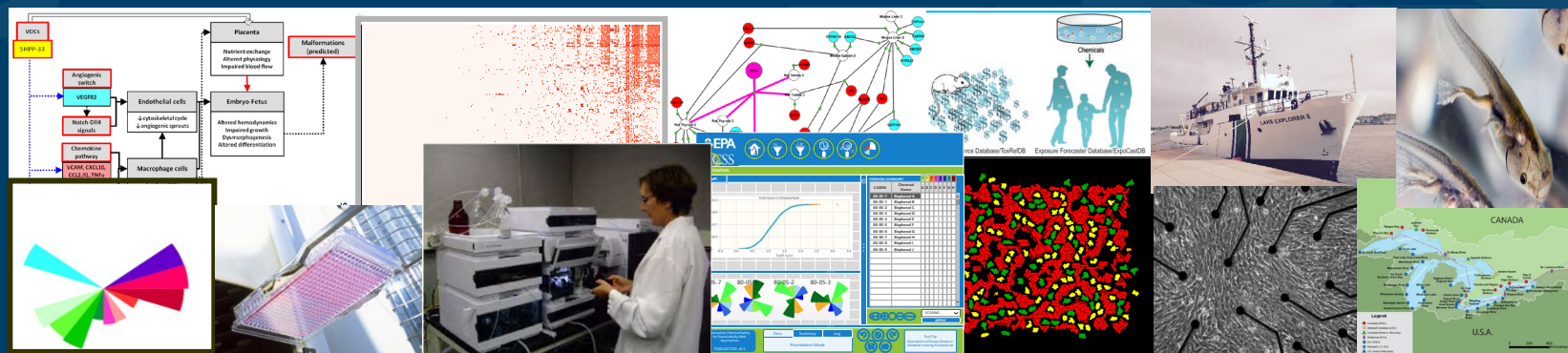


# State of the Science on Development and Use of NAMs for Chemical Safety Testing



## Lessons Learned from the Application of NAMs

ToxForum Workshop

July 28, 2021

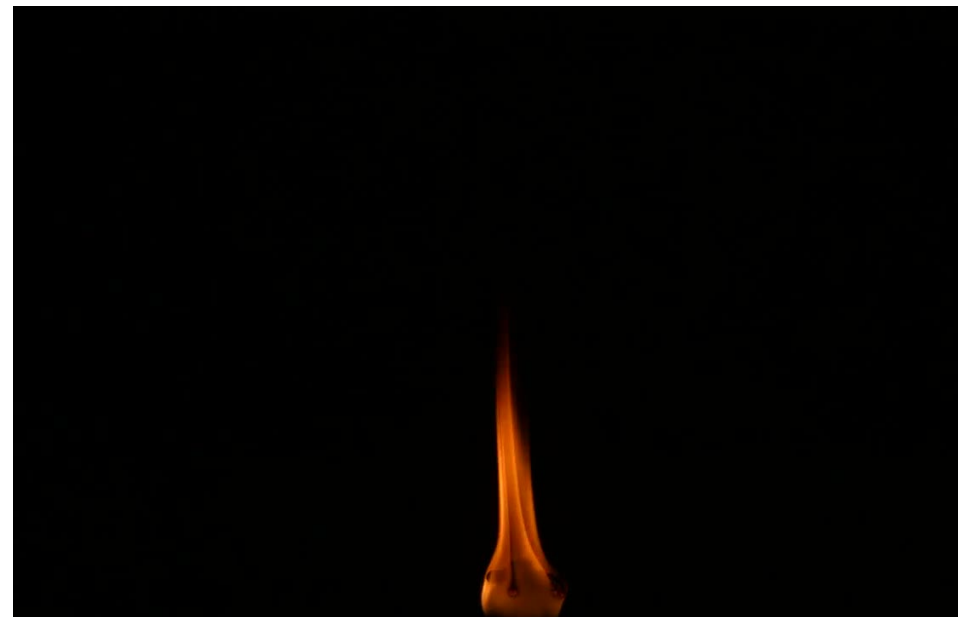
**Rusty Thomas**  
**Director**  
**Center for Computational Toxicology and Exposure**

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

# The Focus of the Session...

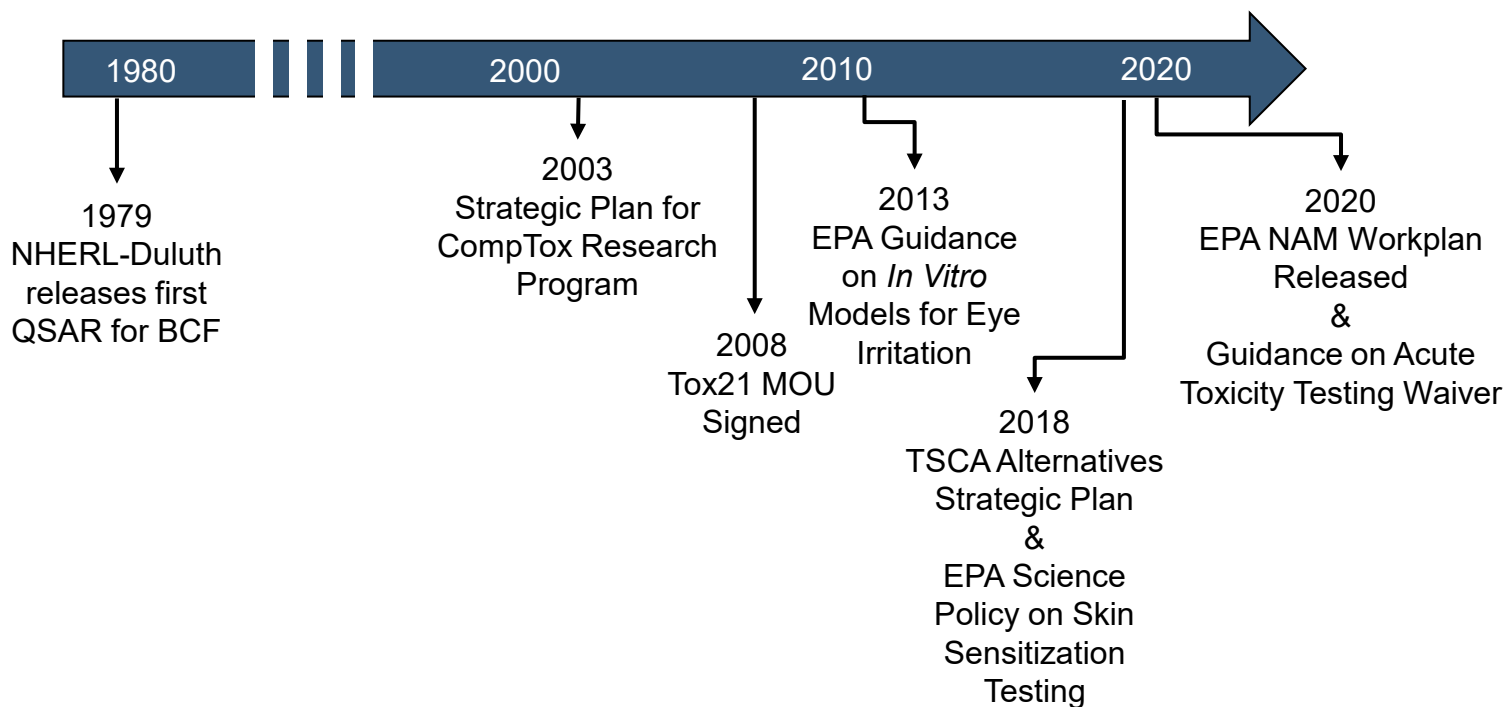


Lots of talk about NAMs...



Not enough application.

# While NAMs May Be The New Buzzword, Work on Alternatives/NAMs Has Been Around for Decades



## Old Fashion Becomes New Fashion

Bell Bottoms  
VS  
“Flared” Jeans

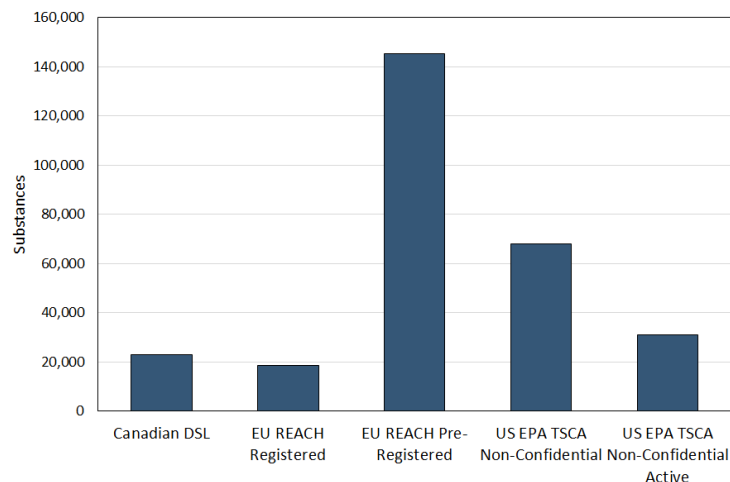


Original Mullet  
VS  
“Modern” Mullet



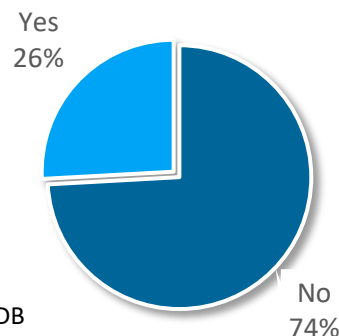
# Underlying Challenges Driving Development and Application of NAMs are the Same

Number of Substances



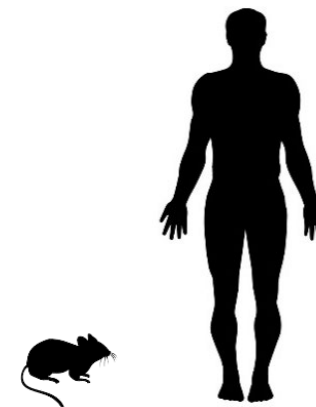
Amount of Data

% of Non-Confidential, Active TSCA Inventory with Repeat Dose Toxicity Studies

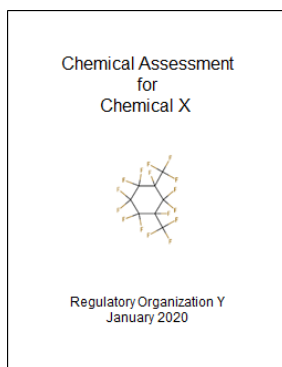


\*Data from ToxValDB (Dec 2019)

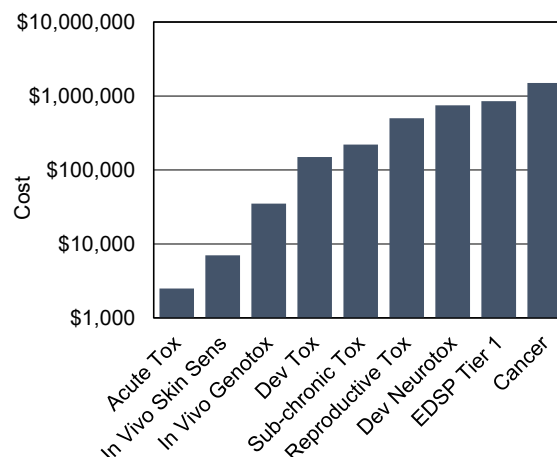
Reliability/Relevance



Time



Economics



Broad Range of Decision Contexts

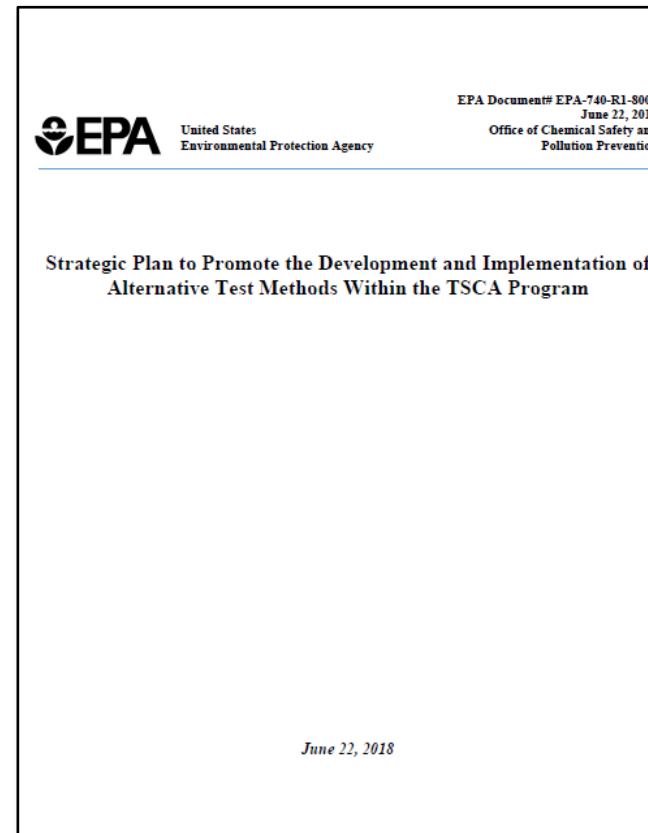


# Trendy or Not, Making Progress Requires a Plan

Similar common goal of reducing use of animals in chemical safety testing/research, but different focus...



*Focused on Agency-wide action*



*Focused on TSCA*



# NAM Work Plan Identified Objectives, Strategies and Deliverables to Apply NAMs to Agency Decisions



- Five objectives for reducing animal testing and research while ensuring that Agency decisions remain fully protective of human health and the environment
  - Evaluate Regulatory Flexibility
  - Develop Baselines and Metrics
  - Establish Scientific Confidence and Demonstrate Application
  - Develop NAMs to Address Information Gaps
  - Engage and Communicate with Stakeholders
- Short- and long-term strategies EPA will use to accomplish the objectives
- Specific deliverables and timelines linked with each objective
- Recognition that the EPA NAMs Work Plan represents a snapshot in time and will evolve as EPA's knowledge and experience grows

# Many of These Strategies Were Themes in the EPA NAM Conferences

## STATE OF THE SCIENCE ON DEVELOPMENT AND USE OF NEW APPROACH METHODS (NAMs) FOR CHEMICAL SAFETY TESTING

**Location:** U.S. Environmental Protection Agency  
William Jefferson Clinton East Building  
Room 1153 (the Map Room)

**Date:** December 17, 2019

**Time:** 9:30 am – 5:30 pm\*



### Agenda

8:30 am – 9:45 am	Registration	
9:45 am – 10:00 am	Welcome	Alexandra Dunn (EPA)
	Charge to the Group	Andrew Wheeler (EPA)
<b>Establishing Baselines for Animal Use at EPA and Opportunities for Reduction</b>		
10:00 am – 10:20 am	Retrospective analysis of the statutory requirements, study requests, and research utilization in OCSP and ORD	Anna Lowit (EPA)
<b>Variability and Relevance of Current Animal Tests and Expectations for NAMs</b>		
10:20 am – 10:40 am	Concordance of the toxicity of pharmaceuticals in animals and human	Thomas Monticello (Amgen)
10:40 am – 11:00 am	Variability of animal studies for acute toxicity, skin sensitization, and mechanistic responses	Nicole Kleinstreuer (NICEATM)**
11:00 am – 11:20 pm	Qualitative and quantitative variability of repeat dose animal toxicity studies	Katie Paul-Friedman (EPA)
<b>State of the Science in Development and Application of NAMs</b>		
11:20 pm – 11:40 pm	Development of NAMs to predict acute toxicological responses	Dave Allen (Integrated Laboratory Systems)
11:40 pm – 12:00 pm	Application of NAMs for quantitative screening level risk decisions	Tara Barton-Maclaren (Health Canada)
12:00 pm – 1:00 pm	Lunch	
1:00 pm – 1:20 pm	State of the science for predicting developmental toxicity using NAMs	George Daston (Proctor & Gamble)

## EPA NAMs Conference 2020: State of the Science on Development and Use of NAMs for Chemical Safety Testing

**Location:** Virtual – Video link to be provided to registered participants

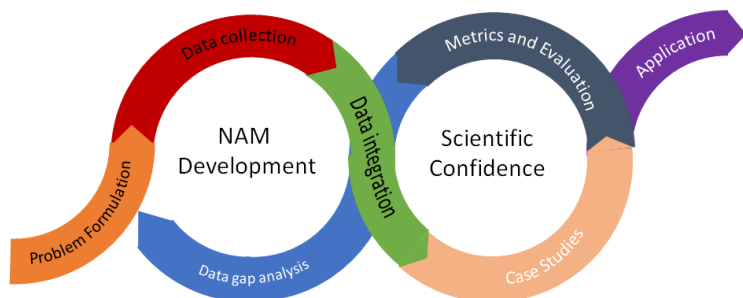
**Day 1:** October 19, 2020 | 9:00 a.m. – 1:00 p.m. ET\*

**Day 2:** October 20, 2020 | 9:15 a.m. – 1:00 p.m. ET\*

### Day 1 Agenda

Time	Topic	Speaker (Affiliation)
9:00 – 9:15 a.m.	Welcome ( <i>recorded remarks</i> )	Andrew Wheeler (EPA)
9:15 – 9:30 a.m.	Charge to the Group	Jennifer Orme-Zavaleta (EPA)
<b>Implementation of Animal Testing Reduction at EPA</b>		
9:30 – 10:00 a.m.	Overview of EPA NAMs Work Plan	Russell Thomas (EPA)
10:00 – 10:30 a.m.	Progress on Implementing the TSCA Alternatives Strategic Plan	Gino Scarano (EPA)
<b>State of the Science in Development of NAMs</b>		
10:30 – 11:00 a.m.	Using Chemical, Biological, and <i>In Vivo</i> Data for NAMs: Which data do we have, and what can we do with it?	Andreas Bender (Cambridge)
11:00 – 11:15 a.m.	Break	N/A
11:15 – 11:45 a.m.	Transcriptome-Based Derivation of an <i>In Vivo</i> POD: Current and Future Utility	Kamin Johnson (Corteva)
11:45 a.m. – 12:15 p.m.	Drugmonizome and Drugmonizome-ML: Integration and Abstraction of Small Molecule Attributes for Drug Set Enrichment Analysis and Machine Learning	Avi Ma'ayan (Mount Sinai)
12:15 – 12:45 p.m.	"Fit for Purpose" for Organotypic Models in Environmental Health Protection	Ivan Rusyn (Texas A&M)
12:45 – 1:00 p.m.	Closing Remarks	David Fischer (EPA)

# Key #1: Continue to Develop and Refine NAMs to Address Information Gaps and Current Limitations

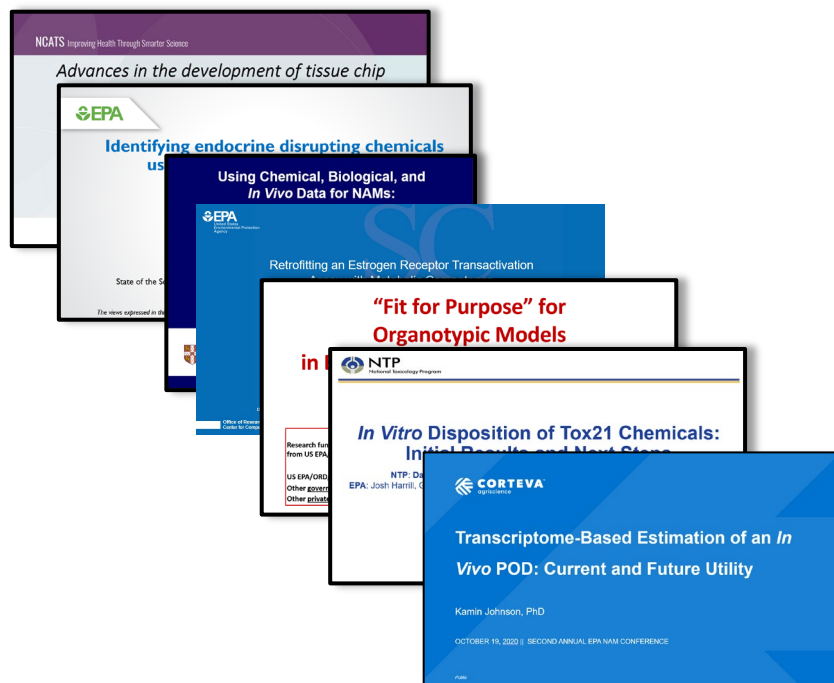


## EPA NAM Work Plan Strategies:

- Joint planning of NAM development by EPA research scientists and regulators
- Encourage development and evaluation of NAMs by external parties

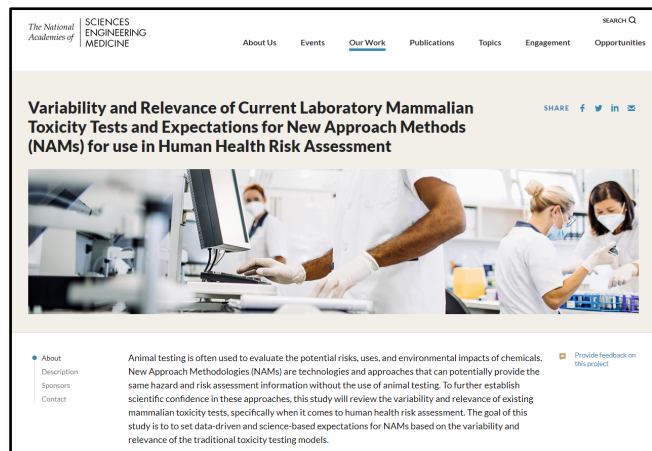
## NAM Conferences:

- Research to develop and refine methods across a variety of hazard endpoints, mechanisms, and dose response applications
- Multiple ongoing activities to address current limitations
  - Tissue and organ effects using organotypic culture models and microphysiological systems
  - Relevant xenobiotic metabolism across *in vitro* models
  - Broad understanding of disposition within *in vitro* systems
  - Technologies to comprehensive characterize chemical impacts across biological space





# Key #2: Establish Appropriate Expectations and Confidence in NAMs

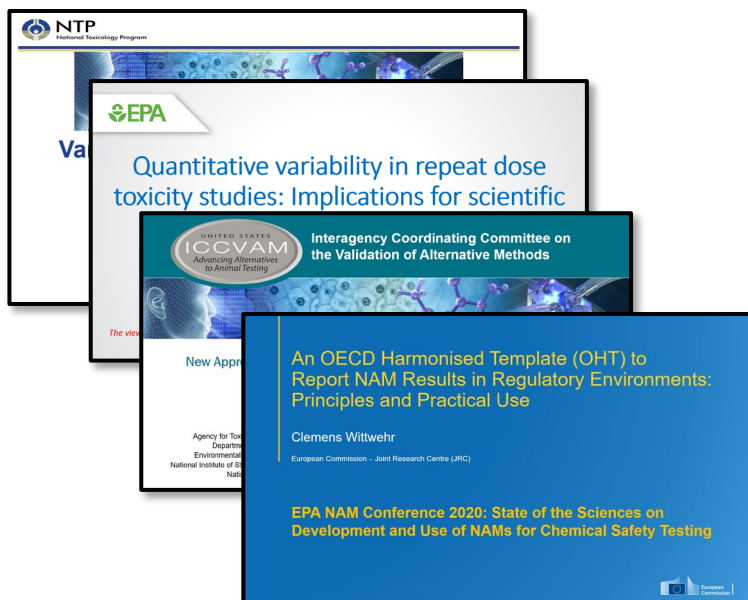


## EPA NAM Work Plan Strategies:

- Characterize the scientific quality and relevance of existing animal tests
- Develop a scientific confidence framework to evaluate the quality, reliability, and relevance of NAMs
- Develop recommended reporting templates

## NAM Conferences:

- Activities to evaluate concordance of pharmaceutical toxicity in animals and humans
- Research to understand variability of animal studies for acute toxicity, skin sensitization, and mechanistic responses
- Characterizing qualitative and quantitative variability of repeat dose toxicity studies
- Developing new approaches to validation and characterizing NAM performance
- OECD harmonized templates to report NAM-related results



# Key #3: Demonstrate Application of NAMs in Different Decision Contexts

## EPA NAM Work Plan Strategies:

- Demonstrate application of the NAMs to regulatory decisions through case studies

## NAM Conferences:

- Application of *in vitro* methods for evaluating respiratory irritants
- Integrating *in vitro* and computational approaches for identifying endocrine active compounds
- Integrating NAM data for evaluating potential developmental neurotoxicity
- Utilizing NAMs for quantitative risk assessment of cosmetic ingredients
- Incorporating threshold of toxicological concern in TSCA



# Key #4: Identify Regulatory Flexibilities for Utilizing NAMs

Table 1. Initial Survey Results of Mammalian Testing Requirements in Major Environmental Statutes

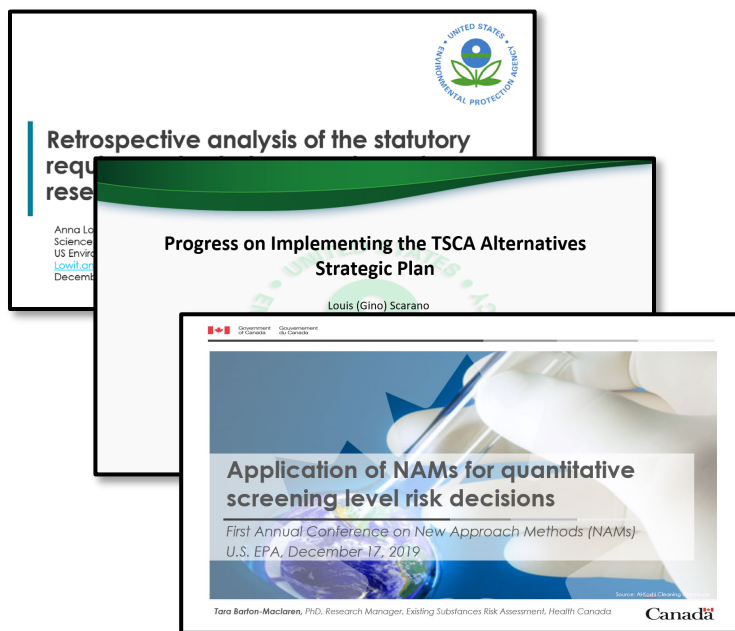
Major Environmental Statute	Statutory Requirements for Mammalian Testing	Regulatory Requirements for Mammalian Testing
Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and Federal Food, Drug, Cosmetic Act (FDCA)	None	40 CFR Part 156 specifies FIFRA and FDCA data requirements that include use of animals (pesticide registration, registration review, and tolerance or exemptions from the requirements of a tolerance for a pesticide chemical residue).
Endangered Species Act (ESA)	None	None <sup>a</sup>
Food Quality Protection Act (FQPA) amendments to the FDCA and the Safe Drinking Water Act (SDWA) amendments	None	None <sup>a</sup>
Toxic Substances Control Act (TSCA)	None, but TSCA Section 4(h) requires reducing use of vertebrate animals in testing.	40 CFR Parts 790 through 799 apply to TSCA Section 4 test rules.
Clean Air Act (CAA)	None	Fuel and Fuel Additive Registration; <sup>a</sup> Significant New Alternatives Policy (SNAP) programs. <sup>b</sup>
Clean Water Act (CWA)	None	None
Comprehensive Environmental Response, Compensation and Liability Act (CERCLA)	None	None
Emergency Planning and Community Right-to-know Act (EPCRA)	None	None
Resource Conservation and Recovery Act (RCRA)	None	None
Safe Drinking Water Act (SDWA)	None	None

## EPA NAM Work Plan Strategies:

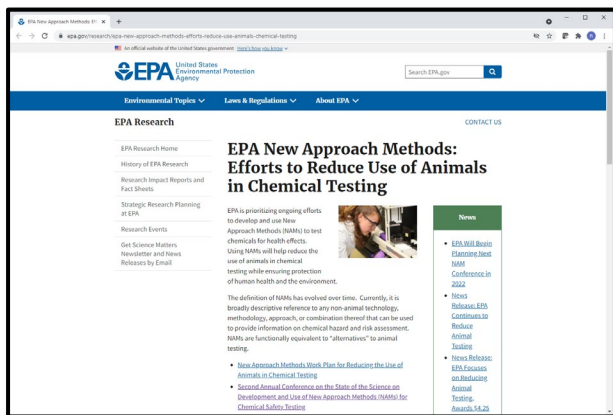
- Review of existing statutes and programmatic regulations, policies and guidance to identify animal testing requirements
- Develop options for introducing flexibility on implementing and/or using appropriate NAMs for regulatory purposes

## NAM Conferences:

- Statutory requirements, opportunities, and application of NAMs in FIFRA
- Utilization of NAMs within TSCA
- Application of NAMs within the Canadian Chemicals Management Plan



# Key #5: Communicate, Train, and Communicate Some More...

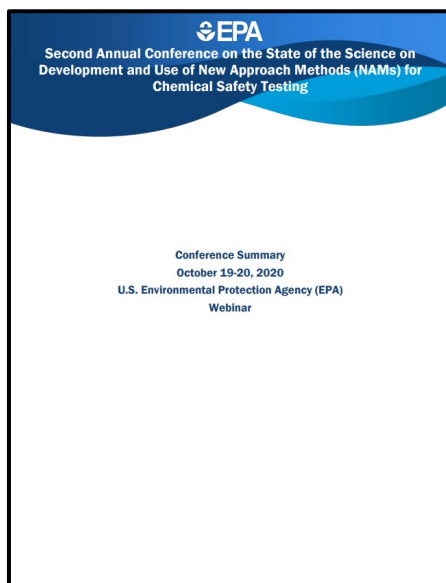


## EPA NAM Work Plan Strategies:

- Develop centralized portal for releasing EPA-related NAM Information
- Actively solicit comment and feedback associated with deliverables
- Develop training courses, workshops, and conferences for stakeholders on NAMs

## NAM Conference:

- Feedback from breakout group discussions during the first annual conference used to inform NAM Work Plan strategies
- NAM Work Plan discussed at second annual conference
- NAM Conference reports are available ([www.epa.gov/nam](http://www.epa.gov/nam))



# Acknowledgements

## EPA NAM Work Plan Leadership and Conference Planning Team

Sarah Stillman*	Anna Lowit	Gino Scarano
Russell Thomas	Evisabel Craig	Monique Perron
Maureen Gwinn	Jeff Frithsen	Monica Linnenbrink

## EPA NAM Work Plan Development and Writing Team Subgroups

Regulatory Flexibility and Existing Statutes	Baselines and Metrics	Scientific Confidence and Demonstration	NAM Development and Scientific Gaps	Communication and Outreach
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Betsy Behl (OW)		William Irwin (OCSPP)	Allison Crimmins (OAR)	
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		Samantha Jones (ORD)		
		Stiven Foster (OLEM)		

\*Left EPA