

From Cells to Solutions:

Using New Approach Methodologies to protect human health and the environment



Rebecca Fry, PhD

Carol Remmer Angle Distinguished Professor and Chair

Director, Institute for Environmental Health Solutions and UNC-Superfund Research Program

New Approach Methodologies (NAMs)



New Approach Methodologies in Regulatory Science

Proceedings of a scientific workshop

Helsinki, 19–20 April 2016

ECHA's Topical Scientific Workshop (19-20 April 2016) addressed the use of data and information from new approach methodologies (NAMs) to support regulatory decisions for the use of chemical substances. The workshop brought together over 200 stakeholders in person and a further 100 online.

New Approach Methodologies (NAMs)

The screenshot shows the EPA website's 'Safer Chemicals Research' section. The main heading is 'EPA New Approach Methods Work Plan: Reducing Use of Vertebrate Animals in Chemical Testing'. Below the heading is a graphic with five icons representing the work plan's objectives: Evaluate regulatory flexibility, Develop baselines and metrics, Establish scientific confidence, Develop NAMs to address challenges, and Engage and communicate with stakeholders. The text explains that EPA uses information from vertebrate animal tests to evaluate risks and assess impacts, and that the updated NAMs Work Plan was released in December 2021. A list of objectives is provided at the bottom of the page.

EPA New Approach Methods Work Plan: Reducing Use of Vertebrate Animals in Chemical Testing

EPA uses information from a broad range of vertebrate animal tests to evaluate the potential risks of chemicals, assess potential impacts on the environment, and approve chemicals for certain uses. EPA's New Approach Methods (NAMs) Work Plan was created to prioritize agency efforts and resources toward activities that aim to reduce the use of vertebrate animal testing while continuing to protect human health and the environment. The original EPA NAMs Work Plan was released in June 2020 and laid out the Agency's objectives and strategies. The updated [EPA NAMs Work Plan](#) was released in December 2021.

The Work Plan includes the following objectives:

- [Evaluate Regulatory Flexibility for Accommodating NAMs](#)
- [Develop Baselines and Metrics for Assessing Progress](#)
- [Establish Scientific Confidence in NAMs and Demonstrate Application to Regulatory Decisions](#)
- [Develop NAMs to Address Scientific Challenges and Fill Important Information Gaps](#)
- [Engage and Communicate with Stakeholders](#)

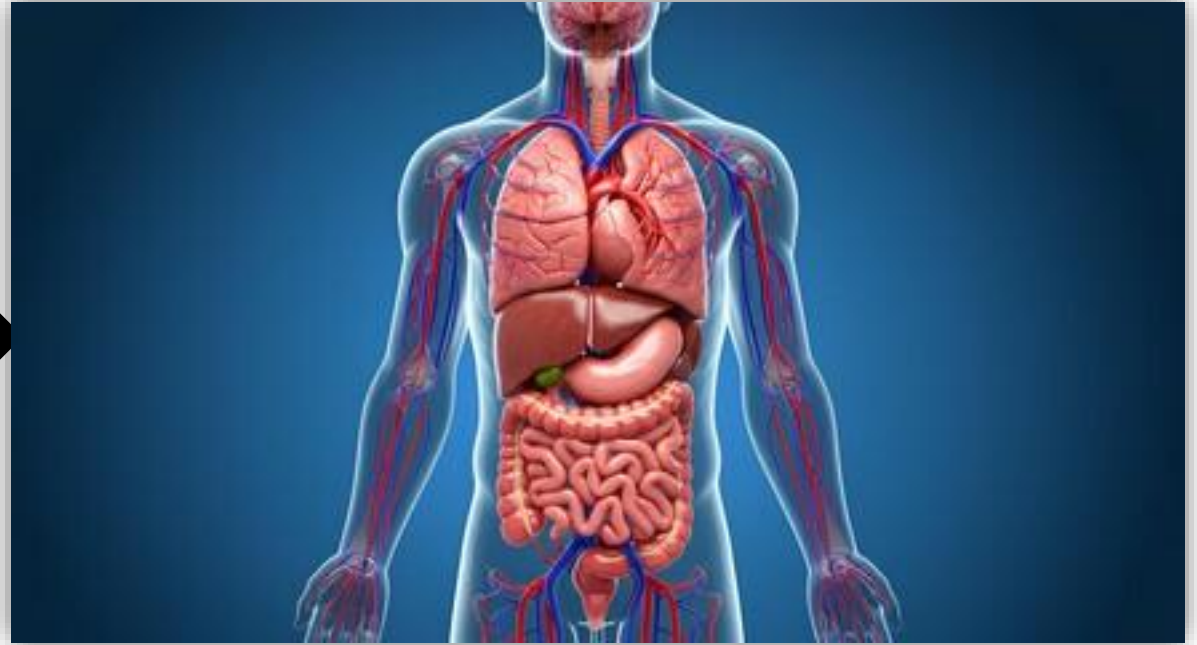
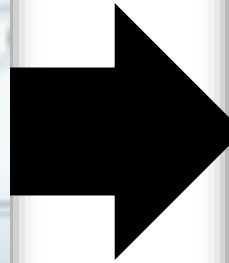
- “any non-vertebrate animals technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment.
- These include *in vitro* tests, *in chemico* assays, and *in silico* models.
- NAMs are functionally equivalent to “alternatives” to mammal testing.”

Epa.gov

New Approach Methodologies (NAMs)

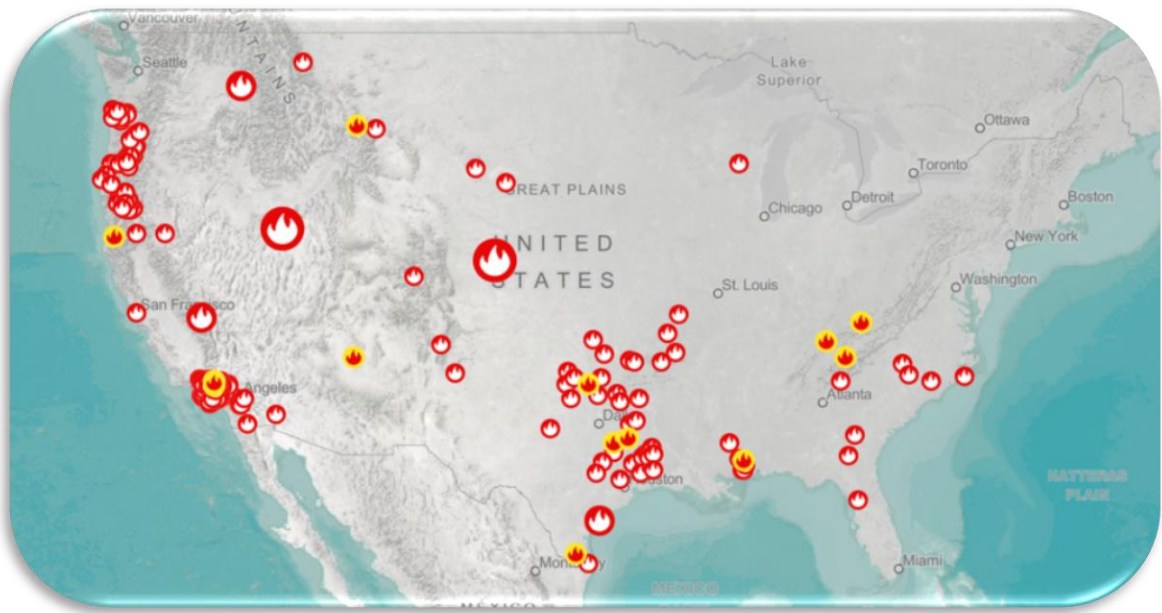


Arsenic, PFAS
Wildfire smoke



Developmental/reproductive toxicity
Adverse respiratory outcomes
Hepatotoxicity

1. Can NAMs be used to better understand the toxicity of wildfire smoke in the lung?

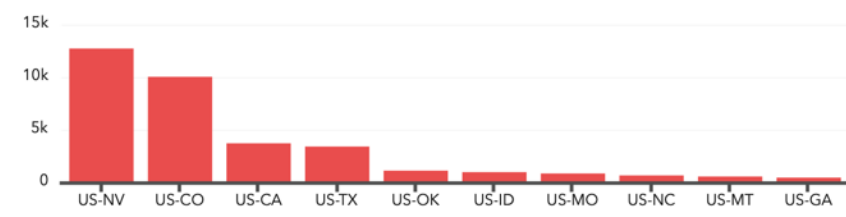


608
Active US Wildfires

36.9k
Active Acres

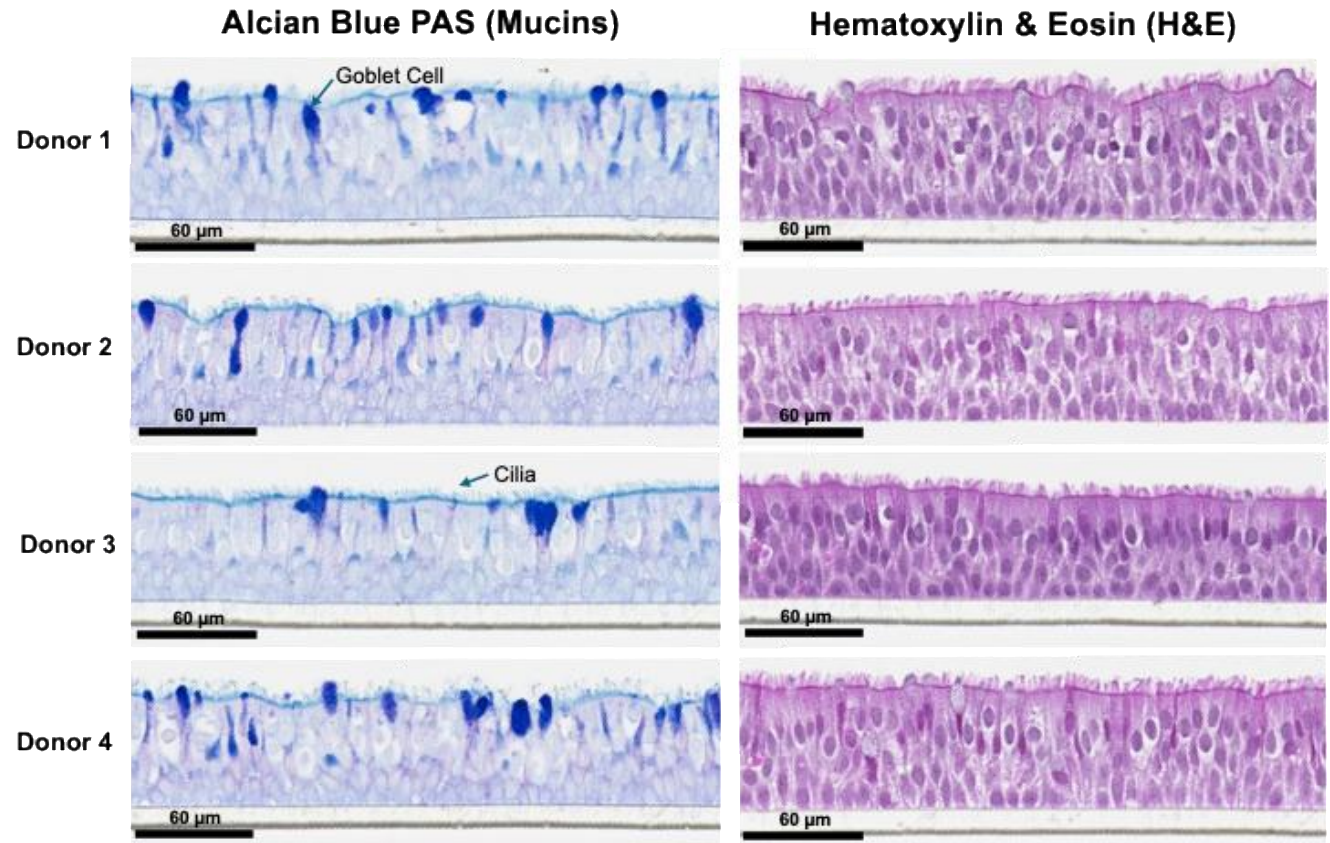
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Top 10 States by Active Acreage



Using *in vitro* models to test for inter-individual differences in response to wildfire smoke

- Smoke from wildfire events often localize over communities, causing chronic exposures and adverse health effects
- The team is using *in vitro* techniques that allow for repeat exposures using lung cells from human donors acquired through UNC Hospitals



Using *in vitro* models to test for inter-individual differences in response to wildfire smoke

Alcian Blue PAS (Mucins)

Hematoxylin & Eosin (H&E)

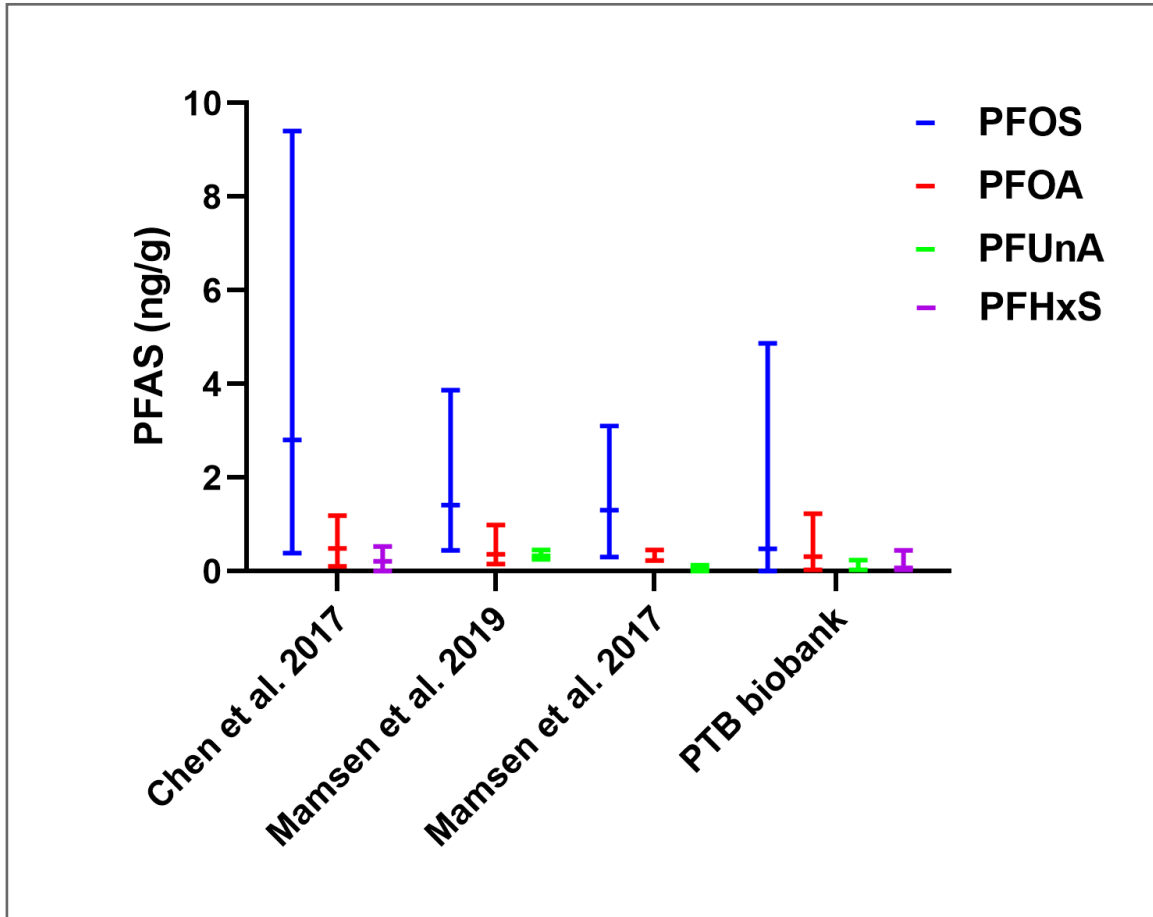
These studies will help identify why some individuals may experience more severe respiratory effects during wildfire events.

2. Can NAMs be used to identify the mechanisms of developmental/reproductive toxicity of PFAS?

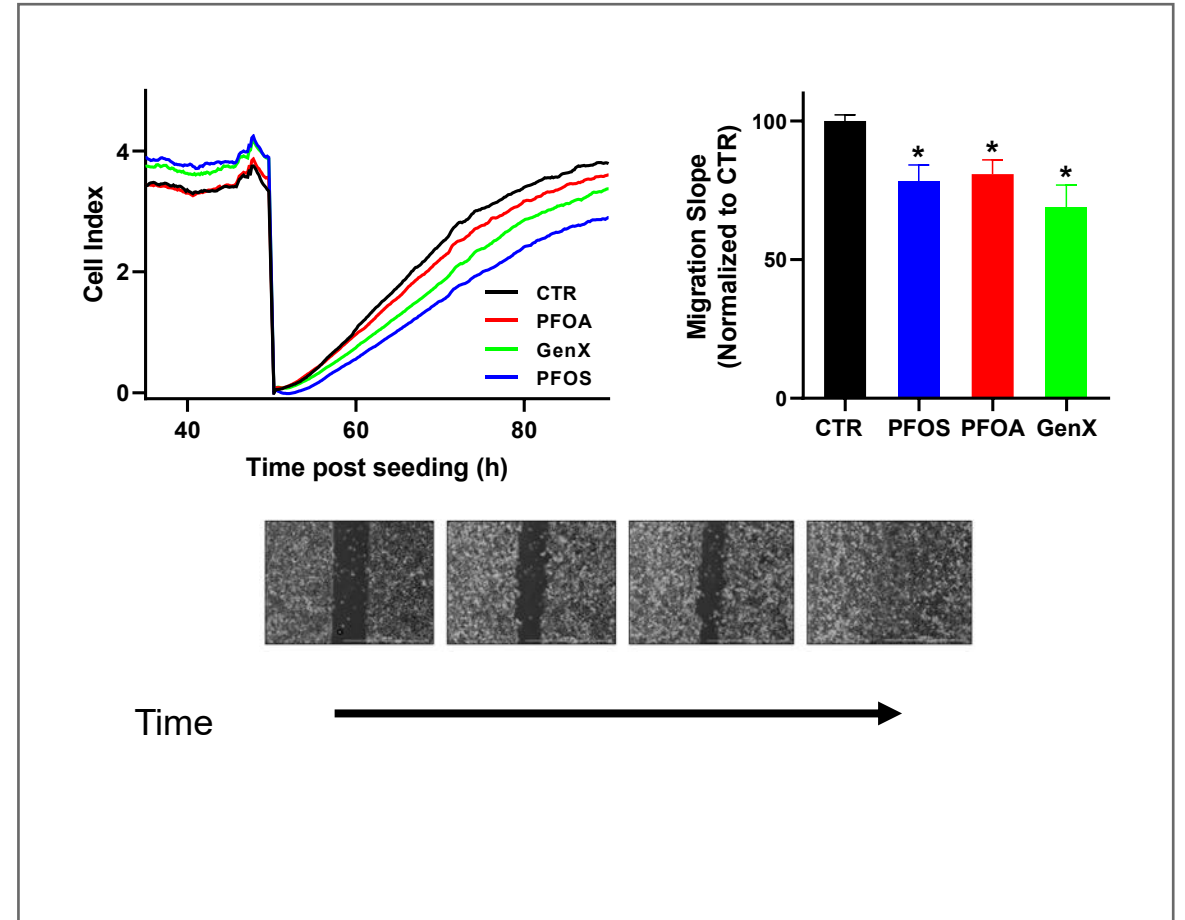


including low birth weight, thyroid disruption, harm to the male reproductive system, pregnancy-induced high blood pressure

Identifying PFAS in human placentas and toxicity in placental cells *in vitro*



(Bangma et al. 2020)



(Szilagyi et al. 2020)

Identifying PFAS in human placentas and toxicity in placental cells *in vitro*

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PFAS accumulate in the human placenta and are associated with placental migration – a potential mechanistic link to adverse pregnancy outcomes

(Bangma et al. 2020)

(Szilagyi et al. 2020)

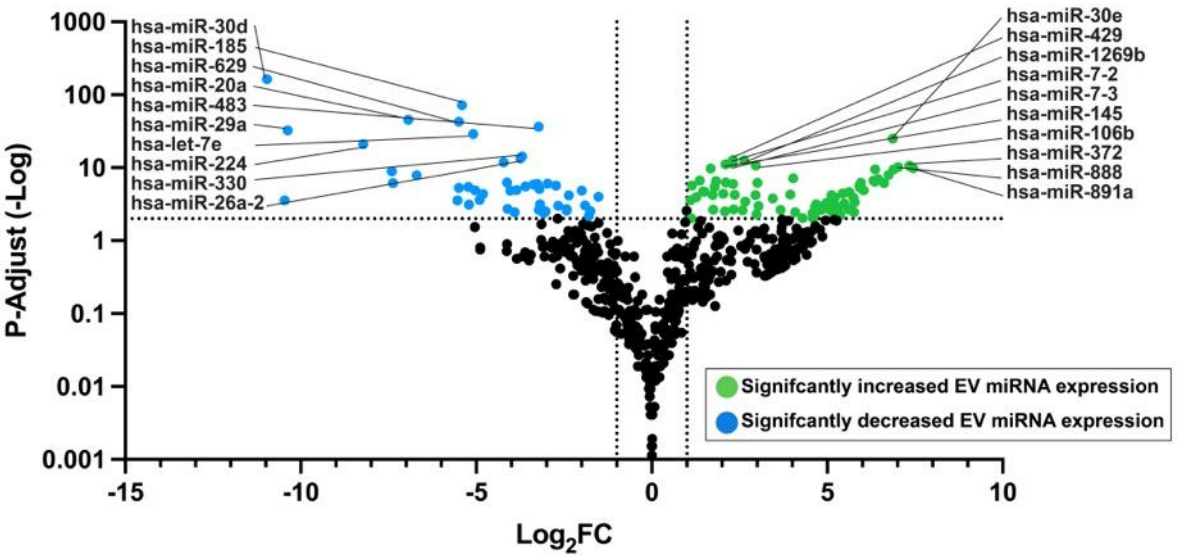
3. Can NAMs be used to identify mechanisms of per and polyfluoroalkyl substances (PFAS)-induced liver toxicity?



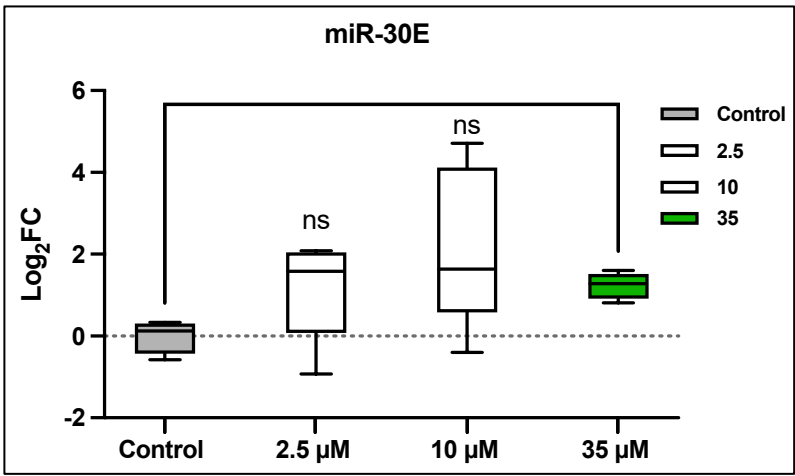
liver damage/toxicity, including non-alcoholic fatty liver disease (NAFLD)

PFAS alter the expression of microRNAs in secreted extracellular vesicles

Human liver cells (HepG2) exposed to various PFAS excreted extracellular vesicles with differential loading of microRNAs involved in liver cell health



Involved in fibrosis, wound healing, and cancer



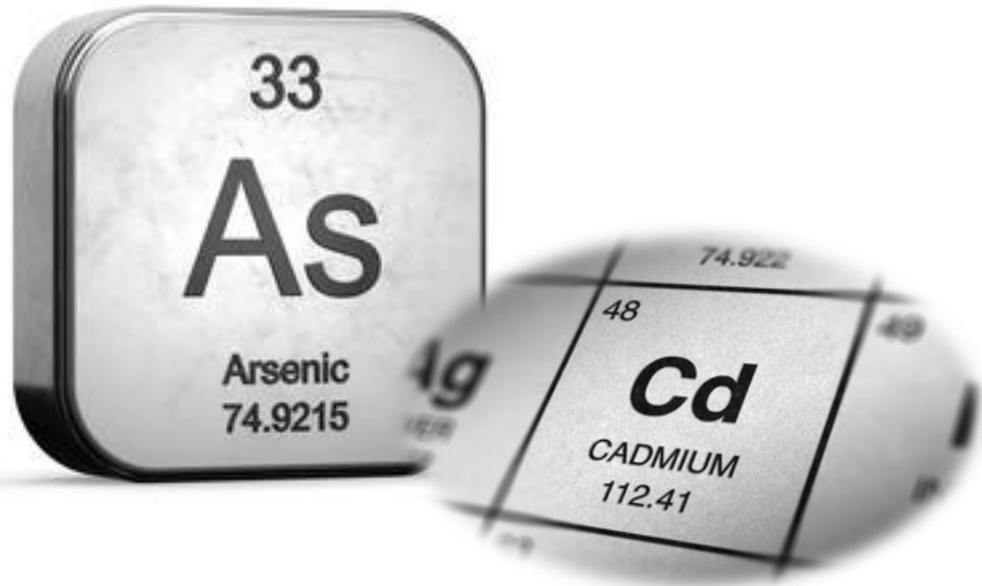
PFAS alter the expression of microRNAs in secreted extracellular vesicles

Human liver cells (HepG2) exposed to various PFAS excreted extracellular vesicles with differential loading of microRNAs involved in liver cell health

P-Adjust (-Log)

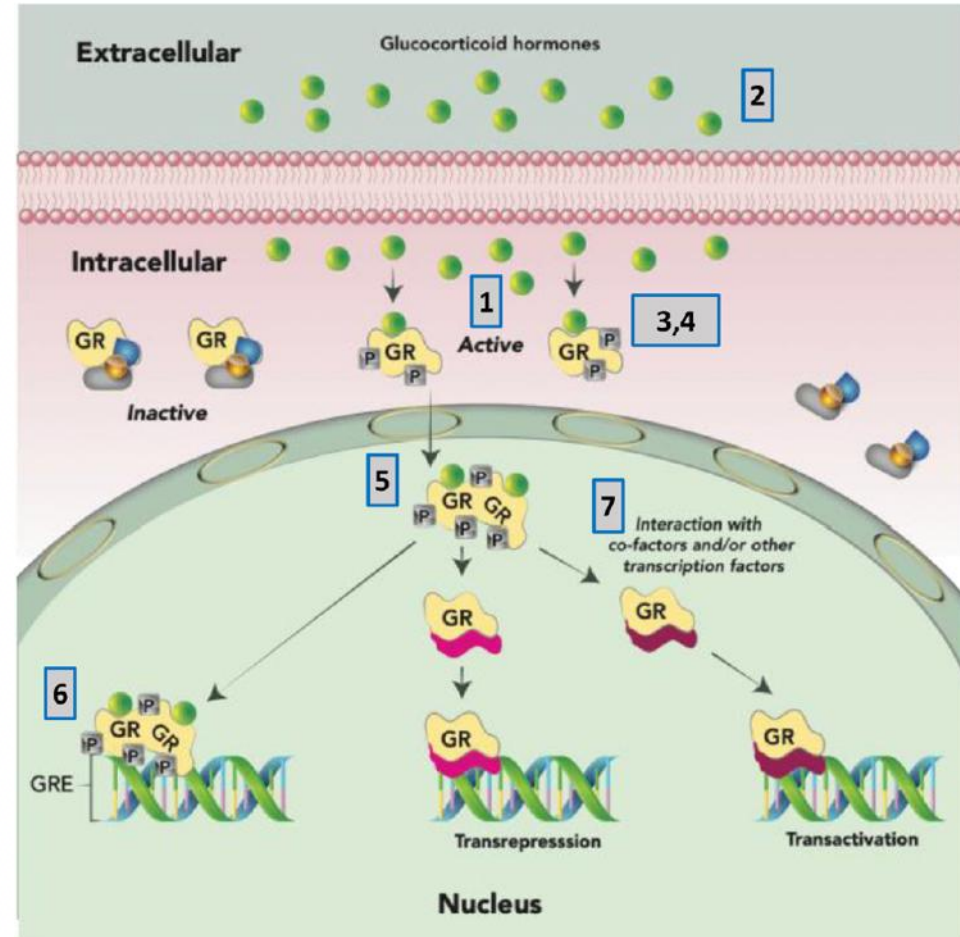
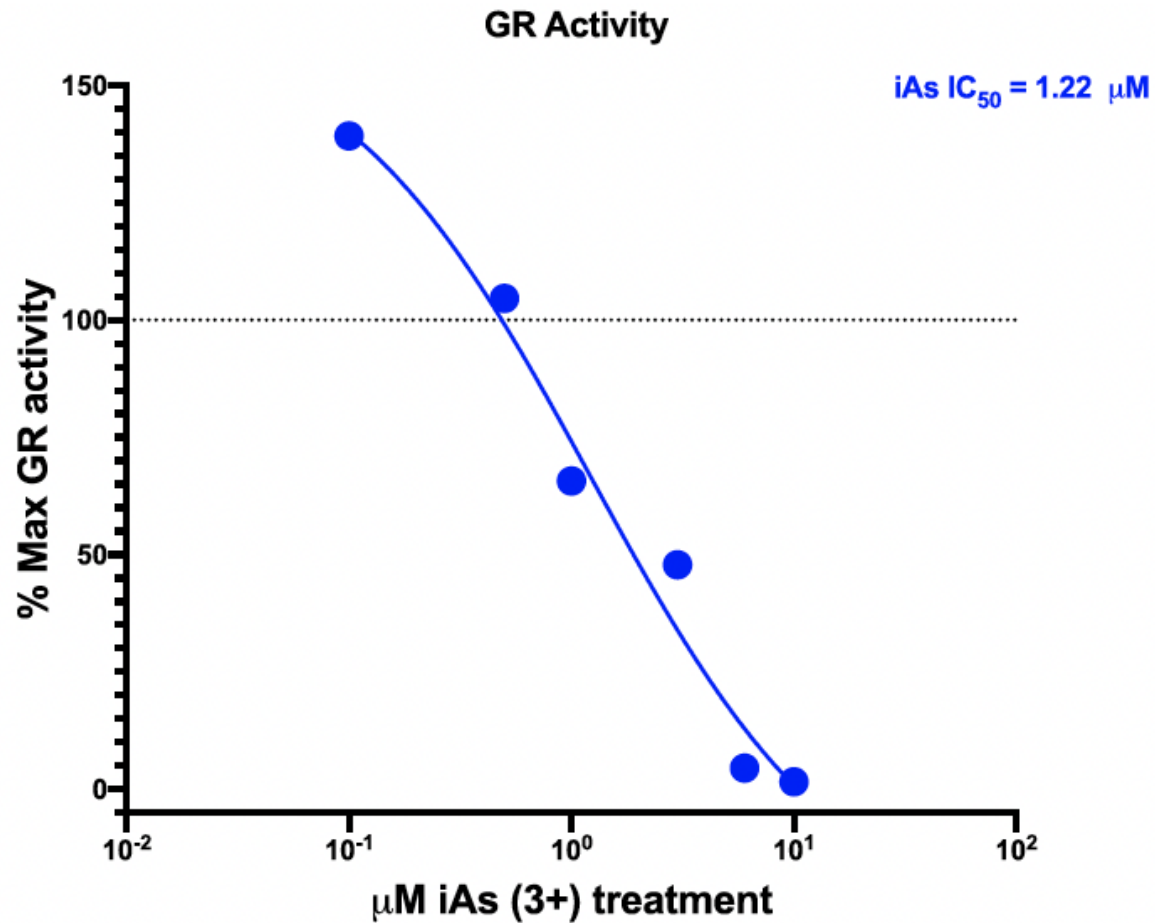
PFAS alter miRNA expression – key epigenetic regulators in cells- and accumulate in extracellular vesicles which can transport from one cell to another

4. Can NAMs be used to identify the mechanisms of developmental/reproductive toxicity of inorganic arsenic and cadmium?



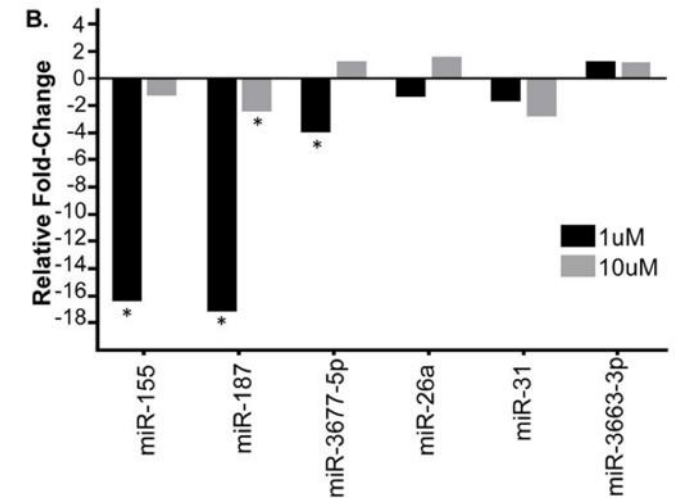
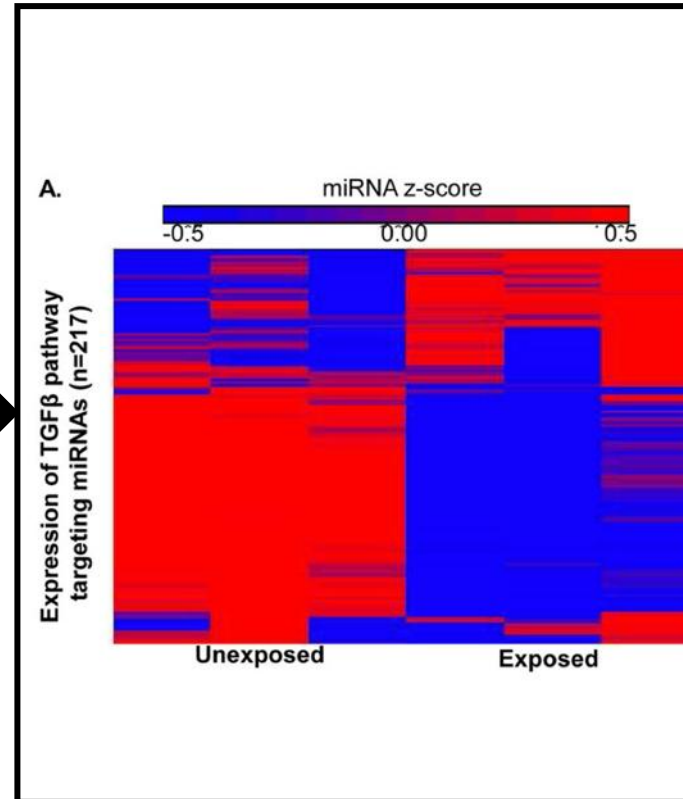
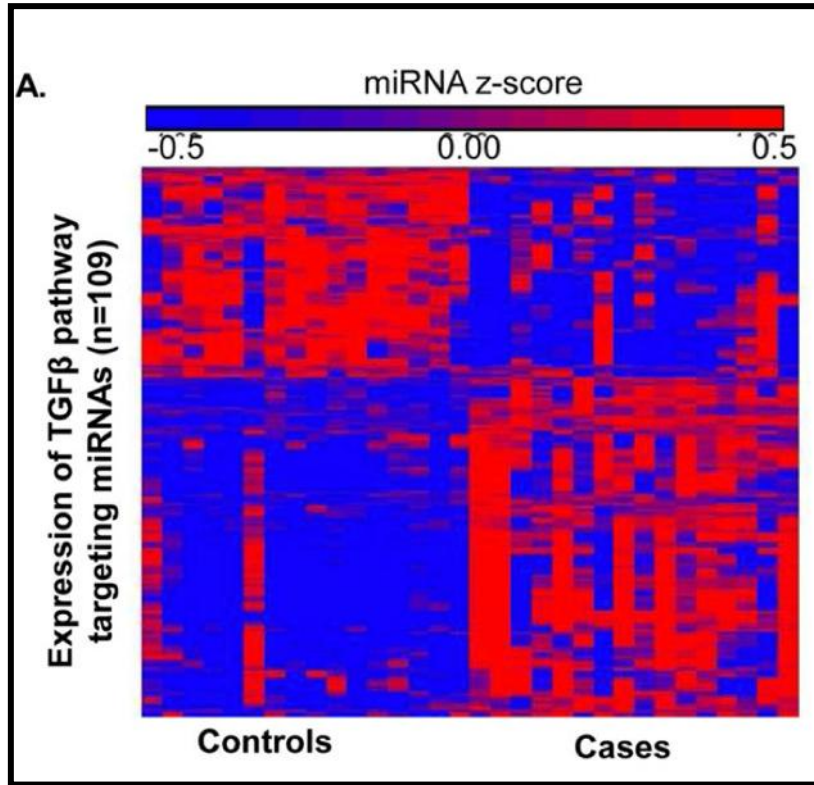
Lower birthweight and preeclampsia

Inorganic arsenic acts as an endocrine disruptor in the placenta acting on the GR pathway



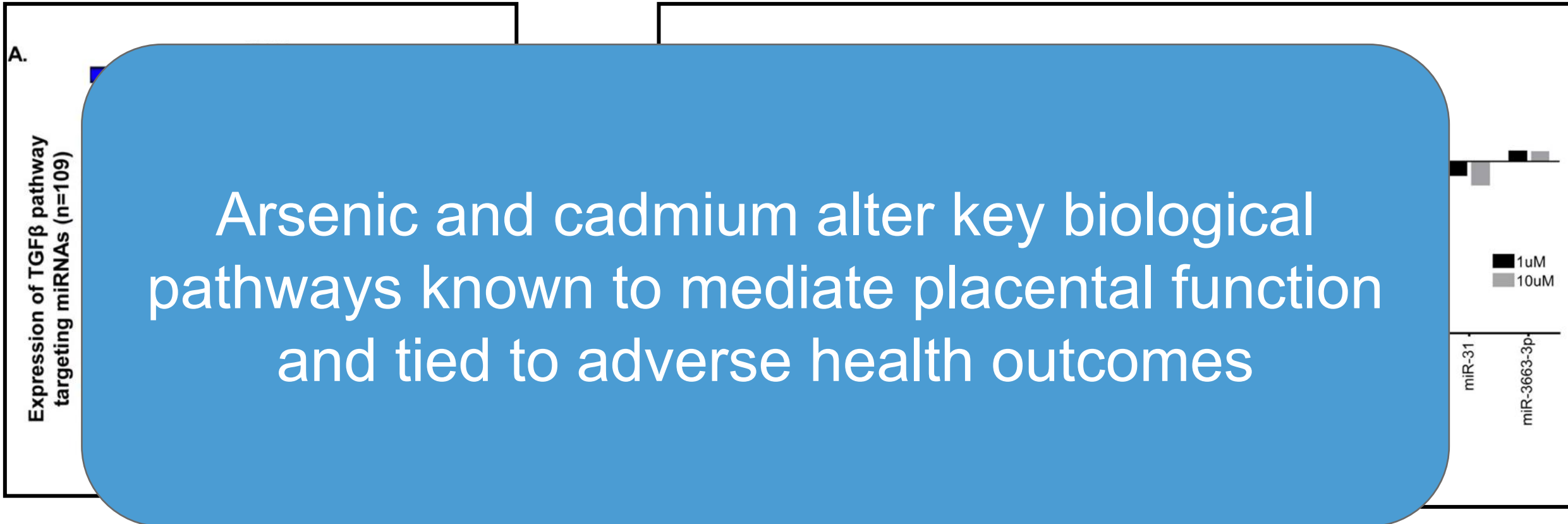
(Meakin et al. 2020)

Cadmium alters miRNA expression and mRNA expression of the TGF- β pathway



(Brooks et al. 2016)

Cadmium alters miRNA expression and mRNA expression of the TGF- β pathway

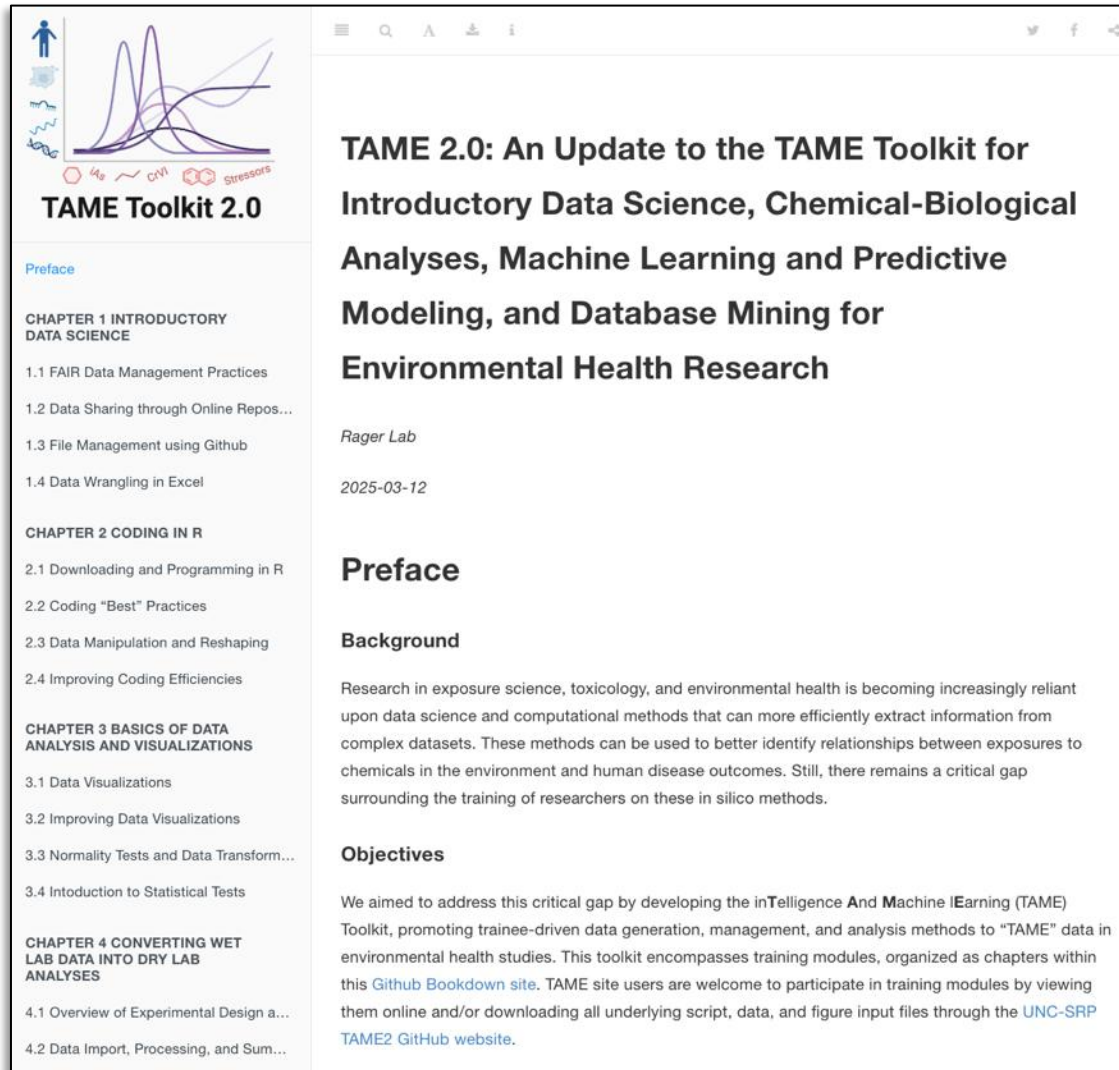


(Brooks et al. 2016)

5. Training students in NAMs Assessments



The TAME Toolkit: to TAME your data



TAME Toolkit 2.0

TAME 2.0: An Update to the TAME Toolkit for Introductory Data Science, Chemical-Biological Analyses, Machine Learning and Predictive Modeling, and Database Mining for Environmental Health Research

Rager Lab
2025-03-12

Preface

Background

Research in exposure science, toxicology, and environmental health is becoming increasingly reliant upon data science and computational methods that can more efficiently extract information from complex datasets. These methods can be used to better identify relationships between exposures to chemicals in the environment and human disease outcomes. Still, there remains a critical gap surrounding the training of researchers on these in silico methods.

Objectives

We aimed to address this critical gap by developing the inTelligence And Machine lEarning (TAME) Toolkit, promoting trainee-driven data generation, management, and analysis methods to “TAME” data in environmental health studies. This toolkit encompasses training modules, organized as chapters within this [Github Bookdown site](#). TAME site users are welcome to participate in training modules by viewing them online and/or downloading all underlying script, data, and figure input files through the [UNC-SRP TAME2 GitHub website](#).

- The inTelligence And Machine lEarning (TAME) Toolkit
- Online website that provide guided script-based examples on how to “TAME” your data in environmental health
- Originally launched in 2022, and recently updated as TAME 2.0 in 2025

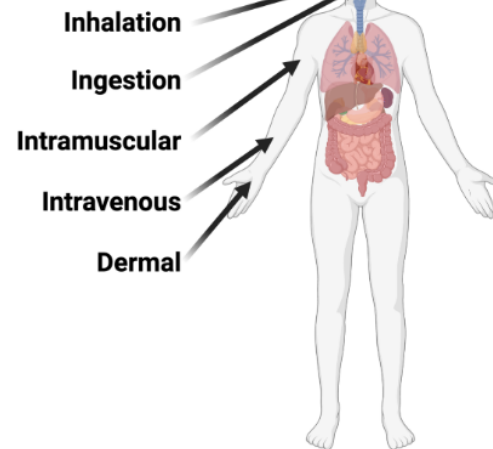
Example TAME training Module for NAMs Assessments

Introduction to Toxicokinetic Modeling

To understand what toxicokinetic modeling is, consider the following scenario:

Scenario: You Are Exposed to a Chemical

Chemical Exposure Routes



Things You Might Want to Know:

- Does the chemical get inside your body?
- If so, how much of it gets inside? For example, what is the concentration of chemical in your blood?
- Is that enough of a concentration to cause any kind of health effect? (desired [e.g., pharmaceuticals] or undesired [e.g., harmful toxicants])
- Does it settle in any particular tissues or organs?
- Does it stay in your body for a long time, or does your body excrete it quickly?

How We Can Get Answers:

Toxicokinetic Modeling! Tells you where the chemical goes in your body, how fast it goes there, and how much of it goes there

- Module 6.6: Toxicokinetic modeling and comparing in vitro-derived bioactivity exposure ratios (BERs) to human exposure estimates to compare toxic doses vs doses humans experience in their everyday lives

Highlights of applications of NAMs



- Understanding toxicity of chemicals (arsenic, PFAS, wildfire smoke)
- Understanding mechanism of action of chemicals (arsenic, PFAS)
- Training students in NAMs

Acknowledgments



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