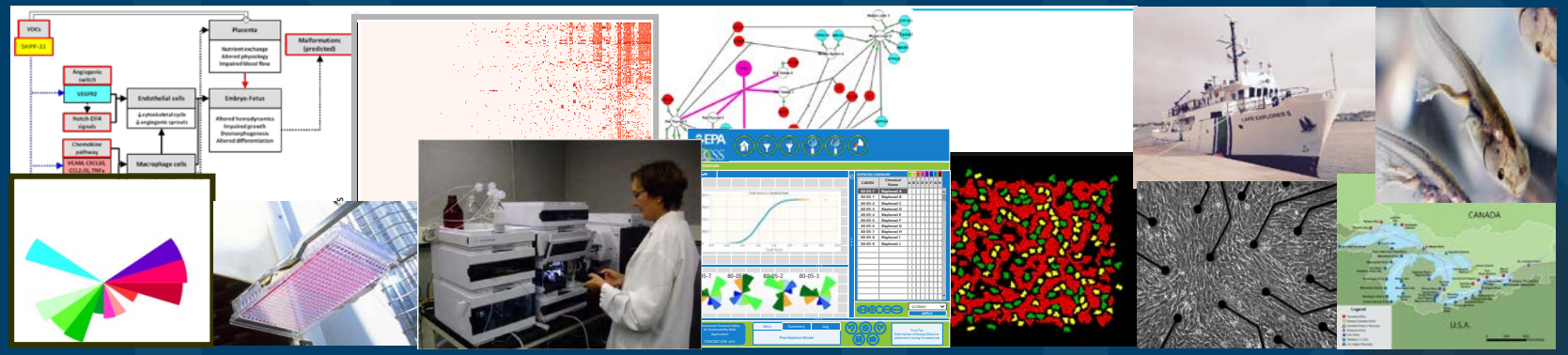
EPA's Work Plan for Reducing Animal Testing: Role of Organotypic, Microphysiological, and *In Silico* Models



NAS Microphysiological Systems Workshop

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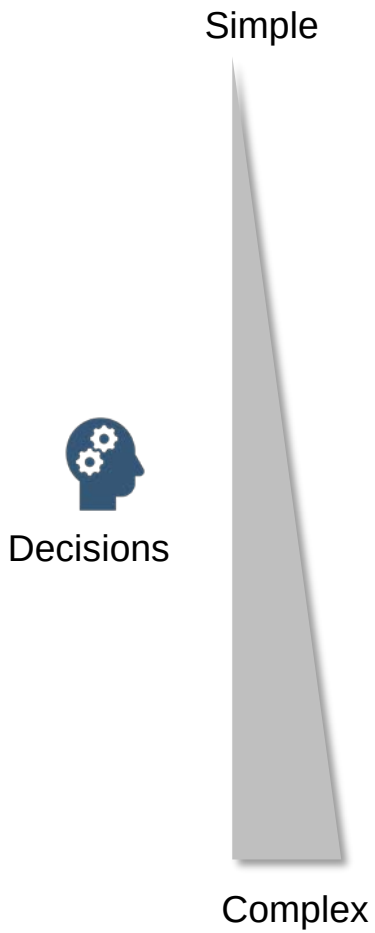
The views expressed in this presentation are those of the presenter and do not necessarily reflect the views or policies of the U.S. EPA

The EPA Makes a Broad Range of Decisions on Chemicals

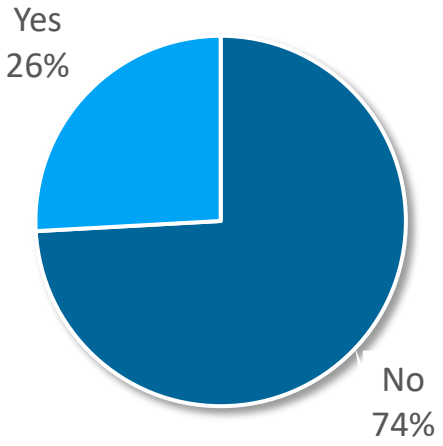


- Different decision contexts exist within statutes governing EPA authority, which determine the type of data and level of certainty required
  - Prioritization (e.g., EDSP, TSCA)
  - Emergency response (e.g., AEGLs)
  - Screening-level assessments (e.g., CCL, PMN)
  - Provisional assessments (e.g., PPRTVs)
  - Toxicity assessments (e.g., IRIS)
  - Endangered species protection (e.g., pesticides)
  - Risk assessments (e.g., MCLs, pesticides, TSCA risk evaluations)
- Organotypic, microphysiological, and *in silico* models can contribute to these decisions in a variety of ways
  - WOE for hazard identification and characterization
  - Cross-species differences
  - Susceptible populations

There is a Lack of Data on Hazard and Toxicokinetics for Most Chemicals

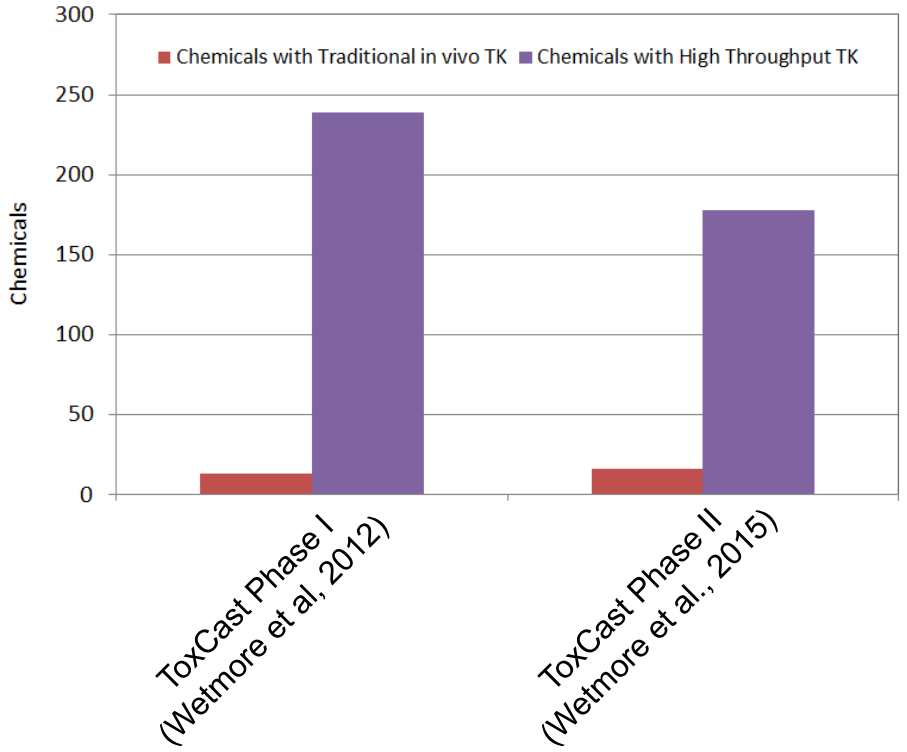
Hazard

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

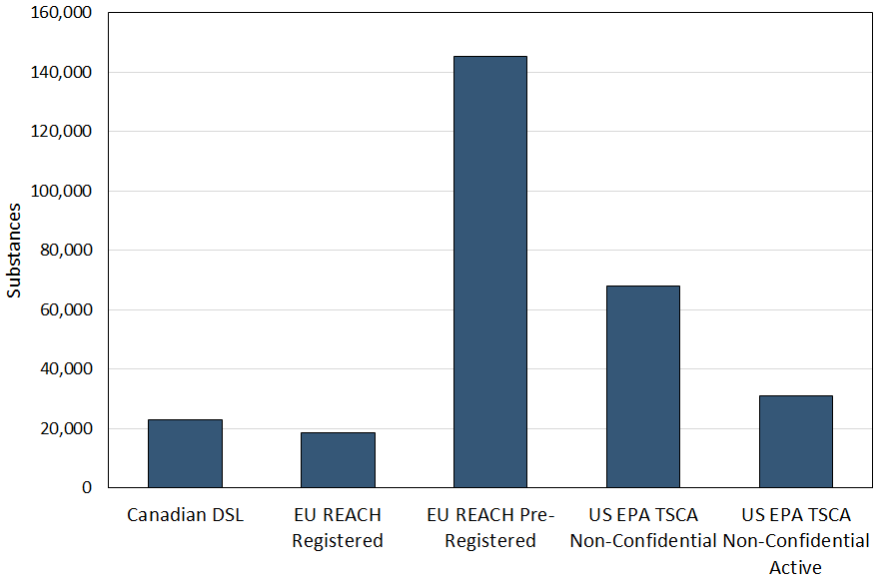


Data from ToxValDB (Dec 2019)

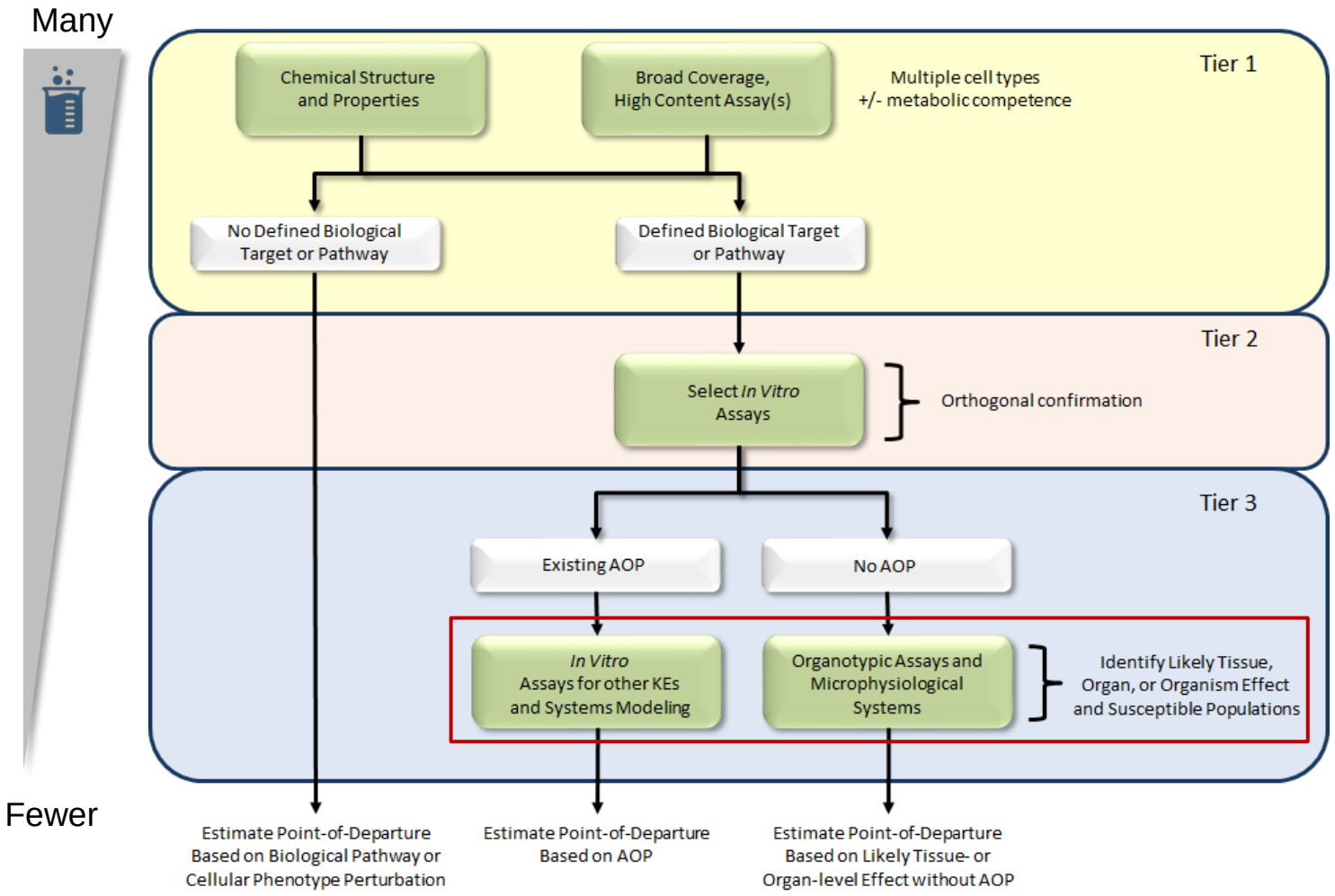
Toxicokinetics



Chemical Inventories



Organotypic, MPS, and *In Silico* Models are Key Components in Efficiently Evaluating Chemicals for these Decisions

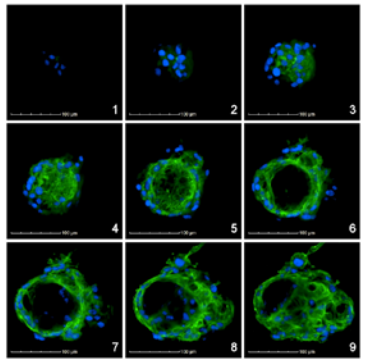


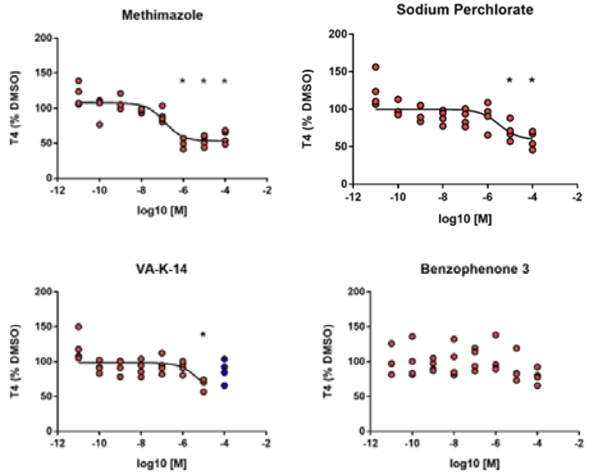
Thomas et al., *Toxicol Sci,* 2019

Example Tiered Testing Application for Thyroid Toxicity

HTS Assay Target	Environmental Chemicals Screened	Active Chemicals	% Active
TSHR	7871	825	10
TPO	1074	314	29
NIS	293	137	47
NIS	768	172	22
DIO 1	292	50	17
DIO 1	1819	221	12
DIO 2	1819	303	17
IYD	293	28	10

3D Organotypic Model





Deisenroth *et al.*, *Toxicol Sci*, 2020

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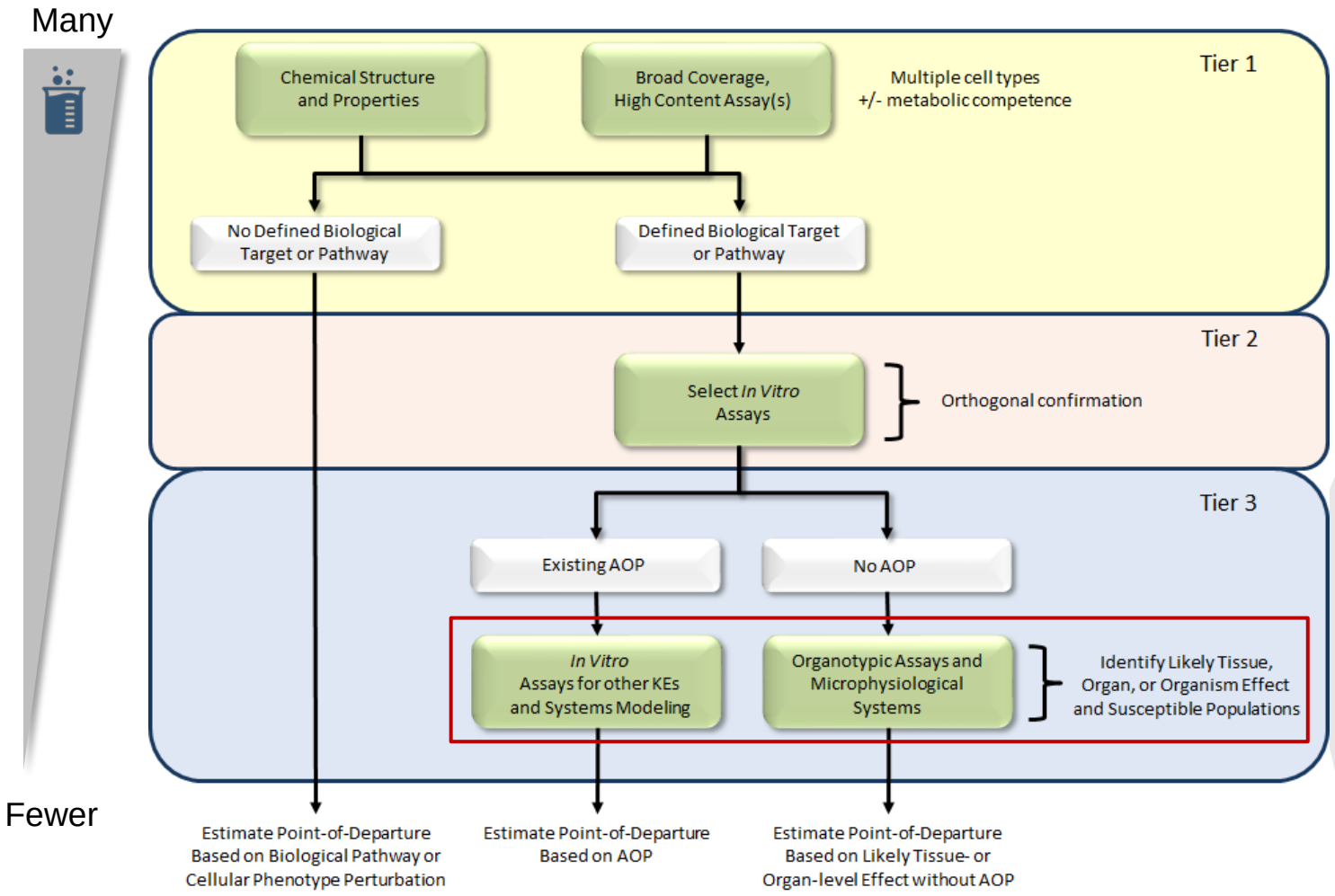
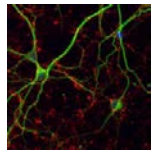
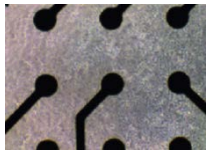


Thomas et al., *Toxicol Sci,* 2019

Example Tiered Testing for Developmental Neurotoxicity

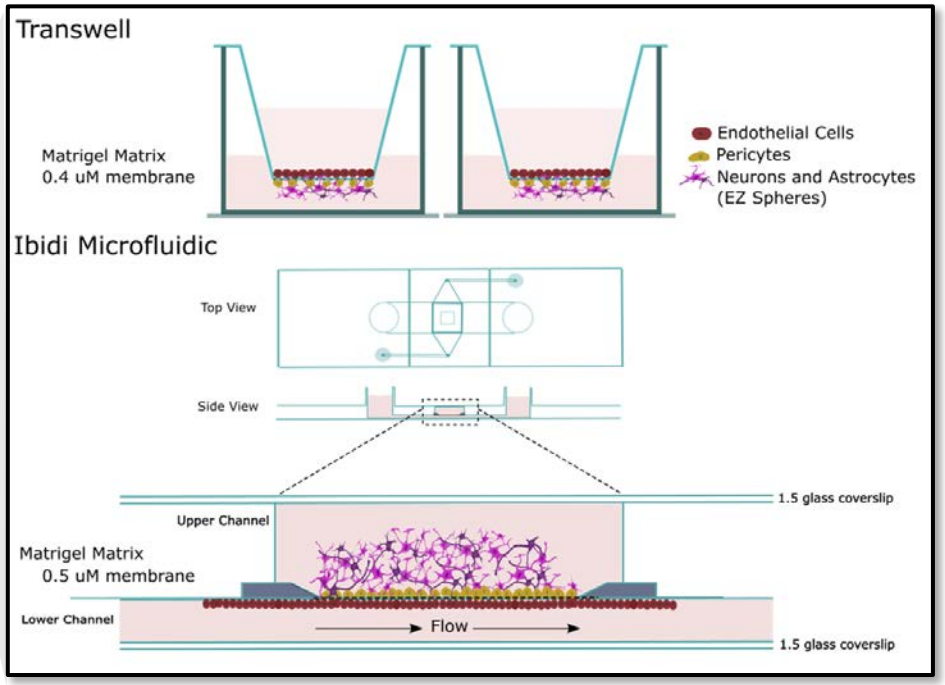
Neuroprogenitor Assays





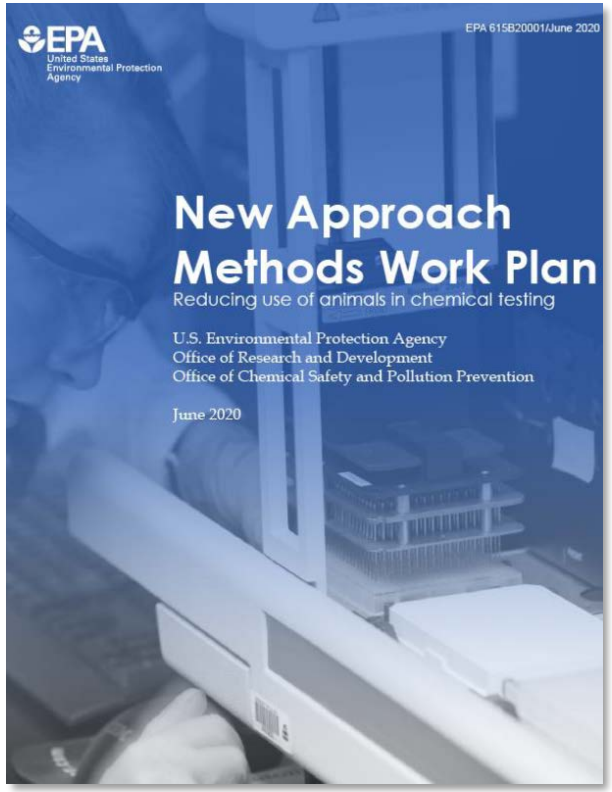
Microelectrode Array Assay

Organotypic and MPS Neurovascular Unit Models



S. Hunter Talk

EPA Intends to Overcome these Challenges while Reducing Animal Testing



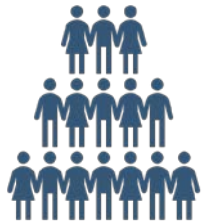
- Aims to:
  - Reduce requests for, and funding of, mammalian studies by 30% by 2025
  - Eliminate all mammalian study requests and funding by 2035
  - Come as close as possible to excluding reliance on mammalian studies from its approval process (subject to applicable legal requirements).
  - Achieve reduction in animal use through the development and application of New Approach Methods (NAMs)
- Work Plan includes:
  - Evaluating 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

Multiple Roles and Opportunities for Organotypic, MPS, and *In Silico* Models in the Work Plan

- In establishing scientific confidence in NAMs, the work plan intends to characterize scientific quality and relevance of existing mammalian toxicity tests.
  - May involve human- and rodent-based organotypic models and microphysiological systems.
- To fill important information gaps, the work plan encourages development and evaluation of NAMs both within EPA and by external organizations and consortia
  - Within EPA [e.g., embryo-fetal neurovascular unit (Hunter presentation), development (Knudsen presentation)]
  - External organizations and consortia
    - EPA STAR program (e.g., Organotypic Culture Models for Predictive Toxicology Centers)
    - Tox21
    - Others

Potential Roles of Organotypic, MPS, and *In Silico* Models in Toxicity Testing and Decision Making

- Better defining organ and tissue effects and toxicokinetics in tiered testing paradigms



- Identifying and evaluating potential susceptible subpopulations (e.g., life stage, genetic)

- Bridge to evaluate cross-species similarities/differences between animal models and humans

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Thank you for your attention!