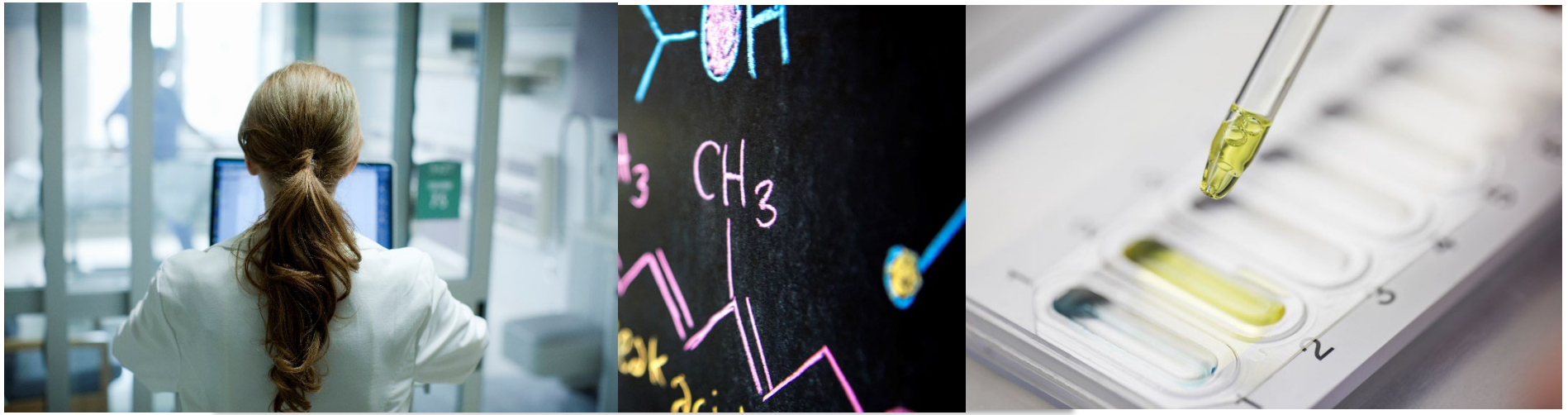
Update on EPA NAMs Work Plan Implementation

Alison Harrill, PhD

Associate Director for Toxicology, EPA Office of Research and Development



The views expressed in this presentation are those of the presenter and do not represent the views or policies of the U.S. EPA

US EPA Office of Research and Development

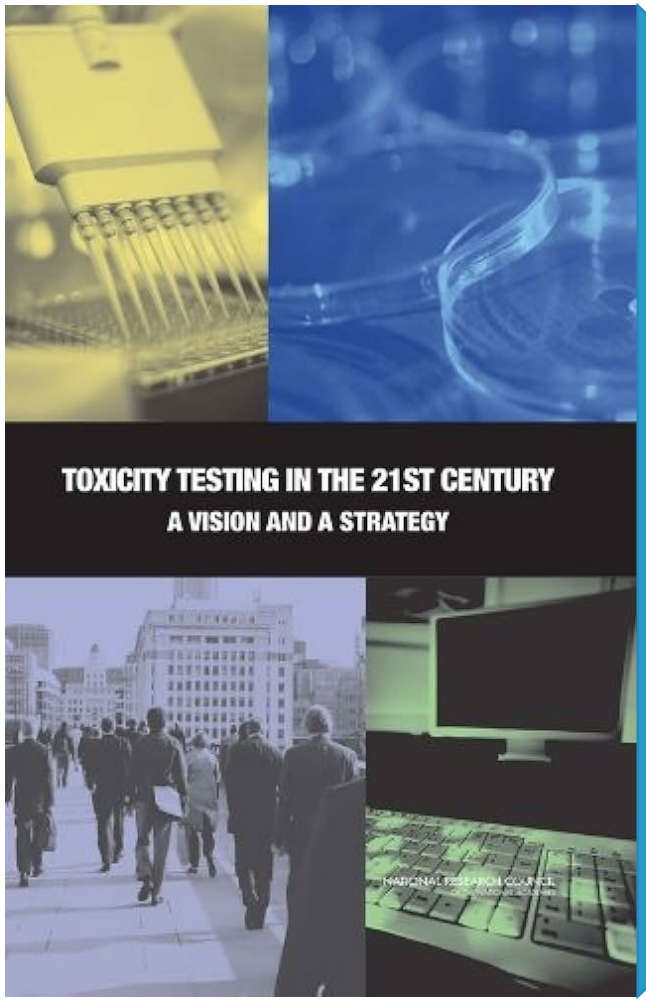
- The Office of Research and Development (ORD) is the scientific research arm of EPA

- Research is conducted by ORD's four national centers, and three offices organized to address:
  - Public health and environmental assessment
  - **Computational toxicology and exposure (CCTE)**
  - Environmental measurement and modeling
  - Environmental solutions and emergency response

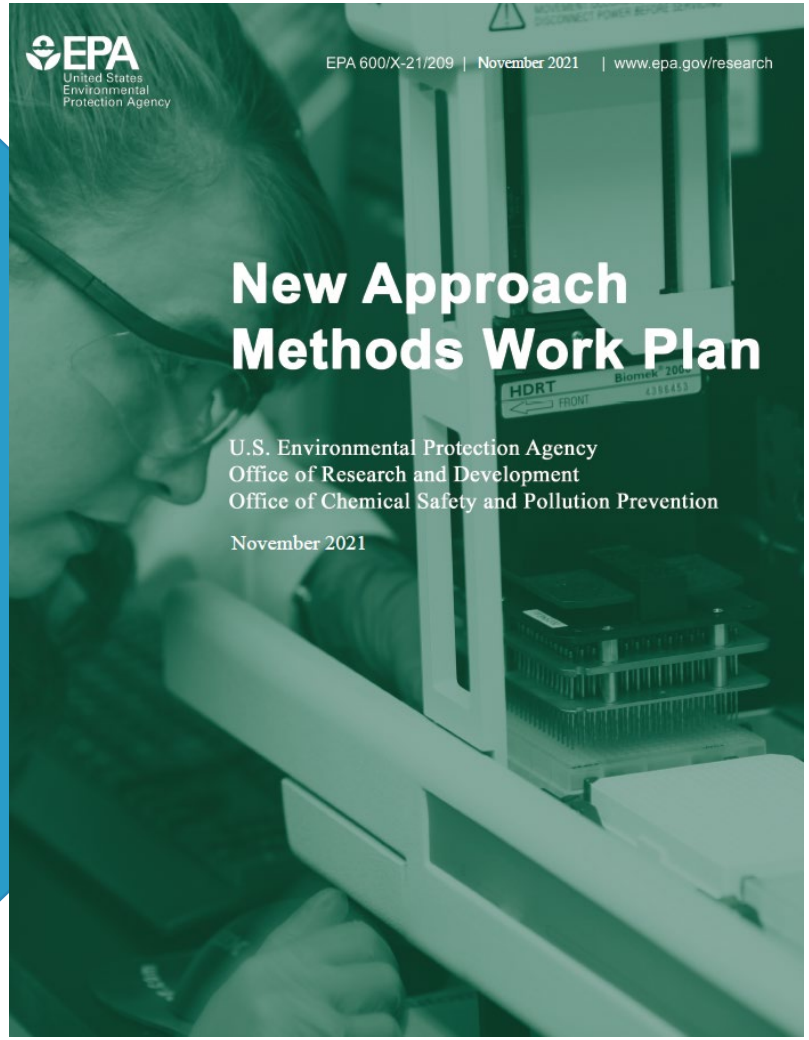
- CCTE published 223 peer-reviewed journal articles from 2022-2023

ORD Facility in
Research Triangle Park, NC
12 additional sites throughout US

The EPA NAMs Work Plan



US National Research Council 2007



US EPA 2021

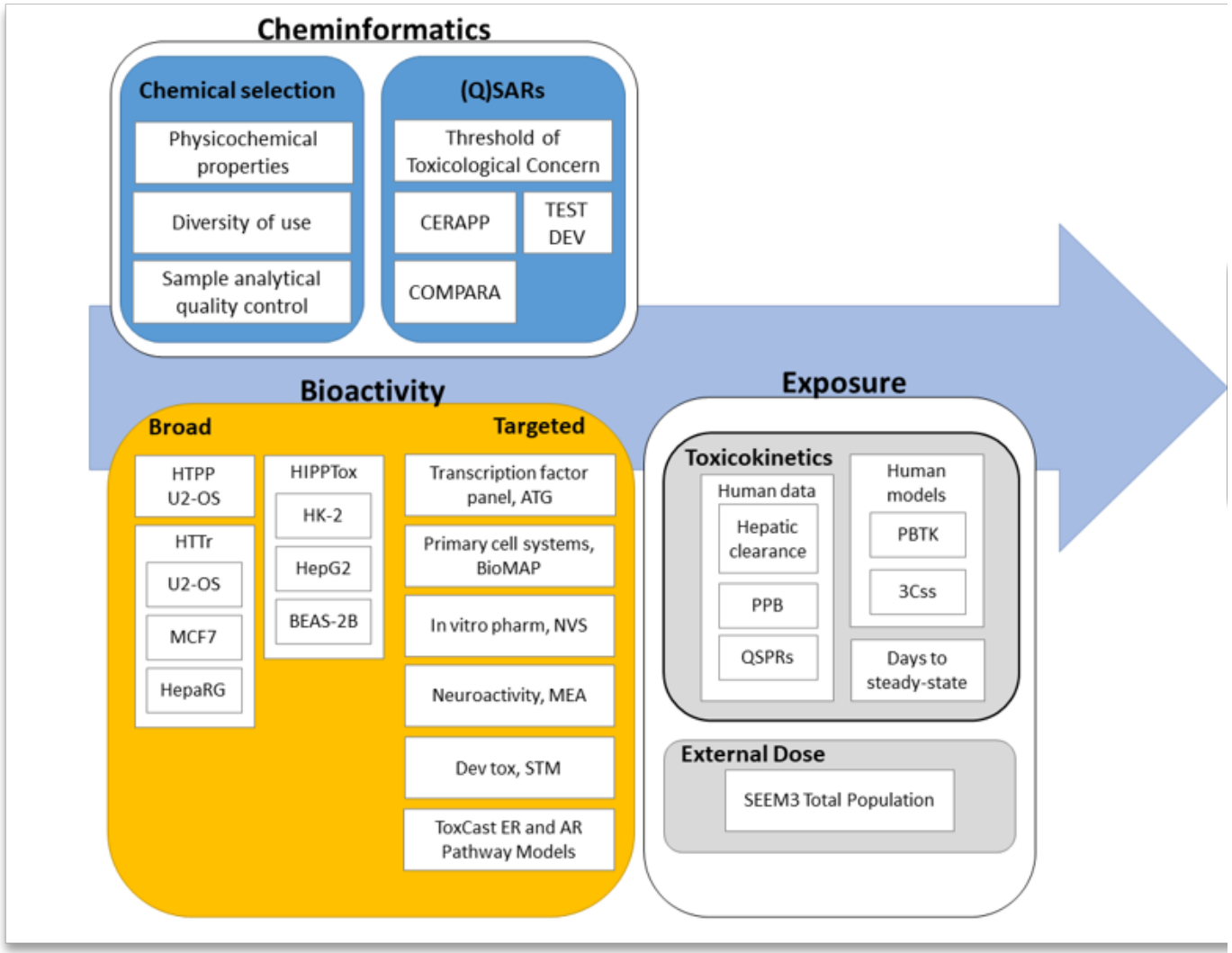
- EPA near-term goals 2021-2024
  1. Develop NAMs to address information gaps
  2. Engage and communicate with stakeholders
  3. Establish scientific confidence and demonstrate application
  4. Develop baselines and metrics
  5. Evaluate regulatory flexibility

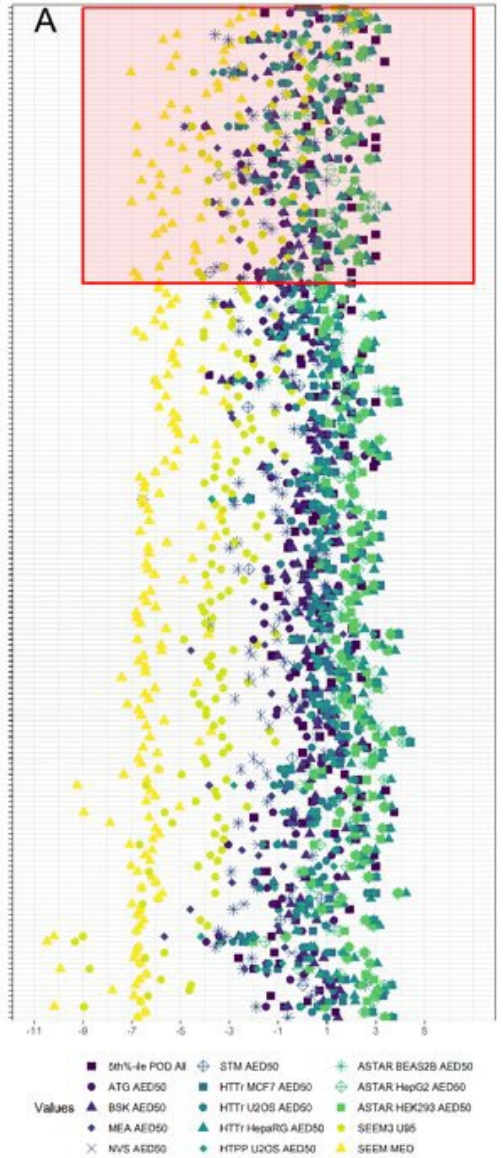
- EPA NAMs Work Plan represents a snapshot in time and will evolve as EPA's knowledge and experience grows

APCRA: International Prospective Case Study on NAMs Integration

- 200 chemicals in ToxCast library
- Generate data
- Derive POD_{NAM}
- Estimate bioactivity:exposure ratio (BER)
- Evaluate hazard flags

#1 – Develop and implement NAMs





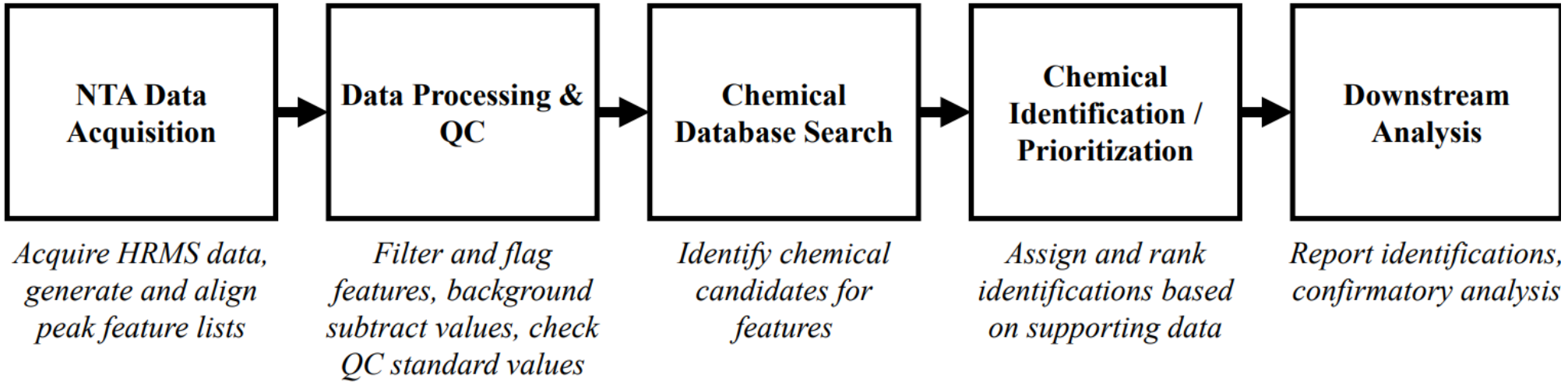
Katie Paul Friedman et al, *in prep.*

NAMs: Assessing Exposure

#1 – Develop and implement NAMs

- Tools for bioactivity assessment are complemented by assessing exposure - we need tools to do that
- Targeted analysis methods are trusted and the inclusion of standards aids identification, but these methods are not amenable to large-scale measurement or surveillance
- Chemical inventories are growing, and there is increasing concern on how to tackle mixtures, degradants, and metabolites

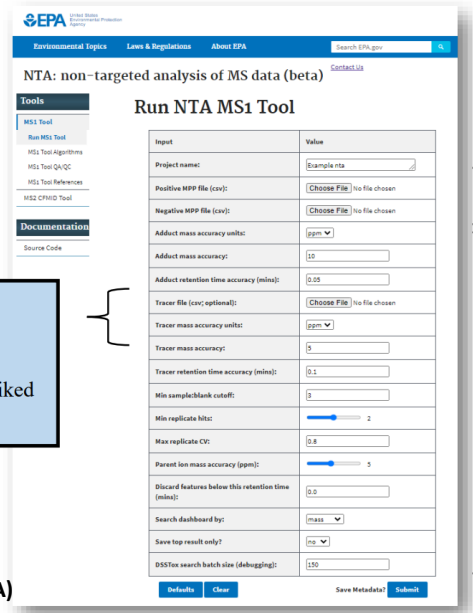
Optimizing exposure assessment to inform NAMs toolbox: Non-targeted analysis (NTA)



#1 – Develop and implement NAMs

Development of analytical methods, data processing, and chemical identification tools are amplifying efforts to assess chemical exposures

NTA WebApp: Input Page (MS1 data)



Tracer Input File

- Tracers: Isotopically labelled standards spiked into samples

NTA Data Input Files:

- Peak-picked, aligned MS1 data (CSV)
- Matrix of feature mass, RT, and sample abundances

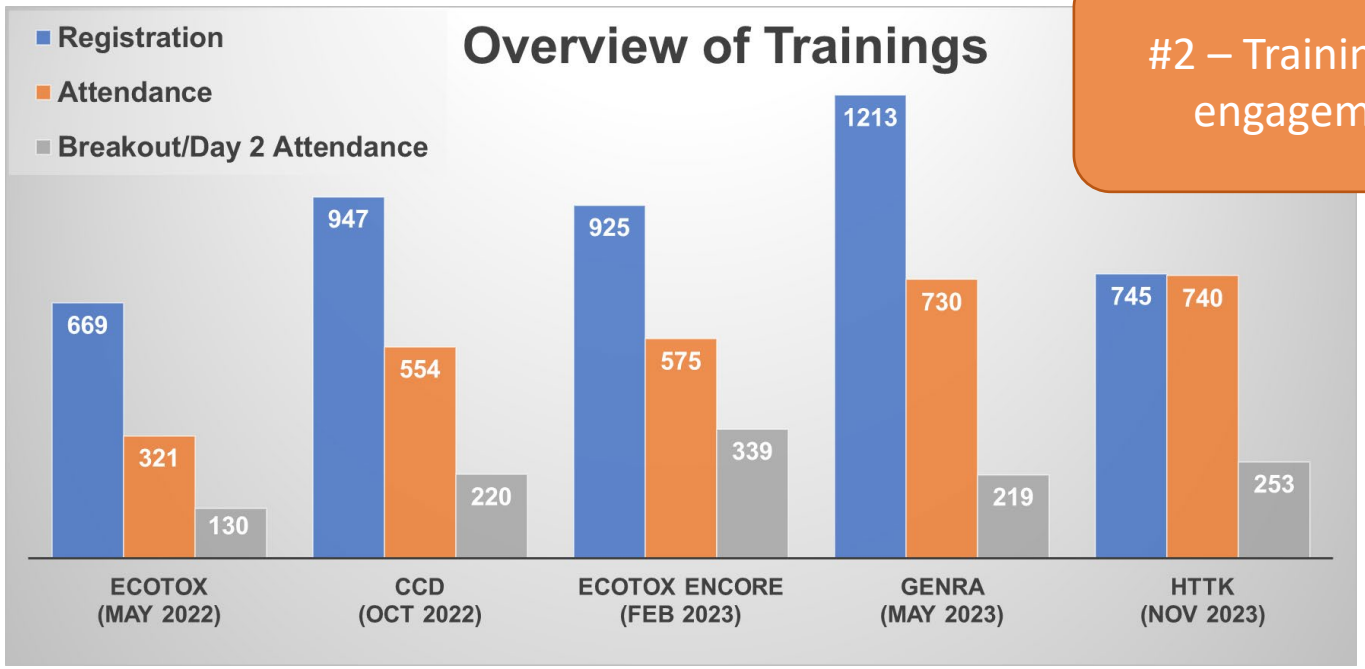
Workflow Parameters:

- Data processing
- Chemical retrieval

Figures: Alex Chao, Jon Sobus (EPA)

Development of a NAMs training program

- Piloting a NAMs Training program is a key deliverable of the EPA NAMs Work Plan and an important avenue to propagating tools and approaches throughout the field



#2 – Training and engagement

Figure: Esra Mutlu (EPA)

Topics to be covered at in person April 2024 training workshop at EPA's RTP campus:

AOP-Wiki, ChemExpo Knowledgebase, Cheminformatics modules, GenRA, ECOTOX Knowledgebase, SeqAPass, ToxCast, APIs for computational toxicology and exposure data, other NAMs resources (data, models)

Building confidence in NAMs requires frameworks

Efforts with significant engagement enable harmonization of concepts and incorporation into EPA practice

Completed: International & United States federal interagency frameworks


REVIEW ARTICLE

A framework for establishing scientific confidence in new approach methodologies

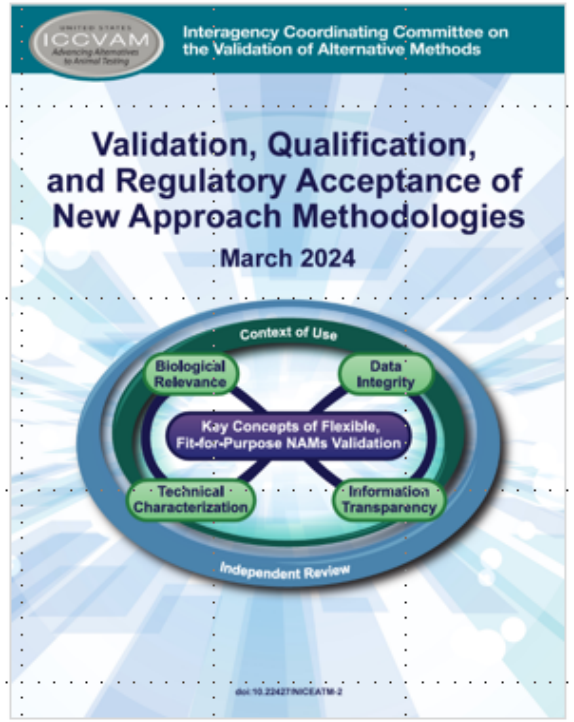
Abstract

Robust and efficient processes are needed to establish scientific confidence in new approach methodologies (NAMs) if they are to be considered for regulatory applications. NAMs need to be fit for purpose, reliable and, for the assessment of human health effects, provide information relevant to human biology. They must also be independently reviewed and transparently communicated. Ideally, NAM developers should communicate with stakeholders such as regulators and industry to identify the question(s), and specified purpose that the NAM is intended to address, and the context in which it will be used. Assessment of the biological relevance of the NAM should focus on its alignment with human biology, mechanistic understanding, and ability to provide information that leads to adult protective decisions, rather than solely comparing NAM-based chemical testing results with those from traditional animal test methods. However, when NAM results are compared to historical animal test results, the variability observed within animal test method results should be used to inform performance benchmarks. Building on previous efforts, this paper proposes a framework comprising five essential elements to establish scientific confidence in NAMs for regulatory use: fitness for purpose, human biological relevance, technical characterisation, data integrity and transparency, and independent review. Universal uptake of this framework would facilitate the timely development and use of NAMs by the international community. While this paper focuses on NAMs for assessing human health effects of pesticides and industrial chemicals, many of the suggested elements are expected to apply to other types of chemicals and to ecotoxicological effect assessments.

Keywords Validation · Framework · NAMs · New approach methodologies · Human health · Regulatory

PETA Science Consortium International
European Commission, Joint Research Centre
Organisation for Economic Co-Operation and Development (OECD)
National Institutes of Health
US Consumer Product Safety Commission
US Environmental Protection Agency
Interagency Center for the Evaluation of Alternative Toxicological Methods (ICCVAM)

https://pubmed.ncbi.nlm.nih.gov/35987941/



https://ntp.niehs.nih.gov/sites/default/files/2024-03/VWG_Report_27Feb2024_FD_508.pdf

Under development: International & US EPA NAMs validation/confidence principles


Unclassified

ENV/JM/MONO(2005)14

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development

18-Aug-2005

English - Or. English

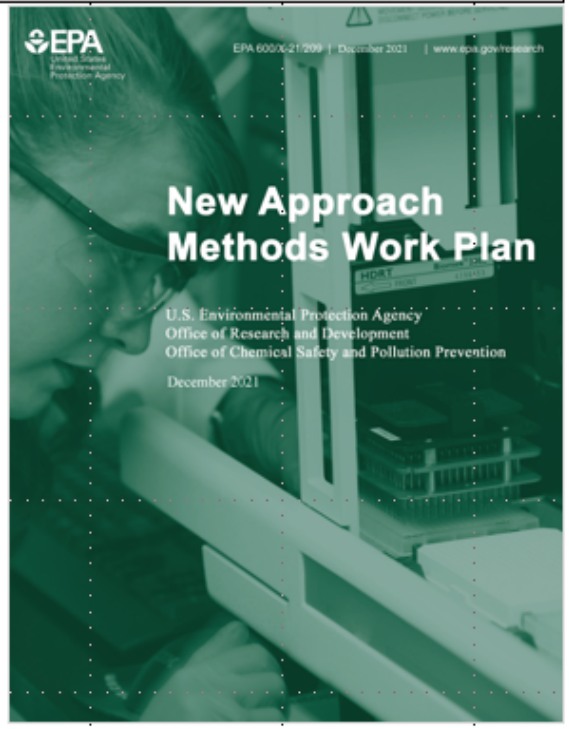
ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

ENV/JM/MONO(2005)14
Unclassified

OECD SERIES ON TESTING AND ASSESSMENT
Number 34

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

US, JRC, Netherlands co-leading project to **modernize** OECD guidance (GD 34) on validation and international acceptance of new and updated test methods for hazard assessment.



https://www.epa.gov/chemical-research/new-approach-methods-work-plan

#3 – Establish scientific confidence

Establishing baselines for EPA

#4 – Develop baselines and metrics

- GAO 2019 report to Congress recommended that Federal agencies develop metrics to assess the progress made toward reducing, refining and replacing animal use in testing
- The 2021 NAMs Work Plan established goals to quantify animal usage for R&D and regulatory testing requirements, starting with mammals
- OPPT and ORD web-publish metrics on an annual basis and have established baselines for mammals
- Process for inclusion of all vertebrate animals is ongoing

Strategic Vision for Adopting New Approach Methodologies – Metrics

The U.S. Government Accountability Office (GAO) released a report to Congress in 2019 recommending that Federal agencies develop metrics to assess the progress made toward reducing, refining and replacing animal use in testing. The activities and policies EPA has implemented over the past several years demonstrate significant impacts in reducing the number of animals used in testing and saving resources for the Agency and stakeholders. Additionally, one of the objectives of the Agency's NAMs Workplan is to begin reporting overall baseline metrics and progress by the fourth quarter (Q4) of 2022.

Details on these reduction and replacement activities are described on their respective pages. EPA's Pesticide Program began to release specific metrics on NAMS implementation, including animal reduction and replacement, in the FY 2015 Annual Report on PRIA Implementation within the Process Improvements in the Pesticide Program chapter. Links to the PRIA reports between FY2015-FY2018 can be found here.

On this page:

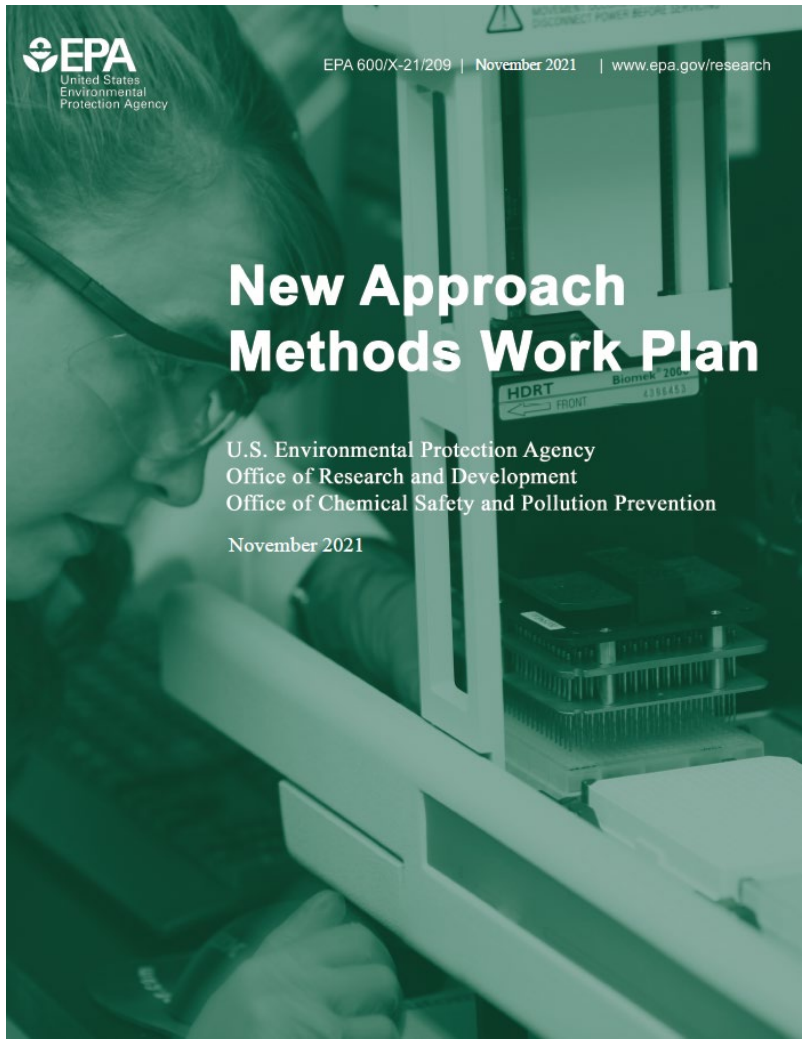
- Hazard and Science Policy Council (HASPOC) Metrics
- Chemistry and Acute Toxicology Science Advisory Council (CATSAC) Metrics
- Acute Dermal Retrospective Waiver Requests Metrics
- *In Vitro* Assay Metrics

Opportunities to use NAMs data to inform decisions

- Draft document assessing regulatory requirements and flexibilities to use a variety of information sources has been drafted
- Incorporation of new scientific approaches into regulatory decision-making is an iterative process, in which several statutory and regulatory barriers must be considered
- Although the majority of EPA's statutory mandates do not specify the types of testing the Agency must require, language across statutes generally indicates that the scientific information considered should be of high quality, based on scientifically sound methodologies, and be subjected to peer-review
- Specific statutory and regulatory flexibilities to utilize alternative methods and information sources will be discussed

#5 – Evaluate regulatory flexibilities

The EPA NAMs Work Plan



US EPA 2021

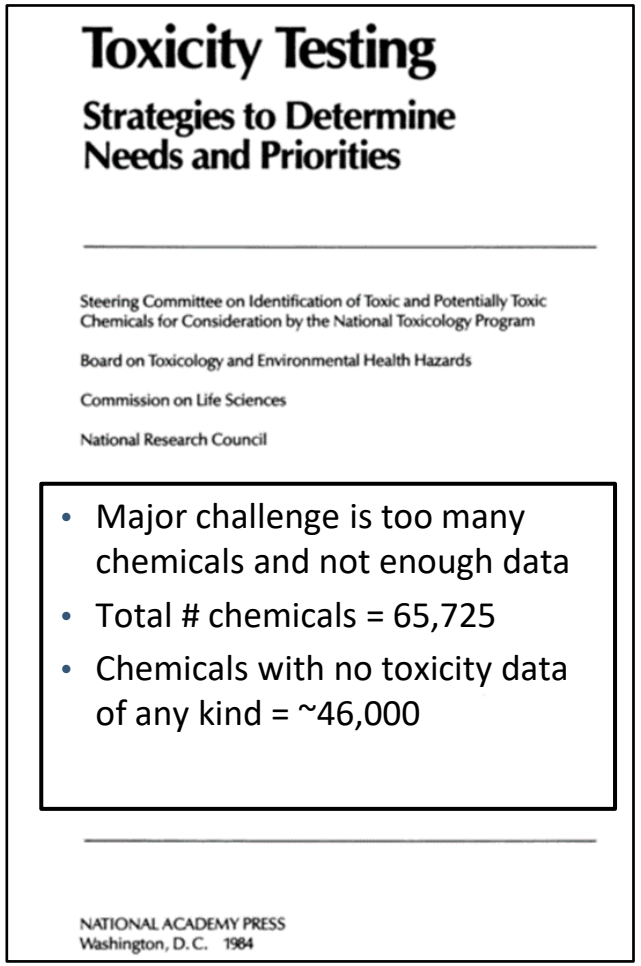
- EPA near-term goals 2021-2024

1. ☑ Develop NAMs to address information gaps
2. Engage and communicate with stakeholders
3. Establish scientific confidence and demonstrate application
4. ☑ Develop baselines and metrics
5. Evaluate regulatory flexibility

- Work Plan goals – by Q4 2024
- The Agency will continue working with national and international partners to identify the decision contexts where available NAMs are demonstrated to be the best available science

Toxicity data and health assessments are needed

1984 NAS Report



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

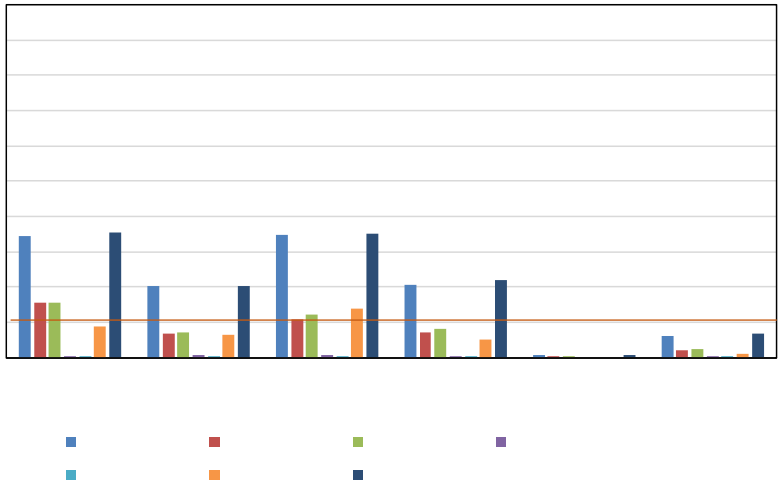
Commission on Life Sciences

National Research Council

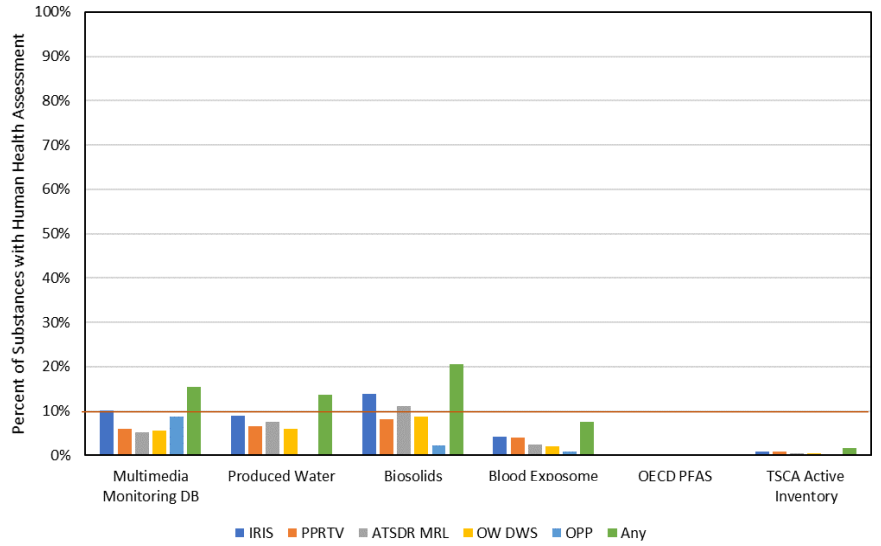
- Major challenge is too many chemicals and not enough data
- Total # chemicals = 65,725
- Chemicals with no toxicity data of any kind = ~46,000

NATIONAL ACADEMY PRESS
Washington, D.C. 1984

2020 survey of 19 countries and regions: **350,000 chemicals and mixtures of chemicals** are registered in one or more inventories[1]



Toxicity Data and Human Health Assessments: 2022



[1]Wang et al. *Environmental Science & Technology* 2020.

Time and resources from no data to a human health assessment using traditional approach is significant

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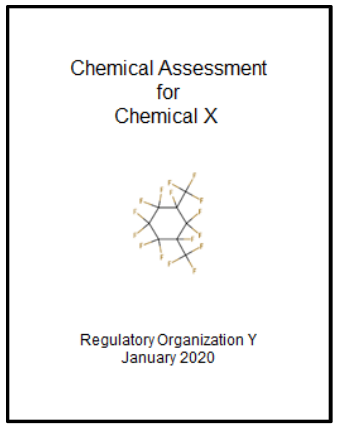

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6 – 14+ years

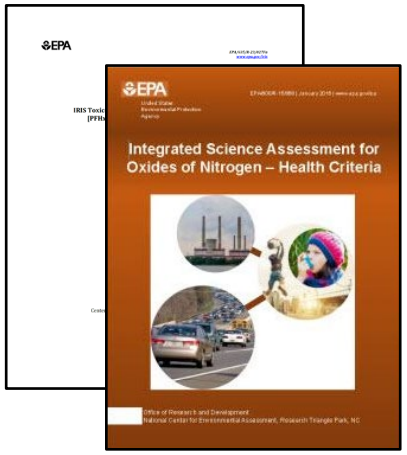
- Time from chemical identification to finalizing report can range from 2 – 10 years

- Time to perform a typical chemical assessment is 4+ years (Krewski *et al., Arch Toxicol.,* 2020).
- More complex assessments can take substantially longer (NASEM, 2009).

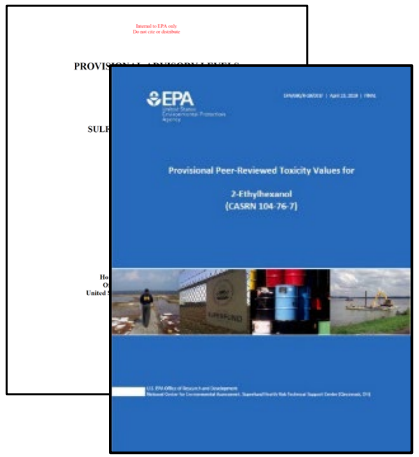
ORD: A Portfolio of Human Health Assessment Products

ORD is developing new assessment products to provide **actionable information** for a variety of decision contexts.

Data-Rich **Relative Data Availability** Data-Poor



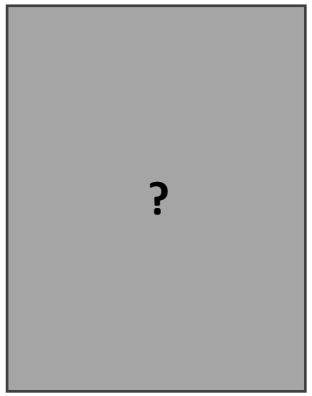
ISAs, IRIS



PPRTVs, PALs

Human Health Toxicity Assessments

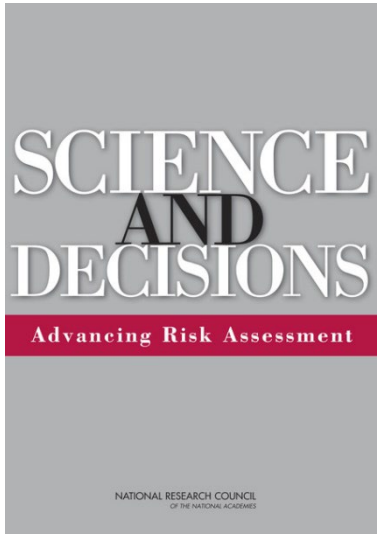
Fit-for-purpose



ETAP, NAMs, others?

Longer **Relative Development Time** Shorter

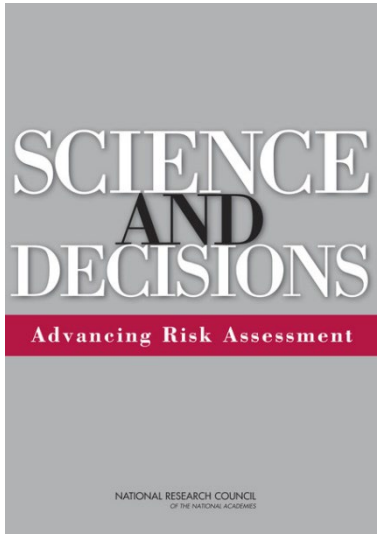
Case study quantifying trade-offs of uncertainty, cost, and time comparing short-term, lower cost assay compared to traditional chronic bioassay



	Short-Term Transcriptomic Study and Assessment	Traditional Toxicity Testing and Human Health Assessment
Time Required	6 months*	8+ years*
Uncertainty	Higher	Lower
Costs	~$200,000	~$4 million

- The NAS committee reflected that **time** is a “major and rarely acknowledged influence in the nature and quality” of a risk assessment
- VOI is a method for quantifying the expected gain in economic terms for reducing uncertainty through the collection of additional data or information

Case study quantifying trade-offs of uncertainty, cost, and time comparing short-term, lower cost assay compared to traditional chronic bioassay



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"…if health-related dangers are detected, what are we as people willing to spend to correct the situation? How much risk are we willing to accept? Who's going to pick up the tab?"

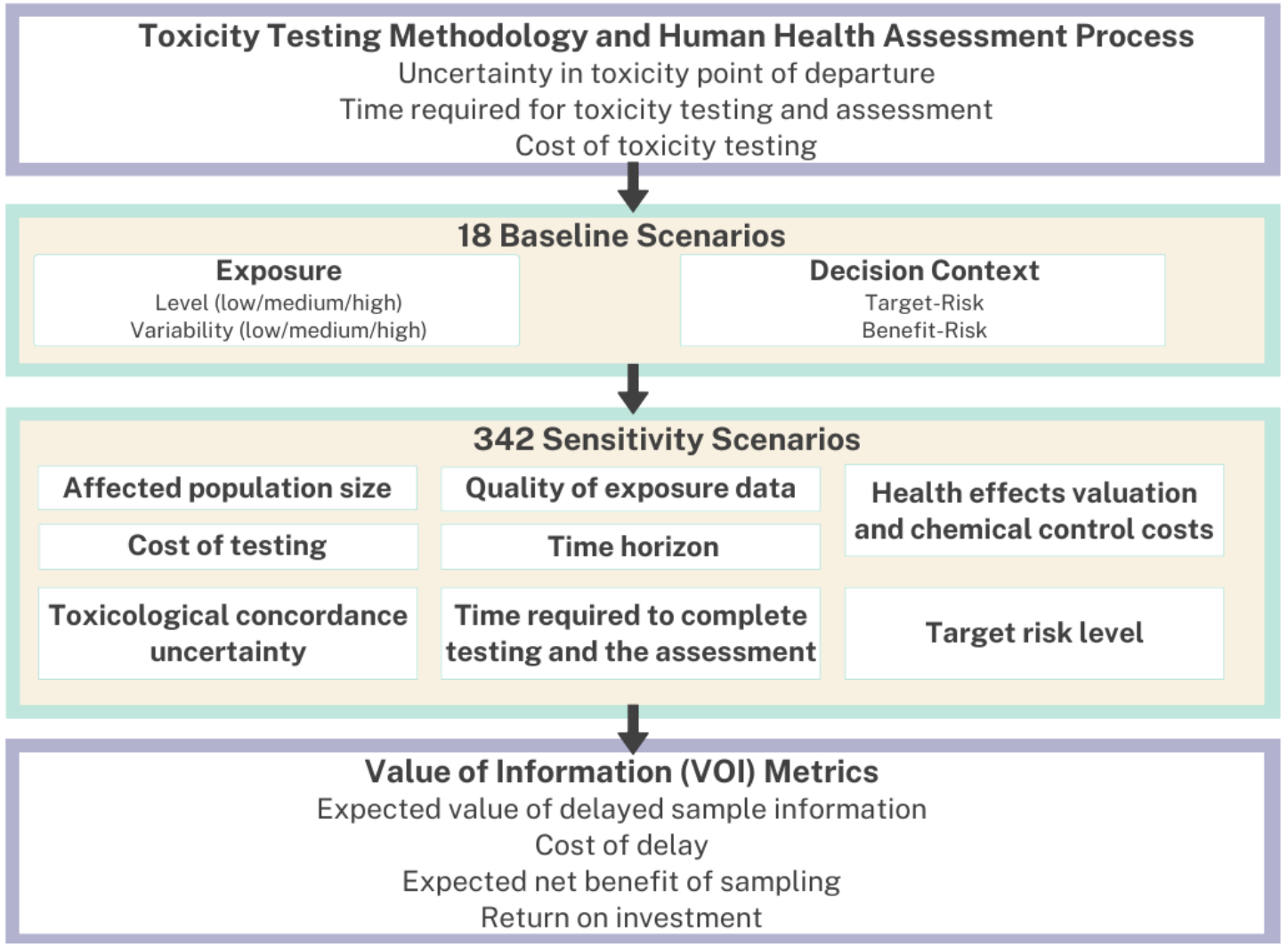
-- Eckardt C. Beck, EPA Region 2 Administrator (1977-1979)
EPA Journal - January 1979

Case study quantifying trade-offs of uncertainty, cost, and time comparing short-term, lower cost assay compared to traditional chronic bioassay

Decision scenario 1:

- Benefit-risk
- 83% favored shorter duration assessment
- 17% favored no testing

- **Decision scenario 2:**
  - Target-risk
  - 87-99% favored shorter duration assessment
  - 7% favored no testing



Toxicity testing and human health assessment approaches evaluated (Traditional/Non-Traditional)

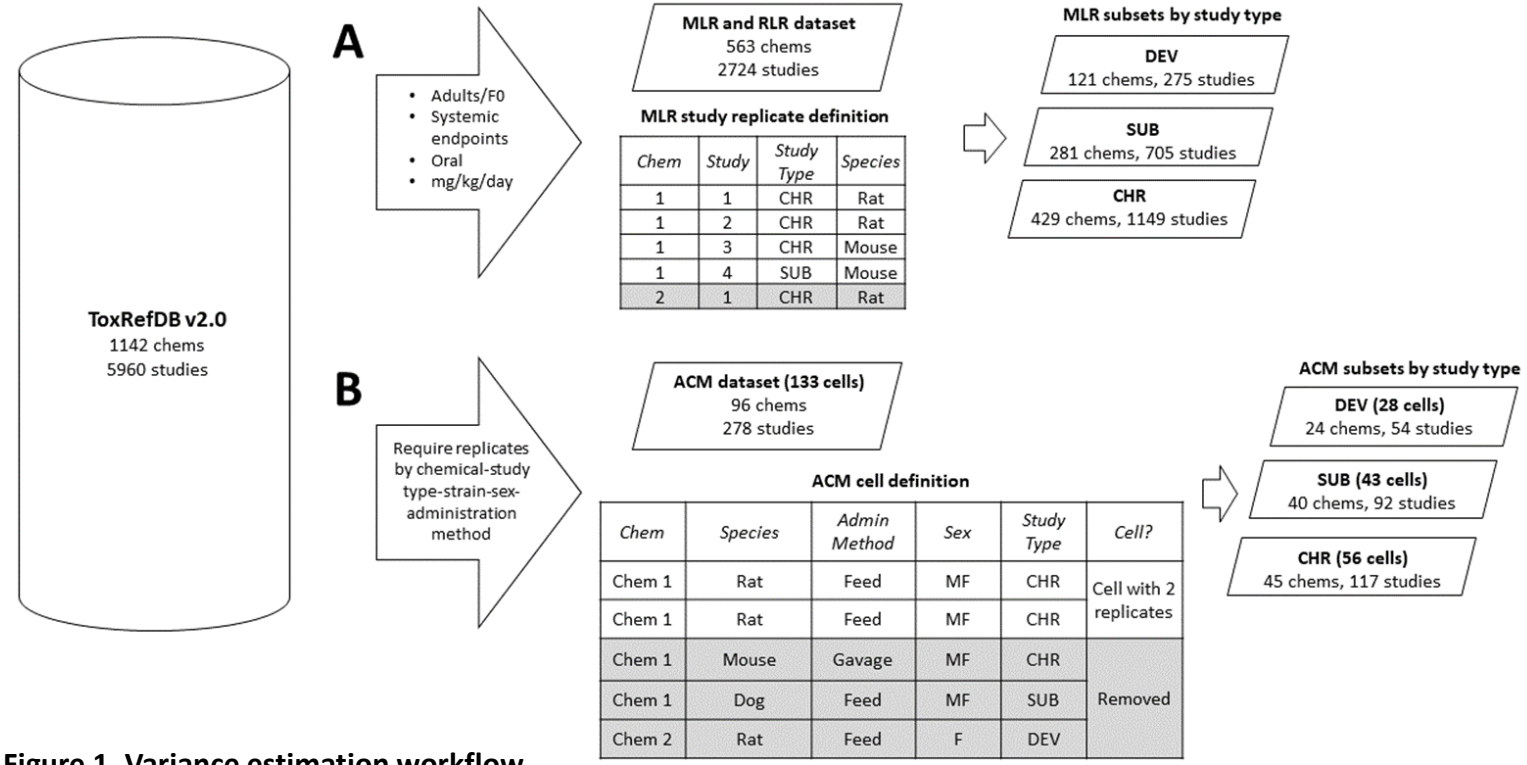
Baseline scenarios reflecting multiple exposure circumstances and decision contexts

Sensitivity analysis exploring the effects of key VOI parameters to capture potential additional sources of uncertainty and chemical characteristics

Key VOI metrics used to compare traditional and non-traditional testing and assessment strategies

Benchmarking NAMs: Evaluating reproducibility of traditional repeat dose toxicity studies in adult animals

Katie Paul-Friedman and team built 28 different statistical models to approximate total variance, unexplained variance, and the spread of the residuals from statistical models of study-level points-of-departure in adult animals.



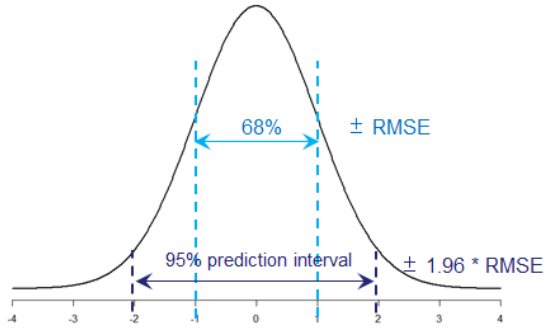
Chem	Study	Study Type	Species
1	1	CHR	Rat
1	2	CHR	Rat
1	3	CHR	Mouse
1	4	SUB	Mouse
2	1	CHR	Rat

Chem	Species	Admin Method	Sex	Study Type	Cell?
Chem 1	Rat	Feed	MF	CHR	Cell with 2 replicates
Chem 1	Rat	Feed	MF	CHR	
Chem 1	Mouse	Gavage	MF	CHR	Removed
Chem 1	Dog	Feed	MF	SUB	
Chem 2	Rat	Feed	F	DEV	

Figure 1. Variance estimation workflow.

CHR = chronic; DEV = developmental (adults only); SUB = subchronic; cells are defined by the factor of all categorical variables; MF = males and females; F = females; MLR = multilinear regression; POD = point of departure; RLR = robust linear regression; ACM = augmented cell means.

The variance, as approximated by RMSE, approaches 0.4-0.6 log10-mg/kg-bw/day regardless of the dataset or approach used. This helps us estimate a minimum prediction interval for a new estimation of study-level point-of-departure and to set a benchmark for NAMs to predict these values.



Using an RMSE=0.59, the minimum 95% PI of an LEL/LOAEL is:

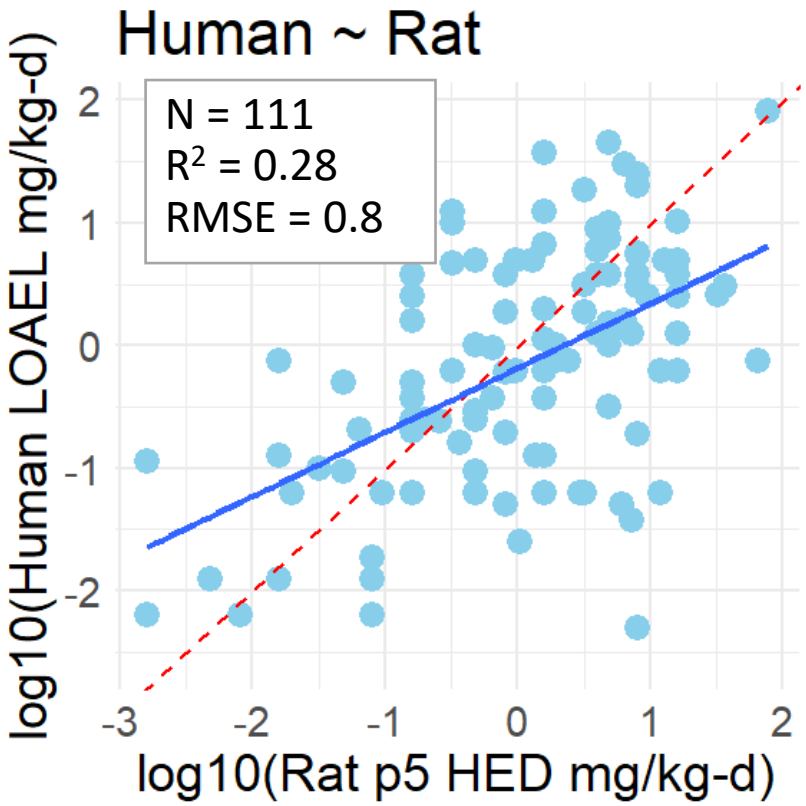
1 mg/kg/day ➔ 0.07 – 14 mg/kg/day.

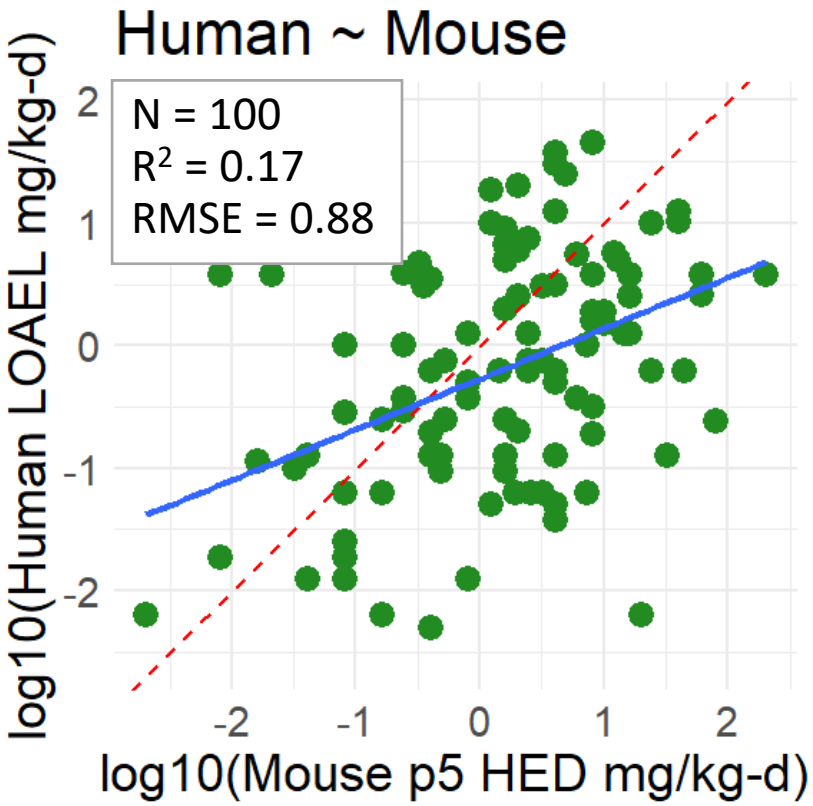
10 mg/kg/day ➔ 0.7 – 143 mg/kg/day.

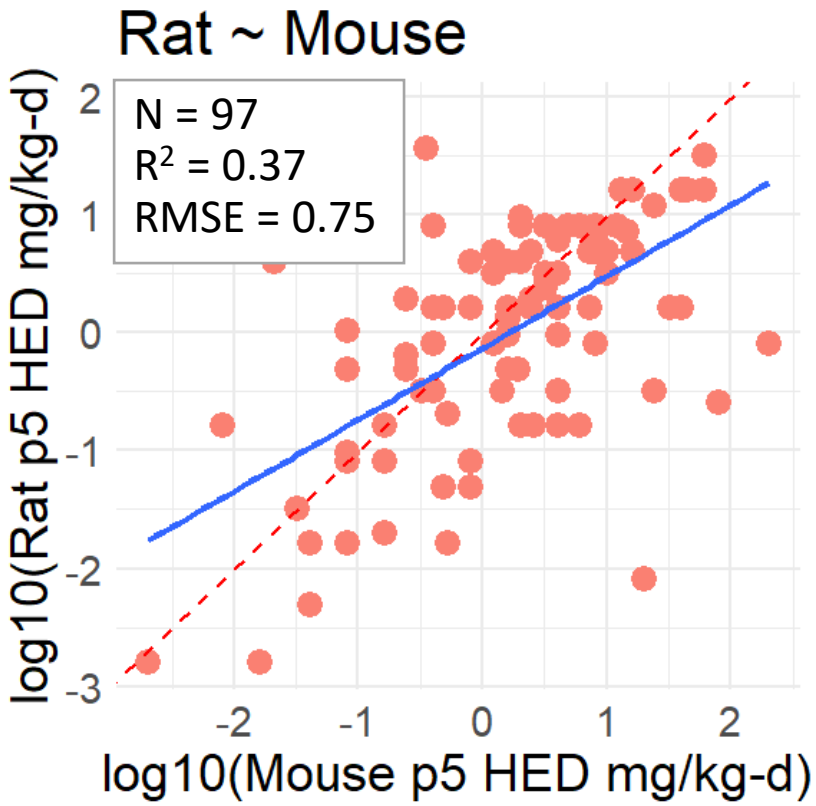
APCRA case study evaluating concordance of species- and organ-level effects

Pharmapendium database – assessing dose concordance in allometrically scaled values between rodent species and human (nonclinical and clinical studies)

Preliminary/draft analysis – process improvements in data curation are ongoing



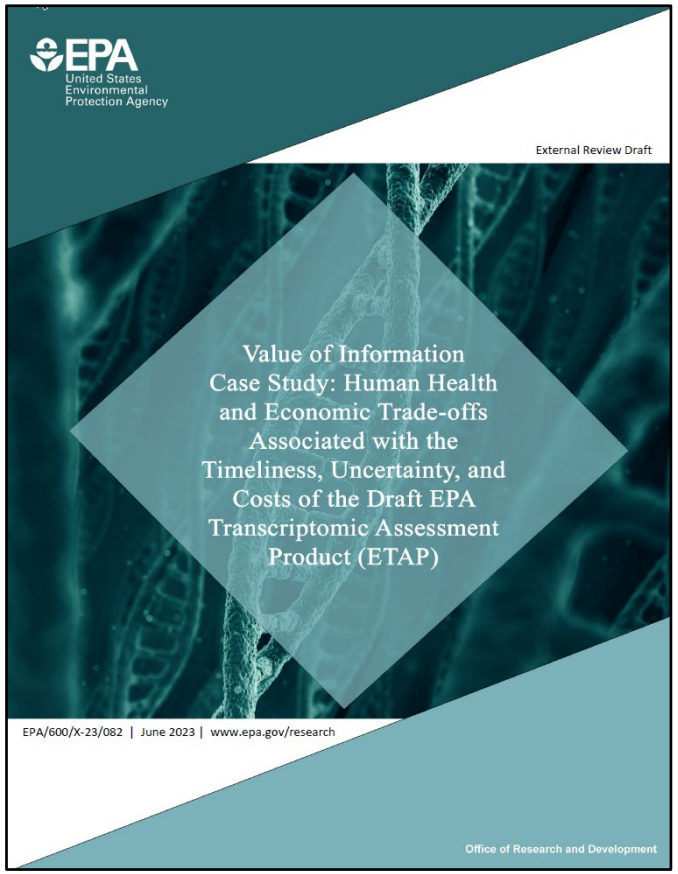




Credit: Chelsea Weitekamp (EPA), presented at APCRA 2023 annual meeting

What are the implications for NAMs?

- Work ongoing to complete deliverables of NAMs Work Plan
- NAMs data is often more efficient to obtain than traditional animal study data, uncertainties can be compared to traditional tox study concordance and error estimates
- VOI analysis contextualizes the trade-offs in uncertainty with the return on investment and socioeconomic public health benefits realized by reducing time to a regulatory decision
- However, barriers to adoption of NAMs for regulation still necessitate confidence building through ICCVAM, including
  - Case studies
  - Adding details to assay validation frameworks
  - Consensus building and peer review



Thank you

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