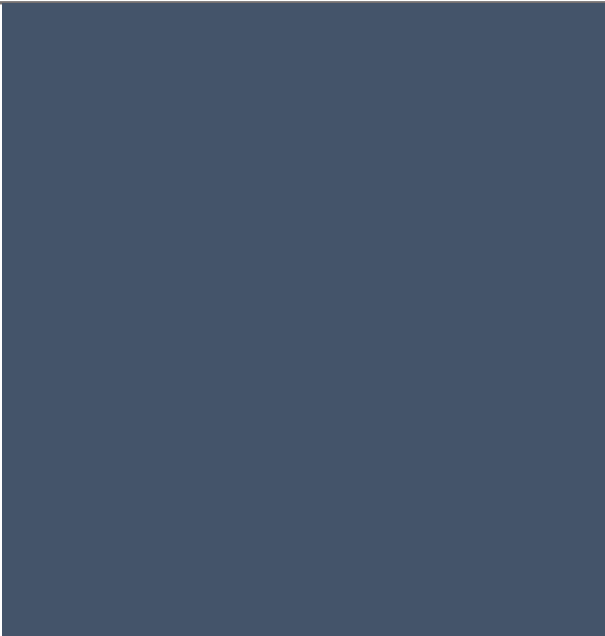


Note: this document may contain some elements that are not fully accessible to users with disabilities. If you need assistance accessing any information in this document, please contact [ORD\\_Webmaster@epa.gov](mailto:ORD_Webmaster@epa.gov).



# US EPA CSS-HERA Board of Scientific Counselors Chemical Safety Subcommittee Meeting

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US EPA CSS-HERA BOSC Meeting – February 2-5, 2021

## CSS-HERA Introduction Slides



The work presented within represents US EPA Office of Research and Development research activities. Material includes both peer reviewed, published results and work-in-progress research. Please do not cite or quote slides.

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The work presented within represents US EPA Office of Research and Development research activities. Material includes both peer reviewed, published results and work-in-progress research. Please do not cite or quote slides.



# Chemical Safety for Sustainability (CSS) National Research Program

## Board of Scientific Counselors (BOSC) Chemical Safety Subcommittee Implementation Meeting

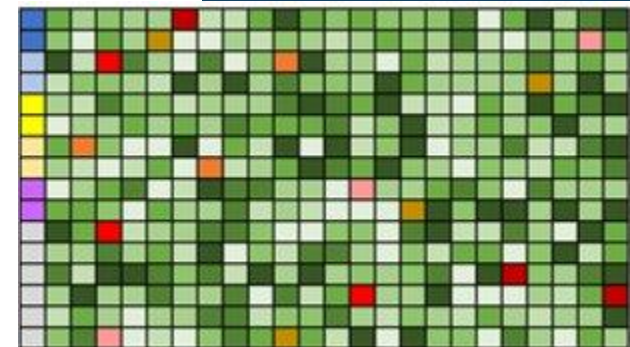
Jeffrey Frithsen National Program Director (NPD)

Joe Tietge, Principal Associate NPD

Kathie Dionisio, Associate NPD

Heidi Bethel, Associate NPD

February 2, 2021



- **CSS Focus:**
  - Presentation of selected research demonstrating examples of the development, testing and implementation of **New Approach Methods (NAMs)**;
  - Demonstration of selected tools.
- **HERA Focus:**
  - Presentation of research related to applying **NAMs** in **HERA** assessments;
  - **Systematic review tools and approaches**;
  - **Dose-response analyses and models**.
- **NAMs:** Any technology, methodology, approach or combination thereof that can be used to provide information on chemical hazard and risk that avoids the use of intact animals.



Topic	Research Areas	Outputs	Products	Presentations
Chemical Evaluation	High-Throughput Toxicology (HTT)	8	36	Sessions 1A; 1C; 1D; 2
	Rapid Exposure Modeling and Dosimetry (REMD)	8	50	Session 1B; 2; 3
	Emerging Materials and Technologies (EMT)	2	13	
Complex Systems Science	Adverse Outcome Pathways (AOP)	8	42	Session 2
	Virtual Tissue Modeling (VTM)	3	16	Session 1D
	Ecotoxicological Assessment and Modeling (ETAM)	10	34	Session 1C
Solutions-Based Translation and Knowledge Delivery	Chemical Safety Analytics (CSA)	4	24	Session 3
	Informatics, Synthesis, and Integration (ISI)	5	29	Sessions 2; 3

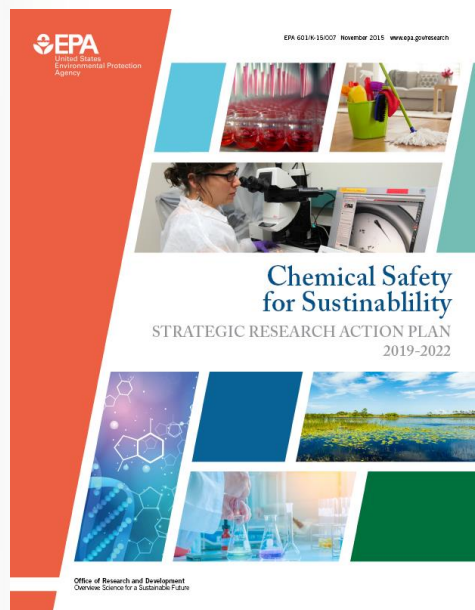
CSS Research Areas that support work on NAMs.

# BOSC Review of Other Parts of CSS Portfolio



Meeting Date	Primary Topic	HTT	REMD	EMT	AOP	VTM	ETAM	CSA	ISI
February 2021	NAMS	XXX	XXX		XX	X	X	X	X
Summer 2021	PFAS	XXX	XXX		XXX		XXX	X	X
Fall 2021	Complex Systems				XXX	XXX	XXX	X	
	Knowledge Delivery			X	X		X	XX	XXX

## Planning



- National Programs Lead
- Strategic Focus
- Resources allocated at Research Area level

RACTs

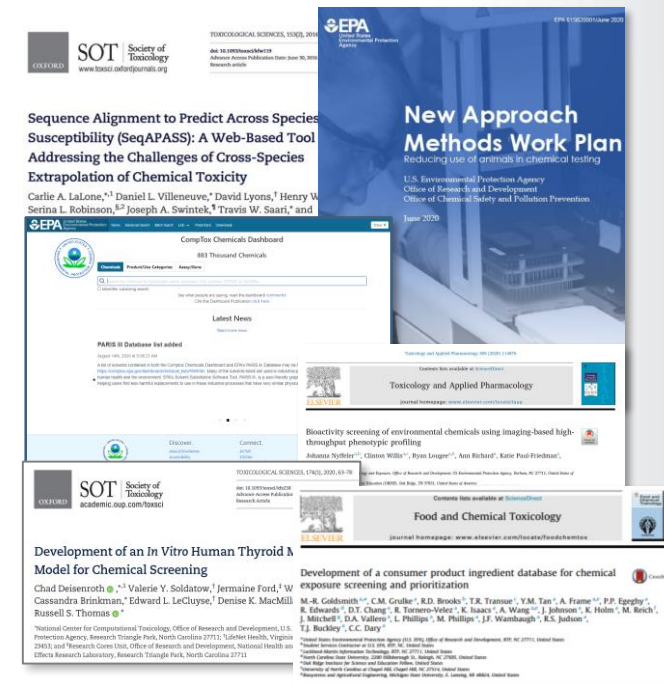


## Implementation

Research Area  
Implementation Plans

- Center Lead
- Tactical focus
- Resources allocated for specific products

## Delivery



- Includes data, models, methods, EPA and journal publications
- Joint activity of National Programs and Centers

# Why NAMs?



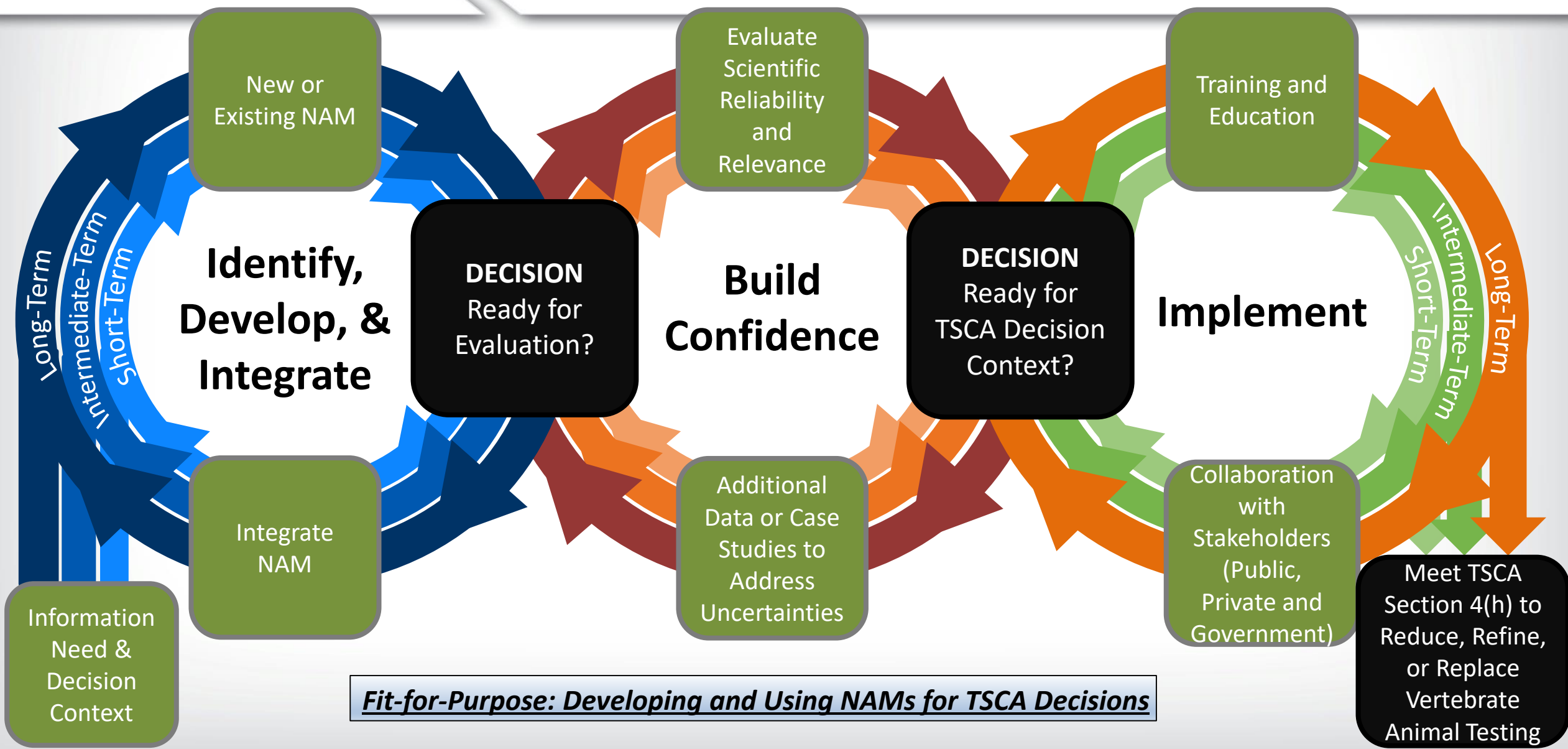
- **Strong focus of the CSS Program for over a decade.**
- **Critical component of the CSS Program's long-term vision:**
  - Provide the information needed to inform Agency decisions about chemicals;
  - Accelerate the pace of chemical assessment and decision-making;
  - Replace, Reduce and Refine vertebrate animal testing;
  - Provide scientific innovation and leadership to transform chemical screening and assessment.
- **Supports Agency objectives, regulatory drivers, and the needs of multiple partners and stakeholders.**

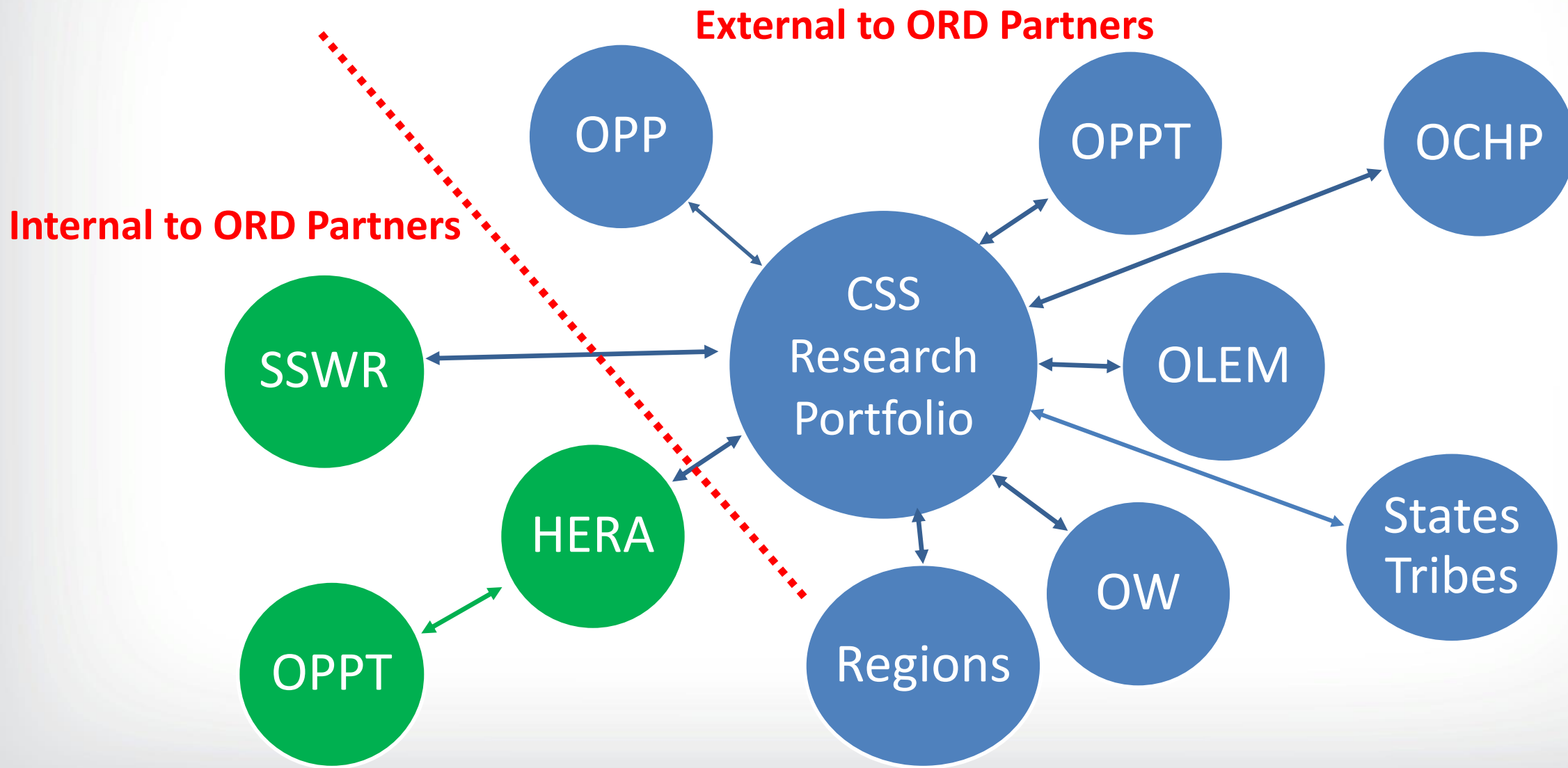


Establish  
scientific  
confidence and  
demonstrate  
application



Develop NAMs  
that fill critical  
information  
gaps







- **Presentations focus on examples of the development of NAMs to address specific research needs and topics.**
- **Presentations align with CSS Charge Question I:**
  - *Please provide specific suggestions or recommendations to improve approaches to advance the development and testing of NAMs conducted under the CSS program.*
- **Four concurrent sessions, each having three focused presentations by ORD scientists.**

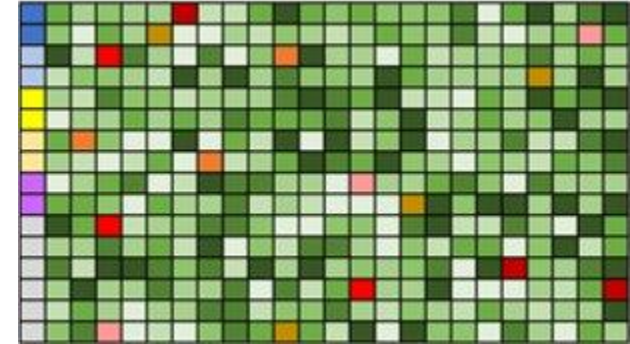
- **Highlights research aimed at facilitating the application of NAMs in decision-making.**
- **Presentations align with CSS Charge Question 2:**
  - *Please comment on the extent to which these selected research activities have the appropriate approach, structure, and components to increase confidence in, and to facilitate use of, NAMs in Agency decision making.*
- **Four presentations will be made.**

- **Provides demonstrations of three selected CSS tools.**
- **Tools utilize the results of NAM research. However, these tools have a broader focus.**
- **Presentations align with CSS Charge Question 3:**
  - *Please provide suggestions or recommendations regarding how these CSS products can be improved and best implemented to serve EPA partners and external stakeholders?*



## Final Comments:

- Presentations contain peer-reviewed published results, works in press, and results from works in progress.
- **ORD** investigators welcome this opportunity to engage with the **BOSC** and talk about our science.
- **Have fun!**





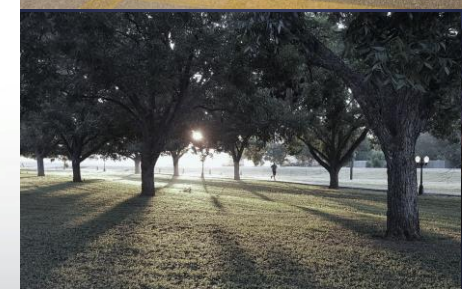
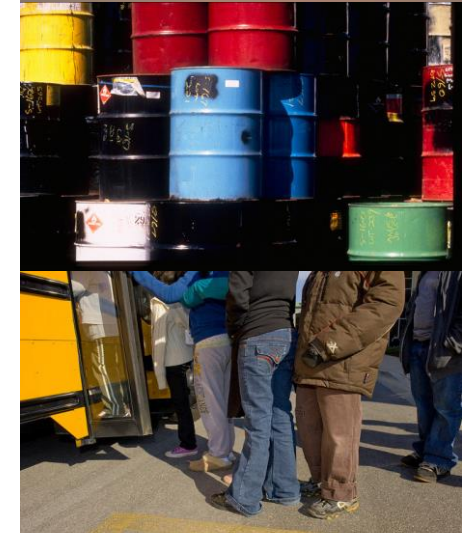


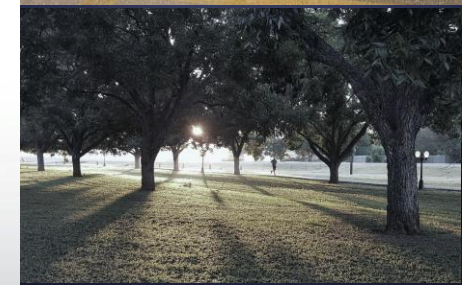
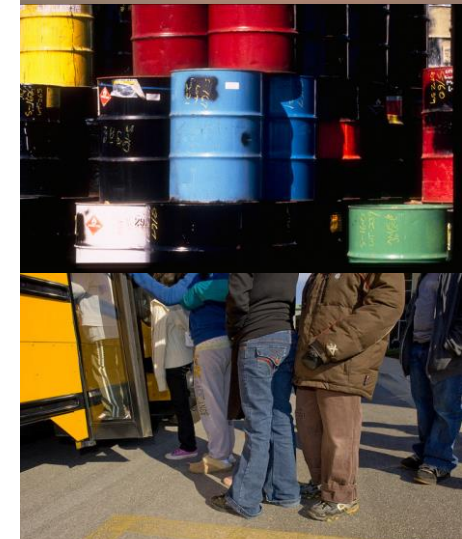
# Health and Environmental Risk Assessment (HERA) National Research Program

## Board of Scientific Counselors (BOSC) CSS-HERA Subcommittee – Implementation Meeting

Samantha Jones, National Program Director (NPD)  
Beth Owens, Principal Associate NPD

February 2, 2021

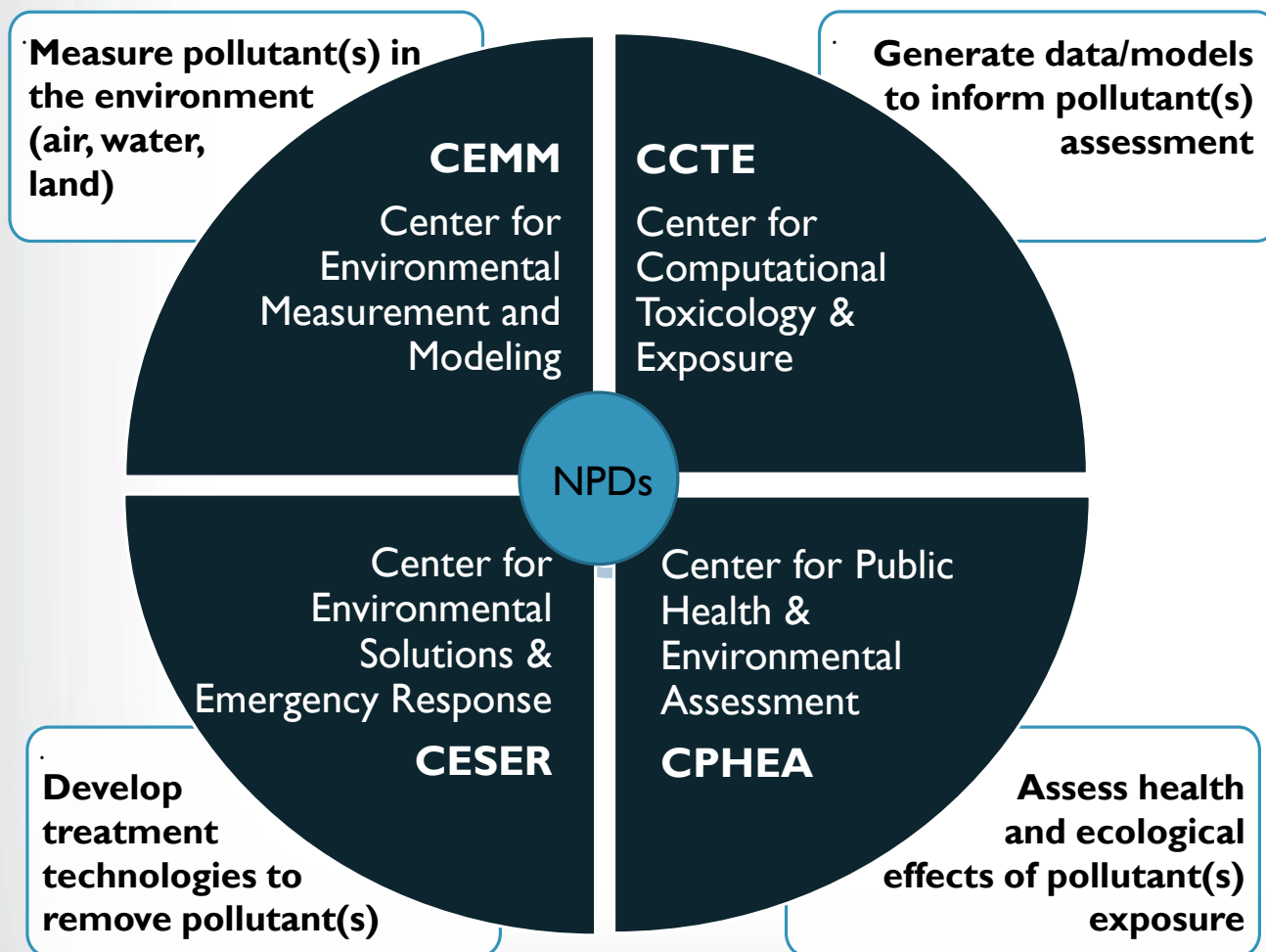




# Implementation of HERA Research - Advancing the Science and Practice of Risk Assessment



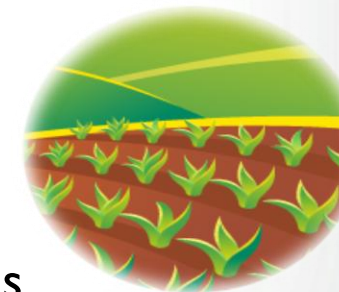
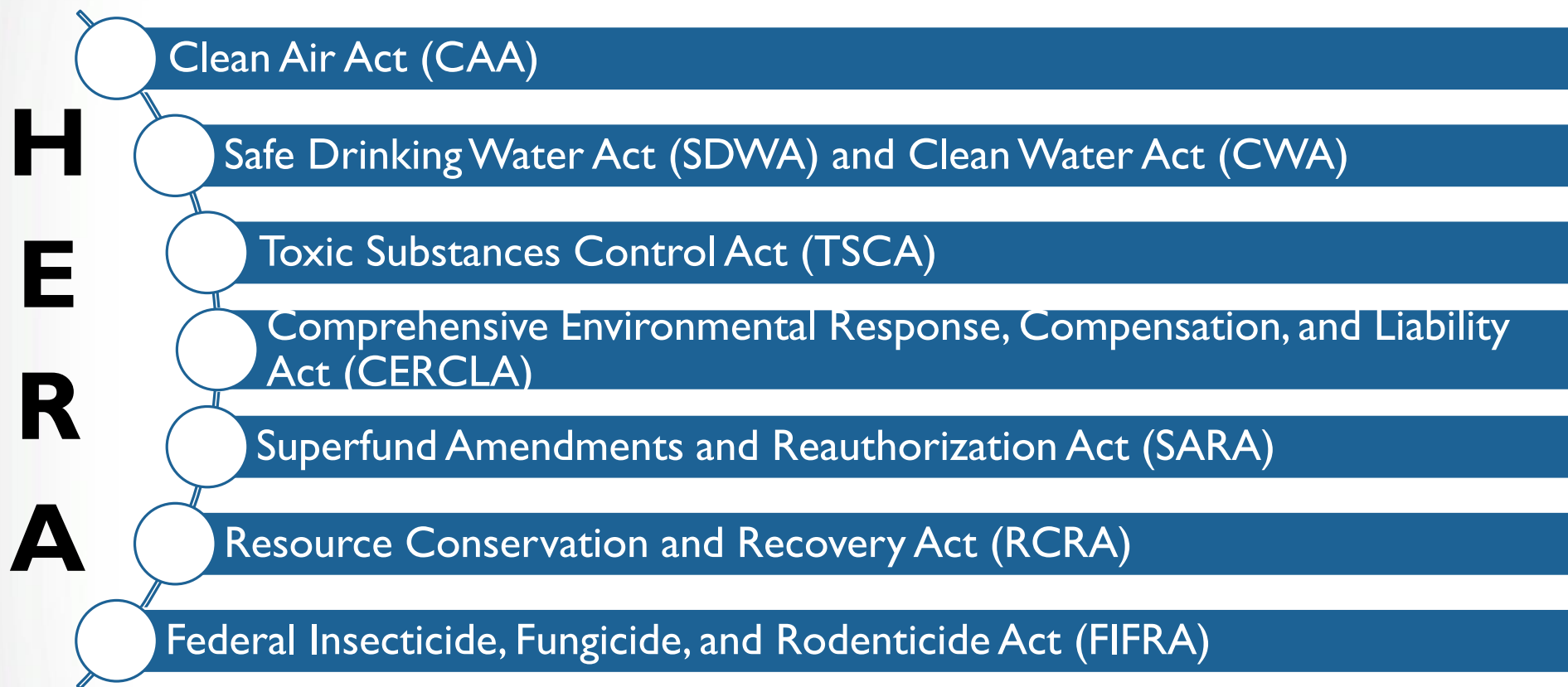
# ORD Implementation of Planned Research



Organizational structure is designed to enhance our scientific leadership, better integrate scientific approaches to problems, support mission and partner focused solutions, create communities of practice, and align the size and structure to optimize the use of our workforce.



# Addressing Agency Priorities and Mandates



**Broad Input to Support**



- Agency and ORD Strategic Goals
- Children's Health
- Environmental Justice

## To innovate and advance the science and practice of assessments

By developing a portfolio of fit-for-purpose human health and environmental assessment products and assessment research that meet the needs and priorities of EPA programs and regions, states, tribes, and external stakeholders.

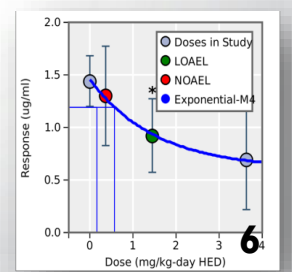
Topic	Research Area
Science Assessments & Translation	1. Science Assessment Development
	2. Science Assessment Translation
Advancing the Science and Practice of Risk Assessment	3. Emerging and Innovative Assessment Methodologies
	4. Essential Assessment and Infrastructure Tools

## Assessment products such as:

- Integrated Science Assessments (ISAs) for the health criteria for particulate matter and ozone, and the ecological criteria for oxides of nitrogen, oxides of sulfur, and particulate matter.
- Integrated Risk Information System (IRIS) assessment materials for inorganic mercury salts, methylmercury, and 5 PFAS.
- Provisional Peer-Reviewed Toxicity value (PPRTV) assessments for 2-ethylhexanol, 2-nitropropane, p- $\alpha,\alpha,\alpha$ -tetrachlorotoluene.

## Models, databases, and software products such as:

- Advancements to Health and Environmental Research Online (HERO) and Health Assessment Workplace Collaborative (HAWC) databases.
- Benchmark dose software (BMDS) and All Ages Lead model (AALM).



Arzuaga, X. et al. (2019). **Use of the Adverse Outcome Pathway (AOP) framework to evaluate species concordance and human relevance of Dibutyl Phthalate (DBP)-induced male reproductive toxicity.** Reproductive Toxicology.

Alman, B. et al. (2019). **Associations between PM<sub>2.5</sub> and risk of preterm birth among liveborn infants.** Annals of Epidemiology.

Kirrane, E. et al. (2019). **A Systematic Review of Cardiovascular Responses Associated with Ambient Black Carbon and Fine Particulate Matter.** Environment International.

Radke-Farabaugh, E. et al. (2019). **Development of outcome-specific criteria for study evaluation in systematic reviews of epidemiology studies,** Environment International.

Lizarraga, L., J. Dean, J. Kaiser, S. Wesselkamper, J. Lambert, and J. Zhao. (2019). **A Case Study on the Application of An Expert-driven Read-Across Approach in Support of Quantitative Risk Assessment of p,p'-Dichlorodiphenyldichloroethane.** Regulatory Toxicology and Pharmacology.

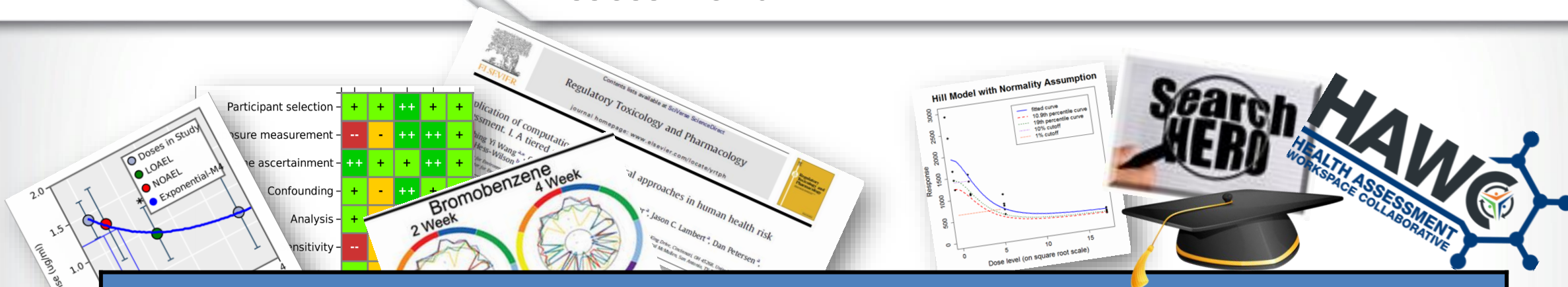
Reyes, J., and P. Price. (2018). **Temporal Trends in Exposures to Six Phthalates from Biomonitoring Data: Implications for Cumulative Risk.** Environmental Science & Technology.





Research and  
Development

## Topic 2 – Advancing the Science and Practice of Risk Assessment

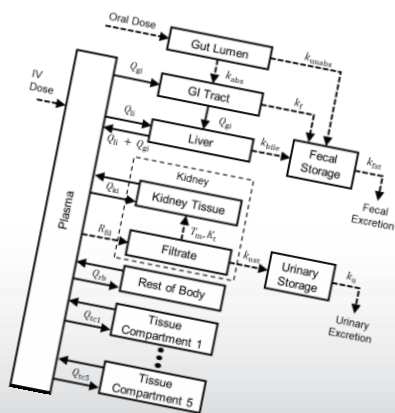


### Advancing the Science and Practice of Risk Assessment

Research Area 3	Emerging and Innovative Assessment Methodologies	Essential Assessment and Infrastructure Tools	Research Area 4
	Focused on incorporating new and innovative methodologies in predictive toxicology, rapid evidence evaluation, systematic review, and toxicokinetic and dose-response modeling across a landscape of decision contexts and assessment products	Supports maintenance and development of new and existing tools and databases used in the assessment process and provides training on such tools and resources to stakeholders	



- Focus on evaluating and optimizing the integration of existing, new, and emerging data streams, techniques, models, tools, or other methodologies for practical implementation in assessing human and environmental health.
- Anchored in assessment development.
- Improve the accuracy, efficiency, flexibility, and utility of applications across the large landscape of assessment activities served by the HERA program.

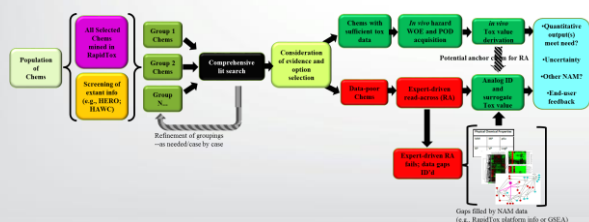


- Delivering state-of-the-science assessment products requires the use of software and database tools to provide the necessary infrastructure.
- Enables the maintenance and development of new or existing tools and databases used in the assessment process and provides training on these resources and applications.

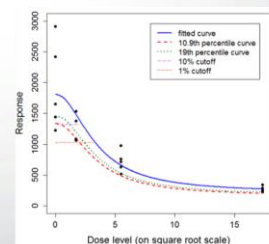
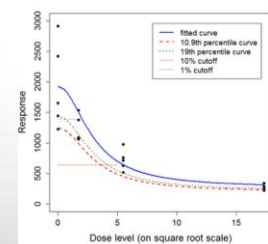
**Advance, translate, and build confidence in the application of new approach methods (NAMs) and data:** As NAMs' science advances, risk assessors still encounter many chemicals with little-to-no data that require assessment. Research is required to translate and build confidence in the application of these NAMs in HERA science assessment contexts.

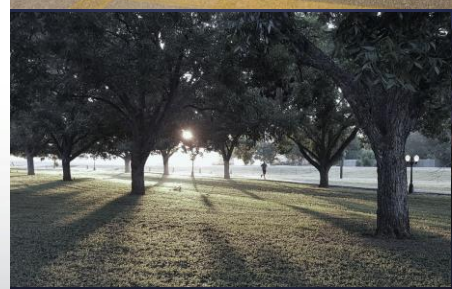
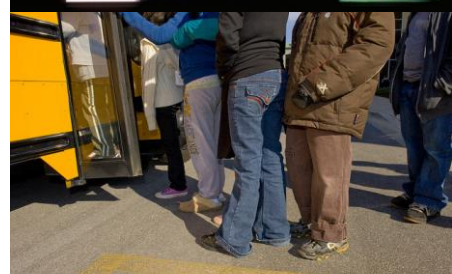
**Advance methods for systematic review:** Incorporating the principles of systematic review into the HERA portfolio of assessment products has been a goal of the HERA program for the last several years. In order to achieve this goal, the HERA program intends to advance the field of systematic review more broadly.

**Advance methods in dose-response modeling and tools:** Dose-response modeling is a critical step in human health assessment. Existing methods have improved upon older methodologies; however, unresolved issues, uncertainties, and complications remain that require targeted research. HERA has planned research products that will result in dose-response methods that are more precise, robust, and meet varied needs.



	acute single dose	single dose	short-term		30 d	developmental, F1 GD7-GD17	Grand Total
Developmental						1	1
Gastrointestinal	1	1			1		2
Hematologic		1			1		1
Hepatic			1		1		2
Immune		1			1		1
Metabolic		1			1		1
Nervous			1				1
Renal	1	1	1		1		3
Reproductive			1			1	1
Respiratory	1						1
Systemic/Whole Body	1	1	1	1	1		3
Grand Total	1	1	1	1	1	1	4





# THANK YOU!

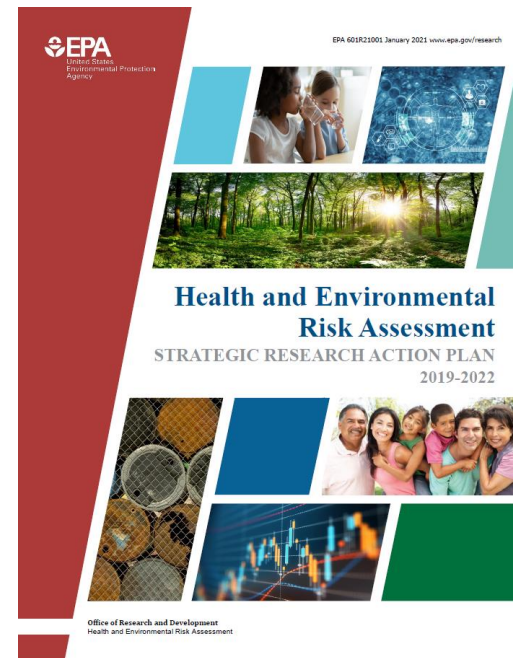
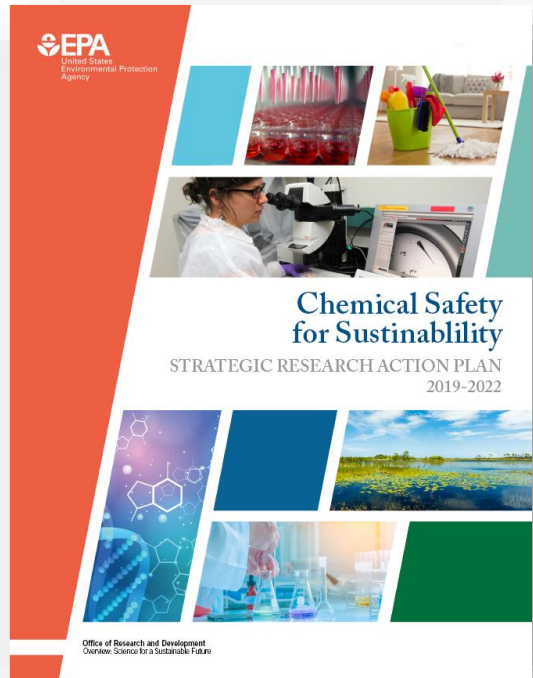
<https://www.epa.gov/research/health-and-environmental-risk-assessment-strategic-research-action-plan-2019-2022>

# Moving from the StRAPs to Implementation by ORD Investigators

Jill Franzosa, PhD



# 2019 – 2022 Strategic Research Action Plans



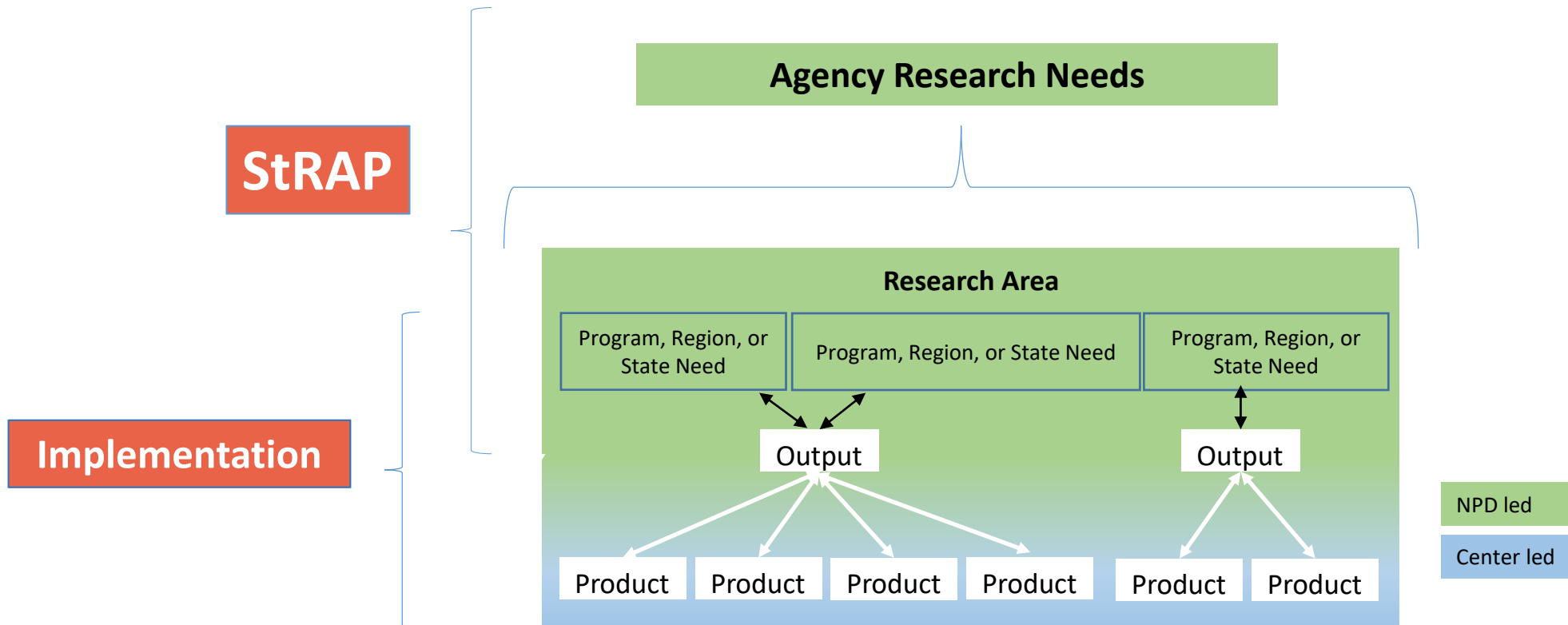
- StRAPs finalized and published on EPA internet
- Focused on defining national program structure and identifying specific outputs to meet the needs of partners
- Informed design and planning of research activities to fulfill the outputs

<https://www.epa.gov/research/strategic-research-action-plans-2019-2022>

# StRAP Implementation

**Output** is a body of work that addresses partner needs through delivery of one or more products

**Products** can be peer-reviewed journal articles, models, databases, software, methods, reports or assessments





# Research Area Coordination Team (RACT)



## Objective

- Expand involvement of partners
- Improve understanding what is needed
- Ensure proposed products are what is needed by partners



## Who

- Program Office representative(s)
- Regional Representative(s)
- State Representative
- NPD Representative
- ORD Scientists

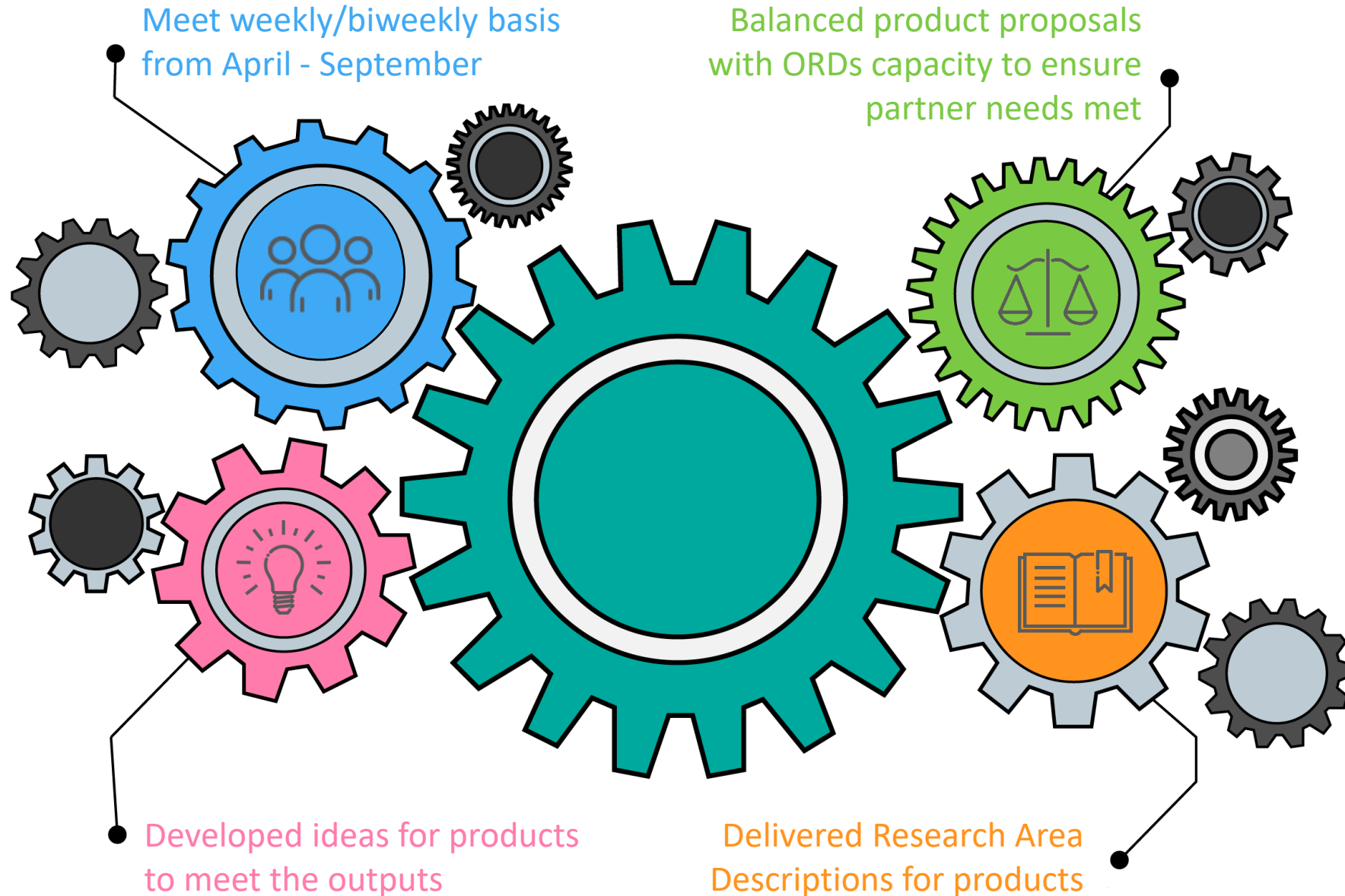


## Outcome

- Products responsive to outputs
- By-in from partners
- Collaboration with partners

**Purpose:** Define the products that ORD will develop to meet the objectives of the outputs

# The Process for RACTs



# Delivery of Research Area Descriptions

## **Program/Regional/State Needs:**

- *How this research will be applied to meet the needs of EPA programs/regions, states, tribes, and/or other partners*
- *Key statutes and/or regulatory issues that the research will support*

## **Output :**

### Output Description:

- *What information is needed by the program, region, state, or tribal partner(s)*
- *How the products build on each other to form the Output*
- *Description of how the partner will use the Output*

EPA Program/Regional or State/Tribal Partner(s)

## **Product:**

### Brief Description and Research Use:

- *Description of research and how it will be used by the partner to address their identified regulatory, policy, and/or other need(s).*

EPA Program/Regional or State/Tribal Partner(s)




# RACT Output Leads and Product Leads

- Output Leads
  - Nominated by Center management
  - Provide scientific leadership
  - Coordinate and communicate with Product Leads
  - Include representation from across ORD Centers
- Product Leads
  - Develop research products and components to fulfill objectives of the output
  - Lead and coordinate product research teams
  - Include representation from across ORD Centers

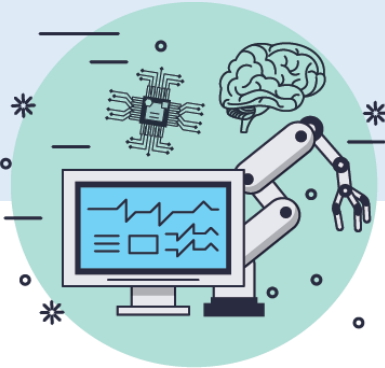


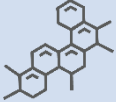



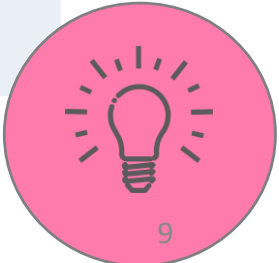
# CSS Example: Translating Partner Needs to Outputs

PARTNER NEED	RESEARCH AREAS	OUTPUTS WITH DNT PRODUCTS
<p><b>Developmental neurotoxicity (DNT):</b> DNT is an important risk assessment endpoint for chemical assessments. However, currently available in vivo methods are costly and do not fully represent important mechanisms and pathways. Therefore, there is a need for alternative approaches for evaluating DNT, including valid in vitro methods and modeling approaches. (OCSPP; OLEM; OCHP)</p> 	HTT	Develop, evaluate, apply, and interpret a developmental neurotoxicity (DNT) battery of assays to reduce uncertainties in chemical safety evaluations
	AOP	Develop and conduct strategic in vitro and in vivo studies for high-priority AOPs to help establish validity of NAMs approaches, support predictive model development, and reduce vertebrate animal testing through in vivo testing refinements for decision-relevant endpoints
	VTM	Integrate and evaluate phenotypic responses in human cell based in vitro and virtual tissue model systems to predict chemical hazard during growth and development
	VTM	Develop and apply in silico agent-based and computational models to evaluate the effects of chemicals on biological pathways critical for lifestage endpoints



# CSS Example: Developing products to fulfill the Output

OUTPUT	PRODUCTS	
<p>HTT: Develop, evaluate, apply, and interpret a developmental neurotoxicity (DNT) battery of assays to reduce uncertainties in chemical safety evaluations</p> 		Behavioral screen for developmental neurotoxicity in zebrafish
		Evaluation of a battery of in vitro DNT NAMs
		Expanded chemical space for developmental DNT NAMs
		Tools for translation and accessibility of DNT NAMs



# What We Developed

Topic	Research Areas	Outputs	Products
Chemical Evaluation	High-Throughput Toxicology (HTT)	8	36
	Rapid Exposure Modeling and Dosimetry (REMD)	8	50
	Emerging Materials and Technologies (EMT)	2	13
Complex Systems Science	Adverse Outcome Pathways (AOP)	8	42
	Virtual Tissue Modeling (VTM)	3	16
	Ecotoxicological Assessment and Modeling (ETAM)	10	34
Solutions-Based Translation and Knowledge Delivery	Chemical Safety Analytics (CSA)	4	24
	Informatics, Synthesis, and Integration (ISI)	5	29

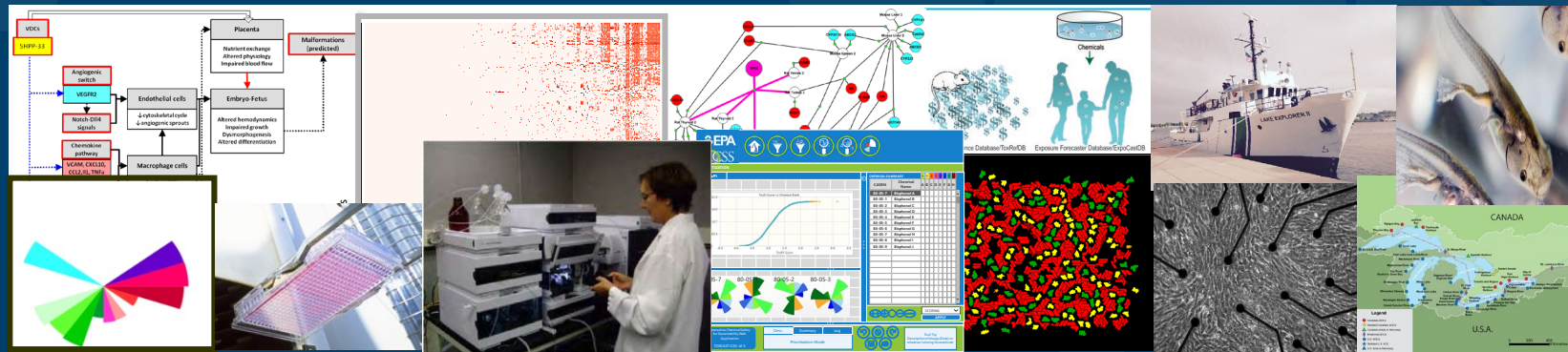


# Thank you!

## Comments/Questions.



# Evolution of NAMs in EPA: From Research to Application



**CSS HERA Board of Scientific Counselors Meeting**

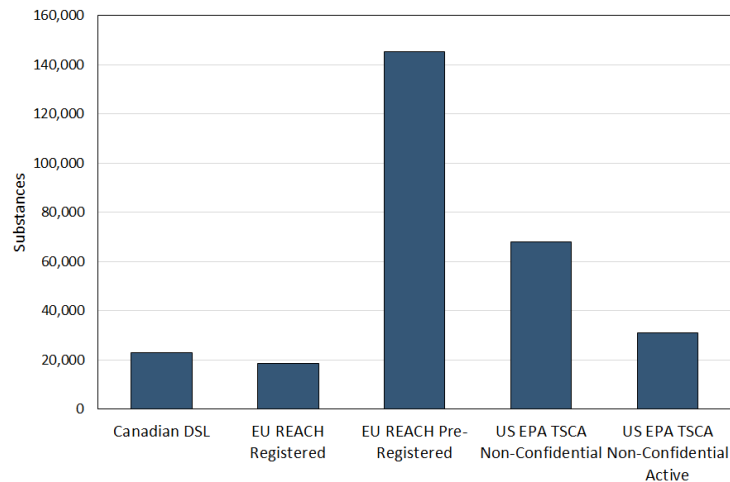
**February 2, 2020**

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

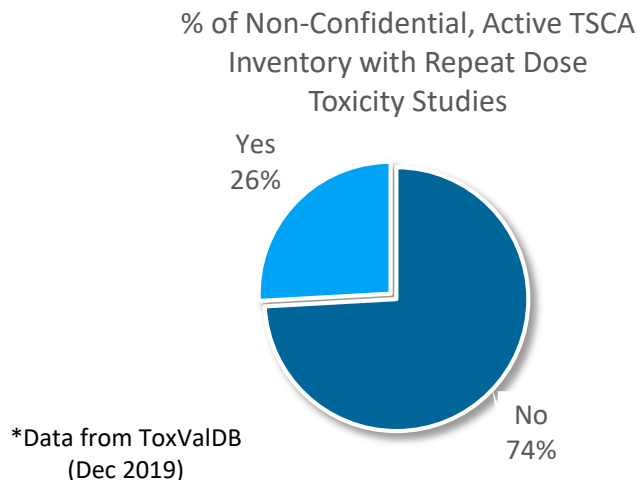
The views expressed in this presentation are those of the presenter and do not necessarily reflect the views or policies of the U.S. EPA

# EPA Faces Multiple Challenges in Evaluating the Human and Environmental Risks of Chemicals

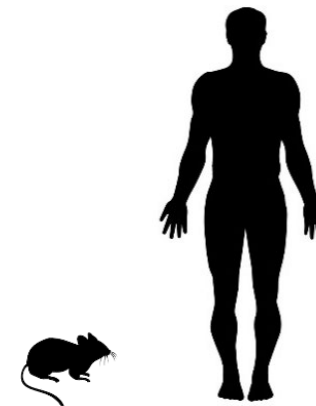
Number of Substances



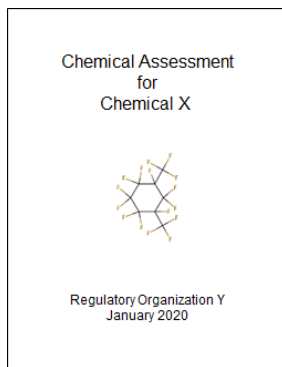
Amount of Data



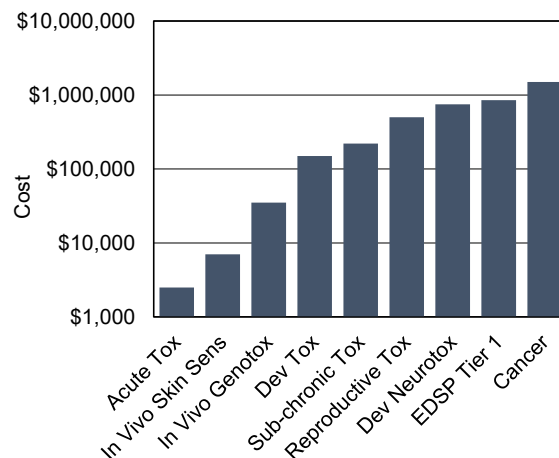
Reliability/Relevance



Time



Economics

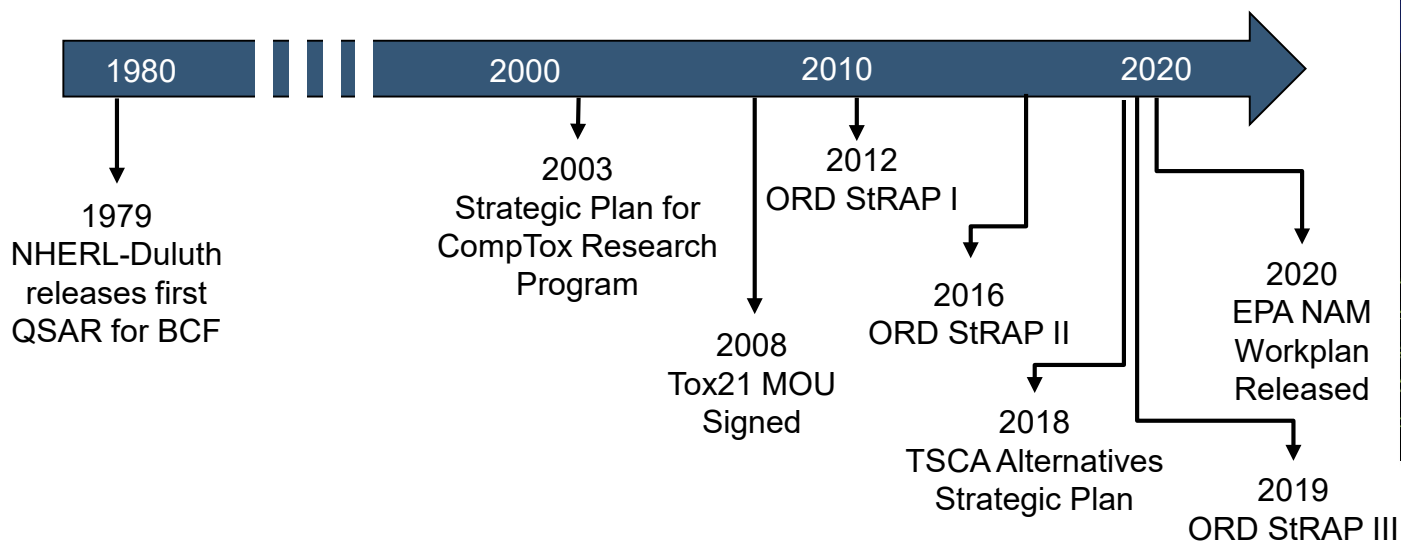


Broad Range of Decision Contexts





# To Address These Challenges ORD has a History in Research on New Approach Methods (NAMs)



# What is a New Approach Method?



- Coined in ~2014, but the definition of a New Approach Method (NAM) has evolved over time
- Currently, it is broadly descriptive reference to any non-animal technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment
- Functionally equivalent to “alternatives”, but can include exposure NAMs, eco NAMs, toxicokinetic NAMs, etc.

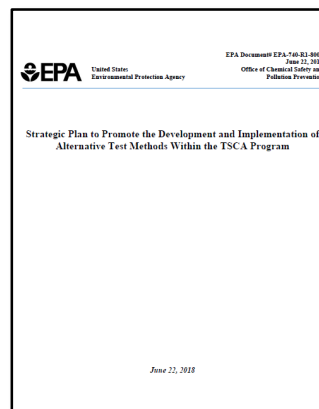
# Despite this History, NAM Development and Application is Still in its Formative Years...



We are here...

# Directing NAM Research Through Formative Years Involves an Integrated Strategy

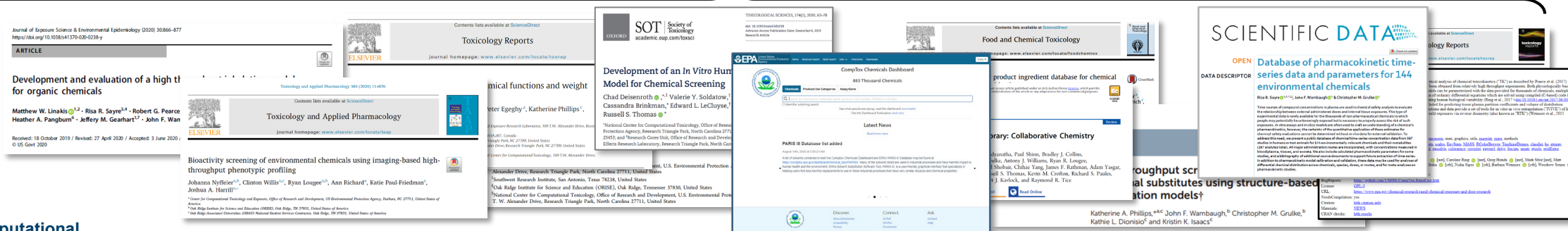
Long Term  
Research  
Strategies



Four Year  
Research Plans

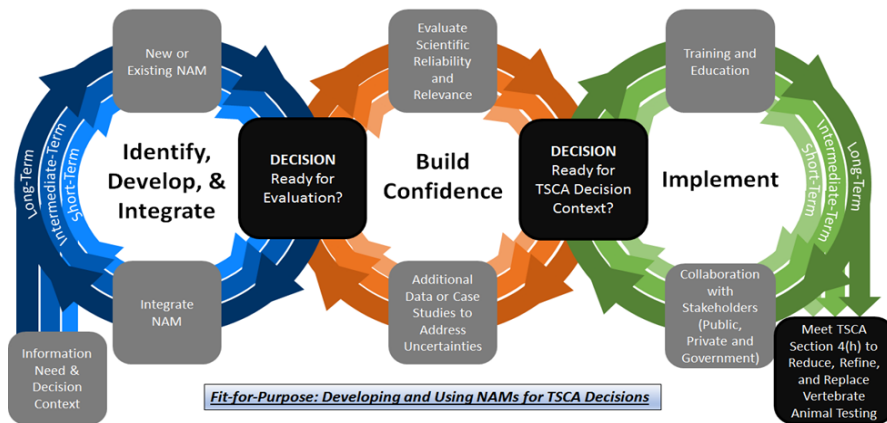


Research  
Products

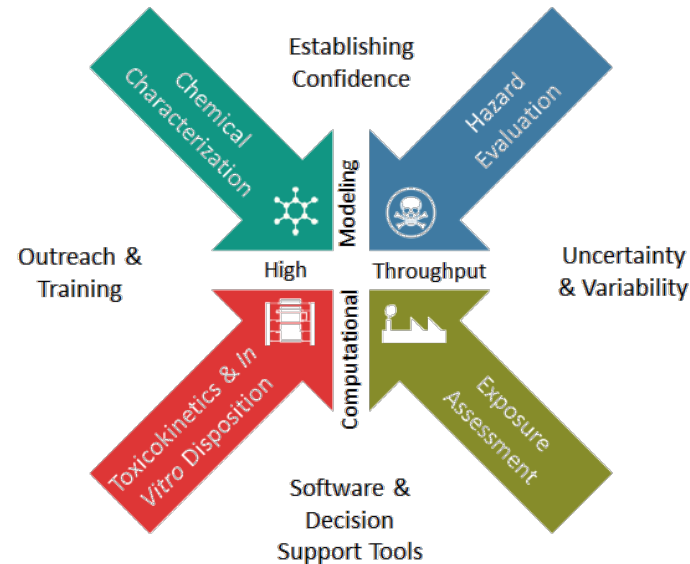


# There is a Significant Overlap Between Elements of the EPA NAM Research Strategies...

## TSCA Alternatives Strategic Plan



## EPA CompTox Blueprint



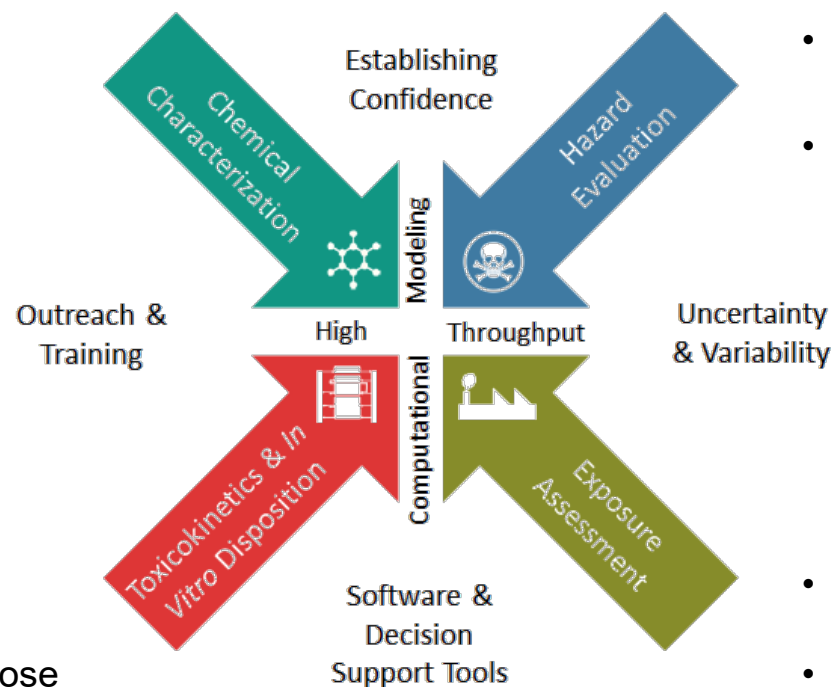
## EPA NAMs Work Plan



and the research activities you will hear about over the next few days.



# Highlights of the Research You Will Hearing About Today



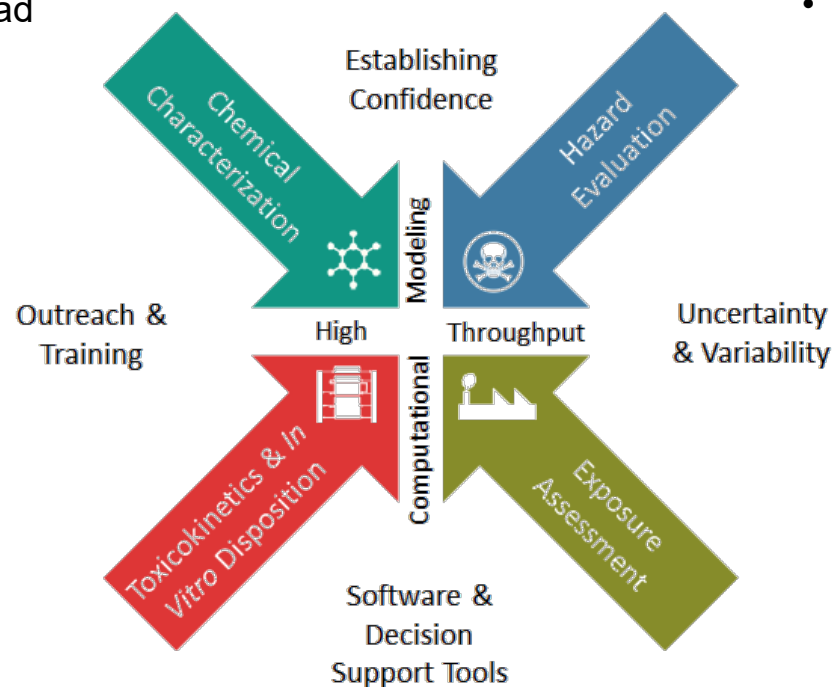
- Estimate toxicokinetic parameters for hundreds of chemicals
- Put *in vitro* testing concentrations in a dose context

- Broadly evaluate potential impacts of chemicals across biological space and species
- Systematically address limitations in *in vitro* test systems
- Identify likely tissue, organ and organism effects and susceptible populations

- Estimate chemical exposures with uncertainty for thousands of chemicals
- Put hazard in a risk context
- Identify potential exposure pathways for unknown chemicals
- Establish consistency and confidence in non-targeted methods

# Highlights of the Research You Will Hearing About Tomorrow and Thursday

- Case studies and proof-of-concept applications with State, Region, and Program Partners
- Incorporating metabolite similarity into read across
- Application of AOPs for evaluating mixtures



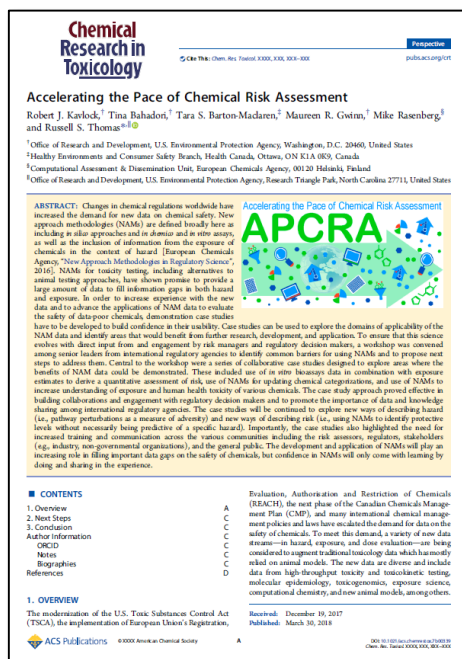
- Data extraction and curation for model training and evaluation
- Data integration, data visualization, and decision support tools

# But, There are LOTS of Activities You Won't Hear About This Time



# Working with Federal, State, and International Collaborators to Develop, Evaluate, and Apply NAMs

## APCRA Inter-Governmental Consortium



## Bi- and Tri-Lateral Engagements

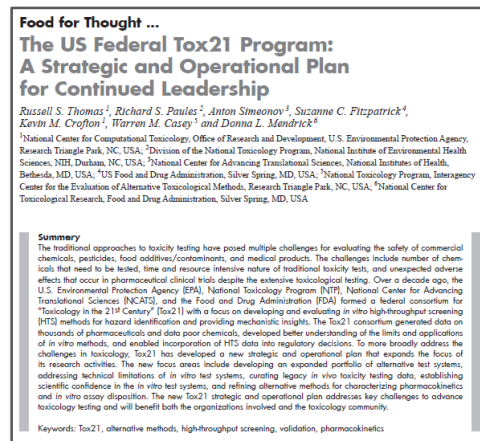


Health  
Canada



Environment and  
Climate Change Canada

## Cross-Federal Collaborations



## Other



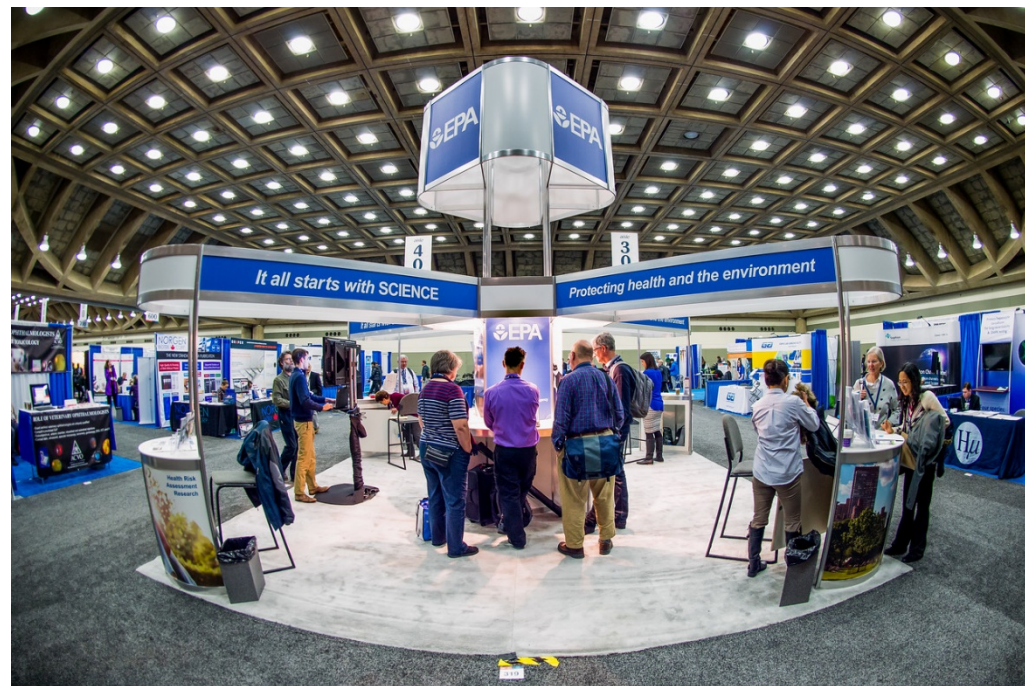
DEPARTMENT OF  
ECOLOGY  
State of Washington





# Outreach and Training

- Ongoing development of EPA NAM Training Program
- Collaboration with organizations with interest and expertise in NAMs
- Active solicitation of feedback from stakeholders through Agency NAM email address, workshops, and communities of practice
- Ongoing communications and outreach via NAMs website, webinars, conferences and social media





# Questions?



Where we are going...

# References

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