**Presentation to the Scientific Review Panel on Toxic Air Contaminants** 

# **Computational Toxicology and New Approach Methodologies**

**Office of Environmental Health Hazard Assessment** 

August 16, 2024



# Outline

- 1. New Approach Methodologies (NAMs) in toxicology and risk assessment
- 2. Components of the NAMs effort at OEHHA
  - Staffing (NTES)
  - Academic Collaborations
  - Expert Panel



# **New Approach Methodologies (NAMs)**

- **Traditional approaches**: human epidemiological and animal toxicological data (focus on duration and route of exposure).
- **NAMs**: in vitro data (cell culture), in silico data (computational predictions of binding of chemicals to macromolecular targets), alternative animal models (e.g., transgenic mouse models).
- NAMs will **reduce** and **replace animal use** in chemical risk assessment.



## **Broad Use of the Term "NAMS"**

#### Computational, modeling and read-across methods

Quantitative structureactivity relationships (QSAR) Physiologically based kinetic (PBK) models Absorption, distribution. metabolism and excretion (ADME) In vitro to in vivo extrapolation (IVIVE) Machine learning and artificial intelligence (AI)

Read-across

High-throughput screening (HTS) and imaging (HTI) bioassays

#### Advanced imaging/scanning techniques

Magnetic resonance imaging (MRI) **Functional magnetic** resonance imaging (fMRI) Computerized axial tomography (CAT) with three-dimensional reconstruction

Positron emission tomography (PET)

### **Omics applications** Genomics Transcriptomics **Proteomics** Lipidomics Metabolomics Interactomics **Nutrigenomics** Epigenomics Exposomics



### **Tissue/organ engineering** Organoids Microphysiological

systems (MPS) Organ-on-a-chip, human-on-a-chip

In vivo systems Alternative animal models Genetically diverse (e.g., collaborative cross)



















Adapted from Schmeisser et al., 2023 PMC10858683 PMID: 37422975 PMCID:

# Illustrative Example 1: Read-across Method for Data gap filling





## Illustrative Example 2: In-vitro-to-in-vivo Extrapolation (IVIVE) Method



Adopted from Chang et al. 2022, PMID: 35622645



# Increasing need for NAMs in toxicology and risk assessment

- More chemicals detected in the environment (novel detection methods, lower detection limits) do not have health assessments.
- New chemical alternatives needing assessments (e.g., novel PFAS, disinfectant quaternary ammonium compounds).
- On-going focus to reduce/replace animal use in toxicological studies.
- NAMs are the main proposed alternative to animal studies.



# **Examples of NAMs use by agencies**

## • IARC Monographs:

- Mechanistic evidence organized according to the key characteristics of carcinogens framework.
- **US EPA PPRTV** (provisional peer-reviewed toxicity value)
  - Read-across based on three similarity domains
    - structural/physicochemical
    - metabolic/toxicokinetic
    - toxicodynamic/mode-of-action



# **New Toxicology Evaluations Section (NTES)**

- Created in 2023
- Works with CalEPA BDOs, academic partners, and other stakeholders to address assessment needs of data-poor chemicals
- 5 staff:
  - two toxicologists
  - two chemical scientists (toxicokinetics, molecular chemistry)
  - one bioinformatics scientist



# Academic Partnerships on new assessment methodologies

- UC Berkeley: Predictive methods in carcinogenesis
- UC Davis: Comparison of in vitro and in vivo effects for emerging pollutants
- UC San Francisco: Development of alternative methods in assessing developmental toxicity
- **Texas A&M**: Toxicokinetic and transcriptomic studies



# **Kickoff NAMS Workshops**

## Workshop 1: January 2024



### Workshop 2: May 2024



- Presentations by academia, industry and government agencies
- Discussion of case studies relevant to CalEPA chemicals of interest



# **Proposed NAMS expert panel**

- EPERA: Expert Panel on Emerging Risk Assessment Approaches
  - Includes experts in relevant scientific fields
  - Provides expert advise and feedback on research activities on NAMs
  - Meets twice a year (current plan)
  - Is not a mandated committee like SRP or SAP
- EPERA involvement is peer input and not a substitute for peer review process
- First EPERA meeting ~ fall 2024



# Wrap up

• New approach methodologies (NAMs) are becoming part of landscape of tools for informed decision-making for data-poor chemicals.

- OEHHA's efforts in NAMs include:
  - Creation of New Toxicology Evaluations Section (NTES)
  - Academic collaborations and
  - Assembling an expert panel (EPERA)

