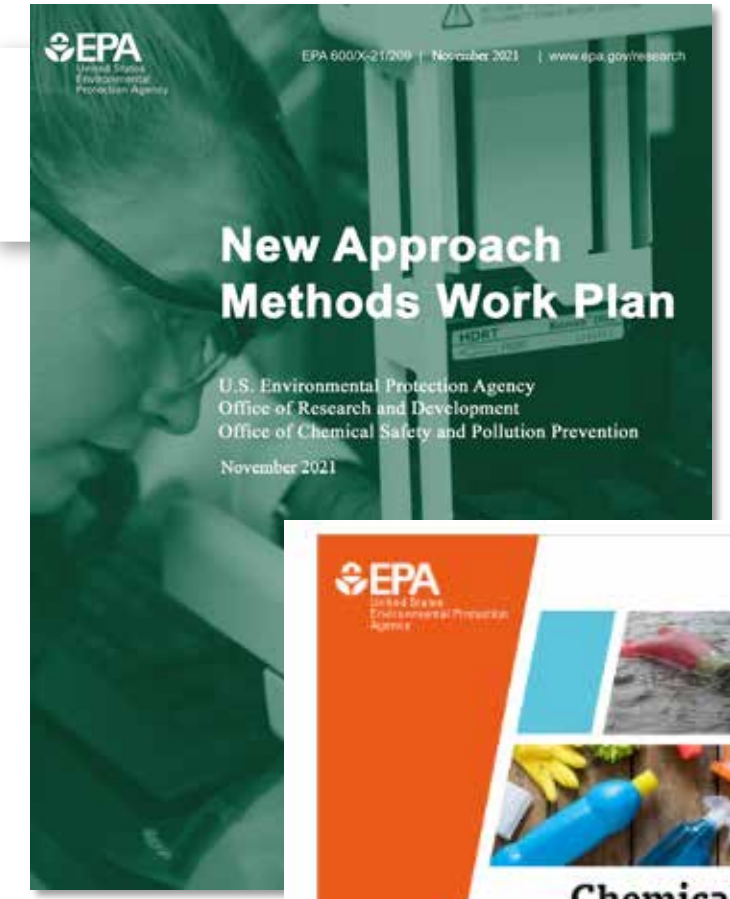
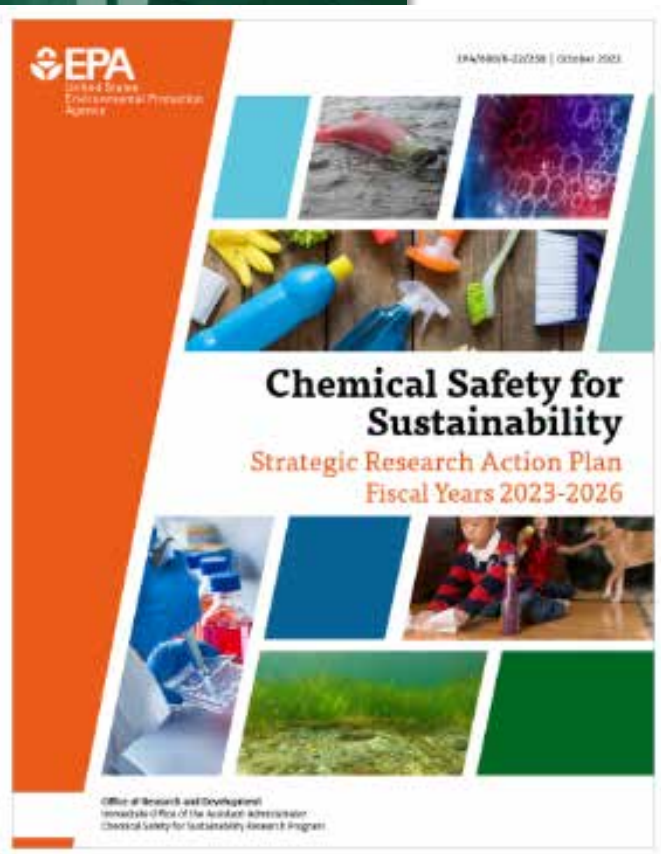




Development of New Approach Methods for Decision Making

Maureen R. Gwinn, Ph.D.

Principal Deputy Assistant Administrator

Chief Scientist

U.S. Environmental Protection Agency

Office of Research and Development

Presentation for the **Trust Your Gut: Establishing Confidence in Gastrointestinal Models**

An Overview of the State of the Science and Contexts of Use

Preliminary Webinar Series

September 18, 2023

New Approach Methods (NAMs)

- NAMs are defined as any technology, methodology, approach, or combination that can provide information on chemical hazard and risk assessment to avoid the use of animal testing
- Commonly defined to include *in silico* approaches, *in chemico* and *in vitro* assays, as well as information from the exposure of chemicals in the context of hazard assessment.
- Challenges
  - Multiple decision contexts
  - Scientific confidence in the use of NAMs in regulatory decision-making
  - Addressing complex issues (*e.g.*, cumulative impacts)

https://echa.europa.eu/documents/10162/22816069/scientific_ws_proceedings_en.pdf

https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/alternative-test-methods-and-strategies-reduce

Questions to consider in developing NAMs for use in regulatory decision-making

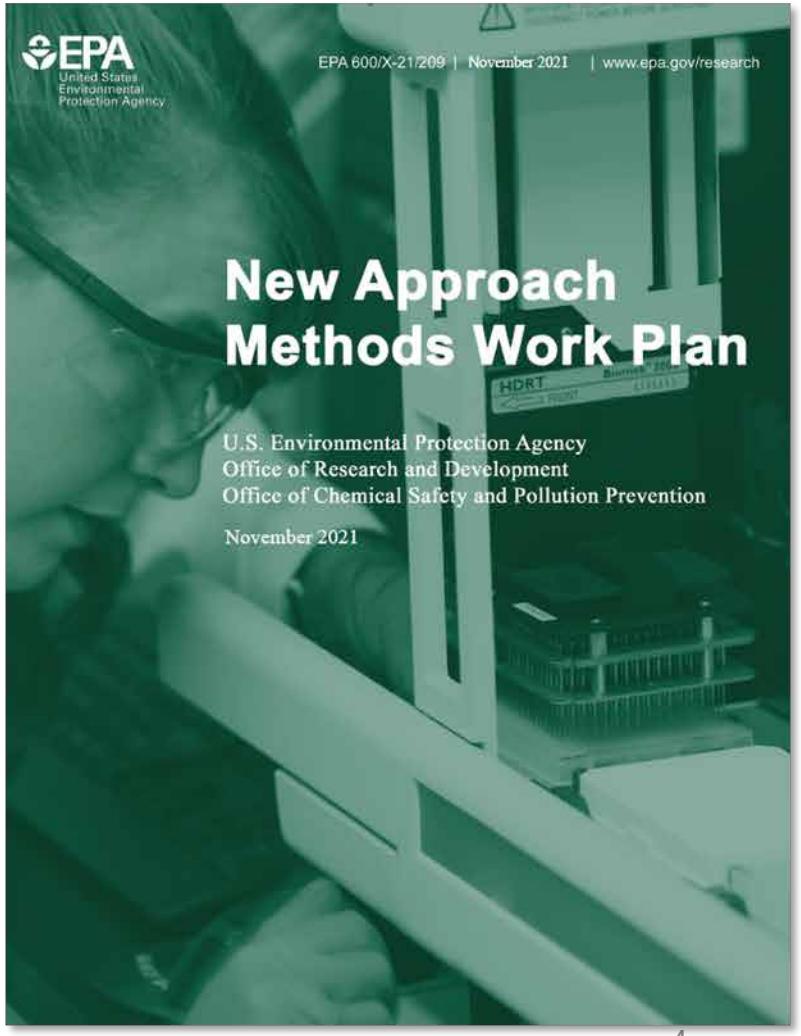
How are agencies prioritizing and/or integrating NAMs into scientific aims and/or regulatory processes?

Where are new tools/capabilities particularly positioned to complement and/or replace traditional models?

What are the biggest challenges in the development/use of NAMs from a regulatory perspective?

EPA NAMs Work Plan

Five objectives for reducing animal testing and research while ensuring that Agency decisions remain fully protective of human health and the environment.



Status of NAM Work Plan Deliverables

Milestones/Deliverables	Proposed Dates
Evaluate Regulatory Flexibility for Accommodating the Use of NAMs	
EPA report on a review of existing statutes, programmatic regulations, policies, and guidance that relate to vertebrate animal testing and the implementation and use of appropriate NAMs for regulatory purposes.	Draft completed September 2023 – entering internal review
Develop Baselines and Metrics for Assessing Progress	
Progress and summary metrics on reducing vertebrate animal testing requests and use.	Annually starting in Q4 2022
Establish Scientific Confidence in NAMs and Demonstrate Application to Regulatory Decisions	
U.S. National Academies of Sciences, Engineering, and Medicine study that evaluates the variability and relevance of existing mammalian toxicity tests and reviews frameworks for validation and establishing scientific confidence in testing methods. The study was funded by the EPA.	2023
A scientific confidence framework to evaluate the quality, reliability, and relevance of NAMs.	Q4 2024 Key principles presented at 2022 EPA Biannual NAMs Workshop
An initial set of reporting templates which may be used by EPA and stakeholders that capture the range of specific NAMs used for Agency decisions.	Q4 2024
Case studies for evaluating application to risk assessment and demonstrating protection of human health and the environment.	Ongoing

Status of NAM Work Plan Deliverables

Milestones/Deliverables	Proposed Dates
Develop NAMs to Address Scientific Challenges and Fill Important Information Gaps	
EPA Strategic Research Action Plans outlining research products to develop and apply NAMs.	Q1 2023 ✓
Encourage development of NAMs through mechanisms such as the STAR program and facilitate partnerships with organizations focused on establishing scientific confidence in alternative methods.	Ongoing ✓
Engage and Communicate with Stakeholders	
EPA website to house information about NAM efforts and progress upon release of the work plan. https://www.epa.gov/nam	2020 ✓
Public webinars and, where appropriate, peer-review on deliverables from this work plan.	Ongoing ✓
Complete NAMs pilot training program in the fourth quarter (Q4) of 2023 and provide regular scientific exchanges and progress updates through Agency sponsored and partner organized events. **https://www.epa.gov/chemical-research/new-approach-methods-nams-training**	Q4 2023 and Ongoing ✓

Still time to register for httk training on November 8-9, 2023!

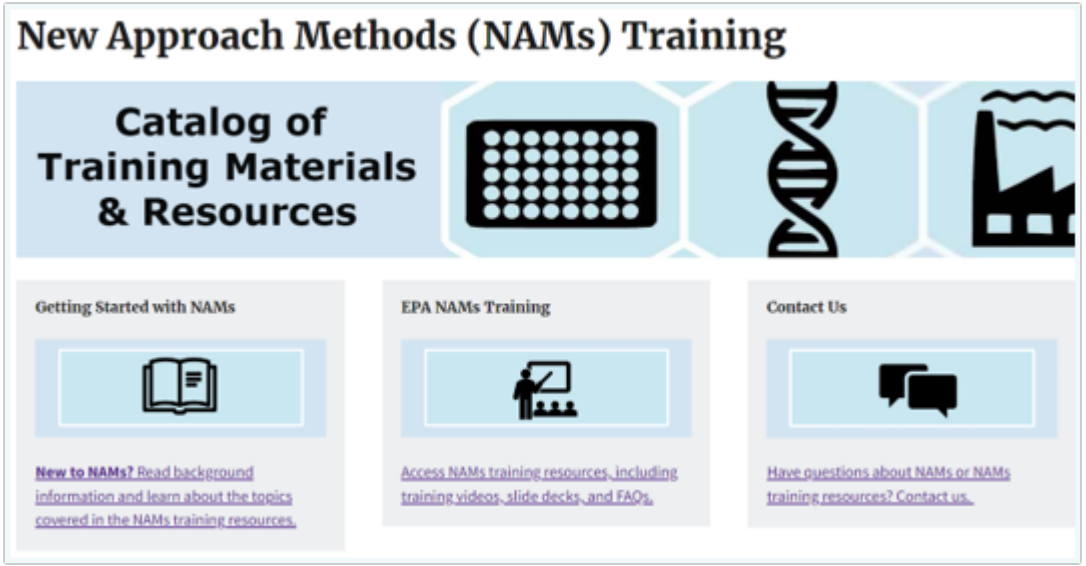
NAMs Confidence Framework

- EPA NAMs Work Plan Implementation Team members developed the ICCVAM white paper *Validation, Qualification, and Regulatory Acceptance of New Approach Methodologies* in partnership with 9 other US federal agencies.
  - https://ntp.niehs.nih.gov/go/ICCVAM-submit (draft submitted for public comment August 2023)
- EPA's Confidence Framework will build on these principles and v be comprehensive – going beyond *in vitro* biological systems to include *in silico* and *in chemico* approaches in both human and ecological health decision contexts.
  - Fit for purpose
  - Transparent
  - Reliable
  - Relevance
  - Uncertainty
- Framework development will be informed by the NASEM report OECD parallel activities to update GD34, the new OECD QSAR framework in development, international APCRA case studies, and ICCVAM activities, among others.

Training: Encouraging NAMs Use and Adoption

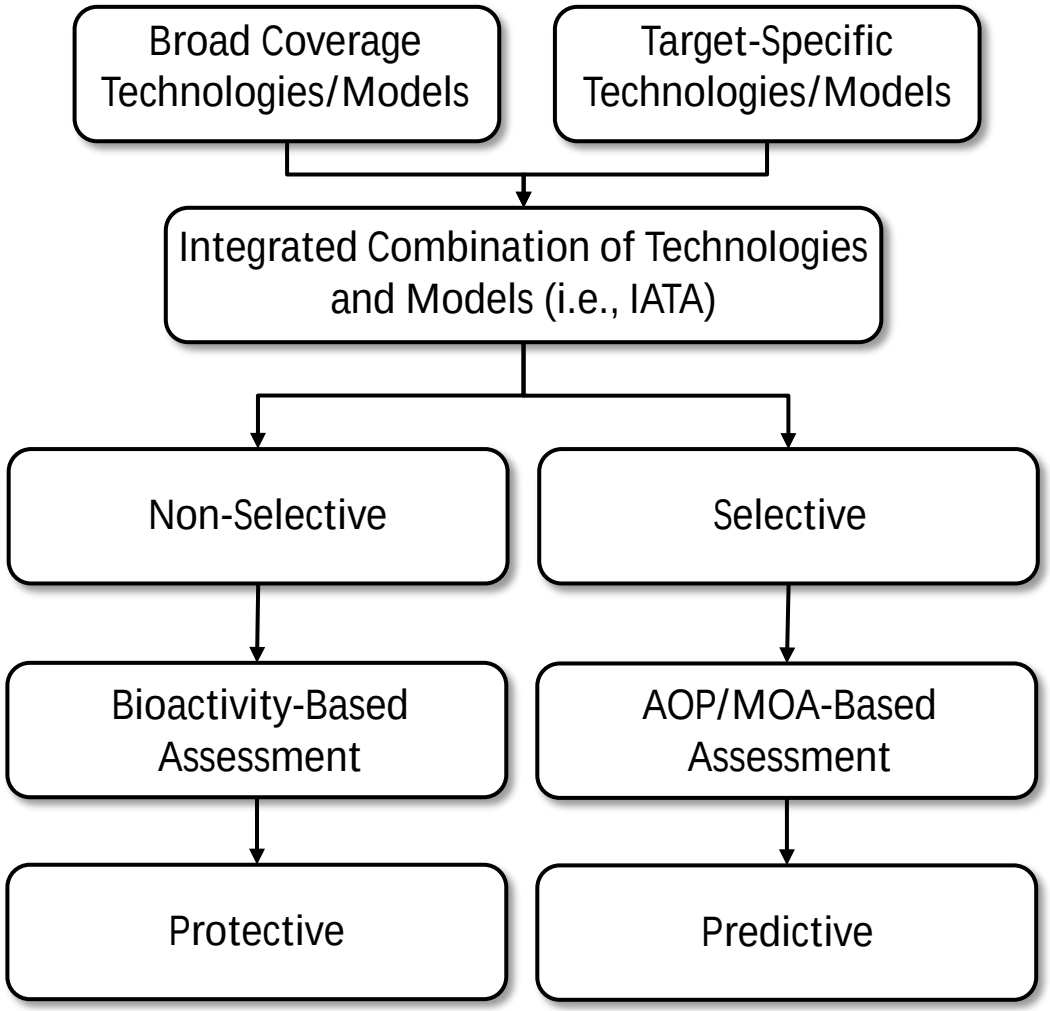
Effective engagement and communication with stakeholders essential to increasing understanding, obtaining feedback, and improving acceptance of NAMs to inform decisions

- EPA NAMs Training
  - Public NAMs training website released to serve as a resource for training materials and recordings for EPA tools and databases
  - Live, interactive trainings are recorded and available on the website for: ECOTOX Knowledgebase, CompTox Chemicals Dashboard, Generalized Read-Across (GenRA)
  - New NAMs Update email bulletin established to share progress and updates
  - Two-way communication via NAM@epa.gov
  - Upcoming Training: Nov 8-9, 2023 on High throughput toxicokinetic modeling (httk)
- EPA NAMs Conferences
  - Most recent held October 2022
  - Planning ongoing for next one anticipated Fall 2024

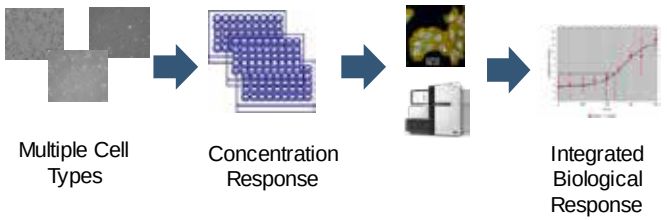


https://www.epa.gov/chemical-research/new-approach-methods-nams-training

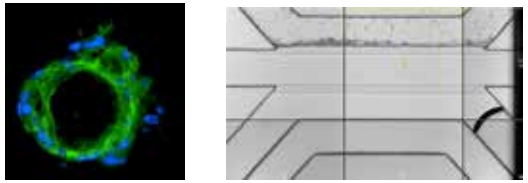
Develop and Refine Methods to Address Key Information and Capability Gaps



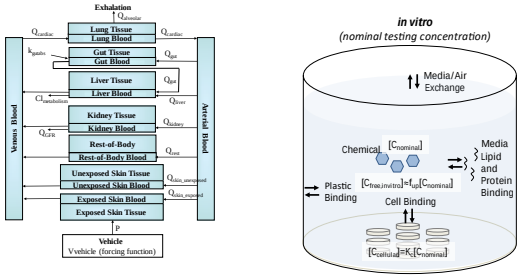
Broad Coverage Assays



Complex Culture and MPS Models

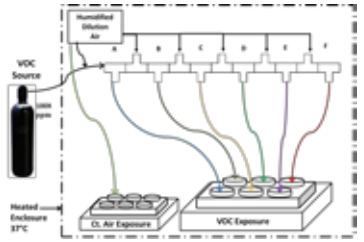


HTTK and Disposition Models

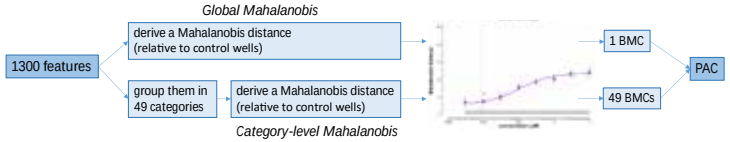


Integrating Metabolism

Exposure Systems

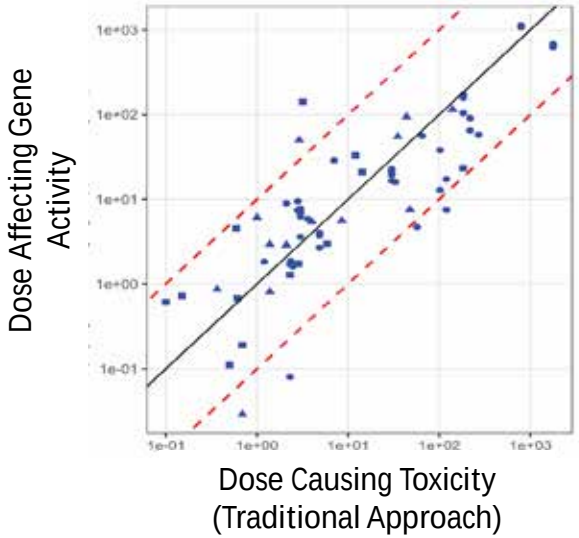


Data Analysis/Integration Models



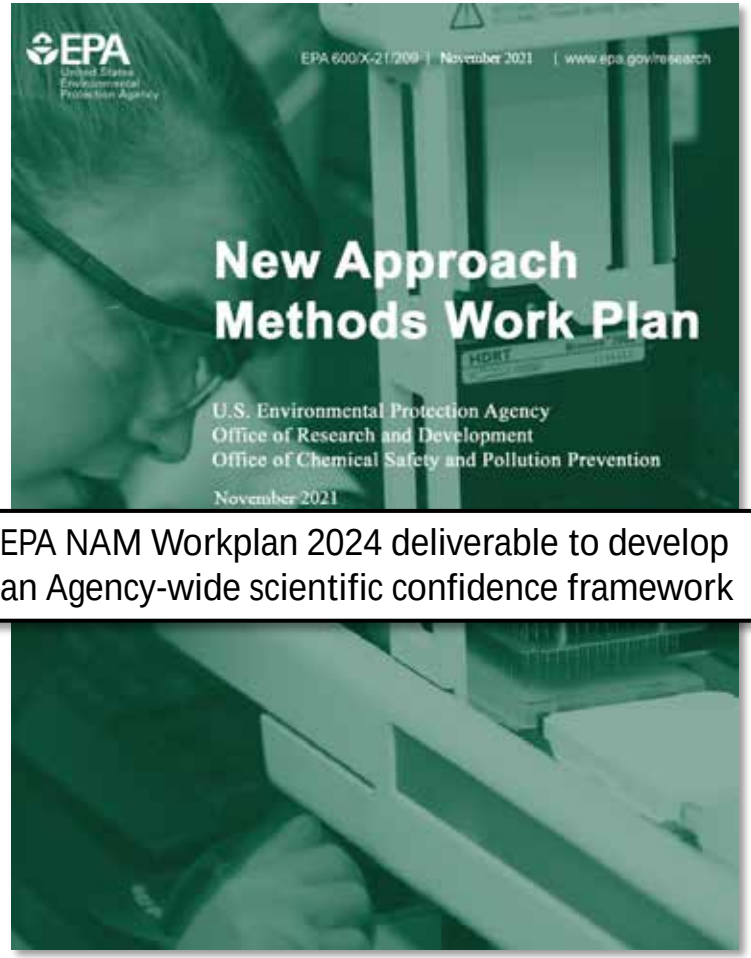
Developing Bridges from the Old to the New Methods

Application of Genome Sequencing Technology and Research Increased Potential for Application to EPA Needs

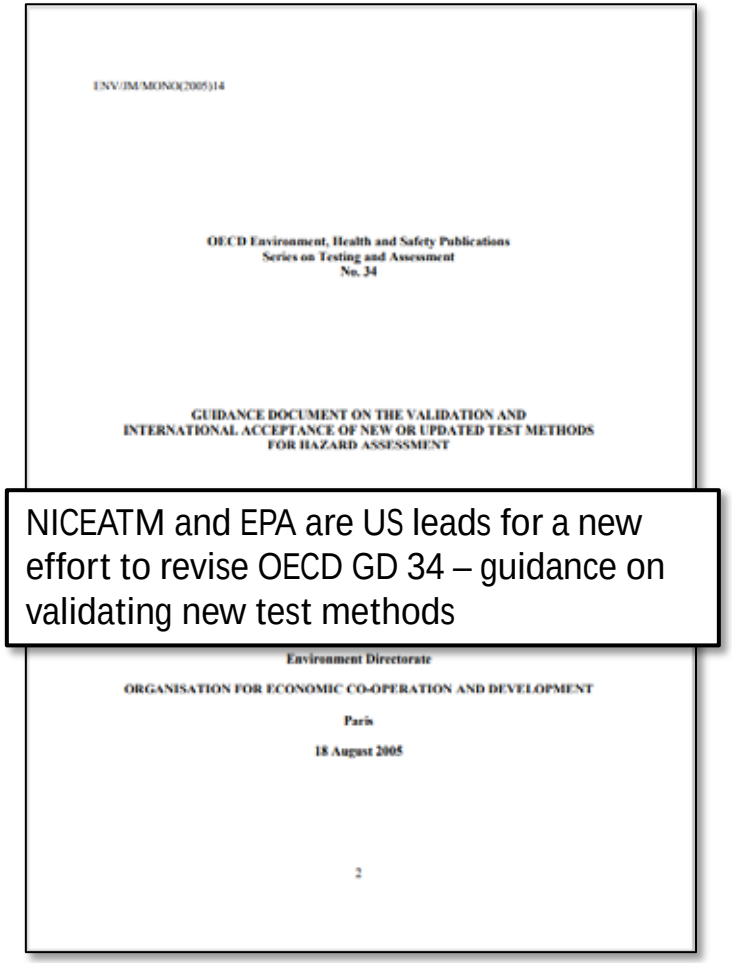


- EPA has developed a potential new assessment product based on transcriptomics. The study paradigm follows the principles of 3Rs to *refine* chronic toxicity assessment by reducing the number of animals needed to assess a reference value.
- It could enable development and release of chemical assessments of data-poor chemicals in as little as 9 months from chemical procurement to assessment release.
- The potential new assessment product and a companion value of information (VOI) case study was presented in July 2023 and is undergoing peer-review via ORD's Board of Scientific Counselors (BOSC).

Evolving Validation and Reporting Processes to be Performance-Based and NAM Compatible



EPA NAM Workplan 2024 deliverable to develop an Agency-wide scientific confidence framework


ENV/JM/MONO(2005)14

OECD Environment, Health and Safety Publications
Series on Testing and Assessment
No. 34

GUIDANCE DOCUMENT ON THE VALIDATION AND INTERNATIONAL ACCEPTANCE OF NEW OR UPDATED TEST METHODS FOR HAZARD ASSESSMENT

Environment Directorate

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

Paris

18 August 2005

2

NICEATM and EPA are US leads for a new effort to revise OECD GD 34 – guidance on validating new test methods


Regulatory Toxicology and Pharmacology

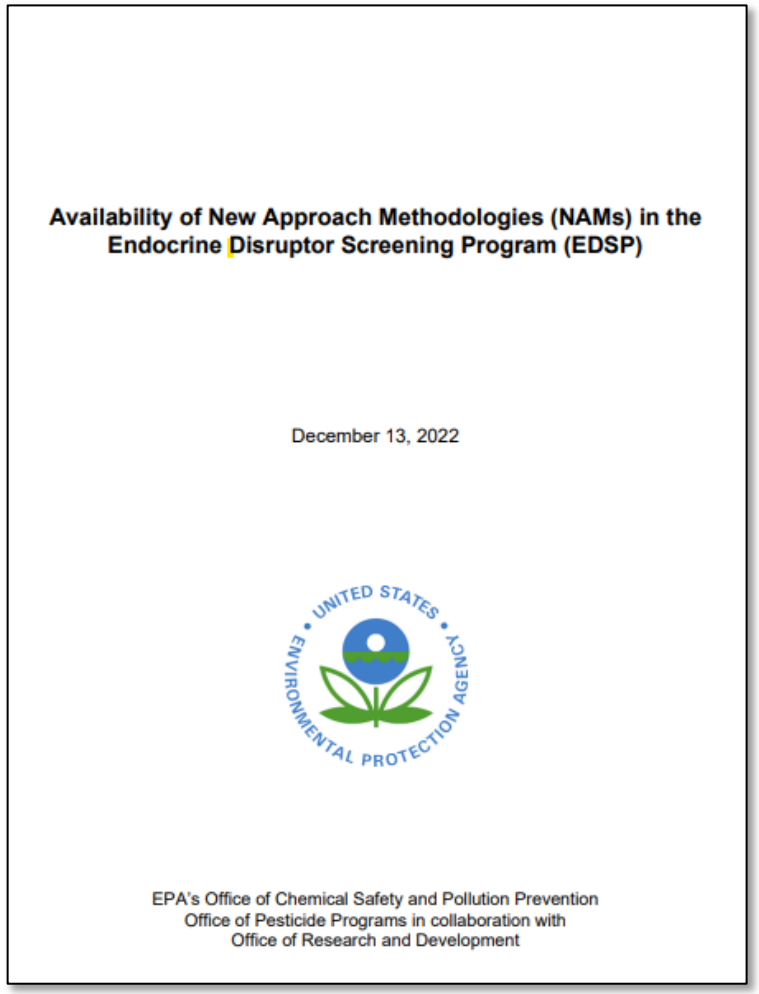
journal homepage: www.elsevier.com/locate/yrtph

Commentary

Progress towards an OECD reporting framework for transcriptomics and metabolomics in regulatory toxicology

OECD project to develop an Omics reporting framework

Developing NAMs to Impact the Needs of the Regulatory Community



Availability of New Approach Methodologies (NAMs) in the Endocrine Disruptor Screening Program (EDSP)

December 13, 2022

EPA's Office of Chemical Safety and Pollution Prevention
Office of Pesticide Programs in collaboration with
Office of Research and Development

Draft document: EPA docket EPA-HQ-OPP-2021-0756-0002

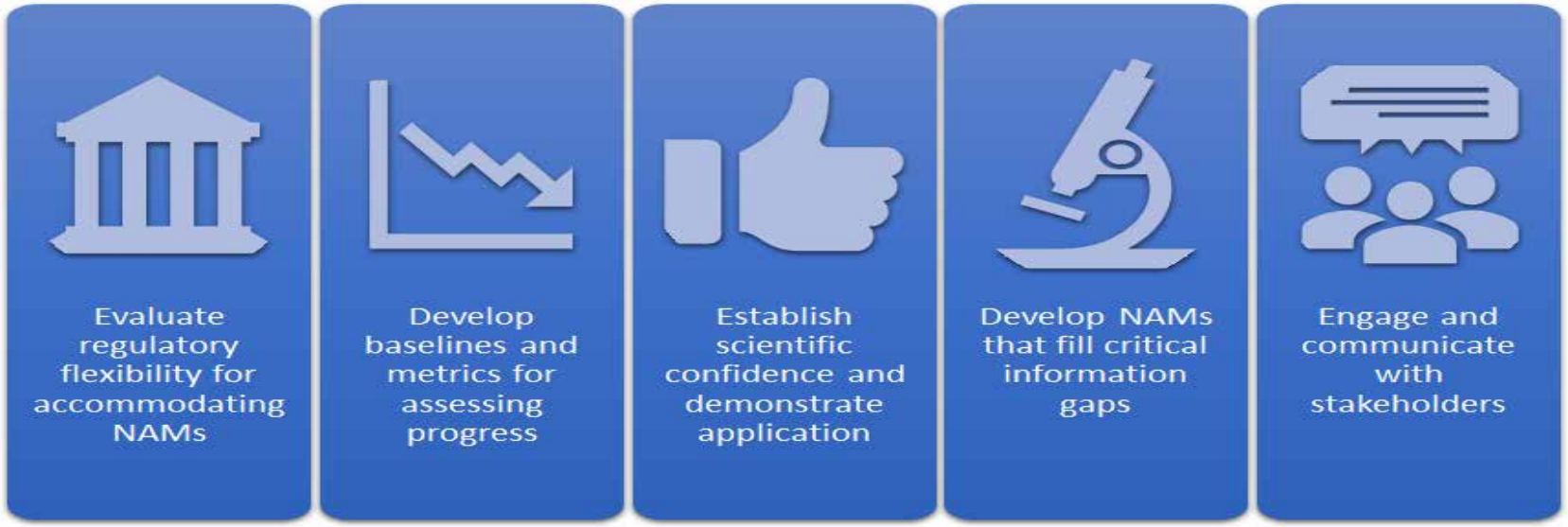
- Recent EPA efforts to develop NAMs in service of the endocrine disruptor screening program resulted in a new 2022 proposal for their inclusion in chemical screening to replace traditional methods
- The Estrogen Receptor (ER) pathway model based on a 18 *in vitro* assay ToxCast/Tox21 battery may be used as an alternative to performing three current EDSP Tier 1 screening assays:
  - ER binding *in vitro* assay (OCSPP 890.1250)
  - ER transcriptional activation (ERTA) *in vitro* assay (OCSPP 890.1300)
  - *In vivo* Uterotrophic assay (rat) (OCSPP 890.1600)
- The Androgen Receptor (AR) pathway model based on a 11 *in vitro* assay ToxCast/Tox21 battery may be used as an alternative for one current EDSP Tier 1 screening assay:
  - AR binding *in vitro* assay (OCSPP 890.1150)

Examples of Recent Accomplishments for *in silico* Tools

CompTox Chemicals Dashboard (CCD)	• Now contains data on over 1 million chemicals, including data generated from testing hundreds of PFAS chemicals in high-throughput screening assays
ECOTOX	• Now includes new PFAS Data and added 20,615 curated records for 134 chemicals
Generalized Read-Across (GenRA)	• Now includes new data and predictive models for PFAS that will help prioritize PFAS for further testing and will help inform categorization efforts
ToxCast/inVitroDB version 3.5	• Contains an updated database, assay information, summary files and concentration response plots
Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS)	• Adds an ECOTOX widget that allows users to draw on the wealth of curated toxicity data from the ECOTOXicology Knowledgebase and compare them to sequence-based predictions of chemical susceptibility.

What are the biggest challenges in the development/use of NAMs from a *regulatory* perspective?

- Performance evaluation of methods and tools
- Build confidence and demonstrate application for regulatory decisions
- Tools interoperability
- Data management and sharing



Questions?