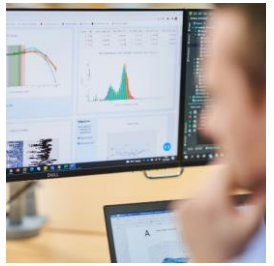
A Decade of Progress with NAMs & NGRA

Prof. Dr. Paul L. Carmichael

Safety, Environmental & Regulatory Science
Unilever, UK

SERS
Safety, Environmental & Regulatory Science



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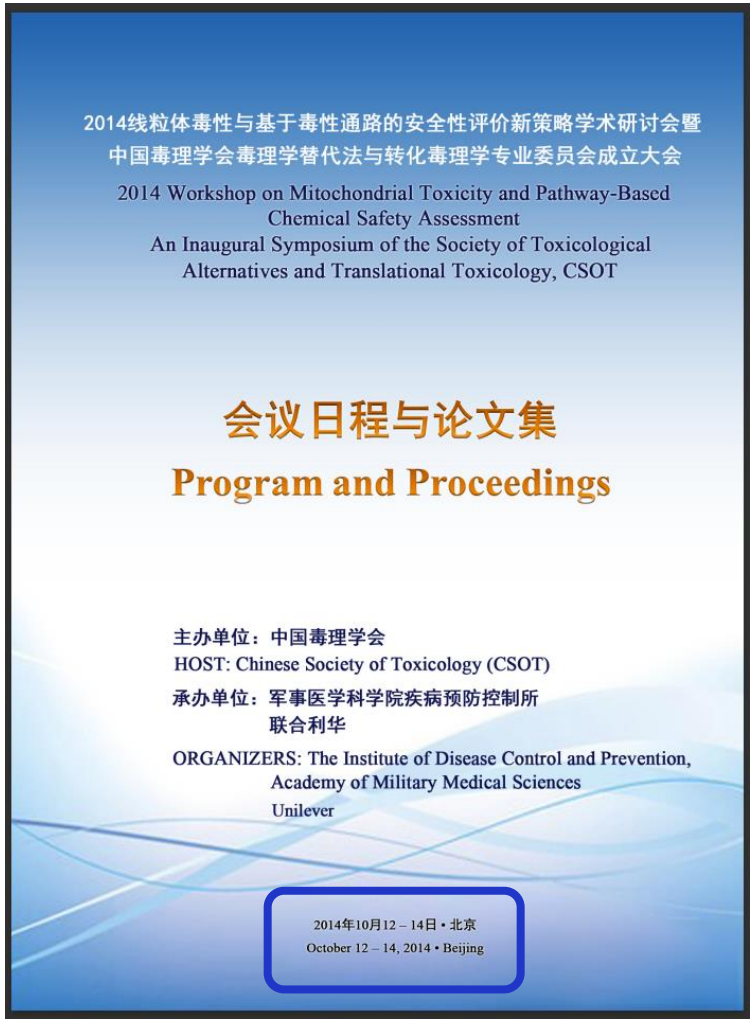
A Decade of TATT



2011 to 2025 – From TT21C to NAMs/NGRA

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A Decade of:
Next Generation Risk Assessment (NGRA)
New Approach (non-animal) Methodologies (NAMs)

NGRA is an exposure-led, risk assessment approach that integrates New Approach Methodologies (NAMs) to assure (human & environmental) safety without the use of animal testing

NAMs are any *in vitro* or computational (*in silico*) method that enables mechanistically based chemical safety assessment and contributes to the replacement of animals

讨论争议点：下/新一代风险评估；Next/New?

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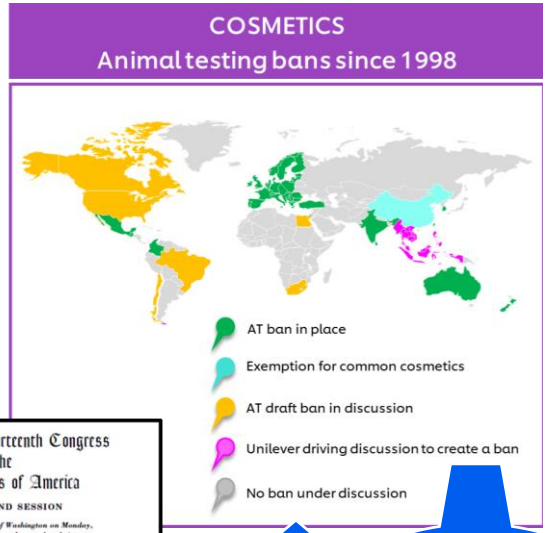
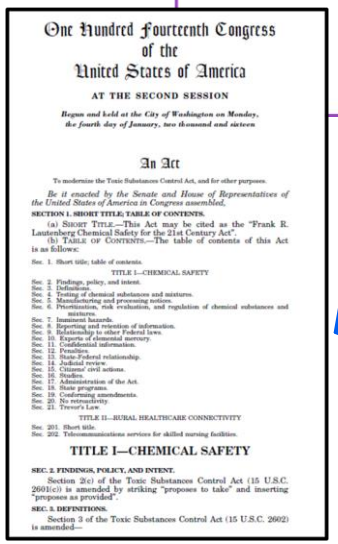
The Need for Implementation of NAM-Based Safety Assessments





One Hundred Fourteenth Congress
of the
United States of America
AT THE SECOND SESSION

Begun and held at the City of Washington on Monday, the fourth day of January, two thousand and sixteen

An Act

To modernize the Toxic Substances Control Act, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the "Frank R. Lautenberg Chemical Safety for the 21st Century Act".

(b) TABLE OF CONTENTS.—The table of contents of this Act is as follows:

Sec. 1. Short title; table of contents.

TITLE I—CHEMICAL SAFETY

Sec. 2. Findings, policy, and intent.
Sec. 3. Definitions.
Sec. 4. Testing of chemical substances and mixtures.
Sec. 5. Manufacturing and processing notices.
Sec. 6. Prioritization, risk evaluation, and regulation of chemical substances and mixtures.
Sec. 7. Imminent hazards.
Sec. 8. Reporting and retention of information.
Sec. 9. Relationship to other Federal laws.
Sec. 10. Exports of elemental mercury.
Sec. 11. Confidential information.
Sec. 12. Penalties.
Sec. 13. State-Federal relationship.
Sec. 14. Judicial review.
Sec. 15. Citizens' civil actions.
Sec. 16. Studies.
Sec. 17. Administration of the Act.
Sec. 18. State programs.
Sec. 19. Conforming amendments.
Sec. 20. No retroactivity.
Sec. 21. Trevor's Law.

TITLE II—RURAL HEALTHCARE CONNECTIVITY

Sec. 201. Short title.
Sec. 202. Telecommunications services for skilled nursing facilities.

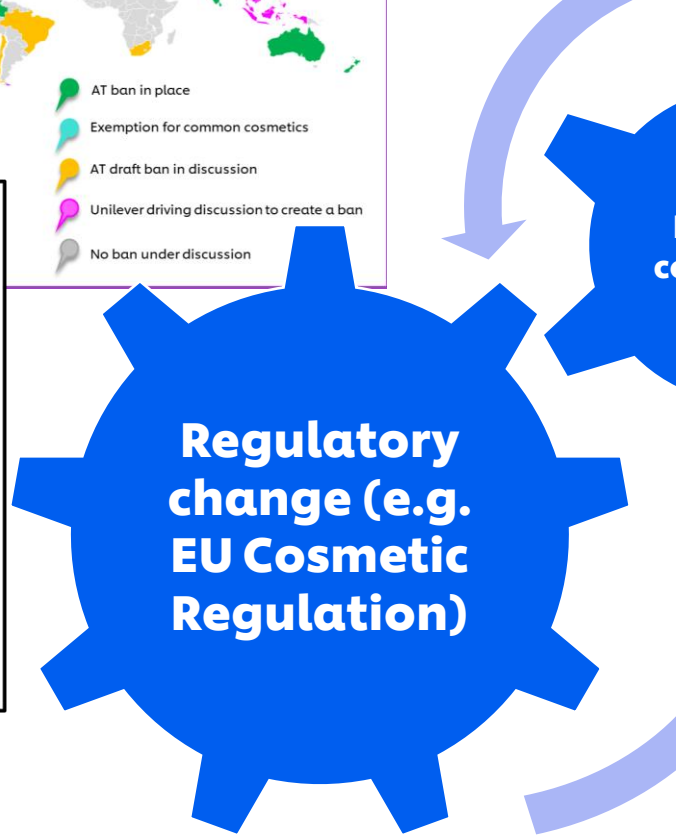
TITLE I—CHEMICAL SAFETY

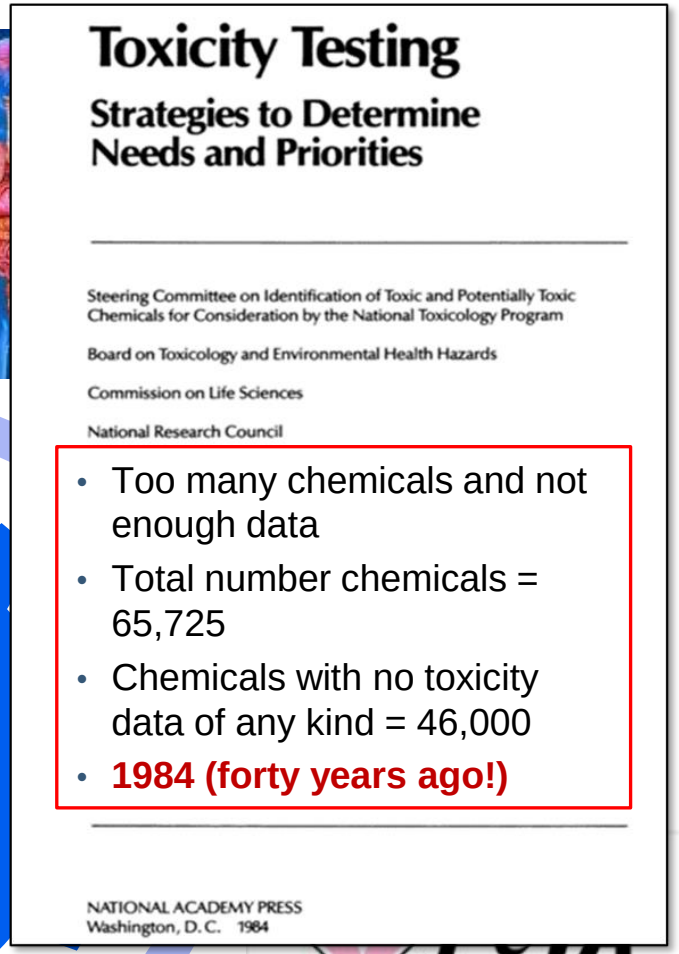
SEC. 2. FINDINGS, POLICY, AND INTENT.

Section 2(c) of the Toxic Substances Control Act (15 U.S.C. 2601(c)) is amended by striking "proposes to take" and inserting "proposes as provided".

SEC. 3. DEFINITIONS.

Section 3 of the Toxic Substances Control Act (15 U.S.C. 2602) is amended—





Toxicity Testing

Strategies to Determine Needs and Priorities

Steering Committee on Identification of Toxic and Potentially Toxic Chemicals for Consideration by the National Toxicology Program

Board on Toxicology and Environmental Health Hazards

Commission on Life Sciences

National Research Council

- Too many chemicals and not enough data
- Total number chemicals = 65,725
- Chemicals with no toxicity data of any kind = 46,000
- **1984 (forty years ago!)**

NATIONAL ACADEMY PRESS
Washington, D.C. 1984

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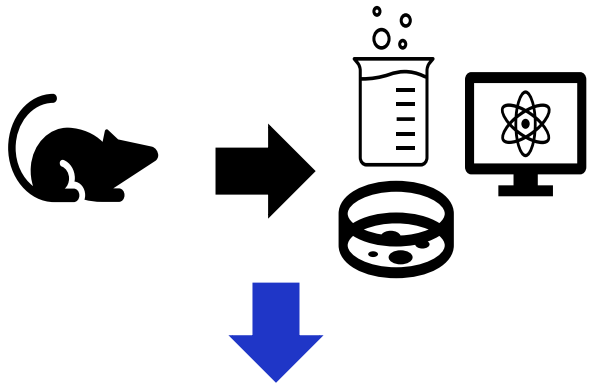
Non-Animal Frameworks for Safety Decisions:

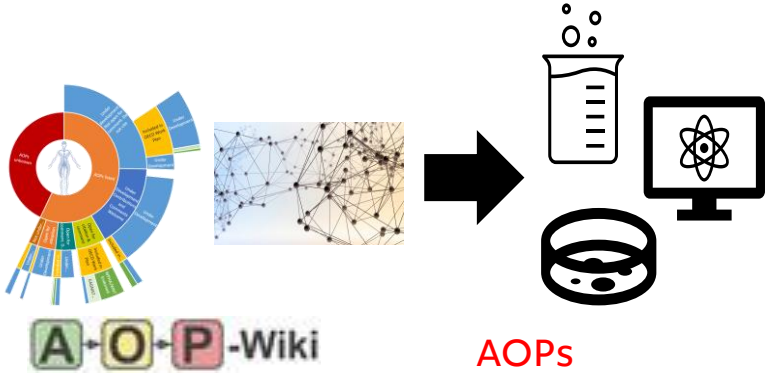
Non-animal NAMs strategies for 1-2-1 replacement – prediction of animal outcome



Prediction of an animal test is **not** necessarily relevant to assess human safety

Rodent studies have been used in a protective manner with the use of uncertainty factors rather than in a predictive way

Development of battery of assays aligned to AOPs



AOPs (currently 481 in AOP wiki; 1789 KE)

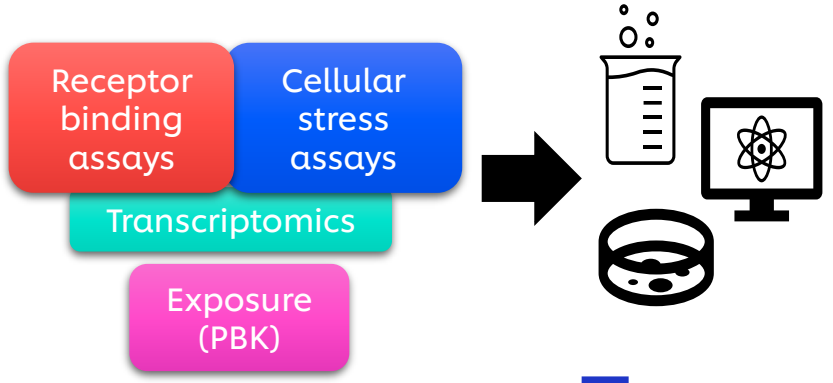
~ Multiple 1000s of assays need to be if multiple AOPs are covered

How to identify the relevant AOP?

Not feasible for initial safety testing

Value in bespoke safety assessment when differentiation between bioactivity & adversity is needed (higher tier)

Development of high-throughput & broad coverage set of non-animal NAMs



Protection Hypothesis:

If biological activity measured using a broad suite of human-relevant test systems is above the predicted exposure in humans, then systemic adverse effects are highly unlikely

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Why Tier NAMs in a Protective NGRA?

- Can then implement the available and valid tools in a measured and logical way
- Maintain a core dynamic system relevant to the risk assessment/safety question
  - Be ever prepared to improve and update
- Can lead from early-tier rapid computational tools to potentially more complex testing systems in later tiers
  - But only as necessary
- Helps give greater confidence to Regulators?
  - Improving
- Early Tiers come at a 'utility' cost – the loss of otherwise useful chemicals?
  - That's what we have encountered but we must build confidence

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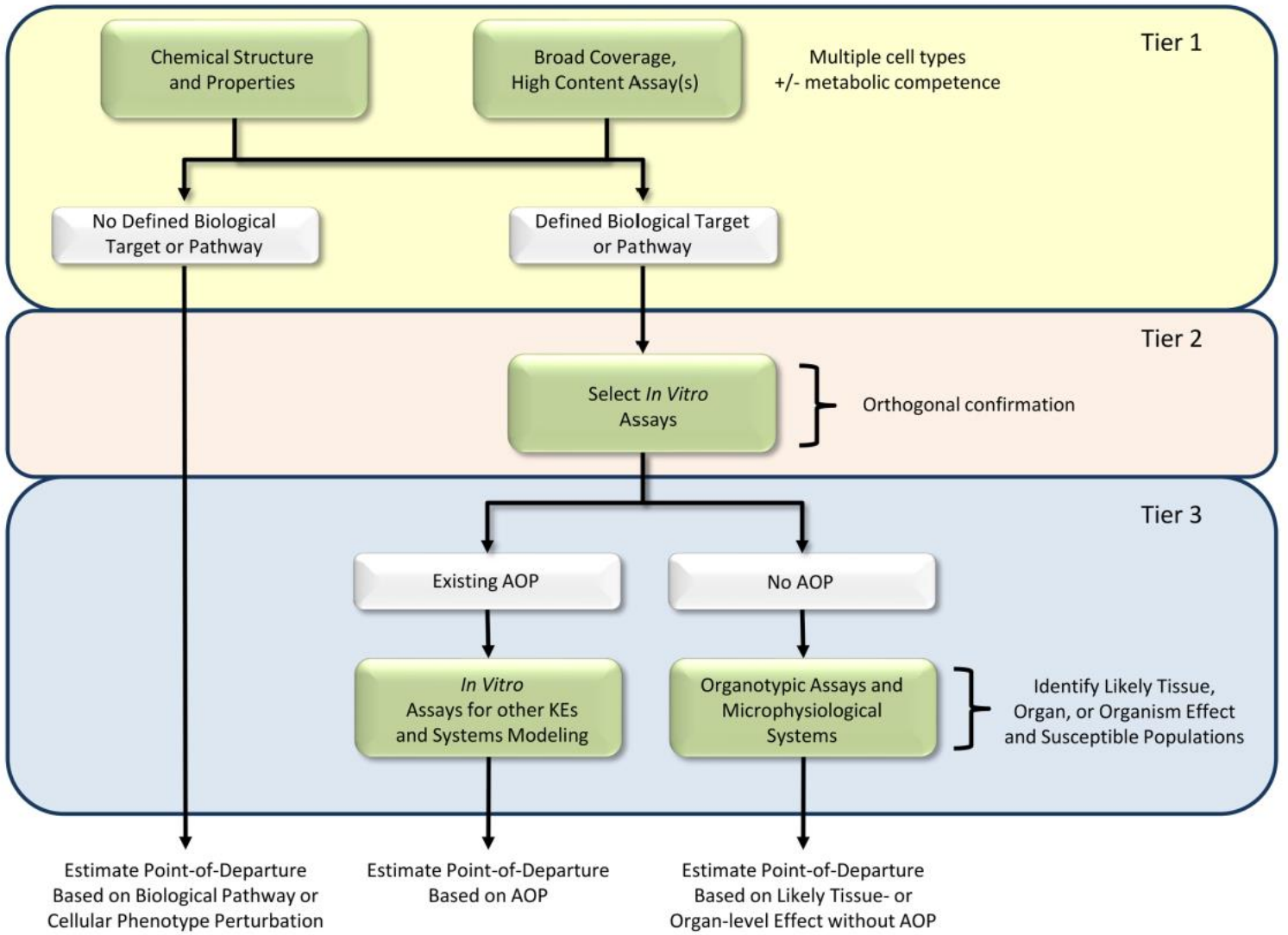
The EPA Blueprint: A 'Tiered' Approach



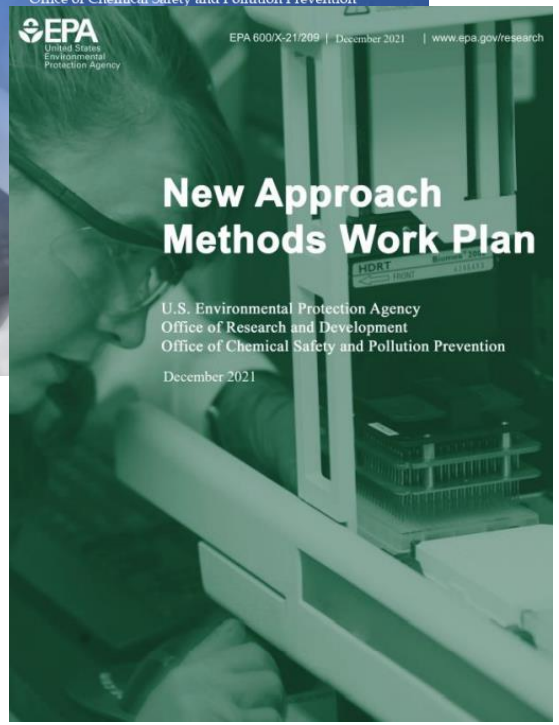
OXFORD SOT Society of Toxicology www.toxsci.oxfordjournals.org

TOXICOLOGICAL SCIENCES, 169(2), 2019, 317–332
doi: 10.1093/toxsci/kfz058
Advance Access Publication Date: March 5, 2019
Forum

FORUM

The Next Generation Blueprint of Computational Toxicology at the U.S. Environmental Protection Agency

Russell S. Thomas,*,[1] Tina Bahadori,[†] Timothy J. Buckley,[‡] John Cowden,* Chad Deisenroth,* Kathie L. Dionisio,[‡] Jeffrey B. Frithsen,[§] Christopher M.



NAMs are Generally *More* Protective than Animal Tests

Accelerating the Pace of Chemical Risk Assessment (APCRA)

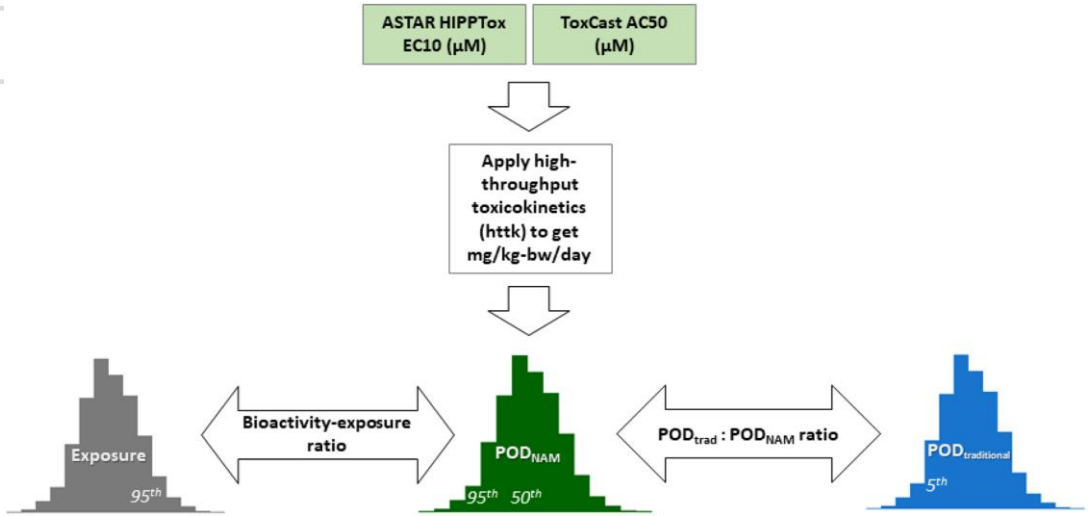
OXFORD SOT Society of Toxicology academic.oup.com/toxsci Tox Spotlight article

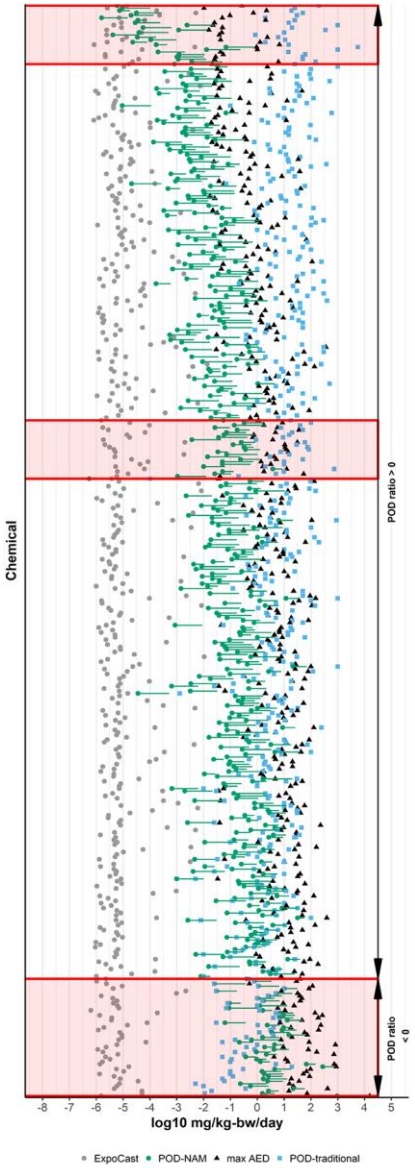
TOXICOLOGICAL SCIENCES, 173(1), 2020, 202–225

doi: 10.1093/toxsci/kfz201
Advance Access Publication Date: September 18, 2019
Research Article

Utility of *In Vitro* Bioactivity as a Lower Bound Estimate of *In Vivo* Adverse Effect Levels and in Risk-Based Prioritization

Katie Paul Friedman ,*,[1] Matthew Gagne,[†] Lit-Hsin Loo,[‡] Panagiotis Karamertzanis,[§] Tatiana Netzeva,[§] Tomasz Sobanski,[§] Jill A. Franzosa,[¶] Ann M. Richard,* Ryan R. Lougee,*,[||] Andrea Gissi,[§] Jia-Ying Joey Lee,[‡] Michelle Angrish,[|||] Jean Lou Dorne,[||||] Stiven Foster,[#] Kathleen Raffaele,[#] Tina Bahadori,[||] Maureen R. Gwinn,* Jason Lambert,* Maurice Whelan,** Mike Rasenberg,[§] Tara Barton-Maclaren,[†] and Russell S. Thomas *



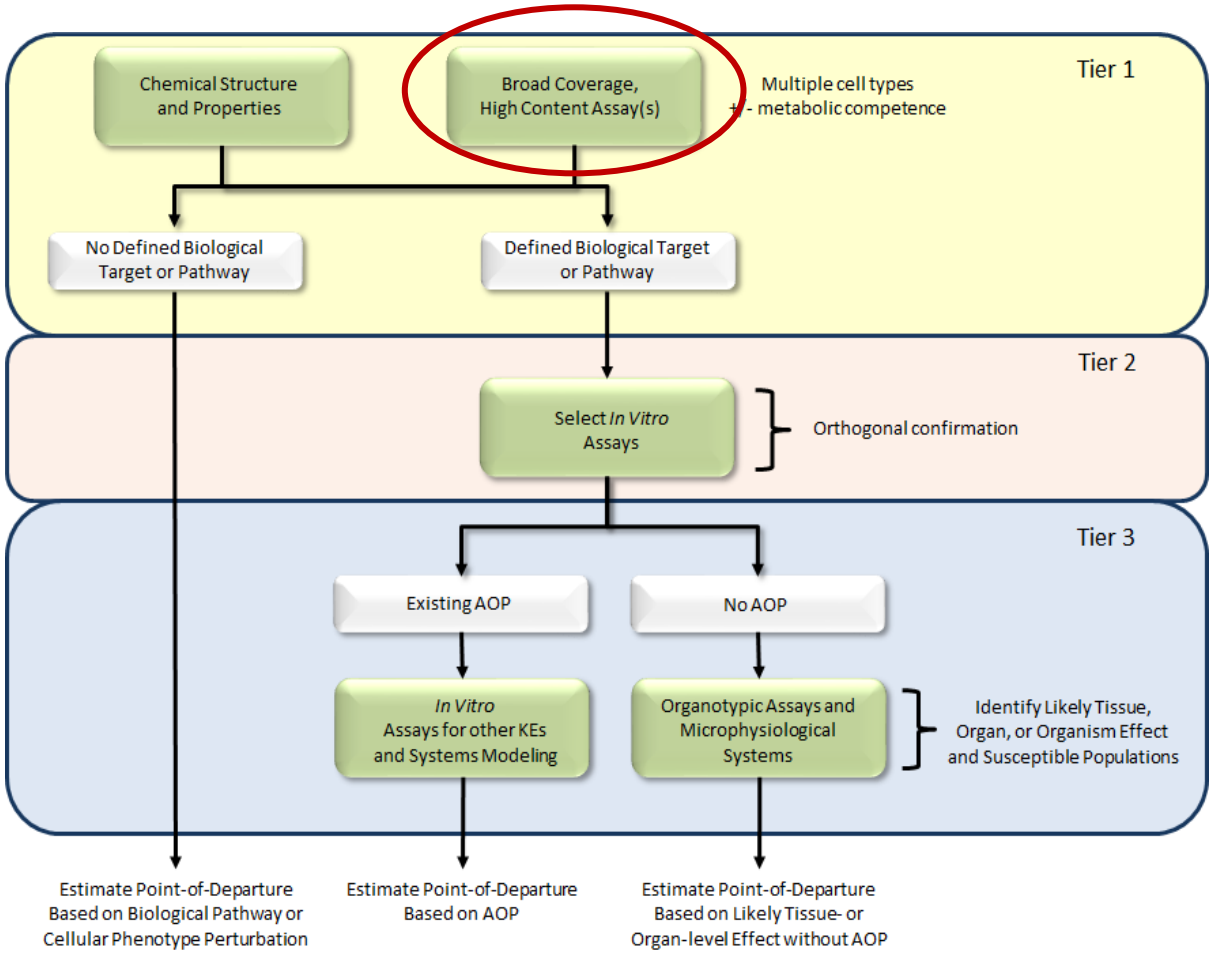


Of the 448 substances, **~90%** had a $POD_{NAM,95}$ that was less than the traditional POD ($POD_{traditional}$) value

Bioactivity:exposure ratios (BERs), useful for identification of priority substances, demonstrated that high-throughput exposure predictions were greater than the $POD_{NAM,95}$ for 11 substances

APCRA ACCELERATING THE PACE OF CHEMICAL RISK ASSESSMENT

EPA Transition from ToxCast to Broad Coverage NAM 'Product'



High throughput profiling (HTP) assays are proposed as the first tier in a NAMs-based hazard evaluation approach

HTP Assay Criteria:

1. Yield bioactivity profiles that can be used for potency estimation, mechanistic prediction and evaluation of chemical similarity
2. Compatible with multiple human-derived culture models
3. Concentration-response screening mode
4. Potential to detect specific and non-specific bioactivity

To date, EPA has identified and implemented two HTP assays that meet this criteria:

- **High-Throughput Transcriptomics [HTTr]**
- **High-Throughput Phenotypic Profiling [HTPP]**

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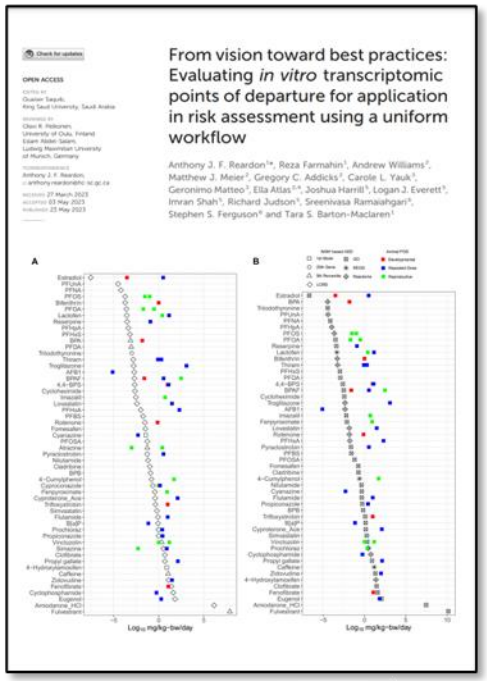
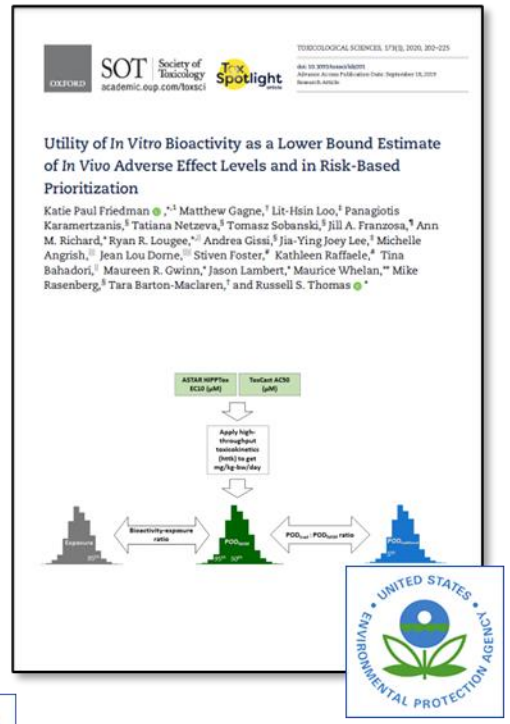
Building NAMs/NGRA Confidence: End-to-End Case Studies

≈40 compounds


From vision toward best practices: Evaluating *in vitro* transcriptomic points of departure for application in risk assessment using a uniform workflow

Anthony J. F. Reardon[1*], Reza Farmahin[1], Andrew Williams[2], Matthew J. Meier[2], Gregory C. Addicks[2], Carole L. Yauk[3], Geronimo Matteo[3], Ella Atlas[3,4], Joshua Harrill[5], Logan J. Everett[5], Imran Shah[5], Richard Judson[5], Sreenivasa Ramaiahgari[6], Stephen S. Ferguson[6] and Tara S. Barton-Maclaren[1]

448 compounds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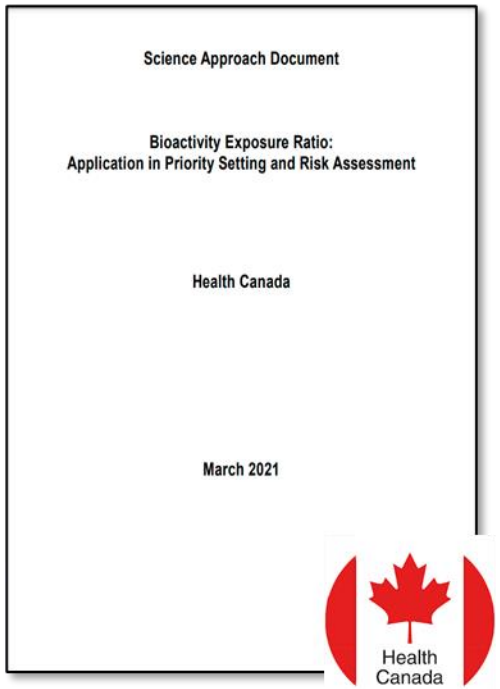
46 compounds


Science Approach Document

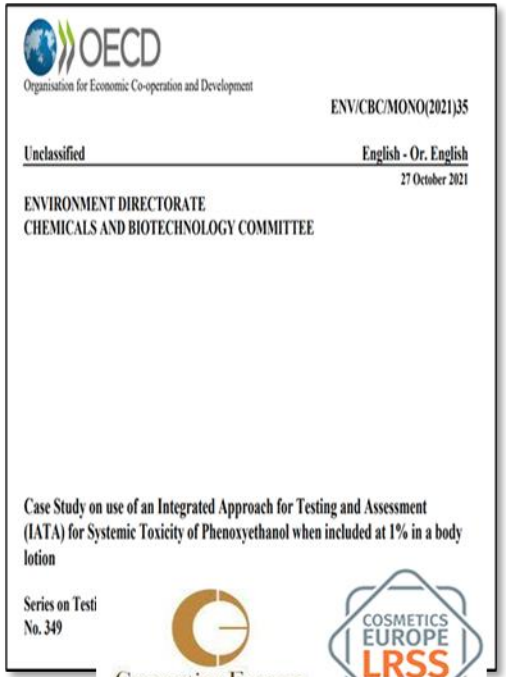
Bioactivity Exposure Ratio:
Application in Priority Setting and Risk Assessment

Health Canada

March 2021

https://www.canada.ca/en/environment-climate-change/services/evaluating-existing-substances/science-approach-document-bioactivity-exposure-ratio-application-priority-setting-risk-assessment.html

30 compounds


OECD
Organisation for Economic Co-operation and Development

ENV/CBC/MONO(2021)35

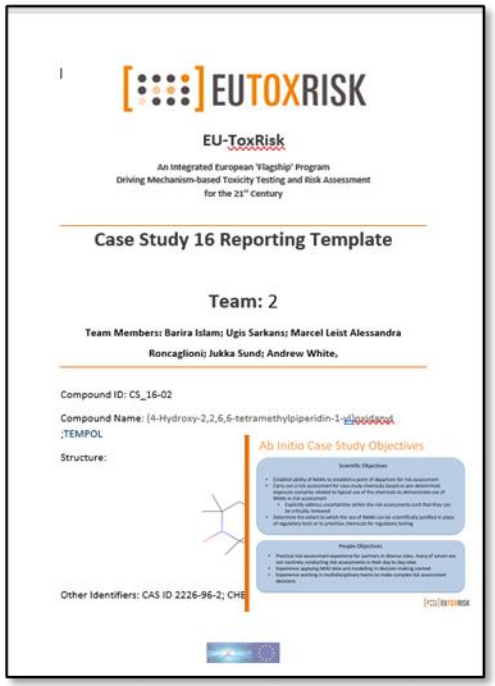
Unclassified — English - Or. English
27 October 2021

ENVIRONMENT DIRECTORATE
CHEMICALS AND BIOTECHNOLOGY COMMITTEE

Case Study on use of an Integrated Approach for Testing and Assessment (IATA) for Systemic Toxicity of Phenoxyethanol when included at 1% in a body lotion

Series on Testi
No. 349

>70 compounds


EUTOXRISK

EU-ToxRisk

An Integrated European 'Flagship' Program
Driving Mechanism-based Toxicity Testing and Risk Assessment
for the 21st Century

Case Study 16 Reporting Template

Team: 2

Team Members: Barira Islam; Ugis Sarkans; Marcel Leist Alessandra Roncaglioni; Jukka Sund; Andrew White,

Compound ID: CS_16-02

Compound Name: (4-Hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl ;TEMPOL

Structure:

Ab Initio Case Study Objectives

Other Identifiers: CAS ID 2226-96-2; CHE

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Unilever: A NAMs/NGRA Tiered Framework Approach:
The overall goal is a human safety risk assessment

TIER 0: Problem Formulation

- Characterise the chemical
- Characterise the consumer exposure scenario
- Collate all available information (literature mining)

→ **Exit** *if safety decision can be made*

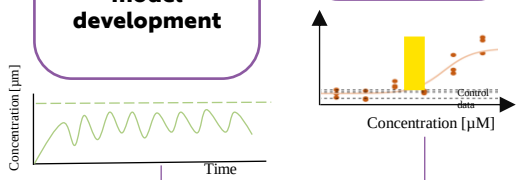
- Use of predictive tools (i.e. *in silico* QSAR models)
- Use of exposure-based waiving approaches such as Threshold of Toxicological Concern (TTC)
- Read Across

→ **Exit** *if safety decision can be made*

Progress if safety decision can't be made

TIER 1: Data Generation

- Exposure refinement including generation of relevant ADME parameter data for PBK model development
- Bioactivity data generation



- Calculate BER

→ **Exit** *if safety decision can be made*

Progress if safety decision can't be made

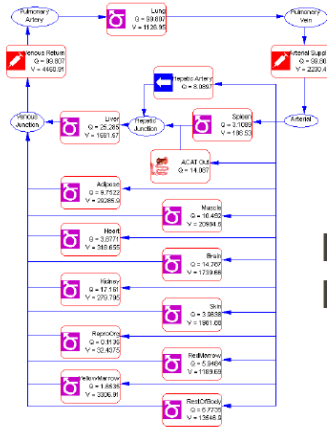
TIER 2: Refine Assessment to Increase Decision Certainty

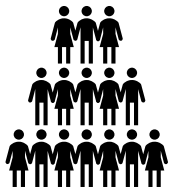
- Bespoke assays to cover remaining uncertainties identified a Tier 0 or Tier 1
- Further exposure refinement, e.g. consideration of transporters, metabolism ..etc...

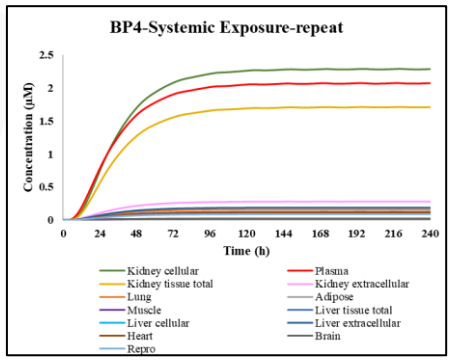
→ **Exit** *Safety Decision*

Unilever: Our Key NAMs

Internal exposure - PBK modelling

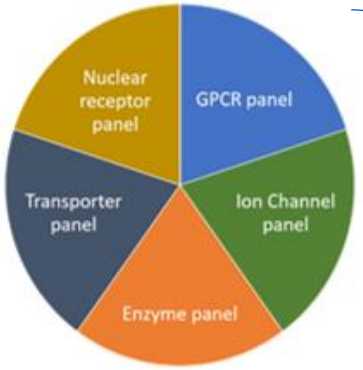






Moxon TE et al., 2020. Toxicology In Vitro, 63, 104746

In vitro pharmacological profiling



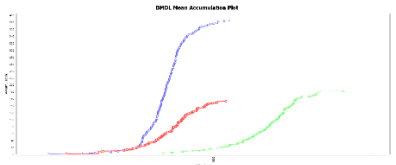
~79 targets

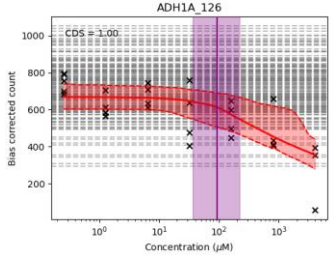
eurofins | Cerep

Bowes et al. 2012. Nat Rev Drug Discov 11(12): 909-22

High-Throughput transcriptomics (HTTr)

- TempO-seq technology – full gene panel
- 24hr exposure
- 7 concentrations
- Various cell models (e.g. HepG2, MCF7, HepaRG)
- Dose-response analysis using BMDExpress2 and BIFROST model





Reynolds et al. 2020. Comp Tox 16: 100138
Baltazar et al. 2020. Toxicol Sci 176(1): 236–252

Cell stress panel (CSP)

- 36 biomarkers covering 10 cell stress pathways
- HepG2
- 24hr exposure
- 8 concentrations
- Dose-response analysis using BIFROST model

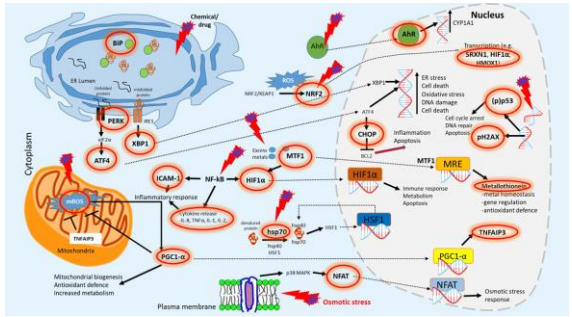


Image kindly provided by Paul Walker (Cyprotex)

Hatherell et al. 2020. Toxicol Sci 176(1): 11-33

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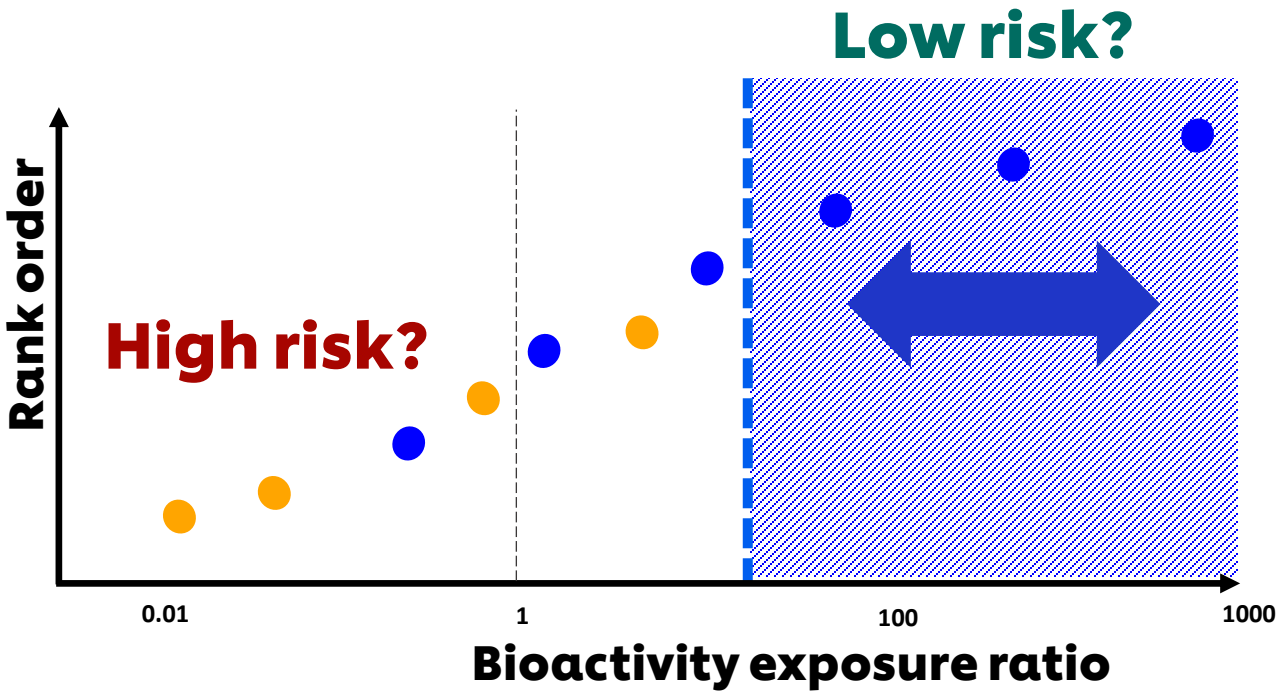
Unilever: Testing the Performance of NAMs in an NGRA

Benchmarking using chemical-exposure scenarios

- Chemicals with well-defined human exposures
- Traditional safety assessment available
- High certainty in the risk classification for each chemical-exposure scenario from a consumer goods perspective
- Risk class is relative to consumer health (N.B. drugs = high-risk)



‘Low’ risk for consumers from systemic perspective

‘High’ risk for consumers from systemic perspective

Protectiveness

How many of the high-risk exposure scenarios are identified as uncertain/high risk?
(i.e. BER < threshold)

Utility

How many of the low-risk scenarios are identified as low-risk at this early tier stage in a risk assessment framework?
(i.e. BER > threshold)

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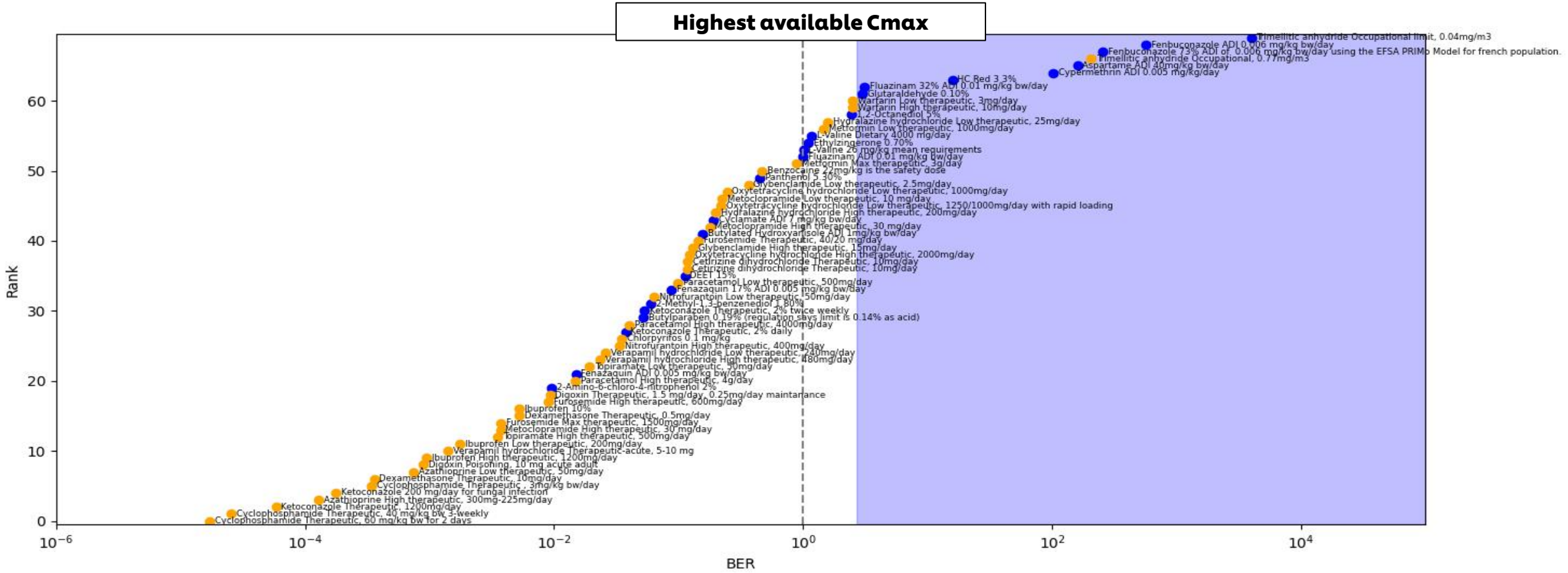
Results for 38 Test Chemicals and 70 Exposure Scenarios



Protectiveness **98% (45 out of 46)**

High-risk exposure scenarios are identified as uncertain/high risk (i.e. BER < threshold)

Utility **33% (8 out of 24)**

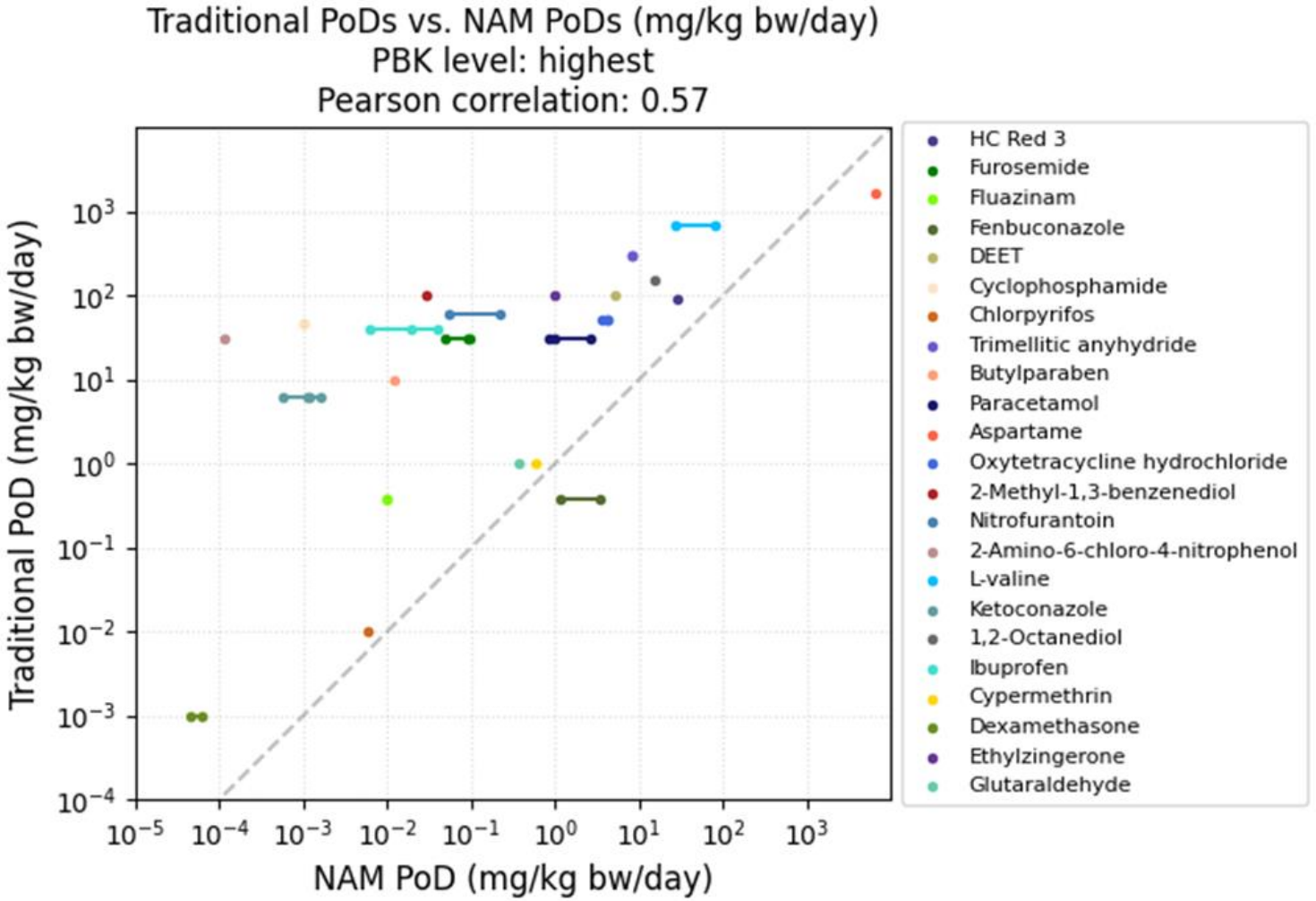
Low-risk scenarios are identified as low risk at this early tier stage in a risk assessment framework (i.e. BER > threshold)

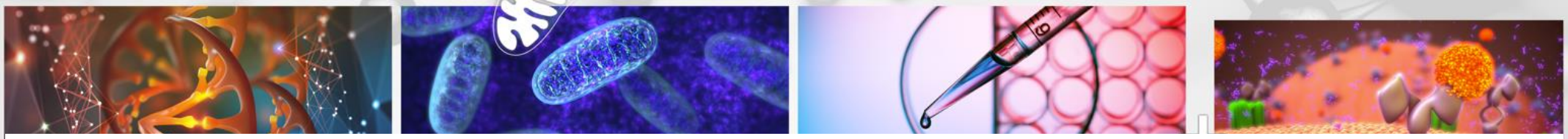
Comparison of NAM-based Tier 1 Toolbox with Decisions Made Using *in vivo* Data – Protective not Predictive

What if we took the same approach with *in vivo* data?

- Repeat dose *in vivo* data identified for 27 chemicals of the 38 tested.
- In most cases NAM PoDs are more conservative than traditional PoDs

In agreement with Paul-Friedman et al. (2020)





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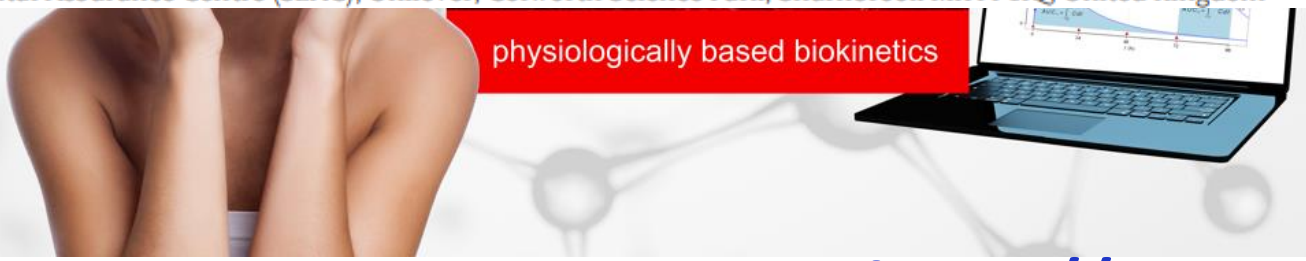
SOT | Society of Toxicology
academic.oup.com/toxsci

Toxicological Sciences, 2025, **204(1)**, 79–95
https://doi.org/10.1093/toxsci/kfae159
Advance Access Publication Date: December 18, 2024
Research article

Advancing systemic toxicity risk assessment: Evaluation of a NAM-based toolbox approach

Sophie Cable*, Maria Teresa Baltazar, Fazila Bunglawala, Paul L. Carmichael, Leonardo Contreas, Matthew Philip Dent, Jade Houghton, Predrag Kukic, Sophie Malcomber, Beate Nicol, Katarzyna R. Przybylak, Ans Punt, Georgia Reynolds, Joe Reynolds, Sharon Scott, Dawei Tang, Alistair M. Middleton

Safety and Environmental Assurance Centre (SEAC), Unilever, Colworth Science Park, Sharnbrook MK44 1LQ, United Kingdom



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https://youtu.be/5Z2S8MnKp7g

A Decade of Progress for TATT with NAMs/NGRA/TT21C

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And Yet, Today, Nearly All Regulatory Safety Testing is **Still** Based on:

Despite the current toxicity testing paradigm not sufficiently serving our needs… woefully limited data, high testing costs, extremely long timelines, lack of human relevance, etc.

What does the USA FDA think?

U.S. FOOD & DRUG ADMINISTRATION

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GUIDANCE DOCUMENT

Considerations for the Use of Artificial Intelligence To Support Regulatory Decision-Making for Drug and Biological Products

Draft Guidance for Industry and Other Interested Parties

JANUARY 2025

THE AMERICAN JOURNAL of MEDICINE

Official Journal of the Alliance for Academic Internal Medicine

The FDA Modernization Act 2.0: Drug Testing in Animals is Rendered Optional

Eli Y. Adashi, MD, MS [a] · Daniel P. O'Mahony, MSLS [b] · I. Glenn Cohen, JD [c]

Affiliations & Notes Article Info

The FDA Modernization Act 2.0 (S.5002), a bipartisan bill co-authored by Senators Cory Booker (D-NJ) and Rand Paul (R-KY), was passed by th Senate on September 29, 2022, by unanimous consent and without amendments. Later ratified by the US House of Representatives, the FDA Modernization Act 2.0, now part of the Consolidated Appropriations Act, 2023, was enacted into law on December 29, 2022.[1] The new law an the Federal Food, Drug, and Cosmetic Act by authorizing sponsors of novel drugs to make use of "certain alternatives to animal testing, incl cell-based assays and computer models, to obtain an exemption from the Food and Drug Administration to investigate the safety and effec of a drug."[1] The new law also "removes a requirement to use animal studies as part of the process to obtain a license for a biological produc biosimilar or interchangeable with another biological product."[1] In this Commentary we review the history of legislative efforts to curtail the mandated use of animals in the testing of drugs for safety and efficacy, discuss the emergence of nonanimal drug testing technology, and r the future prospects thereof.

Congressional expressions of concern over the reliance of the US Food and Drug Administration (FDA) on animals for safety and efficacy test have been a matter of record since 1998. It was in the course of hearings of the Senate Committee on Appropriations that the *Doris Day Ani League* lamented the discontinuation of "all assessments of in vitro, or non-animal test methods, to substantiate the safety of products."[2] Congressional consideration of the authorization of an *Interagency Coordinating Committee on the Validation of Alternative Methods* followe before too long. However, it was not until 2019 that a flurry of Congressional bills were introduced with an eye toward limiting the use of an the testing of new drugs on humane grounds. Examples include, but are not limited to, the *Reducing Animal Testing Act* (S.4288), a bill introc Senator Ben Ray Lujan (D-NM) on May 19, 2022. Perhaps the most compelling illustration of the leanings of the Senate is illustrated by the "S the Senate on Animal Testing" the central missive of which was that "animal testing should not be used for the purposes of safety testing o

FDA

Roadmap to Reducing Animal Testing in Preclinical Safety Studies

Executive Summary

This roadmap outlines a strategic, stepwise approach for FDA to reduce animal testing in preclinical safety studies with scientifically validated new approach methodologies (NAMs), such as organ-on-a-chip systems, computational modeling, and advanced *in vitro* assays. By partnering with federal agencies like NIH and VA through ICCVAM, FDA can accelerate the validation and adoption of these human-relevant methods, improving predictive accuracy while reducing animal use. This transition will enhance public health by streamlining drug development and ensuring safer therapies reach patients faster, while positioning FDA as a global leader in modern regulatory science and innovation.

FDA NEWS RELEASE

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

uncements

For Immediate Release: April 10, 2025

Today, the U.S. Food and Drug Administration is taking a groundbreaking step to advance public health by replacing animal testing in the development of monoclonal antibody therapies and other drugs with more effective, human-relevant methods. The new approach is designed to improve drug safety and accelerate the evaluation process, while reducing animal experimentation, lowering research and development (R&D) costs, and ultimately, drug prices.

The FDA's animal testing requirement will be reduced, refined, or potentially replaced using a range of approaches, including AI-based computational models of toxicity and cell lines and organoid toxicity testing in a laboratory setting (so-called New Approach Methodologies or NAMs data).

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Reflected in Funding at USA National Institutes of Health?

National Institutes of Health
Turning Discovery Into Health

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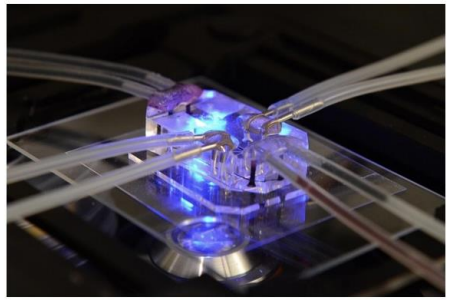
NEWS RELEASES

Tuesday, April 29, 2025

NIH to prioritize human-based research technologies

New initiative aims to reduce use of animals in NIH-funded research.

The National Institutes of Health (NIH) is adopting a new initiative to expand innovative, human-based science while reducing animal use in research. Developing and using cutting-edge alternative nonanimal research models aligns with the U.S. Food and Drug Administration's (FDA) recent initiative to reduce testing in animals. While traditional animal models



Combining microfabrication techniques with

Institute/Center

National Institutes of Health (NIH)

Contact

NIH Office of Communications and Public Liaison
301-496-5787

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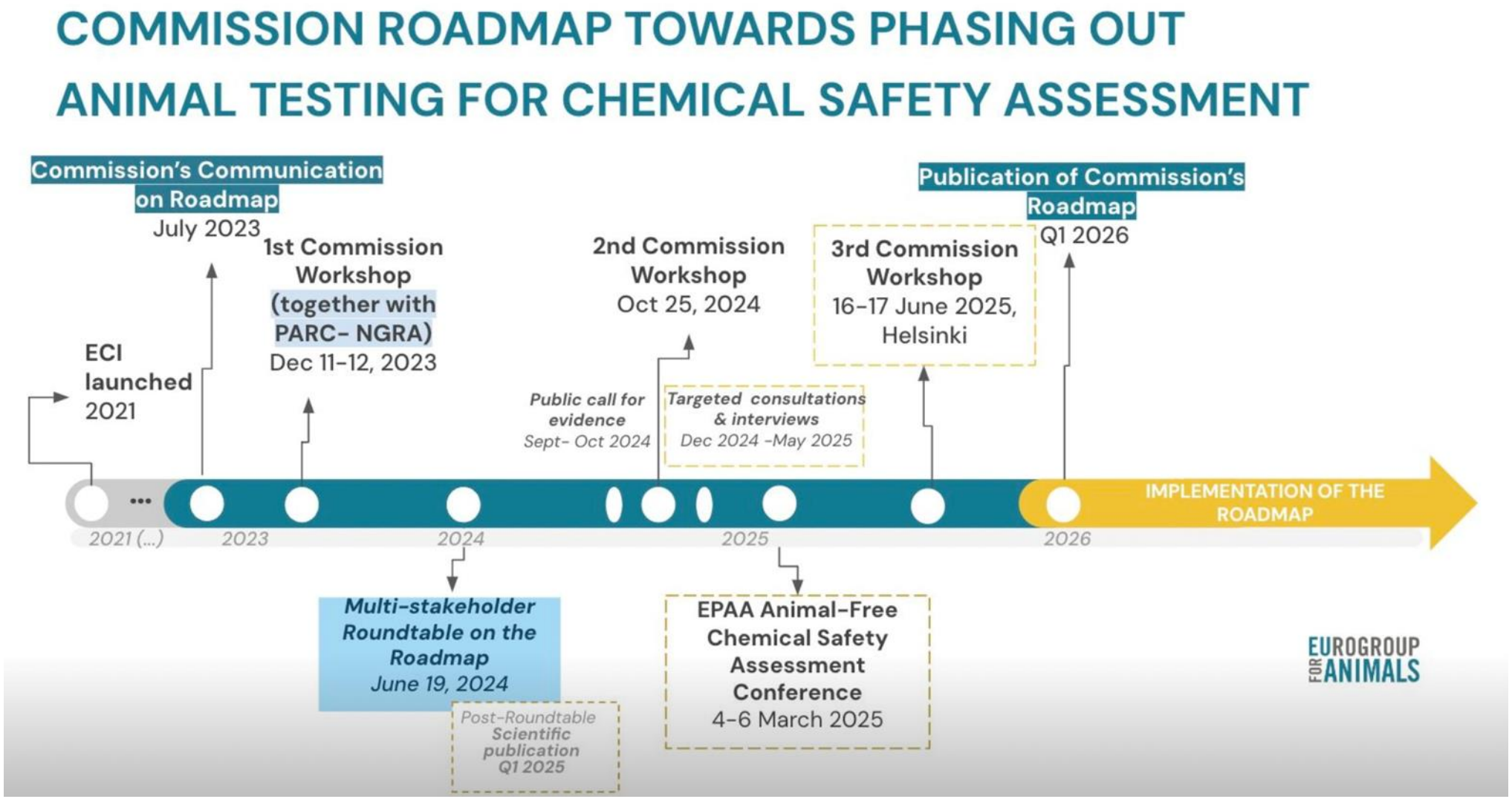
In Europe, A Roadmap? Talk or Action? Lots to Decide On



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In Our Own Work: Selection of Cells?

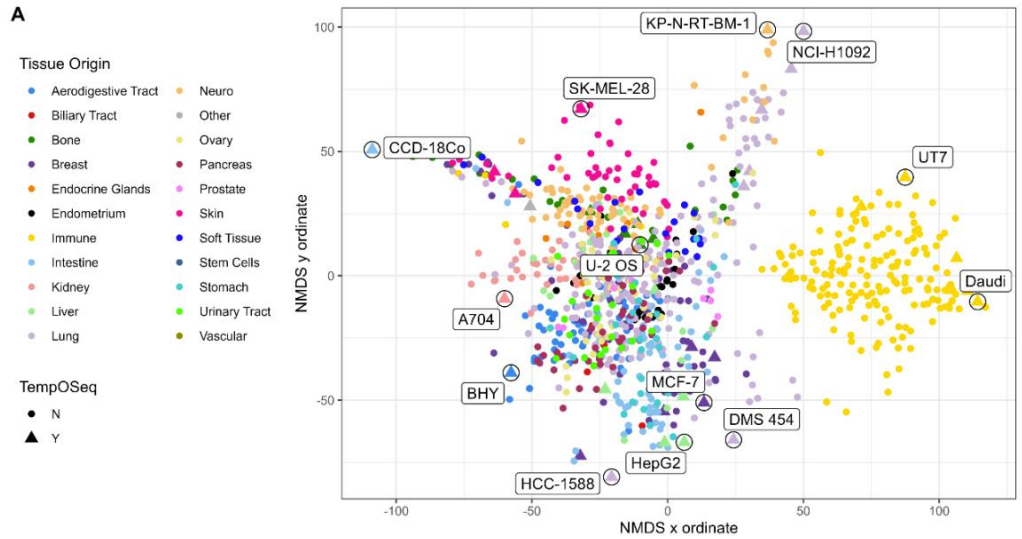
- Initially generated HTTr data in **MCF-7**, **HepG2** and **HepaRG** cell lines for all chemicals, and the Cell Stress Panel is conducted in HepG2 cells.
- Now focussed on using **hTERT** cell lines in place of cancer cell lines for new data generation
- Factors that have been considered:
  - Biological diversity. Using content maximisation methods and baseline gene expression data to rank cells
  - Metabolic capacity. Defining HepaRG 3D as the most competent and using the baseline gene expression data to identify the most and least competent cell lines
  - Presence of DART related genes. Making use of the baseline gene expression data and published lists of DART genes
  - Tissue of origin. Consideration of including most likely target organs or barrier tissues

Already tested:

CHON-001 → Bone
HBEC3-KT → Lung
HepG2 → Liver
hNP1 → Brain
TeloHAEC → Vascular
U-2-0S → Bone

In progress:

RPTEC → Kidney
Ker-CT → Skin
CCD-18Co → Fibroblast
ASC52telo → Mesenchymal stem cell
Two zebrafish cell lines



Are hTERT Cells Likely to be Superseded? YES! By Human iPSCs

2006
- Generation of iPSCs from mouse fibroblasts

2007
- Generation of iPSCs from human fibroblasts
- Generation of iPSC-derived CMs from human fibroblasts

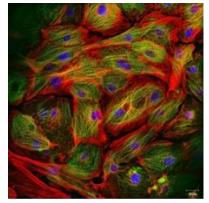
2011
- Use of patient-specific iPSC-CMs for disease modeling [62]
- **Use of iPSC-CMs for drug toxicity testing**

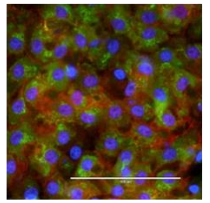
2016
- Use of iPSC-CMs from **patients to recapitulate clinical toxicity of a drug**

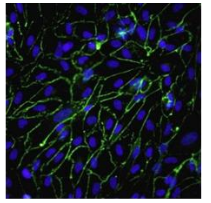
2017
- Use of iPSC-CMs for **non-drug toxicity testing**

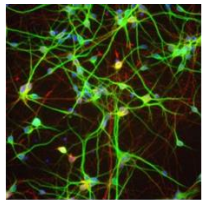
2018
- Use of a healthy population of iPSC-CMs for **environmental chemical toxicity testing**

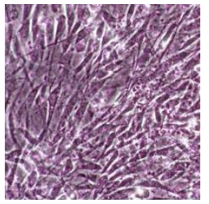
2019
- Use of a healthy population of iPSC-CMs for drug toxicity testing

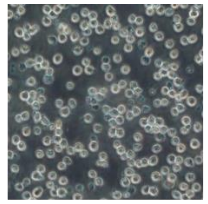

Cardiac Cells

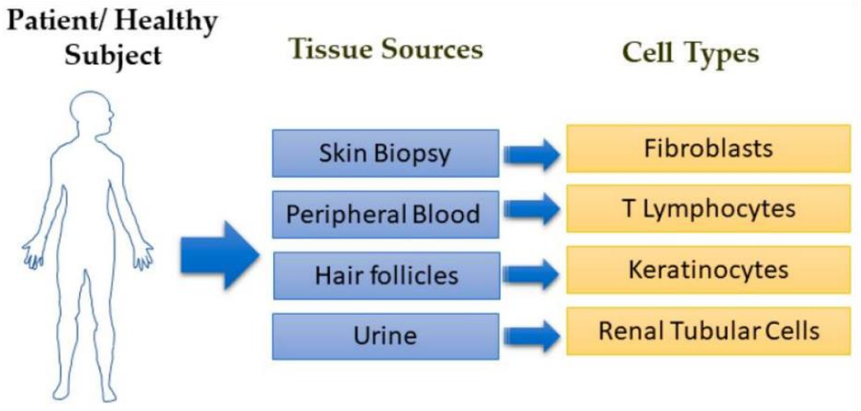

Liver Cells

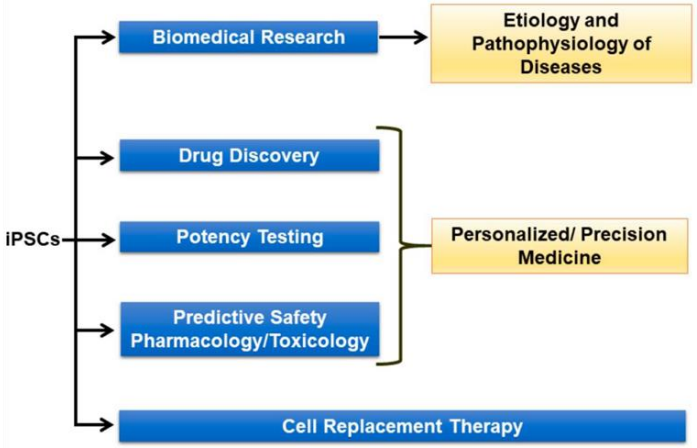

Endothelial Cells


Neuronal Cells


Mesenchymal Cells


Hematopoietic Progenitors





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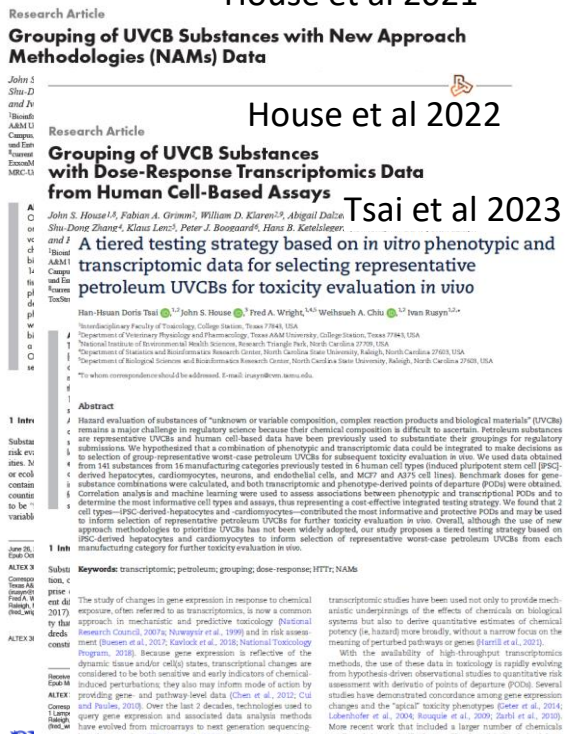
And They Are Being Used in Decision Making:

Grouping of UVCBs to waive (or minimize) animal testing requirements

House et al 2021



Research Article

Grouping of UVCB Substances with New Approach Methodologies (NAMs) Data

House et al 2022

Research Article

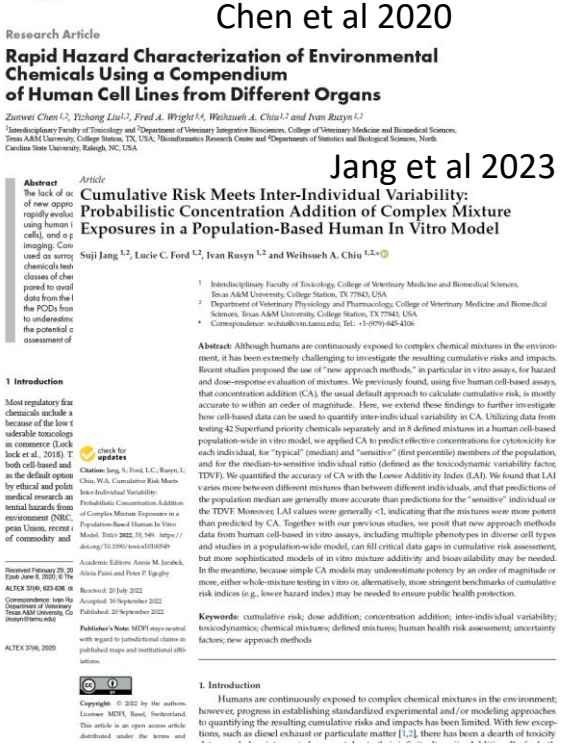
Grouping of UVCB Substances with Dose-Response Transcriptomics Data from Human Cell-Based Assays

Tsai et al 2023

A tiered testing strategy based on *in vitro* phenotypic and transcriptomic data for selecting representative petroleum UVCBs for toxicity evaluation *in vivo*

Deriving "protective" points of departure and bioactivity-exposure ratios

Chen et al 2020



Research Article

Rapid Hazard Characterization of Environmental Chemicals Using a Compendium of Human Cell Lines from Different Organs

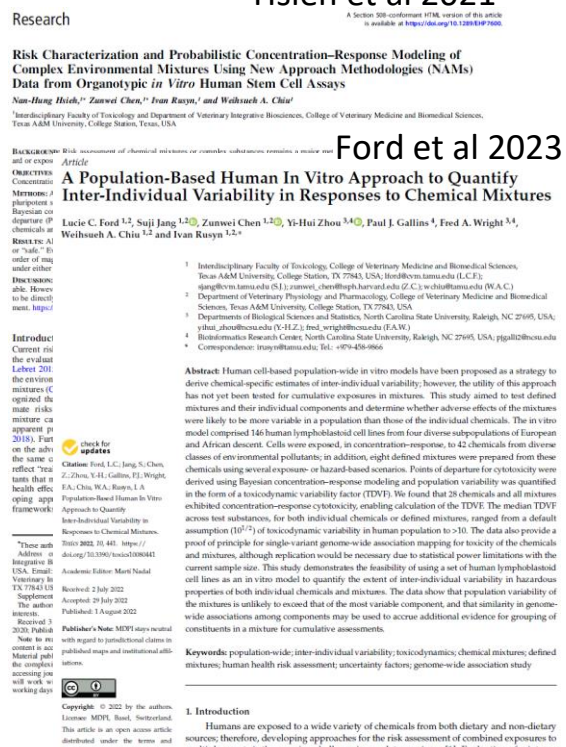
Jang et al 2023

Article

Cumulative Risk Meets Inter-Individual Variability: Probabilistic Concentration Addition of Complex Mixture Exposures in a Population-Based Human In Vitro Model

Testing validity of dose reconstruction assumptions for chemical mixtures

Hsieh et al 2021



Research

Risk Characterization and Probabilistic Concentration–Response Modeling of Complex Environmental Mixtures Using New Approach Methodologies (NAMs) Data from Organotypic *in Vitro* Human Stem Cell Assays

Ford et al 2023

Article

A Population-Based Human In Vitro Approach to Quantify Inter-Individual Variability in Responses to Chemical Mixtures

Rapid hazard screening after disaster events that may involve re-distribution of chemicals

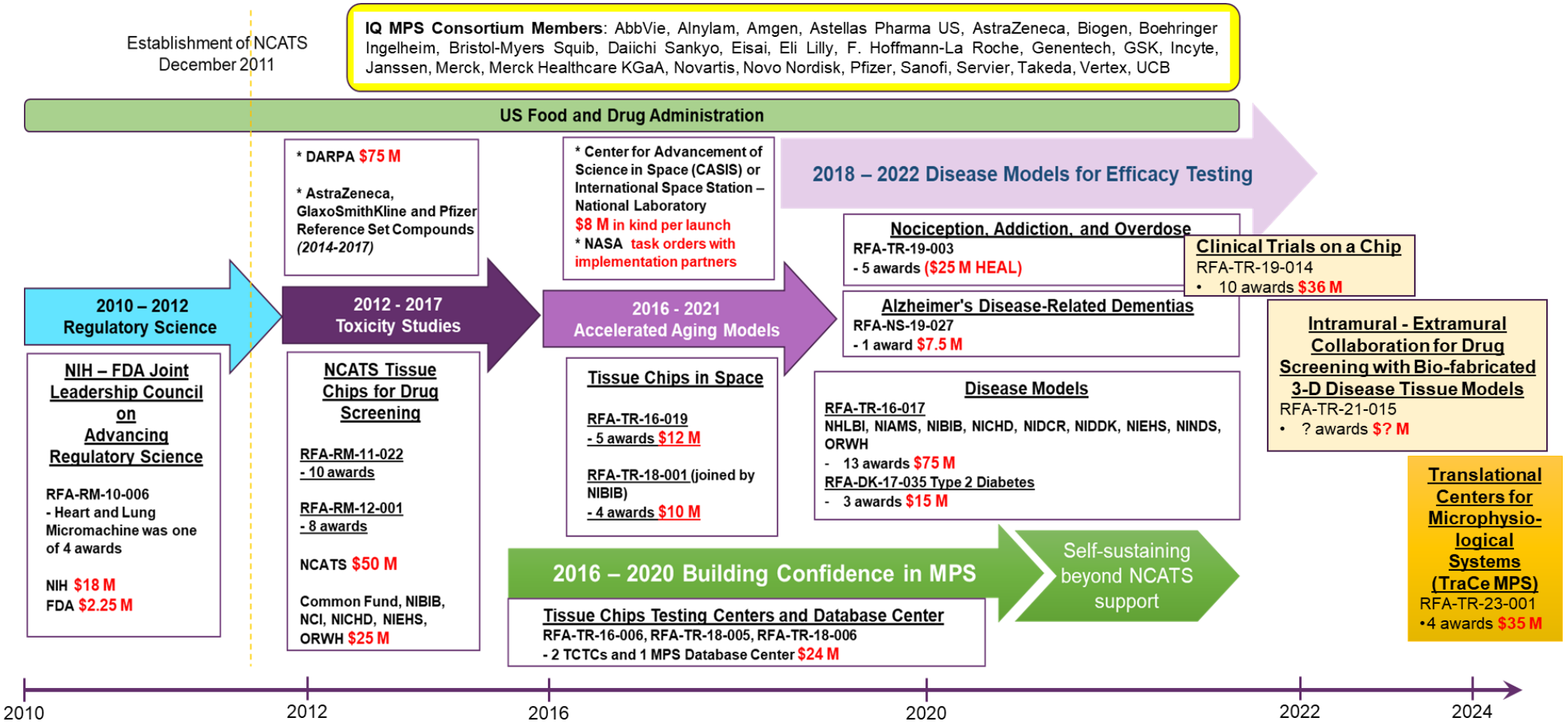
Chen et al 2021

Risk Characterization of Environmental Samples Using *In Vitro* Bioactivity and Polycyclic Aromatic Hydrocarbon Concentrations Data

Chen et al 2021

Potential Human Health Hazard of Post-Hurricane Harvey Sediments in Galveston Bay and Houston Ship Channel: A Case Study of Using *In Vitro* Bioactivity Data to Inform Risk Management Decisions

And That is Without Factoring the MPS/Organ-on-Chip Possibilities!



The USA NIH-funded **'Tissue Chips'** Landscape = >$400m to-date

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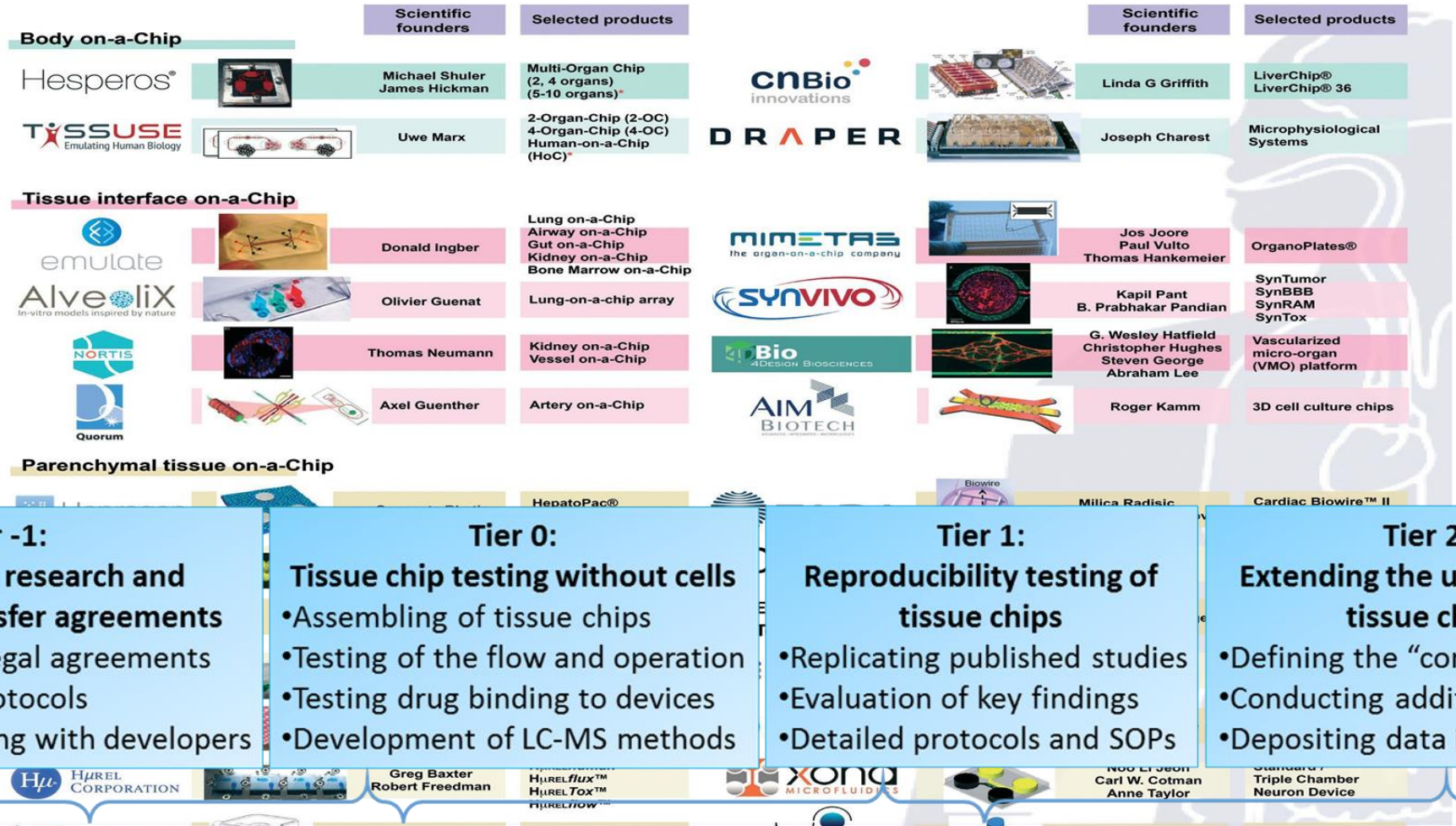
Why Not Spin-Off Your Own Organ-on-Chip Company (NIH Supported):



Tier -1:
Collaborative research and technology transfer agreements
- Execution of all legal agreements
- Sharing of the protocols
- TAMU staff training with developers

Tier 0:
Tissue chip testing without cells
- Assembling of tissue chips
- Testing of the flow and operation
- Testing drug binding to devices
- Development of LC-MS methods

Tier 1:
Reproducibility testing of tissue chips
- Replicating published studies
- Evaluation of key findings
- Detailed protocols and SOPs

Tier 2:
Extending the utility of the tissue chips
- Defining the "context of use"
- Conducting additional studies
- Depositing data into MPS-Db

4-8 months period of testing for each tissue chip/microphysiological system (MPS)

PBK Modelling in NGRA – 'Black Box' or Fully Understood?

Physiologically based kinetic (PBK) models are used to simulate the behaviour of a chemical in the body for a given exposure scenario

- A Bayesian statistical model to quantifies the error for a novel chemical
- **Output: Plasma C_{max} distribution at each PBK level**

- PBK models are composed of multiple coupled ordinary differential equations.
- The model have various parameters that need to be determined.
- Example equation for determining the concentration of chemical in the liver:

$$V_{\text{Liver}} \frac{dC_{\text{Liver}}}{dt} = Q_{\text{Liver}} \left(C_{\text{Arterial}} - \frac{C_{\text{Liver}}}{P_{\text{Liver}}} \right) - CLint \left(\frac{C_{\text{Liver}}}{P_{\text{Liver}}} * Fup \right)$$

- $V_{\text{Liver}} \frac{dC_{\text{Liver}}}{dt}$: [Rate of change of concentration in the liver]
- Q_{Liver}: [Blood flow rate]
- C_{Arterial}: [Concentration of chemical in the arterial blood]
- $\frac{C_{\text{Liver}}}{P_{\text{Liver}}}$: [Concentration of chemical in the liver plasma]
- $CLint \left(\frac{C_{\text{Liver}}}{P_{\text{Liver}}} * Fup \right)$: [Clearance rate via metabolism in the liver]

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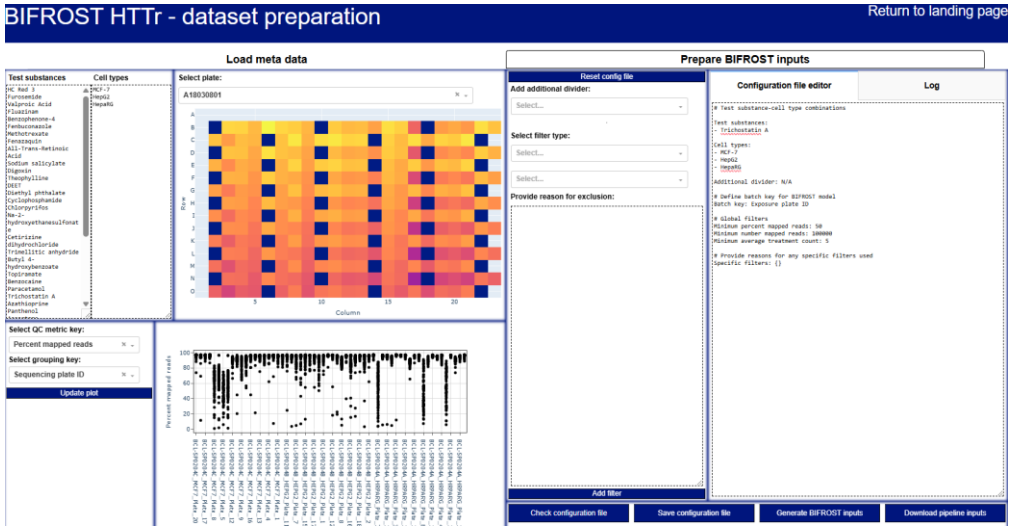
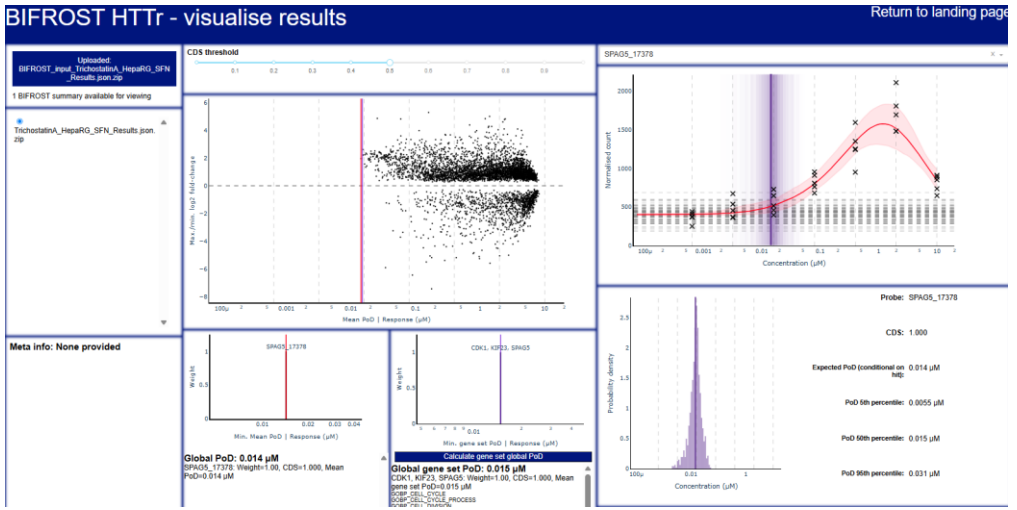
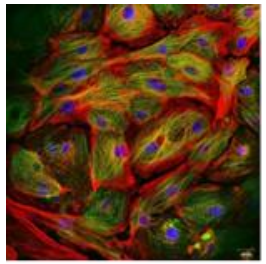
Defined Approaches for Complex Data Integration: POD in HTTr

- High throughput transcriptomic (HTTr) studies provide high dimensional datasets for the bioactivity of a chemical
- Downstream results are highly sensitive to a plethora of decisions around experimental design, data normalisation, modelling choices, summary statistics and more
- For robust inferences, it is critical that the consequence of each decision, as well as the consequence of having made an alternative choice, is understood

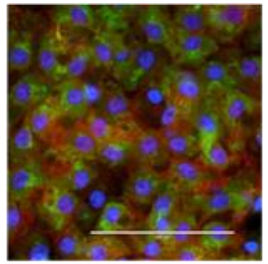




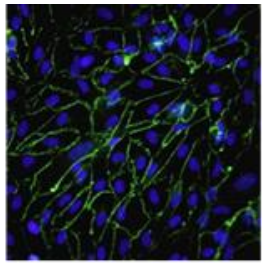
Put Together iPSC of Multiple Lineages, into MPS/OoC, Treat with 'Toxins', Determine POD from HTTr (and other NAMs) by Bayesian Statisics and Compare to Exposure Estimated by Computational PBK with Population Variability... Oh, and VALIDATE THAT!



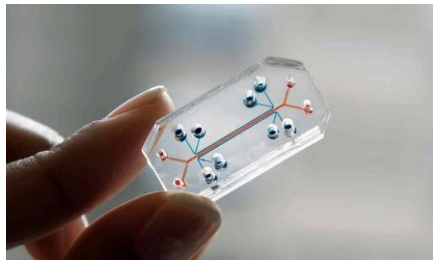
Cardiac Cells

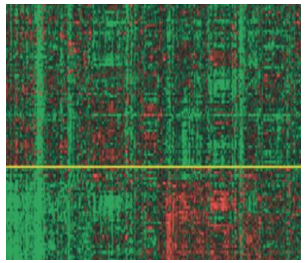


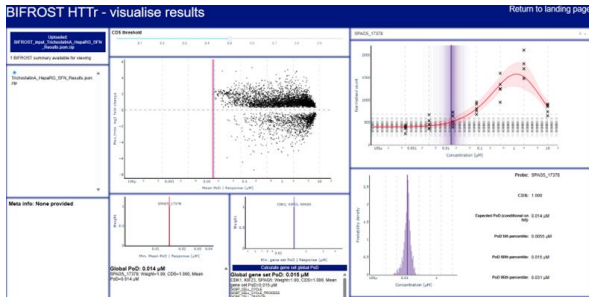
Liver Cells

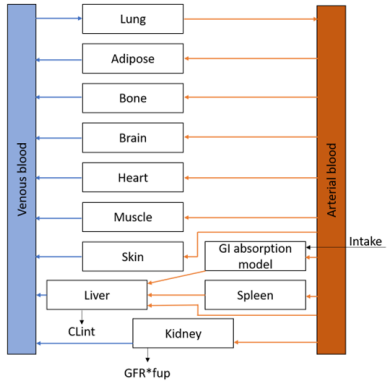


Endothelial Cells









And let AI make the decision on:
Safe or Not-Safe

Reproducible? The Regulators Replication Validation Dilemma

News in focus

NEWS FEATURE | 05 December 2023

Is AI leading to a reproducibility crisis in science?

Scientists worry that ill-informed use of artificial intelligence is driving a deluge of unreliable or useless research.

AI LINKED TO EXPLOSION IN LOW-QUALITY BIOMEDICAL PAPERS

Hundreds of studies seem to follow a template, reporting correlations based on public data sets.

By Miryam Naddaf

NEWS | 25 April 2025

Huge reproducibility project fails to validate dozens of biomedical studies

Unique reproducibility effort in Brazil focuses on common methods rather than a single field — and prompts call for reform.

News Feature | Published: 25 May 2016

1,500 scientists lift the lid on reproducibility

Monya Baker

Nature **533**, 452–454 (2016) | Cite this article

256k Accesses | **5202** Altmetric | Metrics

CAREER NEWS | 20 January 2025

'Publish or perish' culture blamed for reproducibility crisis

Survey of more than 1,600 biomedical researchers also flagged small sample sizes and cherry-picking of data as leading causes of reproducibility problems.

NEWS | 14 October 2024 | Clarification 17 October 2024 | Clarification 23 October 2024

'Doing good science is hard': retraction of high-profile reproducibility study prompts soul-searching

A paper by some of the biggest names in scientific integrity is retracted for issues including misstatements about the research plan.

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Are We Even Scratching the Surface of the Wealth of Data in Transcriptomics?

OXFORD SOT Society of Toxicology academic.oup.com/toxsci Tox Spotlight article

Toxicological Sciences, 2025, **205(2)**, 310–325
https://doi.org/10.1093/toxsci/kfaf036
Advance Access Publication Date: March 20, 2025
Research article

A workflow for human health hazard evaluation using transcriptomic data and Key Characteristics-based gene sets

Han-Hsuan D. Tsai [1,2], King D. Oware [3], Fred A. Wright[1,4,5], Weihsueh A. Chiu [1,2], Ivan Rusyn[1,2,*]

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[2]Department of Veterinary Physiology and Pharmacology, Texas A&M University, College Station, TX 77843, United States
[3]School of Public Health, Texas A&M University, College Station, TX 77843, United States
[4]Bioinformatics Research Center, North Carolina State University, Raleigh, NC 27603, United States
[5]Department of Statistics and Bioinformatics Research Center, North Carolina State University, Raleigh, NC 27603, United States

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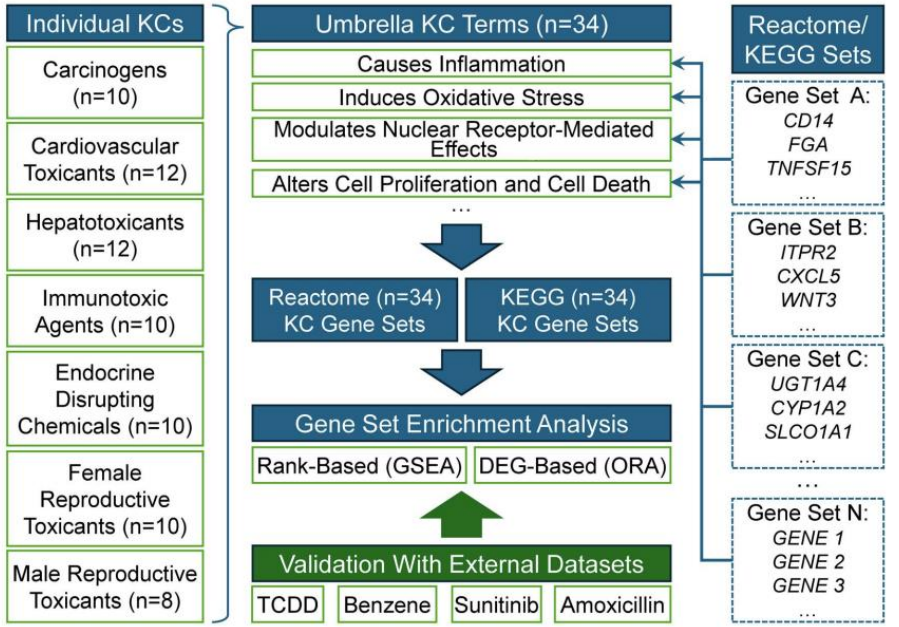


Fig. 1. Overview of the study workflow. Abbreviations: KC, key characteristic; KEGG, Kyoto Encyclopedia of Genes and Genomes; GSEA, gene set enrichment analysis; DEG, differential expressed gene; ORA, over-representation analysis; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin.

Unilever

New Collaboration Between Unilever and CMU for 2026+

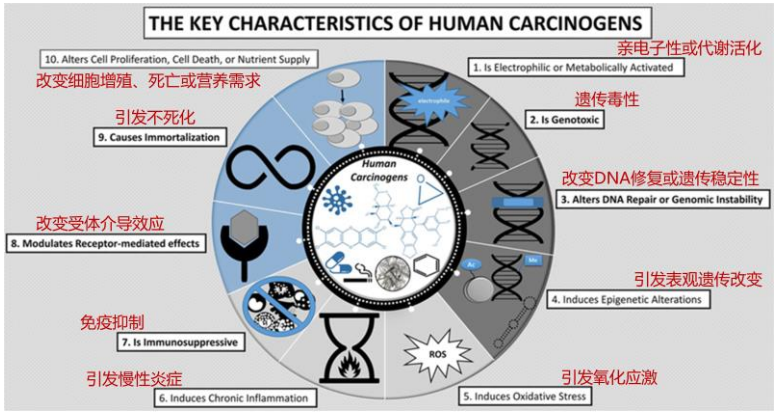
中国医科大学 CHINA MEDICAL UNIVERSITY

Jingbo PI

KEY LAB OF ENVIRONMENTAL STRESS AND CHRONIC DISEASE CONTROL & PREVENTION
环境应激与慢病防控
教育部重点实验室
中国医科大学

Outline

- CMU-Unilever Workshop on NAMs-based NGRA
- Understanding from IARC Monographs
- Key characteristics (KCs) vs. AOPs
- A vision for future: KCs-structured NAMs-based NGRA?



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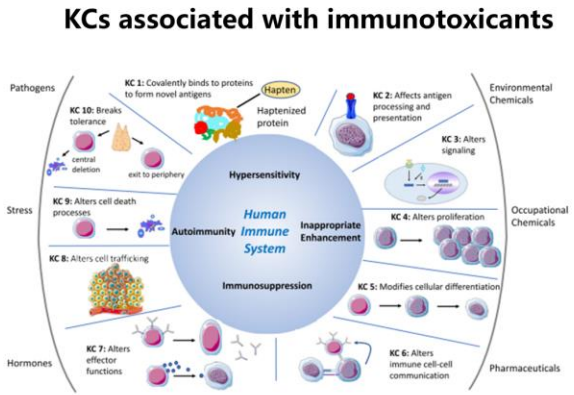

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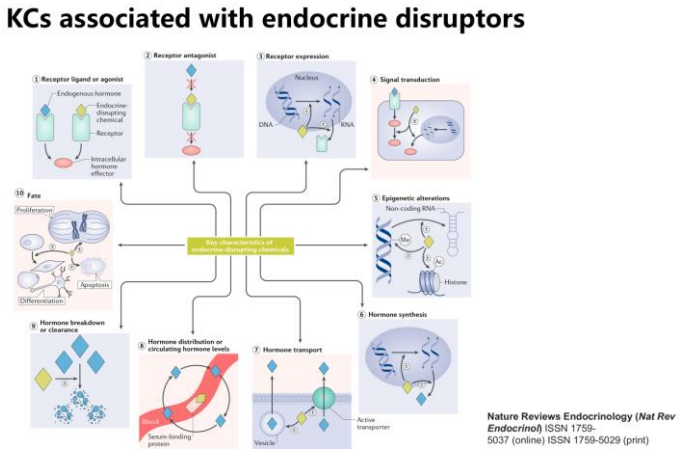

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A Decade of Progress for TATT with NAMs/NGRA/TT21C


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