



3rd Annual STAR Organotypic Culture Models (OCM) for Predictive Toxicology
Research Centers Progress Review

“Implementation of Microphysiological Systems in Toxicological Assessments”

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Planning on EPA Virtual Tissue Modeling Systems (VTM) to produce quantitative cellular, tissue and phenotypic responses

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Scoping the Problem

- Chemical regulation under the *Frank R. Lautenberg Chemical Safety for the 21st Century Act of 2016* ('amended TSCA') requires affirmation of 'low' and 'high' priority substances based on unreasonable risk to vulnerable subpopulations and lifestages.
- New approach methods (NAMs) based on *in vitro* data and *in silico* models can test the majority of chemicals in commerce within a decade but interpretation remains a challenge, especially for complex processes such as developmental toxicity and cancer.





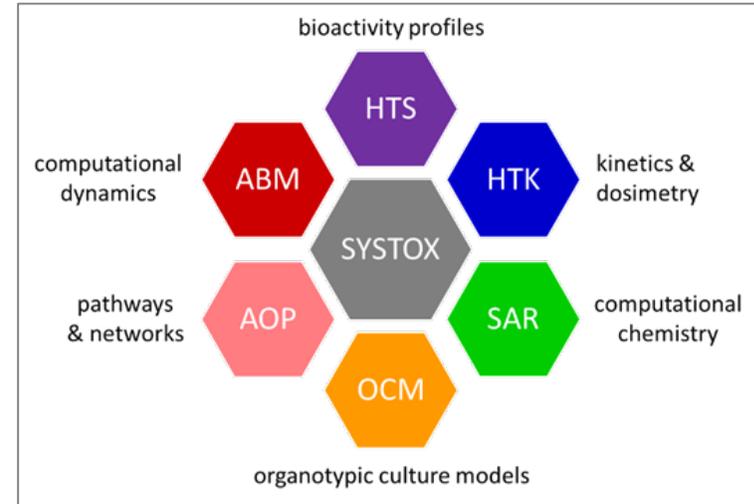
VTM project planning: problem, strategy, and outputs

Program Offices need information that informs the potential effects of chemicals on susceptible populations including early life stages and during development.

Evaluate the effects of chemical exposure during development on phenotypic responses in human cell-based *in vitro* systems (VTMs) to predict chemical hazard.

Utilize new approach methodologies to evaluate the effects of chemicals on developmental endpoints (such as neurodevelopment).

Integrate and translate data generated from agent-based models and organotypic cell culture models to predict potential chemical impacts on developmental endpoints.



Translate ToxCast HTS data into quantitative cellular, tissue and phenotypic responses.

Advance scientific case-studies for developmental health outcomes to reduce uncertainties.



Multiscale Modeling and Simulation

*Quantifiable in
conventional
monoculture*

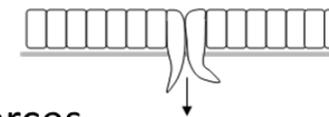
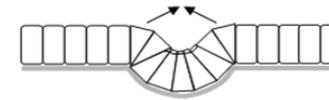
Cellular primitives

- growth (proliferation)
- programmed cell death (apoptosis)
- genetic signals and responses
- differentiation
- cell adhesion
- shape (geometry)
- motility (cell migration)
- ECM (remodeling)



Tissue movements

- folding
- epiboly
- convergent extension
- branching morphogenesis
- cell condensation
- cell sorting
- trans-differentiation (EMT)
- cavitation
- involution
- tractional forces
- ...



*Anatomical
development
requires an
integration of
complex cellular
behaviors*



Microphysiological Systems

Journal List > Exp Biol Med (Maywood) > v.242(16); 2017 Oct > PMC5661772



Experimental Biology and Medicine

Exp Biol Med (Maywood). 2017 Oct; 242(16): 1559–1572. PMID: PMC5661772
Published online 2017 Oct 25. doi: [10.1177/1535370217732765](https://doi.org/10.1177/1535370217732765) PMID: [29065799](https://pubmed.ncbi.nlm.nih.gov/29065799/)

Fitting tissue chips and microphysiological systems into the grand scheme of medicine, biology, pharmacology, and toxicology

David E Watson,¹ Rosemarie Hunziker,² and John P Wikswa^{1,3}

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“Building upon investments by the Defense Advanced Research Projects Agency, National Institutes of Health, Food and Drug Administration, Defense Threat Reduction Agency, and Environmental Protection Agency of more than \$200 million since 2012 and sizable corporate spending, academic and commercial players in the MPS community are demonstrating their ability to meet the translational challenges required to apply MPS technologies to accelerate drug development and advance toxicology.”

Journal List > Exp Biol Med (Maywood) > v.242(16); 2017 Oct > PMC5661771



Experimental Biology and Medicine

Exp Biol Med (Maywood). 2017 Oct; 242(16): 1586–1592. PMID: PMC5661771
Published online 2017 Jun 28. doi: [10.1177/1535370217717897](https://doi.org/10.1177/1535370217717897) PMID: [28658972](https://pubmed.ncbi.nlm.nih.gov/28658972/)

Programming microphysiological systems for children's health protection

TB Knudsen,¹ B Klieforth,² and W Slikker, Jr.³

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“Emerging concepts can be taken forward to a virtual tissue modeling framework for assessing chemical (and non-chemical) stressors on human development. These models will advance children’s health research, both basic and translational and new ways to evaluate complex embryological and reproductive impacts of drug and chemical exposures to inform safety assessments.”



Virtual Reconstruction of Developmental Toxicity

- OCM platforms (eg, biomimetic embryo) in parallel with ABM platforms (eg, virtual embryo) can work together seamlessly in translating HTS data through cellular networks → predicted phenotype.
- Mechanistic models can replace default assumptions with explicit descriptions of the biology that actually determines the shape of a dose-response curve, susceptible lifestage, or regional response.
- Advancing toxicological assessment from *in silico* prediction to mechanistic interpretation will require prioritizing pathways and processes that represent critical determinants of complex phenotype.
- A comprehensive modeling strategy is needed to characterize the genetic logic underlying critical phenomena (eg, mapping cellular networks with Boolean logic).
- Model-driven experimentation has been successful in physics and should be an organizing principle of new approach methodologies aimed at toxicological assessment.

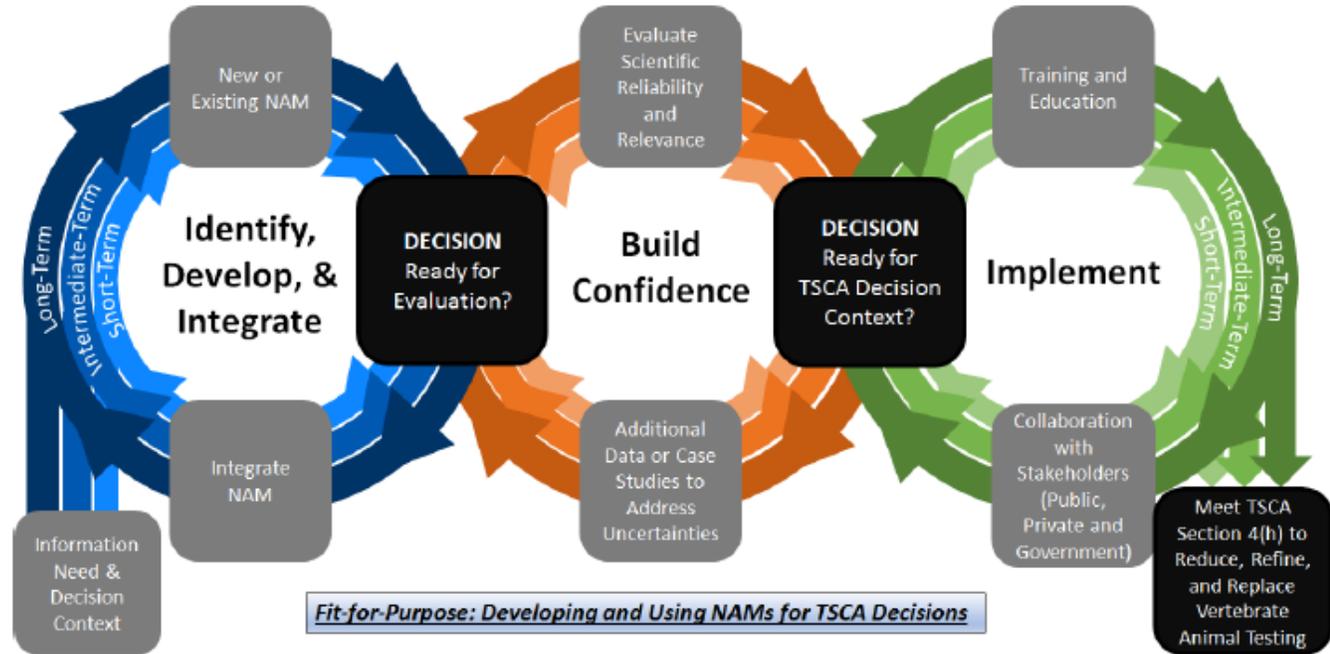


In this document, the EPA outlines its Strategic Plan for the reduction of testing in vertebrates for chemicals regulated under TSCA

Draft for Public Comment

Do Not Cite or Quote

Fig. 1 Core Components of EPA Strategic Plan to Develop and Implement New Approach Methodologies (NAMs) in TSCA



SOT Contemporary Concepts in Toxicology

November 14-16, 2018

Crystal City, VA



Predictive Toxicology for Healthy Children

<https://www.toxicology.org/events/shm/cct/FutureToxIV.asp>