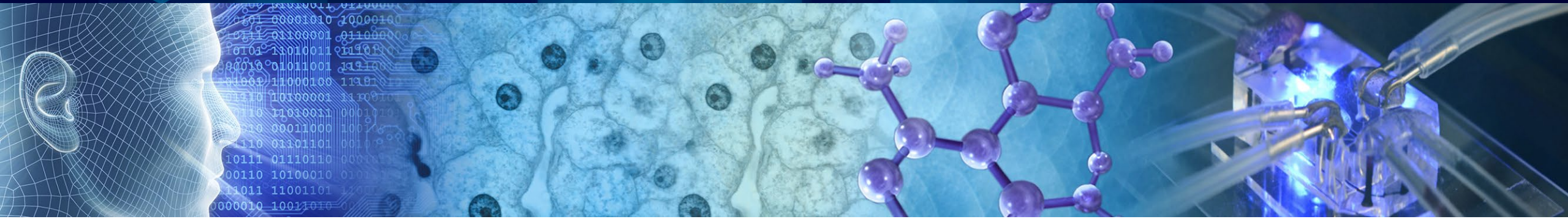
National Institute of Environmental Health Sciences
Division of Translational Toxicology



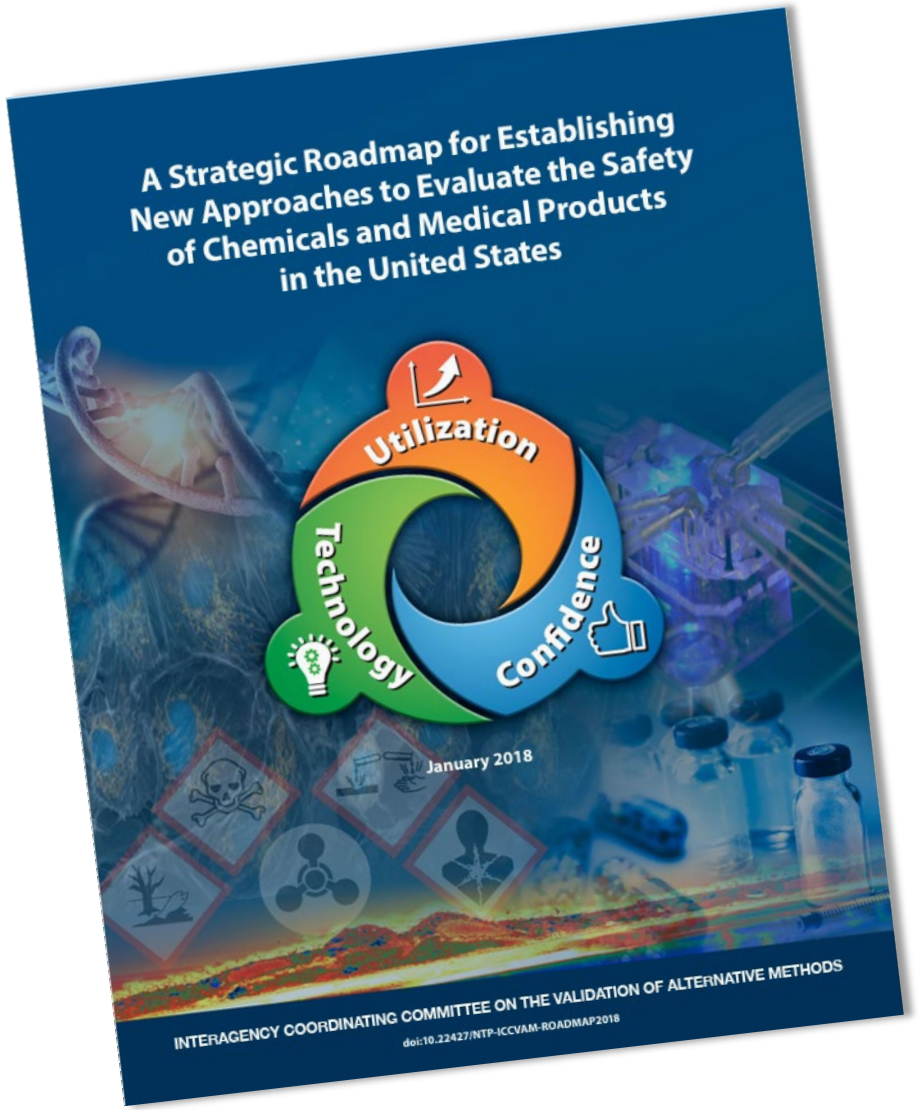
ICCVAM Roadmap and Increased Opportunities

Helena Hogberg, PhD

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

SACATM Meeting
September 11, 2025

ICCVAM Strategic Roadmap - January 2018



- **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/natl-strategy

Agenda Item	Presenter
Session Ia: 5 years into ICCVAM Strategic Roadmap: Full Replacement of the Acute Tox 6-pack	
• Roadmap Implementation Plans: Update on Each of the 6-pack Endpoints, How Close Are We to Replacement?	Dr. Dave Allen, Inotiv
○ Modernizing the Acute Toxicity 'Six-Pack' for U.S. EPA's Office of Chemical Safety and Pollution Prevention	Dr. Monique Perron, EPA
○ Beyond the 6-pack: Strategic Roadmap Future Priorities?	Dr. Nicole Kleinstreuer, NIEHS
Session Ib: 5 Years into ICCVAM Strategic Roadmap: Evolution of Validation	
• ICCVAM Validation Work Group Report	Dr. John Gordon, CPSC
• International Harmonization and Global Considerations	
○ Organizational and Financial Aspects of Validation Studies	Dr. Anne Gourmelon, Organisation for Economic Co-Operation and Development
○ Update of GD 34 and ICATM Position	Dr. Valerie Zuang, European Commission, Joint Research Centre

1. Acute dermal toxicity
2. Acute oral toxicity
3. Acute inhalation toxicity
4. Primary eye irritation
5. Primary skin irritation
6. Skin sensitization

Connect with Method Developers

Connect end users with the developers of alternative methods

More communication is needed between method developers and regulators and among stakeholders from different industries

Training method developers and broader education of stakeholders

Workshops and webinars are good tools for promoting engagement

Need for guidance from agencies to recommend appropriate NAMs

Methods Developer Forum (MDF)

- NAMs developers understand end-user needs to assure fitness-for-purpose
- NAMs developers present their methods to relevant stakeholders
- Each iteration focused on a specific toxicity/endpoint
- Anticipate 1-2 MDFs per year

Methods Developer Forum

Connect end users with the developers of alternative methods

With stakeholder input, the MDF Steering Committee selects an endpoint/toxicity to feature in the MDF main event.

Federal and industry stakeholders record video presentations that summarize their information needs and decision frameworks relevant to the featured endpoint/toxicity.

Recordings are posted on the NICEATM website.

A call for method developer presentations goes out in relevant media platforms.

Participating method developers are asked to view the stakeholder recordings and, using a basic set of questions that correspond to the key concepts in the VWG report, prepare a submission on their method.

The MDF Steering Committee reviews submissions and selects those to be presented at the MDF main event.

The MDF main event features brief presentations from selected method developers.

A panel of stakeholders provides feedback on the featured NAMs' readiness, confidence, and other aspects that should be addressed to strengthen the validation efforts.

Follow up activity?

Organizing the MDF Event

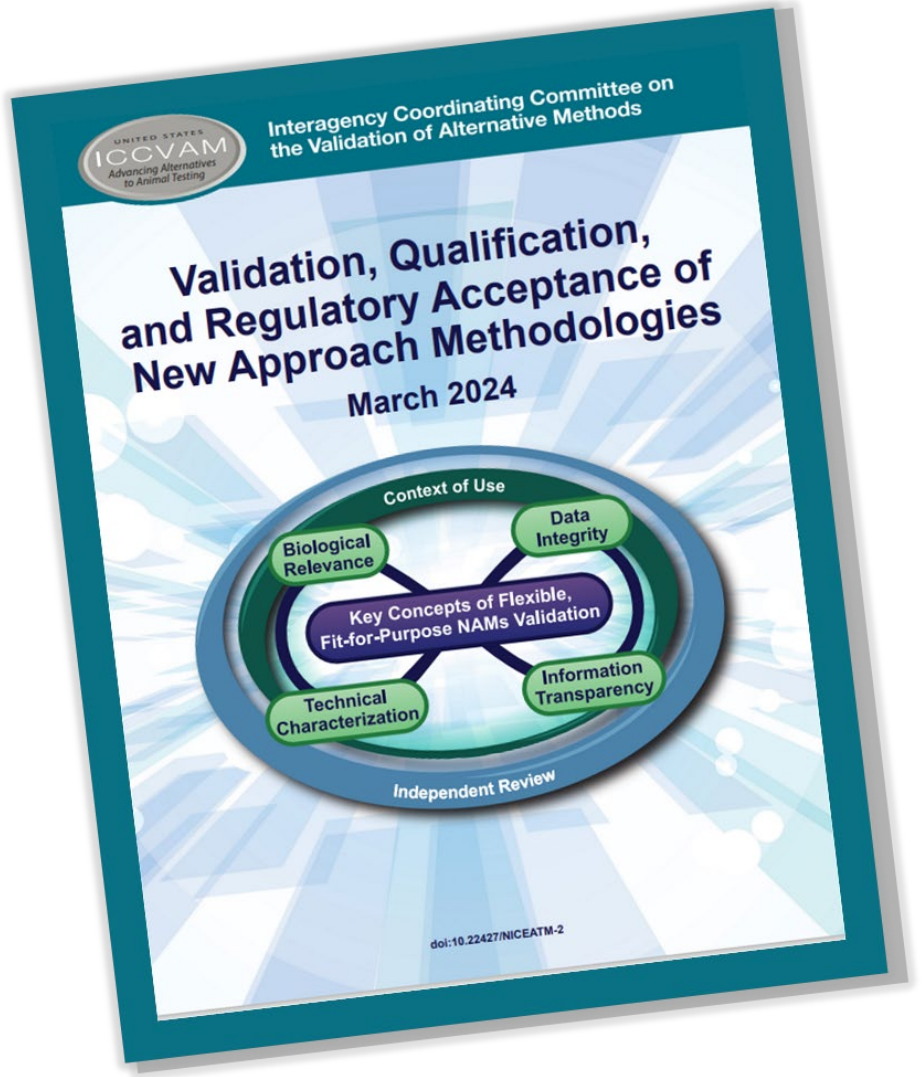
Expand workshops and webinars to hosting focus groups and developing manuscripts in collaboration with method developers

Flexible Validation

Establish new validation approaches that are more flexible and efficient

Standards for validation should be tied to context of use

Demonstration of relevance to human biology is very important



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

Human Relevance

Establish new validation approaches that are more flexible and efficient

Standards for validation should be tied to context of use

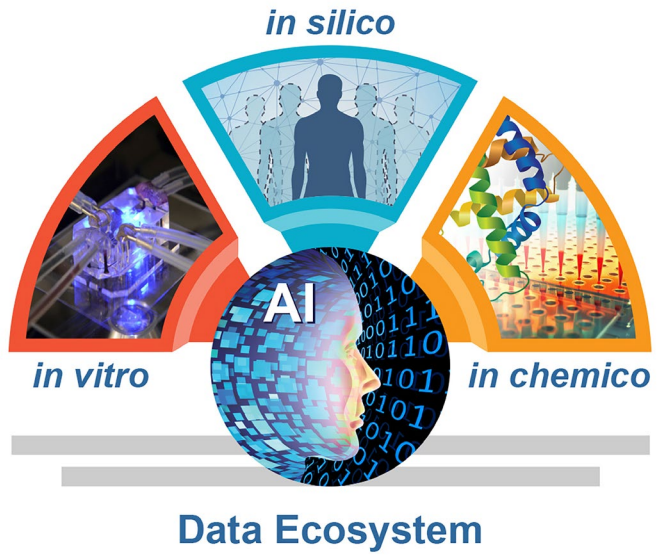
Demonstration of relevance to human biology is very important

A common standard is needed for characterizing NAMs that will bridge the gap between toxicology and medical research

Method developers could also benefit from help with curating data and data review, understanding FAIR concepts and defining what metadata are needed

The question of commercial viability has not been sufficiently addressed

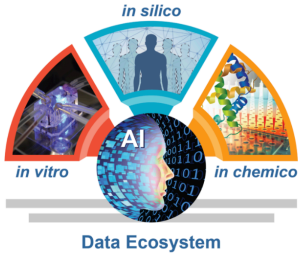
Session II



Validation & Qualification Network Design Phase

Help us build scientific confidence in human-based research platforms. Submit a NAMs project concept.

Researchers have increasingly been working to develop new laboratory models that more accurately represent human biology compared to traditional models. New Approach Methodologies (NAMs) are laboratory (*in vitro* or *in chemico*) or computer-based (*in silico*) research approaches that have the potential to transform basic, translational, and clinical science through the development and use of new human-based biomedical research models. NAMs include pioneering technologies — such as organs-on-a-chip, AI models, and cell lines — that model human biology. The goal of the NIH-funded Complement-ARIE program is to complement, and in some cases replace, traditional animal testing with NAMs, while providing more cost-effective, human-relevant results.



Guidance and Education

Ensure adoption and use of new methods by both regulators and industry

Validation is not sufficient for a new test method to be broadly adopted, it's possible simply educating users might be sufficient

More guidance is also needed about how stakeholders should use in vitro and in silico approaches, especially if they're not to be used as a one-to-one replacement for an animal test

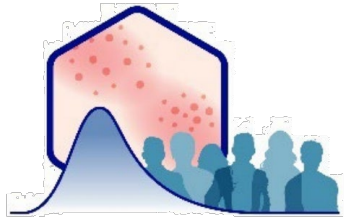
Session III and IV

HPPT App

Classify human predictive patch test data for skin sensitization potency using a weight of evidence approach.

Collection of Alternative Methods for Regulatory Application (CAMERA)

Access validation study reports, data, protocols, SOPs, and other information.



Skin Allergy Risk Assessment-ICE Model (SARA-ICE)

Quantitatively predict a chemical's potential to cause skin sensitization in humans.

DASS App

Predict skin sensitization hazard and potency using defined approaches.

Guidance and Education

Ensure adoption and use of new methods by both regulators and industry

Validation is not sufficient for a new test method to be broadly adopted, it's possible simply educating users might be sufficient

More guidance is also needed about how stakeholders should use in vitro and in silico approaches, especially if they're not to be used as a one-to-one replacement for an animal test

Need for guidance on how to combine methods into Integrated Approaches to Testing and Assessment

Development of implementation plans by agencies will help with harmonization

OECD

DNT IATA Framework Template and Guidance of Support

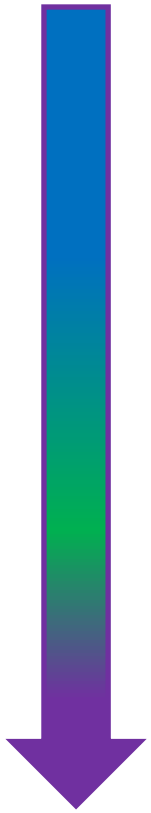
OECD, EU (EFSA) and US (NICEATM) lead project, approved by WHPA in June 2024

Progressing IATA for Systemic Toxicity: Guidance to advance the evaluation of New Approach Methodology (NAM)-based Approaches for Systemic Toxicity

OECD WPHA Systemic Toxicity Leads & Expert Group with support from NICEATM

Increased Standardization of IATA Case Studies

Framework type	Purpose	Level of Flexibility vs Standardisation
IATA Case Study	- Serve as a forum for **exchange** of experience on NAM applications - Share **lessons learned** and publish cases - Regulators can decide if and how to **transpose experience** to their situation - **Data management** system	- Very flexible - Voluntary basis - Annual cycle of cases reviewed
Conceptual Frameworks **IATA workflows [Framework]**	- **Organise** testing and assessment tools - Propose **suite of methods** to address a question and **increase the weight of the evidence** - Clarify **how to use** (interpret/integrate) results - Towards a **knowledge management** system	- Typically makes use of standardised methods (computational, in vitro and in vivo) and proposes consistent way to integrate
Defined Approach	- **Fixed information sources** - **All aspects standardised**	- Fixed data interpretation procedure



Courtesy from Patience Brown, OECD

More Complex Endpoints

- There is also a need to develop human-based testing approaches for more complex endpoints such as **carcinogenesis**, **cardiotoxicity**, and **developmental neurotoxicity**
- Leveraging human data is going to be especially important for addressing complex endpoints
- Establish domain-specific chemical test sets, especially for complex endpoints
- *NAMs to complex mixtures such as pesticide formulations and medical device extracts*

ICCVAM Method Developers Forum

New Approaches for Carcinogenicity Testing

August 21-22, 2024 – 9:00 a.m.-12 noon EDT each day – Online

Agenda

7 ICCVAM Agencies
1 Industry + 1 Academia
10 Methods Developer Presentations

Method Developers Forums

New Approaches for Cardiovascular Toxicity Testing

Planning in progress

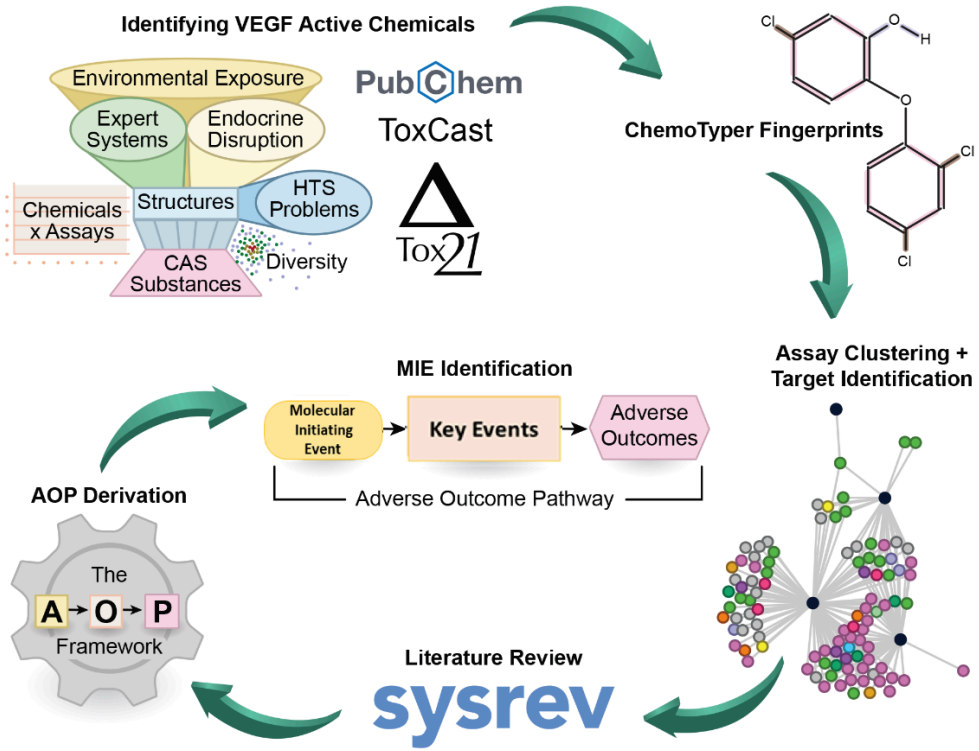
Cardiovascular Toxicity

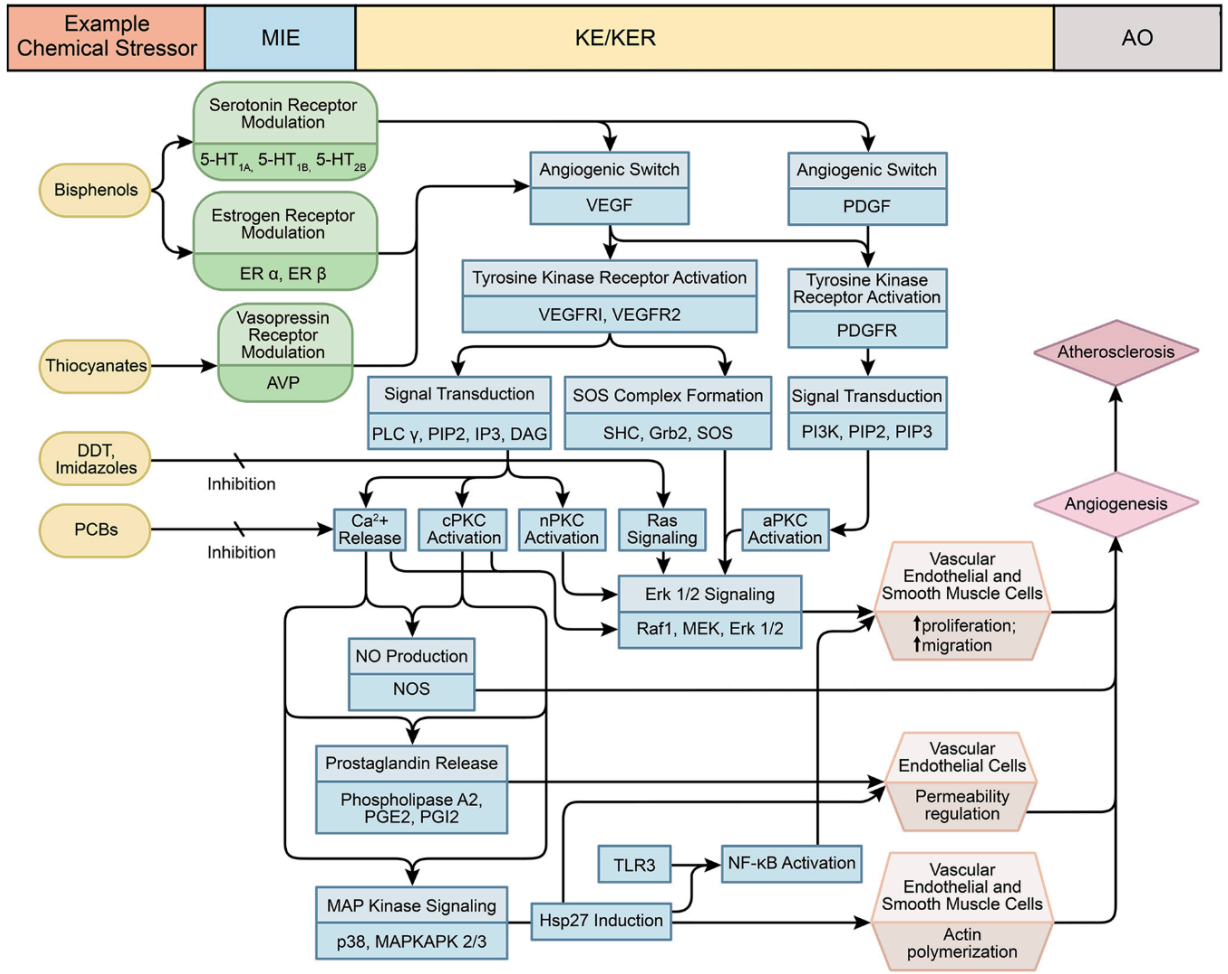
Research Article

Data-Driven Derivation of an Adverse Outcome Pathway Linking Vascular Endothelial Growth Factor Receptor (VEGFR), Endocrine Disruption, and Atherosclerosis

Daniel Ehrlich[# 1], Shagun Krishna[# 2] and Nicole Kleinstreuer[2]

[1]Duke University, Durham, NC, USA; [2]Division of Translational Toxicology, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

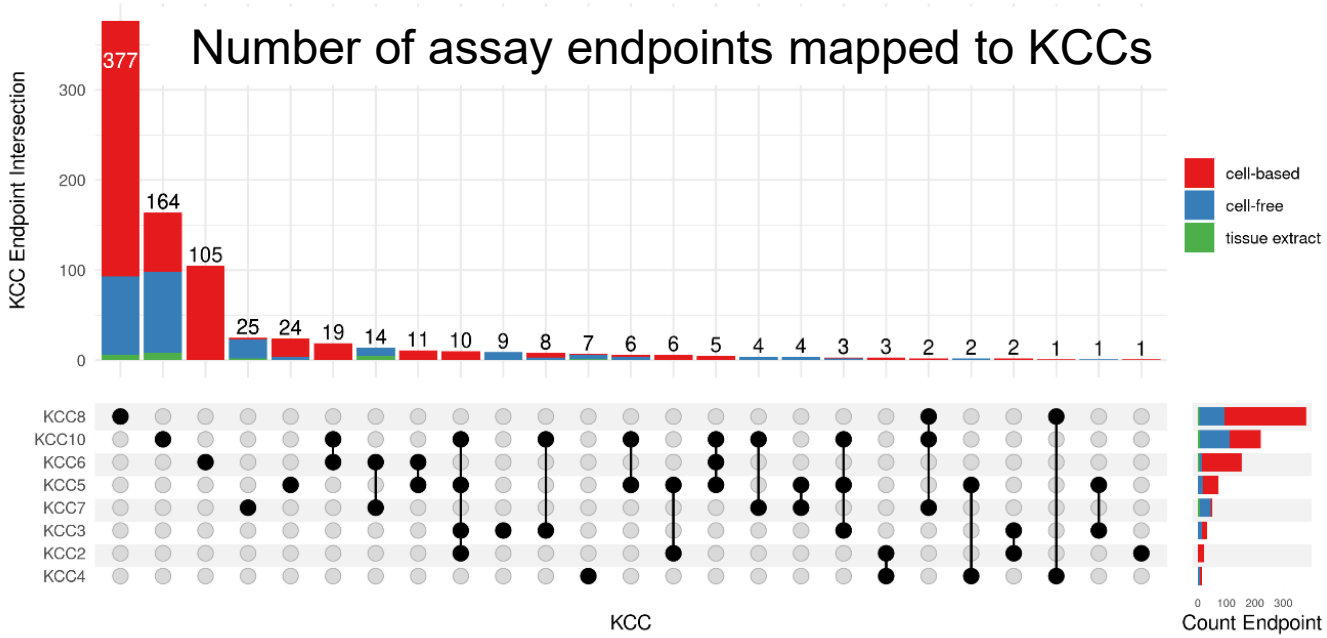




Key Characteristics of Carcinogens (KCCs)

Mapping ToxCast/Tox21 Assays KCCs

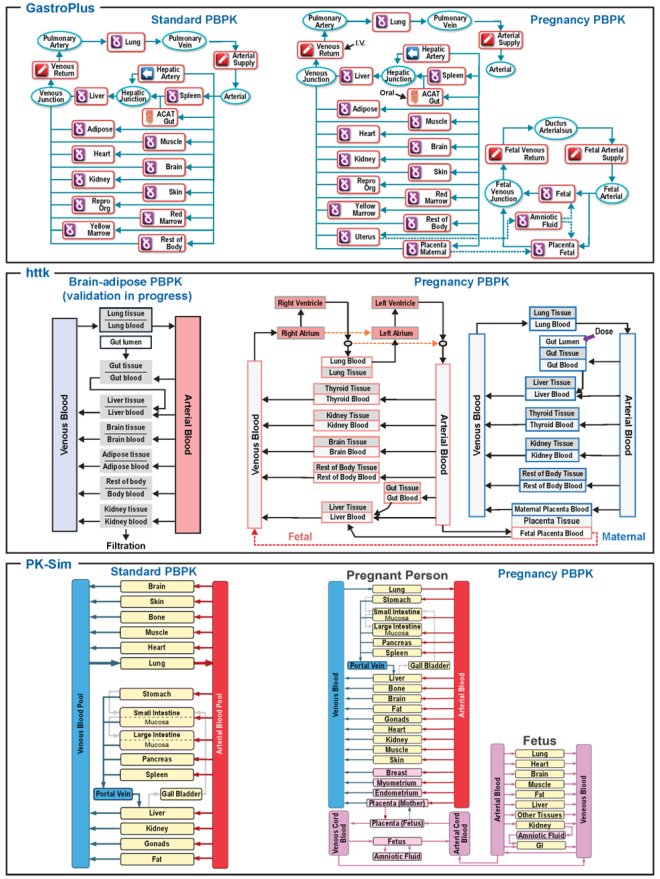
- KCCs are a conceptual framework to integrate mechanistic information into cancer hazard assessments
- A working group was established of 20 scientists with expertise in cancer research
- Expert review of assay technology and biological target led to establishment of a harmonized tiering approach based on relevance to carcinogenesis



- Out of 1570 assays endpoints available in ToxCast/Tox21, 836 assays (56%) have been mapped to the KCCs
- Our updated mapping included information about relevance and assay directionality

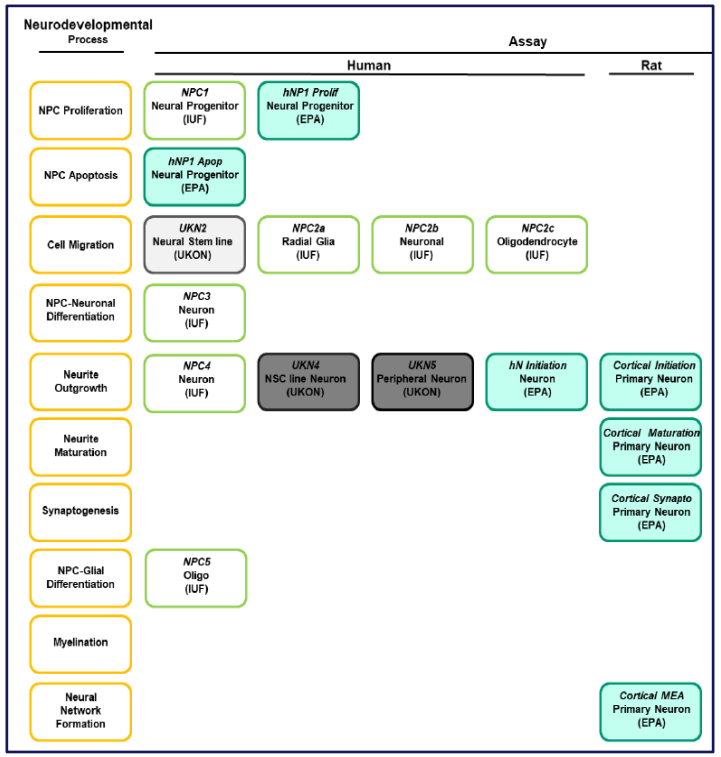
Developmental Neurotoxicity (DNT)

PBPK and IVIVE



Manuscript in revision Tox Sci.

Identification of Reference Compounds for Transfer of Assays



Independent Review of Assay Transfer

IATAs Development

Kreutz et al. 2024 Toxics

Increased Collaborations

NIH to prioritize human-base

New initiative aims to reduce use of animals in N

The National Institutes of Health (NIH) is adopting a new initiative to
innovative, human-based
Developing and using cutti
aligns with the U.S. Food a
to reduce testing in anima
vital to advancing scientifi
can offer unique strengths
can expand the toolbox fo
unanswerable biomedical

"For decades, our biomedi
models. With this initiative
NIH Director Dr. Jay Bhatta
and technology with our g
fundamentally reimagine t
development to real-world
accelerate innovation, imp
changing treatments. It ma

FDA Announces Plan to Phase Out Animal Testing Requirement for Monoclonal Antibodies and Other Drugs

For Immediate Release: April 10, 2025

tentially replaced using a range of
l cell lines and organoid toxicity
es or NAMs data). Implementation of
) applications, where inclusion of
eleased today. To make
g, real-world safety data from other
s already been studied in humans.

NIH Funding Announcements to Align with NIH Initiative to Prioritize Human-based Research

July 10, 2025

On April 29, NIH announced it is prioritizing human-focused research and reducing animal use in research. To further this initiative, all new Notices of Funding Opportunity that relate to animal model systems (NOFOs) must now also support human-focused approaches such as clinical trials, real world data, or new approach methods (NAMs). Examples of NAMs include ex vivo human-based approaches, including perfused human organs and precision-cut tissue slices; in vitro methods, including microphysiological systems and organoids; computational and artificial intelligence-based approaches; and combinations thereof.

Importantly, NIH will no longer issue NOFOs exclusively supporting animal models or limit/specify the types of models that must be used. The intent of this effort is to ensure investigators consider the models most appropriate for understanding human states of health and disease and are not constrained by the NOFO. NIH Institutes, Centers and Program may issue NOFOs that exclude proposals for animal use entirely.

This new emphasis on human-based research will accelerate medical advances, save animals and help NIH achieve its crucial mission of improving human health.

Development of implementation plans by agencies will help with harmonization, and this in turn depends on open communication within and among agencies

Maintain engagement among all agencies, those with less research components appear to be slower to move beyond the animal tests

National Institute of Environmental Health Sciences
Division of Translational Toxicology

Acknowledgments

The NICEATM Group

UNITED STATES ICCVAM
Advancing Alternatives to Animal Testing

Integrated Chemical Environment

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