NTP
National Toxicology Program

Reflections- February 2019 BSC Meeting

Brian R. Berridge, DVM, PhD, DACVP
Associate Director, NTP
Scientific Director, DNTP
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
June 17, 2019

NTP
National Toxicology Program

The Changing Toxicology Landscape: Challenges and the Future of Risk Assessment

Brian R. Berridge, DVM, PhD, DACVP
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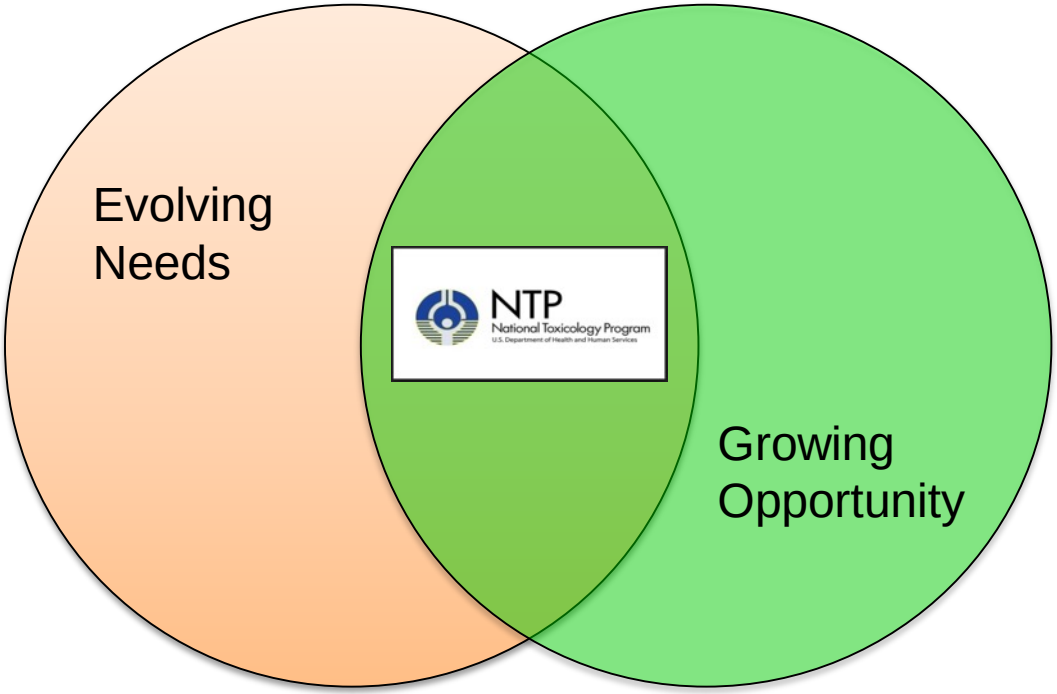
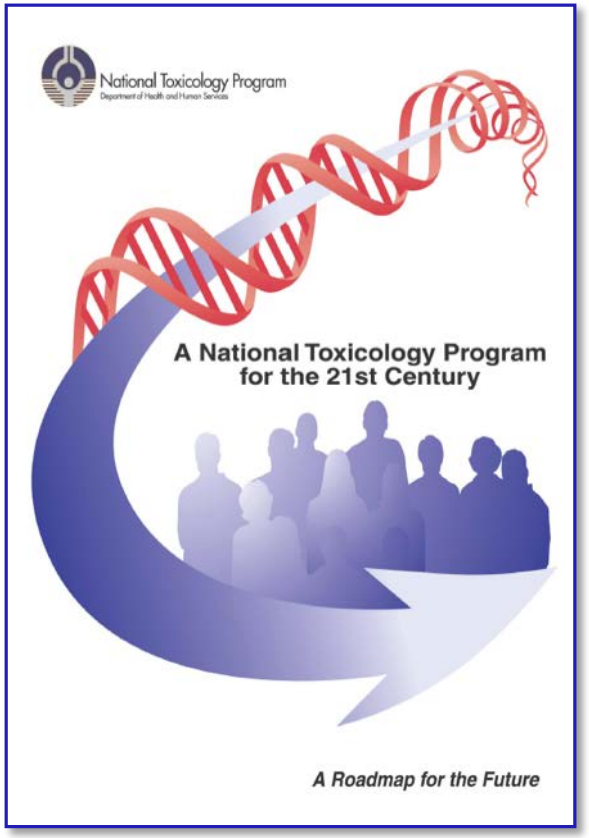
February 15, 2019

An Intersection



Framework for Our Strategic Realignment



21st Century Vision

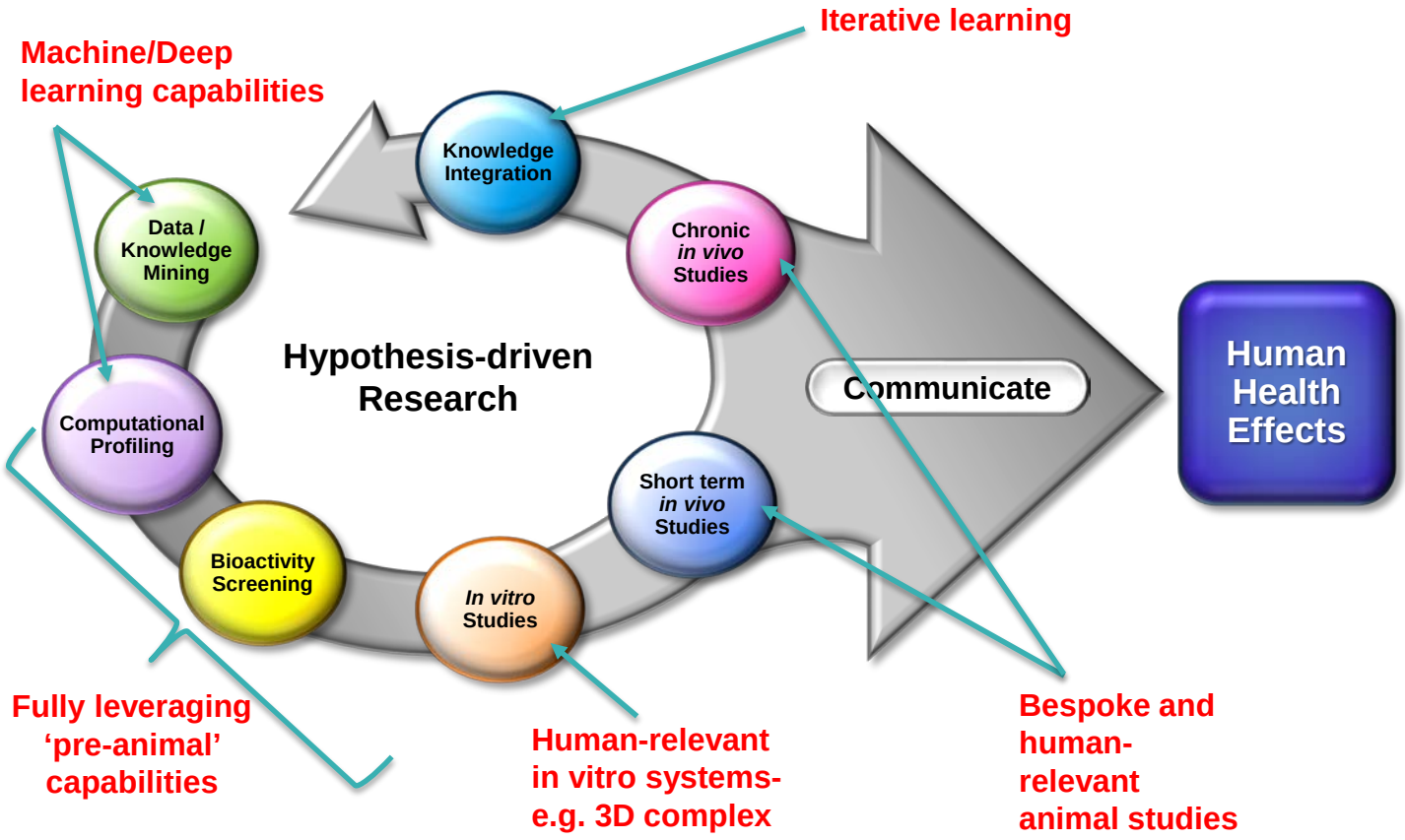
To support the evolution of toxicology from a predominately observational science at the level of disease-specific models to a predominately predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations.

A National Toxicology Program for the 21st Century, November 2004

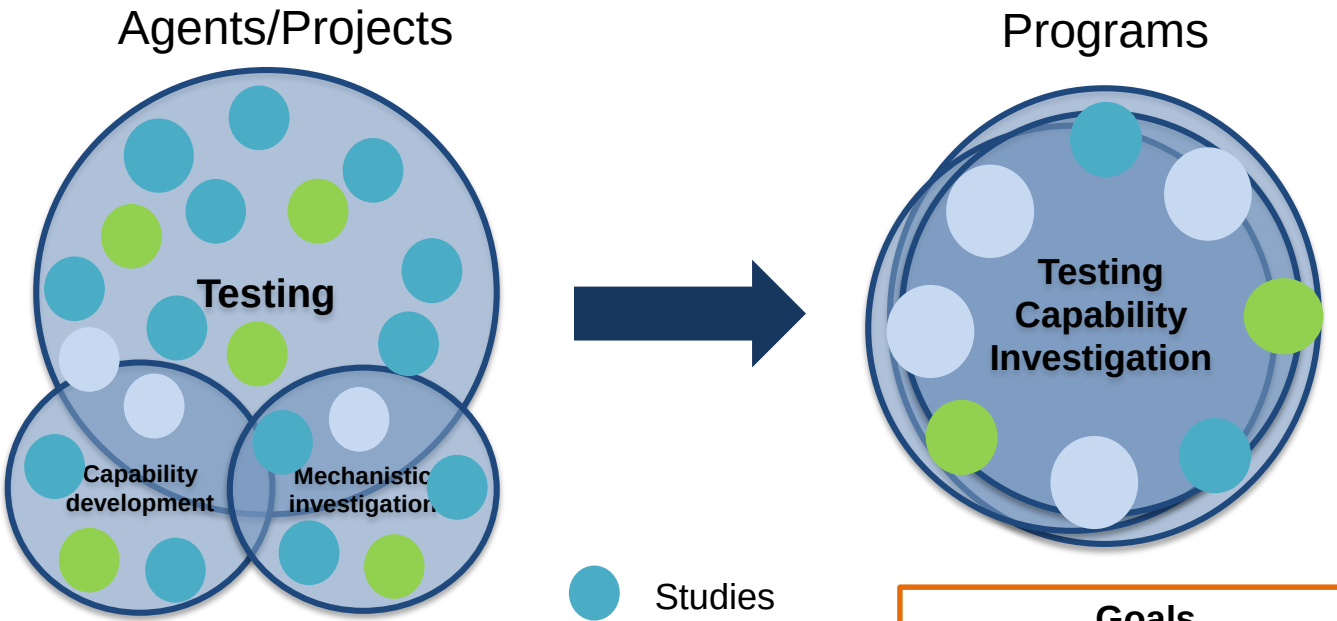
NTP BSC Feedback

- What is NTP's unique value?
  - Ability to focus on complex challenges for prolonged periods of time
  - Impactful science supporting policy and regulation
  - Opportunity to address chronic health effects
  - Build predictive capabilities
- What does it mean to be human-relevant?
  - Studying things of contemporary human concern/importance
  - Studying things in a relevant human context
    - Modeling human exposure context- quantity, route
    - Demonstrating exposure/outcomes relationships
  - Addressing public confusion

Innovating the Paradigm



Evolving Our Portfolio



Goals

- Increase impact
- Improve sustainability
- Increase visibility
- Improve complementarity

Health Effect Innovation

- Carcinogenicity Testing for the 21st Century
- Developmental Neurotoxicity Modeling
- Cardiovascular Hazard Assessment in Environmental Toxicology

Aims

- Fill a gap in current capabilities
- Build on existing effort
- Align to NIH model
- Leverage our key strengths and value

Invited Perspectives

- John Piacentino, MD, MPH- NIOSH
- Bill Slikker, PhD- NCTR/FDA
- Gina Solomon, MD, MPH- UCSF
- Bill Cibulas, PhD, MS- NCEH/ATSDR
- Syril Pettit, DrPH, MEM- HESI
- Fiona Sewell, PhD- NC3Rs
- Rusty Thomas, PhD- EPA

J. Piacentino- NIOSH

National Institute for Occupational Safety and Health

The Changing Toxicology Landscape: Challenges and the Future of Risk Assessment

John Piacentino, MD, MPH
Associate Director for Science, NIOSH

National Toxicology Program
Board of Scientific Counselors
February 15, 2019

NIEHS Spurs NIOSH to Develop Occupational Systematic Review

NIOSH NTP Partnership

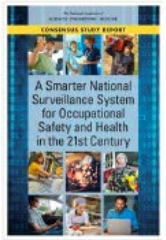
- Characterize occupational exposure to agents of mutual interest to NTP and NIOSH and assess potential health effects
- Workers exposure is greater than non-workers
- Capitalize on NIOSH access to worker populations and work sites to provide real-world context for toxicology studies
- Guide decision-making for NIOSH epidemiologic studies
- Provide toxicologic and epidemiologic evidence for guidan

Evolution of NIOSH approach to examining the immunotoxicity of xenobiotics

Question	Current	Future
What are the long term health effects associated with a xenobiotic?	Conduct a long term animal studies for 1-2 years	Use long term cell culture models (e.g. up to 6 months) with a comparison to animal models
Are cellular interactions required for a toxic effect?	Conduct an animal study for 28 days	Use 2 and 3D cell culture models for 14-21 days to assess chemical and cellular interactions
What biomarkers predict toxicity in animals?	Conduct an animal study for 28 days	Conduct proteomic or metabolomics studies in animals over 7 days and use *machine learning* approaches to predict earlier biomarkers of toxicity
Does this xenobiotic cause sensitization?	Conduct an animal study for 6 weeks	Develop and publish allergenicity screening tests using *in vitro* systems in 30 -60 minutes

Smarter Surveillance for the Future

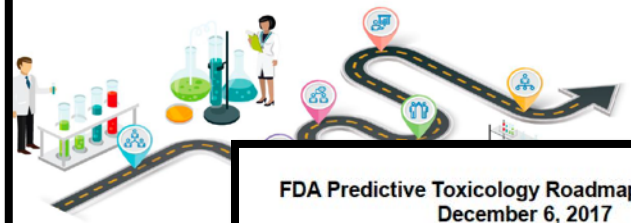
- National Academies of Sciences report on a smarter national surveillance system
- Prioritize and coordinate OSH surveillance
- Improve data collection
- Expand biomedical informatics use and capabilities
- Strengthen data analysis and information dissemination for prevention



http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=24835

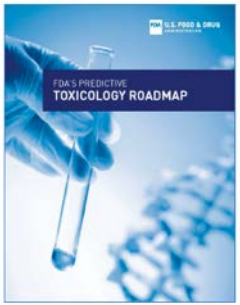
FDA Predictive Toxicology Road Map

National Toxicology Program,
Board of Scientific Councilors
February 15, 2019



FDA Predictive Toxicology Roadmap Announced
December 6, 2017

- https://blogs.fda.gov/fdavoice/index.php/2017/12/fda-launches-predictive-toxicology-roadmap-to-enable-advances-in-toxicity-testing/



RoadMap Goals

- Roadmap identifies the critical priority activities for energizing new or enhanced FDA engagement in transforming the development, qualification, and integration of new toxicology methodologies and technologies into regulatory application
- Implementing the roadmap and engaging with diverse stakeholders will enable FDA to fulfill its regulatory mission today while preparing for the challenges of tomorrow.

- Training of FDA regulators and researchers
- Continued communication
- Collaborations with stakeholders
- Oversight by Office of the Commissioner

The Changing Toxicology Landscape: Challenges and the Future of Risk Assessment

GINA M. SOLOMON, M.D., M.P.H.
PRINCIPAL INVESTIGATOR, PUBLIC HEALTH INSTITUTE
CLINICAL PROFESSOR, U.C. SAN FRANCISCO
FEBRUARY 15, 2019

Summary of Recommendations

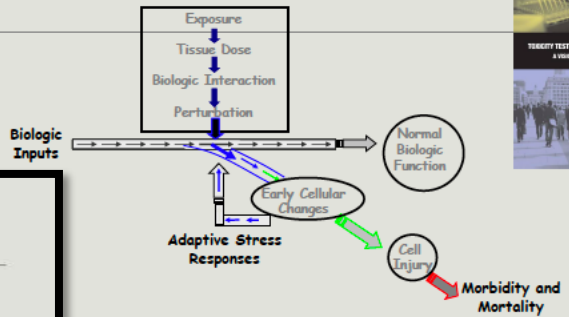
1. Systematically address identified testing gaps in toxicity pathways by developing and incorporating new assays.
2. Follow-up by testing of chemicals that show markedly positive results on important pathways.
3. Move toward making decisions based on the pathway disruption, not on each endpoint.
4. Develop and implement strategies to group chemicals into classes and impute hazards across the class.

multiple stressors, including non-chemical stressors, perturb biological

Thank You!

ucsf.edu

Pathway-Based Toxicity Testing



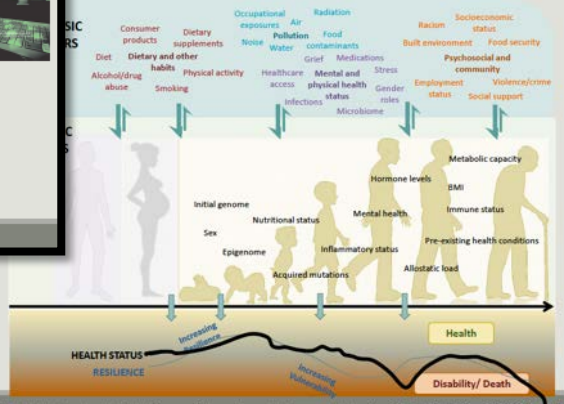
Multiple "Characteristics of Badness"

Endpoints for Trichloroethylene (TCE)

- Kidney cancer
- Non-Hodgkin lymphoma
- Cardiac defects
- Leukemia
- Liver cancer
- Multiple myeloma
- Endstage renal disease
- Parkinson disease
- Scleroderma
- Chronic stress
- Eye defects
- Low birth weight
- Fetal death
- Major malformations
- Miscarriage
- Neural tube defects
- Oral cleft defects (including cleft lip)
- Small for gestational age
- Breast cancer
- Cervical cancer
- Esophageal cancer
- Lung cancer
- Hodgkins disease
- Ovarian cancer
- Prostate cancer
- Rectal cancer
- Impaired immune system function
- Neurological effects (delayed reaction times problems with short-term memory, visual perception, attention, and color vision)
- Neurobehavioral performance deficits (i.e., delayed recall and deficits in visual perception), decreased blink reflex, and mood effects (i.e., confusion, depression and tension)
- Severe, generalized hypersensitivity skin disorder

Specific effect may depend on:

- Metabolic pathway (e.g., GST vs CYP for TCE)
- Timing of exposure
- Concentration and duration
- Other chemical and non-chemical stressors



McHale et al., Assessing health risks from multiple environmental stressors: Moving from G×E to I×E. Mut Res 775 (2018):11-20.

The Changing Toxicology Landscape: Challenges and the Future of Risk Assessment

William Cibulas, Jr., PhD, MS
Deputy Associate Director for Science, NCEH/ATSDR
Director, Division of Toxicology and Human Health Sciences, ATSDR

NTP Board of Scientific Counselors Meeting
NIEHS
February 15, 2019

National Center for Environmental Health
Agency for Toxic Substances and Disease Registry

The Challenge for ATSDR and our Partners

Remove the uncertainties, and improve the precision and timeliness of health/risk assessments for the communities we serve.

What are the toxicology needs for ATSDR?

- Basic biological research on cellular pathways and mechanisms at environmentally-relevant concentrations
- Improved techniques for assessing harmful effects from co-exposures (Mixtures) and cumulative exposures
- Improved methods for assessing cancer risks
- Improved understanding of risks for susceptible populations

What are the toxicology needs for ATSDR?

- Harmonized approaches for developing HGV's for emerging chemicals
- New and improved, validated tools for predictive toxicology
- Better use of probabilistic techniques for communicating 'risk' to communities
- New methods for incorporating 'big data' into health/risk assessments, esp human data (e.g., biomonitoring, epi studies, surveillance, medical health records)

Thinking about the future of 'toxicology'

HESI Presentation to the National Toxicology Program
February 2019

Syril D Pettit, HESI Executive Director

SCIENCE FORESIGHT

PERSPECTIVES FOR 2017-2020

HESI

Objective

Create a broad picture of widely identified global and/or national science and health priorities and align those with priorities identified by our own diverse stakeholder base.

CURRENT

Tox on Defense → Toxicity = Avoid Harms/ 'De-Risk'

FUTURE

Offense → Toxicity = Quality of Life, Public Health

Moving Toxicology from Defense to Offense

Tox-Centric	Health Context
Immunotoxicology	Rheumatology/Immunology
Ecotoxicology	Environmental Stewardship
Mechanistic Tox	Innovation Enabling Biology
Epidemiology	Real-world Evidence
Assay Driven Testing	Decision-driven Strategies
Risk Assessment Methods	Public Health

F. Sewell- NC3Rs

National Centre for the Replacement Refinement & Reduction of Animals in Research

The Changing Toxicology Landscape: Challenges and the Future of Risk Assessment

NTP Scientific Counselors meeting

15 February 2019

Fiona Sewell, PhD
Programme Manager, Toxicology and Regu

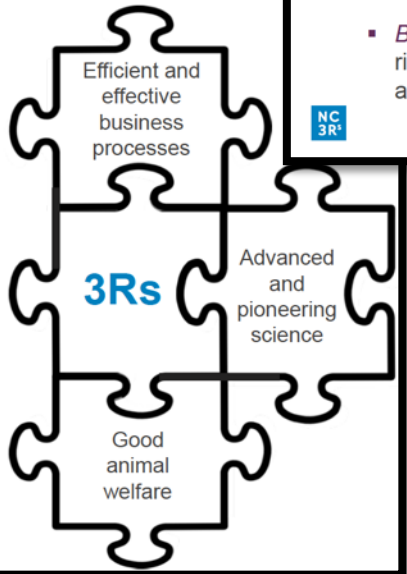
Pioneering Better Science

Benefits of cross company collaboration

Sharing experience & challenging current practices in an open environment can lead to:

- Larger evidence-base.
- More relevant study designs.
- Improved scientific confidence and predictivity.
- Shared and reduced risk.
- Improved interaction with regulators.

- Business advantages:
  - Reduced cost $$$$.
  - Improved efficiency.
  - Streamlined processes.



Global harmonisation is key

- We live in a global marketplace.
- Regulations and data requirements can vary by type of substance and geographical region.
- There can still be variation in practice and interpretation of harmonised guidance.
- Specific tests may be carried out to meet a few regional requirements.
- *Business perspective*: companies may take the most risk-averse/extensive approach to ensure regulatory acceptance of safety assessments.

R. Thomas- EPA

EPA United States Environmental Protection Agency

The Changing Toxicology Landscape

Challenges and Innovations to Adapt at EPA

NTP Board of Scientific Counselors Meeting

February 15, 2019

Rusty Thomas
Director
National Center for Computational Toxicology

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

Addressing the Challenges Will Require Scientific and Policy Advances

EPA United States Environmental Protection Agency

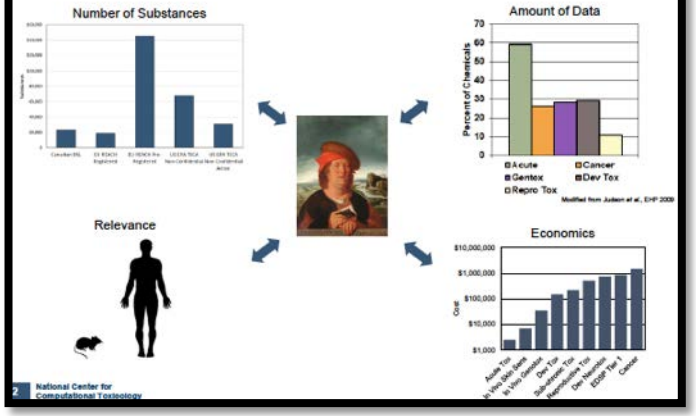
A Strategic Plan to Develop and Integrate New Approach Methods in TSCA

- Amended TSCA requires "Scientifically valid test methods and strategies that reduce or replace use of vertebrate animals while providing information of equivalent or better scientific quality and relevance that will support regulatory decisions" *Section 4(h)(1)(B)*
- Three main parts
  - Identify, develop, and integrate new approach methods
  - Establish relevance, reliability, and confidence
  - Training, education, and collaboration
- Near-term (0 – 3 yr), intermediate (3 – 5 yr), and long-term objectives (>5 yrs)
  - Ex: Identify and maintain a list of most requested studies for new and existing chemicals under TSCA

...educe and eventually ...imal testing"

EPA United States Environmental Protection Agency

Early Versions of Toxicity Testing Left Challenges for Evaluating Chemical Safety



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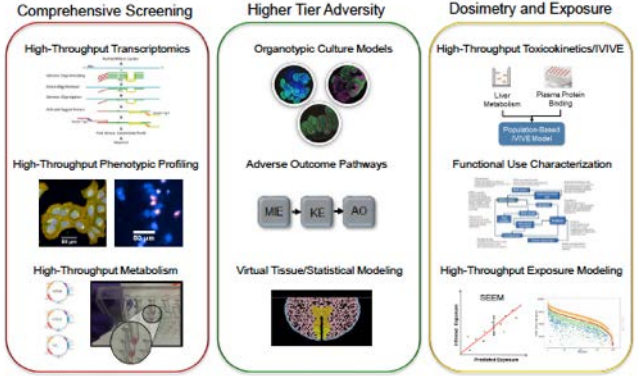
EPA United States Environmental Protection Agency

A Portfolio of Scientific Advances in Toxicity Testing at EPA



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Summary Thoughts

- Good alignment on needs and opportunities
- Much is currently in progress- need to focus on execution and building confidence
- Common themes
  - Need for timeliness
  - Usefulness of understanding mechanisms/modes-of-action
  - Need to collect and leverage relevant data
  - Value of focus on health effects
  - Value of partnerships

Agency Portfolios in Support of NTP

NIOSH:	Dr. John Piacentino Associate Director for Science
FDA/NCTR:	Dr. Gonçalo Gamboa da Costa FDA Liaison Officer to the NTP
NIEHS/DNTP:	Dr. Scott Masten Director, Office of Nomination and Selection
NCATS:	Dr. Christopher Austin Director