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

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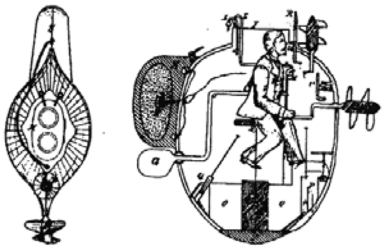
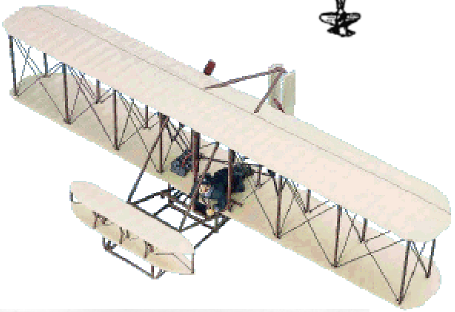
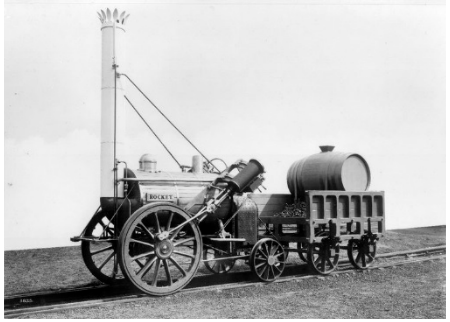
Director
National Center for Computational Toxicology

United States Environmental Protection Agency

Version 1.0 is Seldom Perfect…







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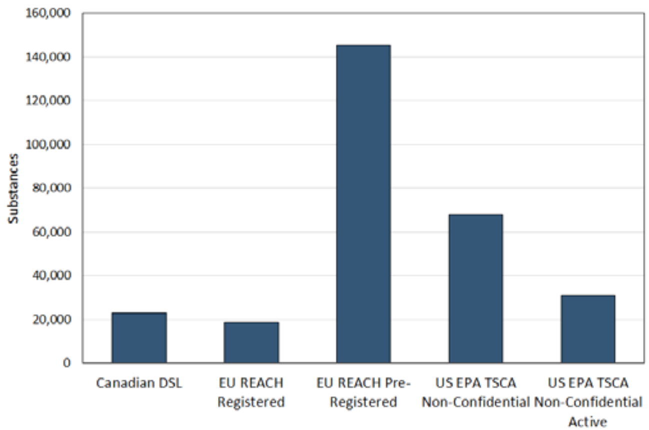
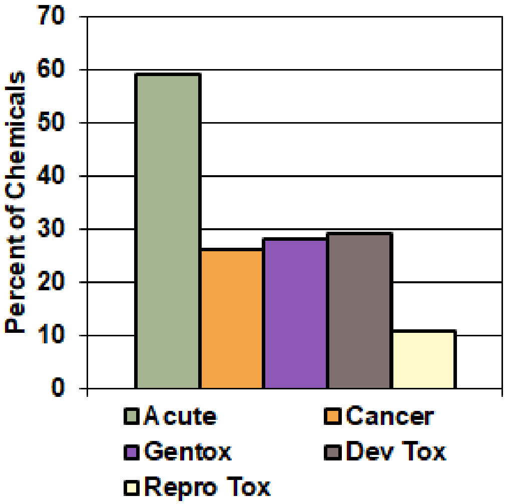
Early Versions of Toxicity Testing Left Challenges for Evaluating Chemical Safety

Number of Substances

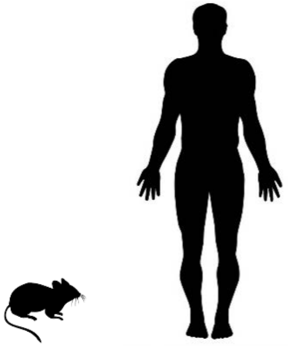


Amount of Data

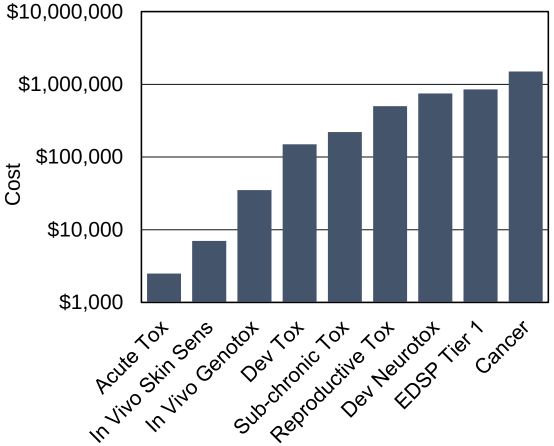


Modified from Judson *et al.*, EHP 2009

Relevance



Economics



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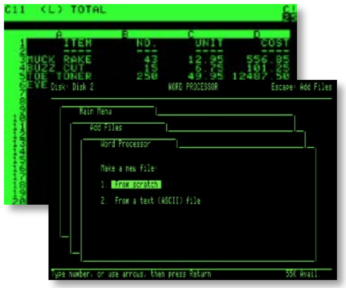
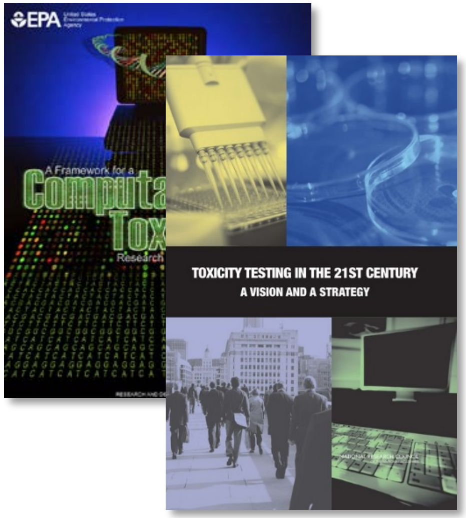
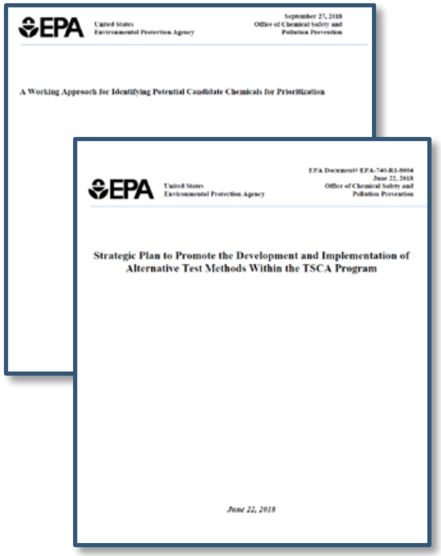
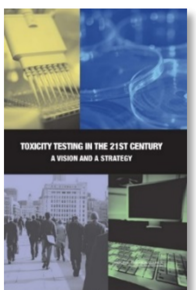
Addressing the Challenges Will Require Scientific and Policy Advances

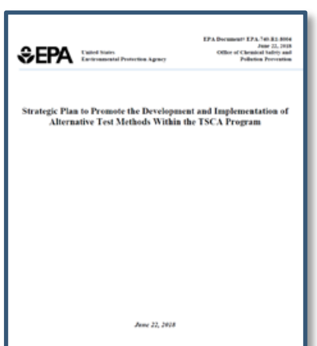






Highlights of a Few Scientific and Policy Advances at EPA

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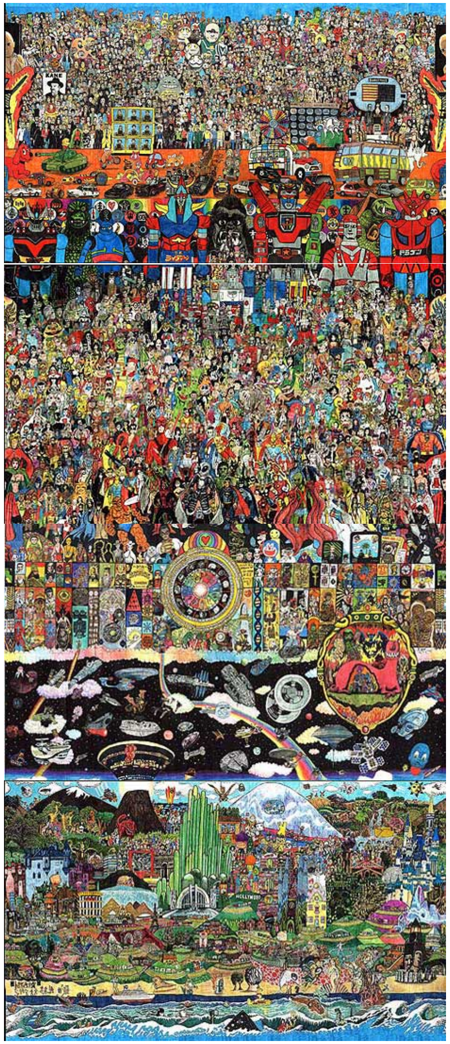
EPA Document# EPA-740-R1-8004
June 22, 2018
Office of Chemical Safety and Pollution Prevention

Strategic Plan to Promote the Development and Implementation of Alternative Test Methods Within the TSCA Program

June 22, 2018

- Technology advances to comprehensively evaluate large numbers of chemicals across toxicological space
- Strategies for incorporating new approach methods in regulatory decisions
- Incorporating new approach methods in identifying potential candidates for prioritization
- Managing and integrating diverse data using visualization and decision support tools

Toxicology is Analogous to Trying to Create a ‘Picture of Everything’



Picture of Everything
Howard Hallis

- In 1997 an artist named Howard Hallis started drawing a 'Picture of Everything', it took 13 years to complete, stands at 15 x 14 feet.
- The ideal toxicity testing approach provides comprehensive coverage of relevant toxicological responses
- It should identify the mechanism/mode-of-action (with dose-dependence)
- It should identify responses relevant to the species of interest and include consideration of metabolism (detoxification/bioactivation)
- Responses should ideally be translated into tissue-, organ-, and organism-level effects
- It must be economical and scalable

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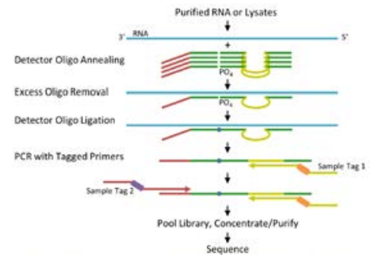
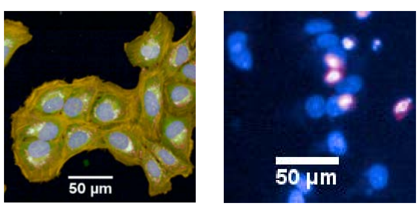
A Portfolio of Scientific Advances in Toxicity Testing at EPA

Comprehensive Screening

High-Throughput Transcriptomics



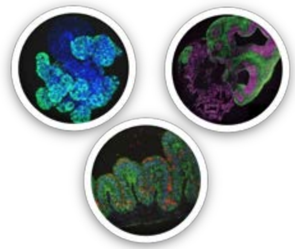
High-Throughput Phenotypic Profiling



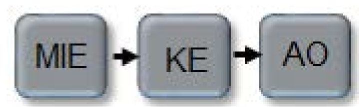
High-Throughput Metabolism

Higher Tier Adversity

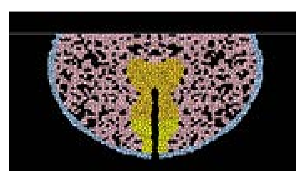
Organotypic Culture Models



Adverse Outcome Pathways

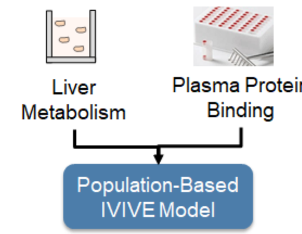


Virtual Tissue/Statistical Modeling

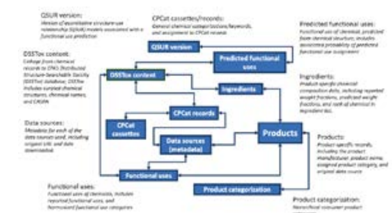


Dosimetry and Exposure

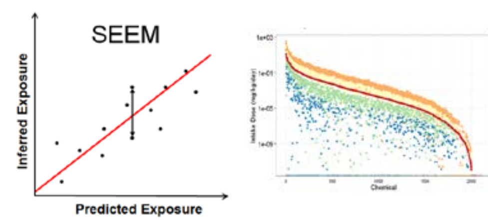
High-Throughput Toxicokinetics/IVIVE



Functional Use Characterization



High-Throughput Exposure Modeling



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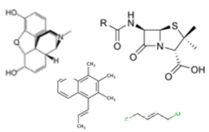
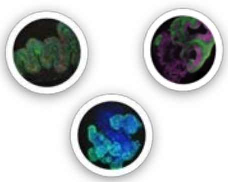
Innovations in High-Throughput and High-Content Screening

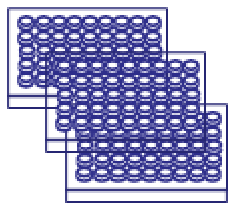


Thousands of Chemicals

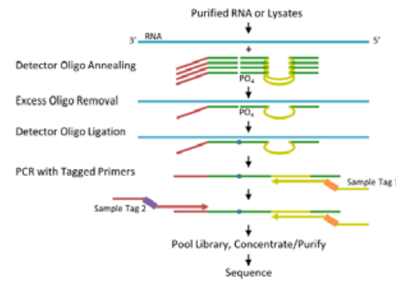


Multiple Cell Types

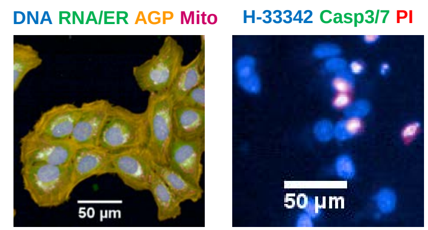
Concentration Response Screening



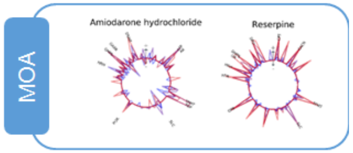
Whole Genome Transcriptomics (HTTr)



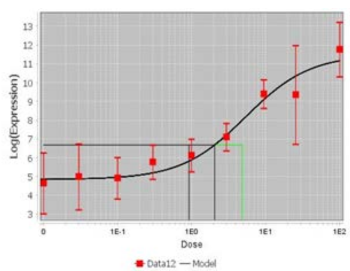
Multi-Parameter Cellular Phenotypic Profiling (HTPP)



Mode-of-Action Identification



Concentration Response Modeling



- 384-well, laboratory automation compatible, portable
- Relatively inexpensive ($2.50 - $1,500 per chemical)
- Broad complementary coverage of molecular and phenotypic responses
- Integration of reference materials and controls for performance standards
- FY18: HTTr – 1 cell type x 2,200 chemicals
- FY19: HTTr – 2 cell types x 1,400 chemicals; HTPP – 4 cell types x 1,400 chemicals

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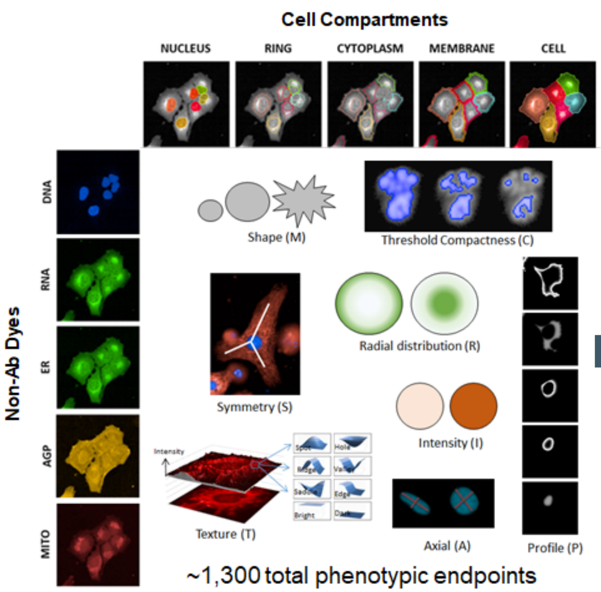
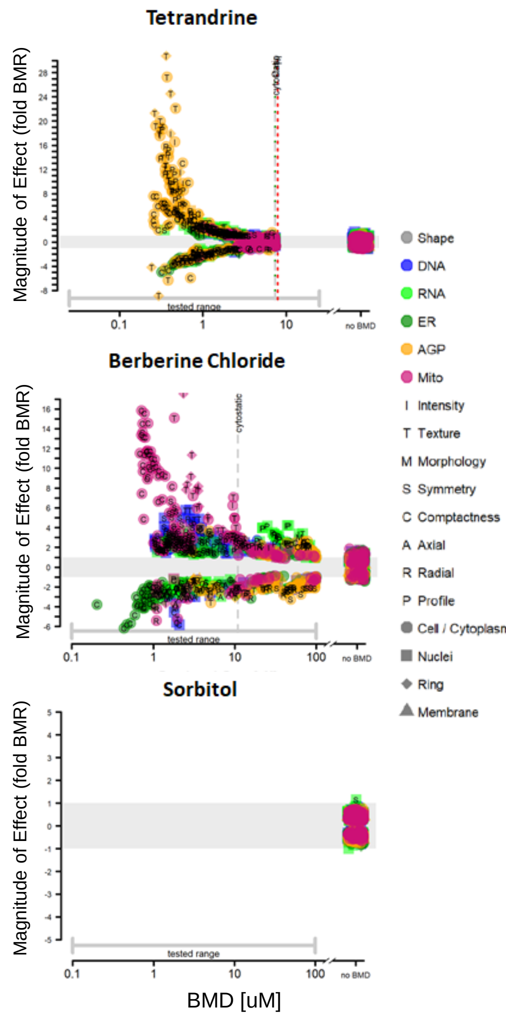
Evaluating ‘Cellular Pathology’ as a Conservative Indicator of *In Vivo* Effects

Phenotypic Profiling

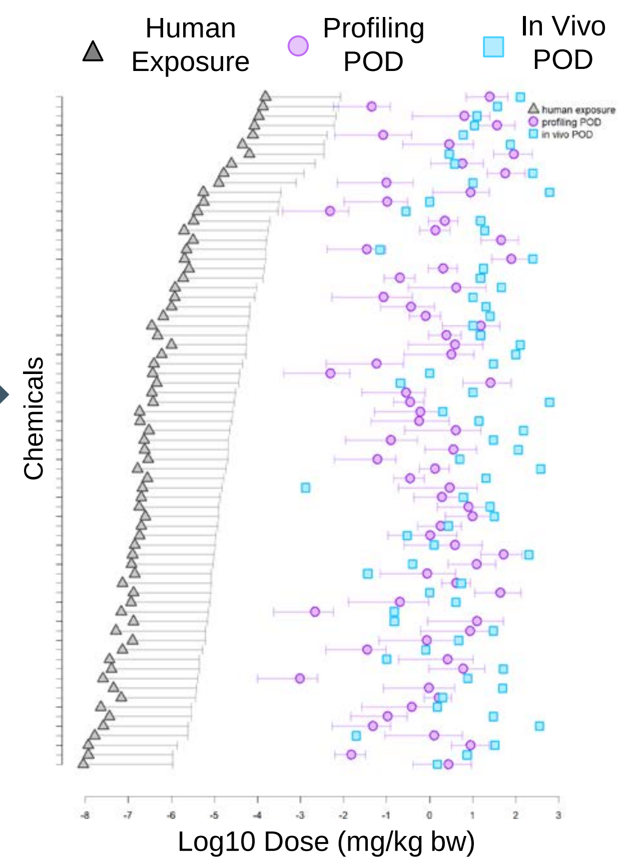


~1,300 total phenotypic endpoints

Concentration Response

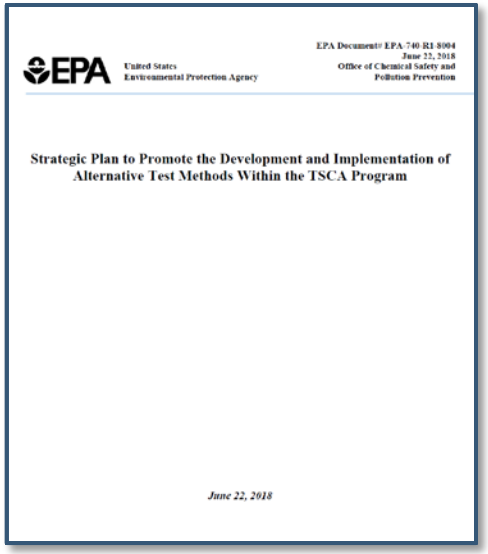


Comparison with *In Vivo* Effects



J. Nyffeler, J. Harrill, Unpublished

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


EPA Document# EPA-740-R1-8004
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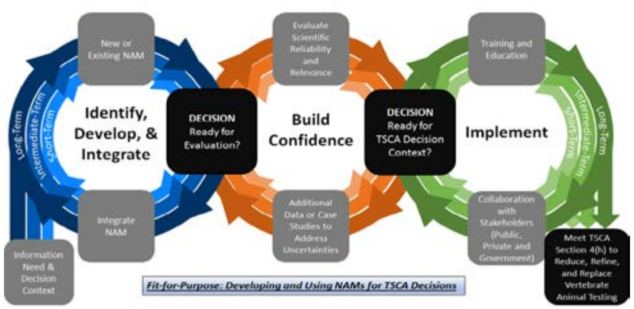
Strategic Plan to Promote the Development and Implementation of Alternative Test Methods Within the TSCA Program

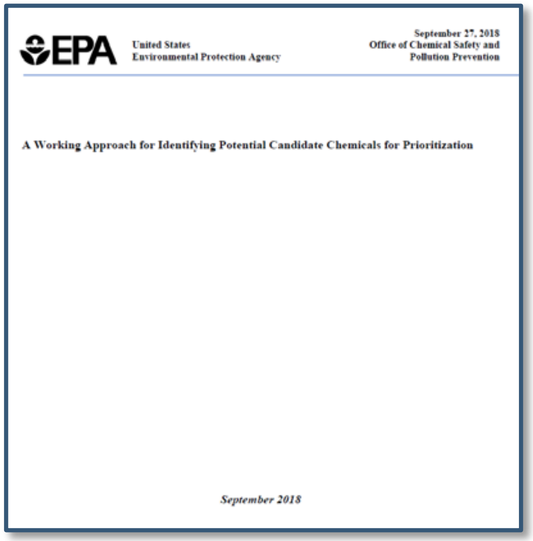
June 22, 2018



https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/alternative-test-methods-and-strategies-reduce

- 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
- Long term goal is to "reduce and eventually eliminate vertebrate animal testing"

Incorporating New Approach Methods to Identify Candidates for Prioritization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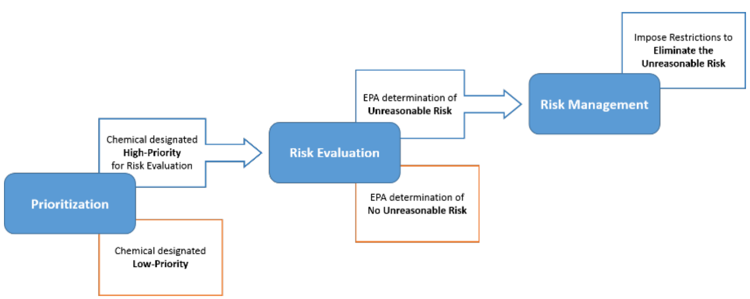
A Working Approach for Identifying Potential Candidate Chemicals for Prioritization

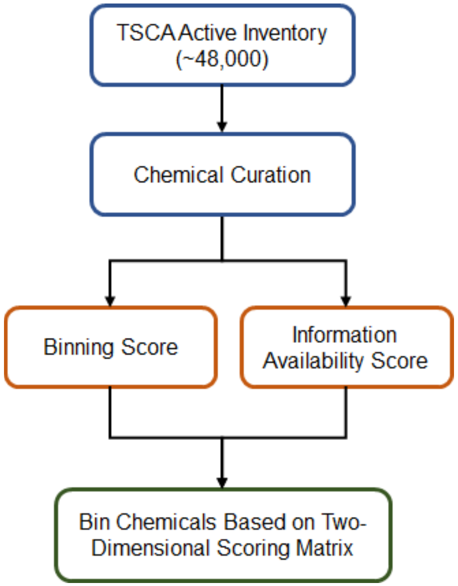
September 2018

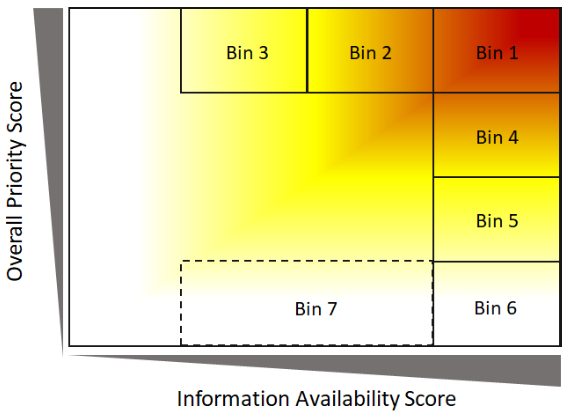


https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/prioritizing-existing-chemicals-risk-evaluation

- Purpose to develop and describe approaches to identify a pool of potential candidates that will inform selection of low and high priority candidates for prioritization
- Two approaches
  - Near-term approach – Identify 20 high and 20 low priority candidates by March 2019
  - Long-term approach – Identify high and low priority candidates beyond 2019
- New approach methods are primarily integrated in long-term approach
- Prioritization is a formal 9 – 12 month process followed by risk evaluation for high priority substances
- High priority substances must have sufficient information for risk evaluation to be completed in 3 years

Characteristics of Proposed Long-Term Approach for Candidate Identification

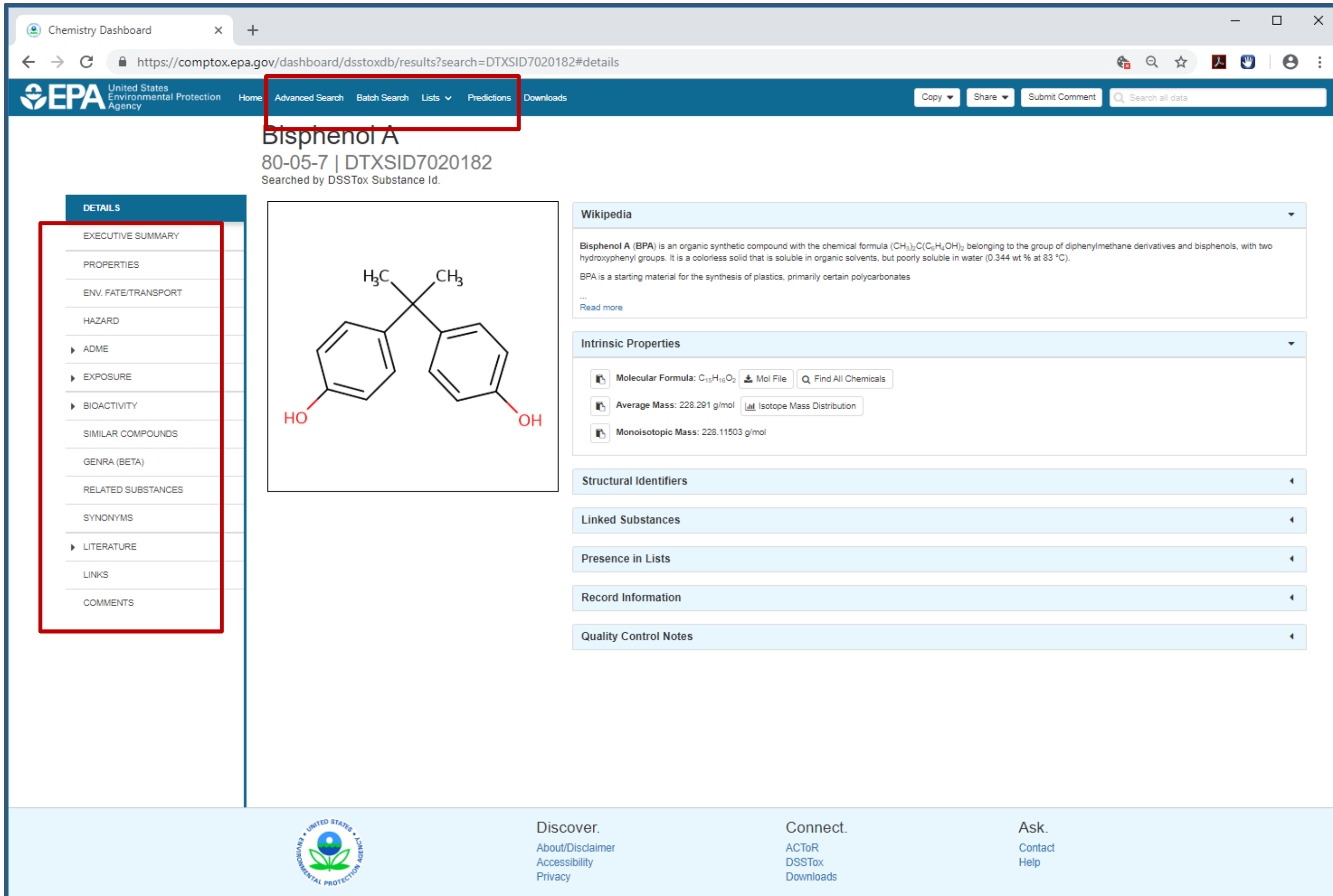




- Long-term approach proposes to bin chemicals based on a combination of risk-related scoring and information availability to inform priority candidate selection
- Risk-related scoring considers human hazard, exposure, genotoxicity/carcinogenicity, ecological hazard, susceptible populations, and persistence/bioaccumulation
- Information availability scoring considers portfolio of potentially relevant human health and ecological toxicity information for risk evaluation
- Relies on a large data management infrastructure and decision support tools that store and integrate information from new approach methods as well as traditional toxicology, exposure, and environmental fate-related studies

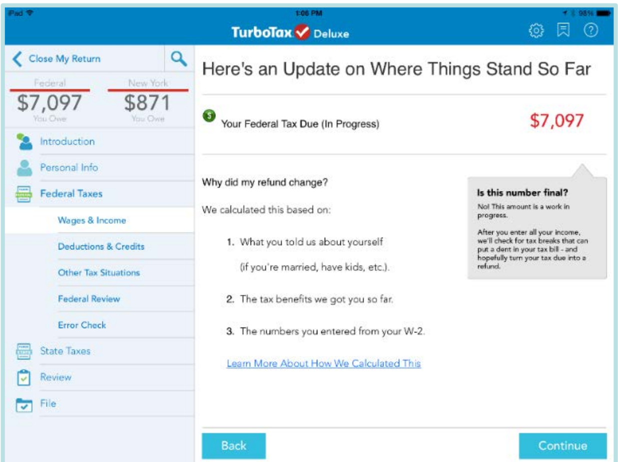
Enabling Translation Through Data Consolidation and Visualization

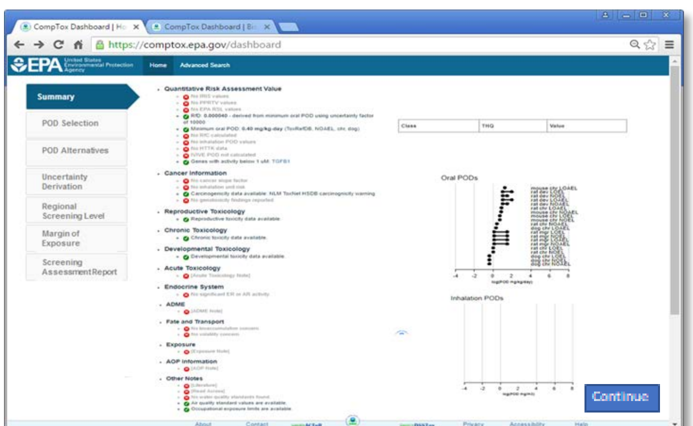
EPA Comptox Chemicals Dashboard



https://comptox.epa.gov/dashboard/

Integrating Data for Regulatory Application with Decision Support Tools





- RapidTox is a suite of workflows that facilitate the application of data surfaced in the CompTox dashboard in diverse assessment decision contexts
- Flexible integration of information related to chemical properties, fate and transport, hazard, exposure, and risk assessment
- Enable expert users to review the assumptions made, refine results, and record the decisions
- Presents data from new approach methods together with traditional toxicology data
- Three workflows currently under development
  - Chemical binning for TSCA (OCSPP)
  - Emergency response (OLEM)
  - Site-specific screening assessments (OLEM)

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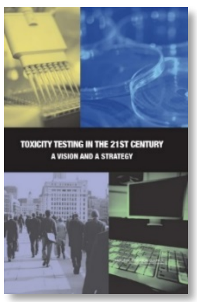
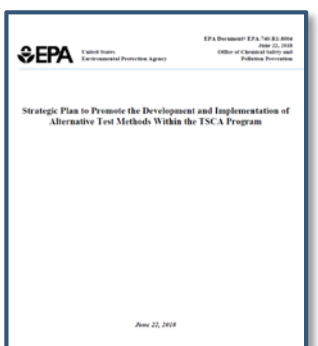
Take Home Messages…

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- Advancing toxicology to the new and improved version will require both scientific and policy advances
- New technologies exist for rapidly and comprehensively covering toxicological space at significantly less cost
- New strategies provide a blueprint for developing and integrating new approach methods for regulatory decisions related to statutes like TSCA
- New approach methods are a key component of the long-term strategy for informing priority candidate selection in TSCA
- Data management systems and decision support tools will be increasingly important for interpreting and integrating the expanding and diverse landscape of chemical safety information

Acknowledgements and Questions

EPA Colleagues:

- NCCT
- NERL
- NHEERL
- NRMRL
- NCEA
- OCSPP
- OLEM
- Regions

Collaborative Partners:

- NTP
- FDA
- NCATS
- Health Canada
- ECHA
- JRC
- EFSA
- A*STAR