New Approach Methodologies (NAMs) and Chemical Risk Assessment

April 24, 2020

EMAP 514 : Introduction to Environmental Health Risk Assessment and Management

Environmental Metrology and Policy Program

Department of Chemistry

Georgetown University

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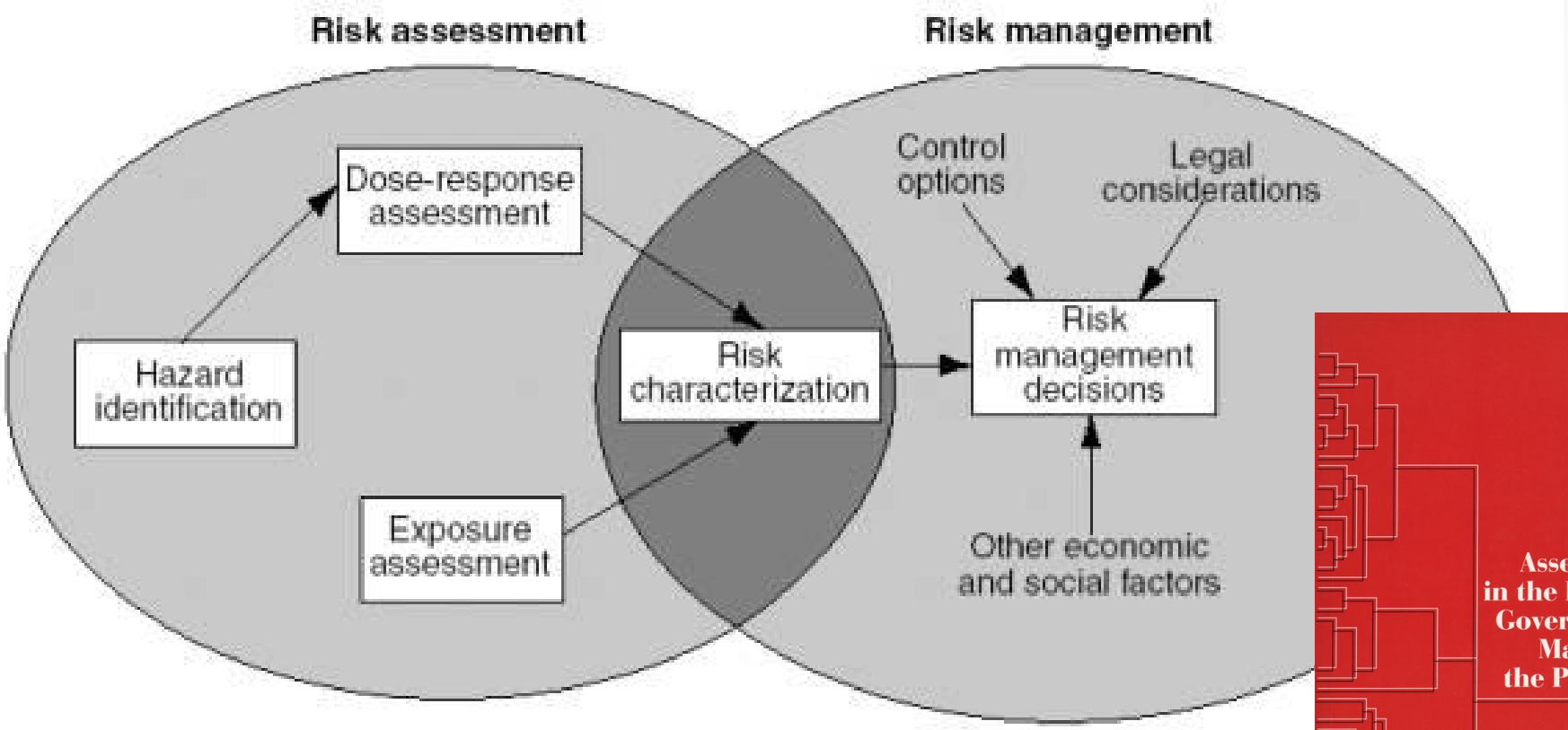
The views presented are those of the author and do not necessarily reflect the views of the US EPA.

Outline

- Environmental Health and Chemical Risk Assessment
- Advancing Risk Assessment
- New Approach Methodologies (NAMs)
- EPA Specific Drivers
- Closing

Environmental Health and Chemical Risk Assessment – A long history



Source: EPA Office of Research and Development.

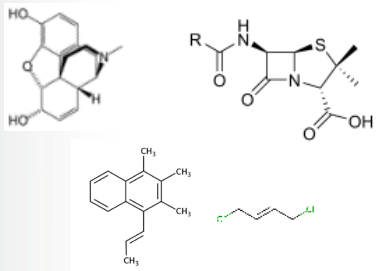
https://www.nap.edu/catalog/366/risk-assessment-in-the-federal-government-managing-the-process

Chemical Risk Assessment

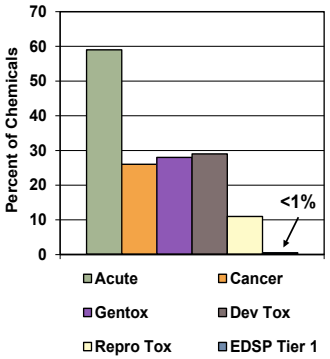
What are we really trying to do?

Regulatory Agencies Make a Broad Range of Decisions on Chemicals…

Number of Chemicals /Combinations



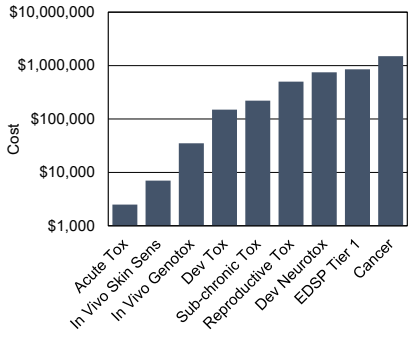
Lack of Data



Modified from Judson *et al.*, EHP 2010

Ethics/Relevance Concerns

Economics



- Number of chemicals and combinations of chemicals is extremely large (>40,000 substances on active TSCA inventory)
- Traditional toxicity testing is expensive and time consuming
- Traditional animal-based testing has issues related to ethics and relevance
- Looking into new ways to address these problems.

EPA-Specific Drivers


UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

September 10, 2019

THE ADMINISTRATOR

MEMORANDUM

SUBJECT: Directive to Prioritize Efforts to Reduce Animal Testing

FROM: Andrew R. Wheeler
Administrator

TO: Associate Deputy Administrator
General Counsel
Assistant Administrators
Inspector General
Chief Financial Officer
Chief of Staff
Associate Administrators
Regional Administrators

Environmental Protection
already making significant
under both statutory and
mended June 22, 2016, by
equires the EPA to reduce
U.S. EPA Strategic Plan
within five years. More
a result of these collective

ct potential hazards for risk
animal testing. These new
pproaches or combinations
potential human exposure

Amy Clippinger

Recycled/R

USEPA Administrator Memo Prioritizing Efforts to Reduce Animal Testing, September 10, 2019

- EPA will reduce its requests for, and our funding of, mammal studies by 30 percent by 2025
- EPA will eliminate all mammal study requests and funding by 2035. Any mammal studies requested or funded by the EPA after 2035 will require Administrator approval on a case-by-case basis.
- Form a working group of agency experts in this field who will provide a work plan within six months.
- https://www.epa.gov/environmental-topics/administrator-memo-prioritizing-efforts-reduce-animal-testing-september-10-2019

EPA-Specific Drivers: OPP

Letter to Stakeholders on OPP's Goal to Reduce Animal Testing from Jack E. Housenger, Director

- https://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2016-0093-0003
- Working in partnership with other governmental entities, industry and non-governmental organizations (NGOs) and need continued robust participation and support to achieve our mutual goal.
- Activities fall under three main objectives
  - Critically evaluating which studies form the basis of OPP decisions;
  - Expanding acceptance of alternative methods and;
  - Reducing barriers such as challenges of data sharing among companies and international harmonization to adopting alternative methods in the U.S. and internationally.

EPA-Specific Drivers: EDSP

- **The US Environmental Protection Agency's (EPA) Endocrine Disrupting Screening Program (EDSP)**
  - established in response to Congressional mandates in the Federal Food Quality Protection and Safe Water Drinking Acts
  - evaluating potential risk of endocrine disruption in humans and wildlife from exposure to pesticide chemicals and drinking water contaminants
  - recommendations from an expert advisory committee established a two tiered system
    - Tier 1 screening for *potential* to interact with the estrogen, androgen or thyroid hormone systems
    - Tier 2 testing to verify interaction and quantify dose-response relationship
  - In 2011, EPA began a multiyear transition to prioritize and screen thousands of EDSP chemicals using high-throughput *in vitro* assays and computational modeling approaches

https://www.epa.gov/endocrine-disruption

EDSP "Pivot" Announcement

FEDERAL REGISTER
The Daily Journal of the United States Government

June 19, 2015
FRL-9928-69

"Use of High Throughput Assays and Computational Tools; Endocrine Disruptor Screening Program; Notice of Availability and Opportunity for Comment"

https://www.federalregister.gov/articles/2015/06/19/2015-15182/use-of-high-throughput-assays-and-computational-tools-endocrine-disruptor-screening-program-notice

35350 Federal Register / Vol. 80, No. 118 / Friday, June 19, 2015 / Notices

may claim all or part of a response confidential. EPA will disclose information that is covered by a claim of confidentiality only to the extent permitted by, and in accordance with, the procedures in TSCA section 14 and 40 CFR part 2.

Burden statement: The annual public reporting and recordkeeping burden for this collection of information is estimated to average 31.5 hours per response. Burden is defined in 5 CFR 1320.3(b).

The ICR, which is available in the docket along with other related materials, provides a detailed explanation of the collection activities and the burden estimate that is only briefly summarized here:

Respondents/Affected Entities: Entities potentially affected by this ICR are companies that manufacture, process or import chemical substances, mixtures or categories.

Estimated total number of potential respondents: 1.

Frequency of response: On occasion.

Estimated total average number of responses for each respondent: 1.

Estimated total annual burden hours: 31.5 hours.

Estimated total annual costs: $2,388. This includes an estimated burden cost of $2,388 and an estimated cost of $0 for capital investment or maintenance and operational costs.

III. Are There Changes in the Estimates from the Last Approval?

There is a decrease of 916 hours in the total estimated respondent burden compared with that identified in the ICR currently approved by OMB. This decrease reflects additional both adjustment changes from a reduction in the assumed number of PAIR reports filed annually, and program changes resulting from mandatory electronic submissions of PAIR reports. In recent years (FY 2011–FY 2014), EPA has received no PAIR submissions and, for the purposes of this analysis, EPA assumes an annual rate of one submission per year. At the time OMB last renewed this ICR, EPA estimated an average of 33 reports from 14.8 submitters based on fiscal year 2006–2010 data. The ICR supporting statement provides a detailed analysis of the change in burden estimate. This change is both an adjustment and a program change.

IV. What is the Next Step in the Process for this ICR?

EPA will consider the comments received and amend the ICR as appropriate. The final ICR package will then be submitted to OMB for review and approval pursuant to 5 CFR 1320.12. EPA will issue another **Federal Register** document pursuant to 5 CFR 1320.5(a)(1)(iv) to announce the submission of the ICR to OMB and the opportunity to submit additional comments to OMB. If you have any questions about this ICR or the approval process, please contact the technical person listed under **FOR FURTHER INFORMATION CONTACT.**

Authority: 44 U.S.C. 3501 *et seq.*

Dated: June 10, 2015.

James Jones,

Assistant Administrator, Office of Chemical Safety and Pollution Prevention.

[FR Doc. 2015–14946 Filed 6–18–15; 8:45 am]

BILLING CODE 6560–50–P

ENVIRONMENTAL PROTECTION AGENCY

[EPA–HQ–OPPT–2015–0305; FRL–9928–69]

Use of High Throughput Assays and Computational Tools; Endocrine Disruptor Screening Program; Notice of Availability and Opportunity for Comment

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: This document describes how EPA is planning to incorporate an alternative scientific approach to screen chemicals for their ability to interact with the endocrine system. This will improve the Agency's ability to fulfill its statutory mandate to screen pesticide chemicals and other substances for their ability to cause adverse effects by their interaction with the endocrine system. The approach incorporates validated high throughput assays and a computational model and, based on current research, can serve as an alternative for some of the current assays in the Endocrine Disruptor Screening Program (EDSP) Tier 1 battery. EPA has partial screening results for over 1800 chemicals that have been evaluated using high throughput assays and a computational model for the estrogen receptor pathway. In the future, EPA anticipates that additional alternative methods will be available for EDSP chemical screening based on further advancements of high throughput assays and computational models for other endocrine pathways. Use of these alternative methods will accelerate the pace of screening, decrease costs, and reduce animal testing. In addition, this approach advances the goal of providing sensitive, specific, quantitative, and efficient screening using alternative test methods to some assays in the Tier 1 battery to protect human health and the environment.

DATES: Comments must be received on or before August 18, 2015.

ADDRESSES: Submit your comments, identified by docket identification (ID) number EPA–HQ–OPPT–2015–0305, by one of the following methods:

- *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the online instructions for submitting comments. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute.
- *Mail:* Document Control Office (7407M), Office of Pollution Prevention and Toxics (OPPT), Environmental Protection Agency, 1200 Pennsylvania Ave. NW., Washington, DC 20460–0001.
- *Hand Delivery:* To make special arrangements for hand delivery or delivery of boxed information, please follow the instructions at *http://www.epa.gov/dockets/contacts.html.*

Additional instructions on commenting or visiting the docket, along with more information about dockets generally, is available at *http://www.epa.gov/dockets.*

FOR FURTHER INFORMATION CONTACT: *For technical information contact:* Jane Robbins, Office of Science Coordination and Policy (OSCP), Office of Chemical Safety and Pollution Prevention, Environmental Protection Agency, 1200 Pennsylvania Ave. NW., Washington, DC 20460–0001; telephone number: (202) 564–6625; email address: robbins.jane@epa.gov.

For general information contact: The TSCA-Hotline, ABVI-Goodwill, 422 South Clinton Ave., Rochester, NY 14620; telephone number: (202) 554–1404; email address: *TSCA-Hotline@epa.gov.*

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this action apply to me?

This action is directed to the public in general, and may be of interest to a wide range of stakeholders including those interested in endocrine testing of chemicals (including pesticides), and the EDSP in general. Since others also may be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action.

B. What is the agency authority for taking this action?

The EDSP is established under section 408(p) of the Federal Food, Drug and

EDSP "Pivot" Goals for Using Computational Toxicology Data

- Use computational tools and models in the EDSP framework to:
  - Rapidly screen chemicals for endocrine bioactivity
  - Contribute to the weight of evidence screening level determination of a chemical's potential bioactivity
  - Provide alternative data for specific endpoints in the EDSP Tier 1 battery

– Similar approaches are common to estrogen, androgen and thyroid pathways; however, estrogen agonist bioactivity is the most mature model and is used to demonstrate the proposed approach.

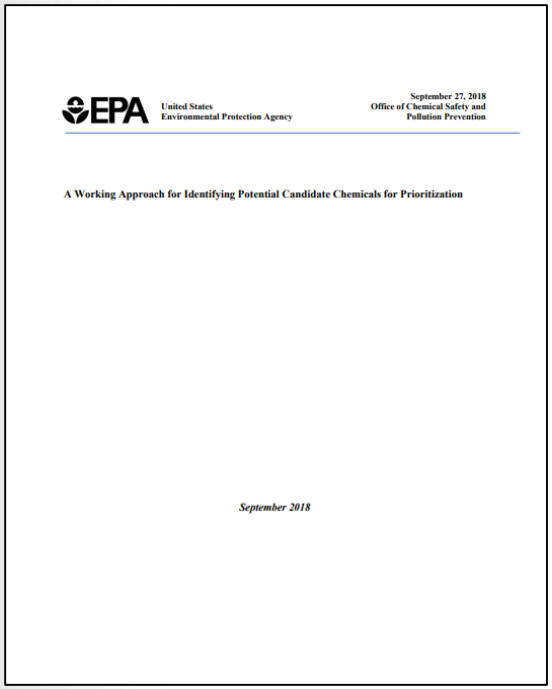
EPA-Specific Drivers: TSCA

Toxic Substances Control Act (TSCA)

- The Toxic Substances Control Act (TSCA) regulates the introduction of new and existing chemicals.
- TSCA was amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act (June 22, 2016):
    - Large bipartisan support in both House and Senate;
    - Broad stakeholder support;
    - First major update to an environmental statute in about 20 years.
- Implementation of TSCA is the responsibility of the Office of Chemical Safety and Pollution Prevention (OCSPP), specifically, the Office of Pollution Prevention and Toxics (OPPT).
- EPA required to make determination if chemical substance presents an unreasonable risk of injury to human health or the environment. Determinations are risk-based.

https://www.epa.gov/chemicals-under-tsca

TSCA Section 6 (Existing Chemicals)



EPA United States Environmental Protection Agency

September 27, 2018
Office of Chemical Safety and Pollution Prevention

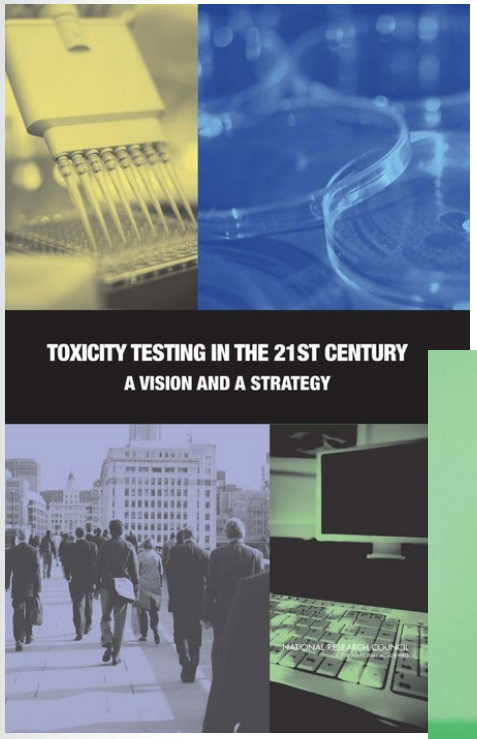
A Working Approach for Identifying Potential Candidate Chemicals for Prioritization

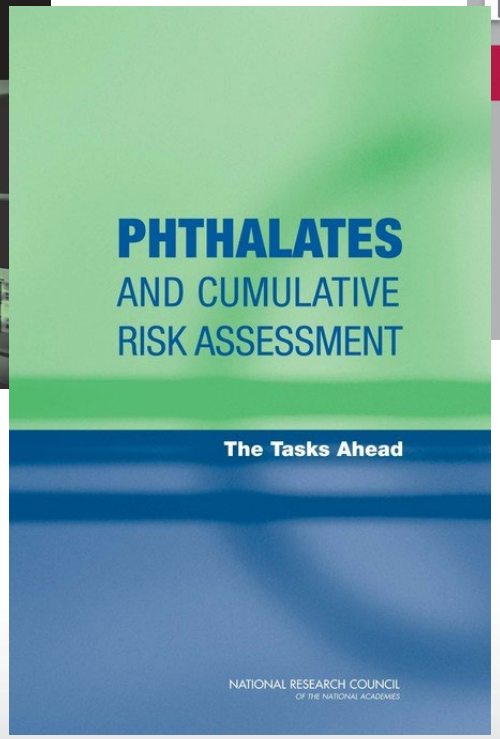
September 2018

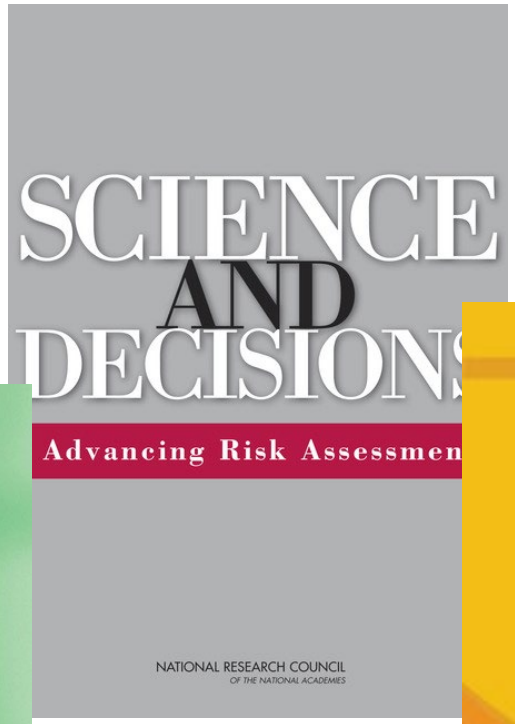
https://www.epa.gov/sites/production/files/2018-09/documents/preprioritization_white_paper_9272018.pdf

- Under Lautenberg, EPA must identify 20 high- and 20 low-priority chemicals (TSCA Section 6).
- EPA developed a document describing two approaches on how EPA may identify candidate chemicals to enter the prioritization process:
  - Short-term approach may be used to identify high-priority chemicals (likely) from the TSCA 2014 Workplan and low-priority chemicals from the Safer Chemicals Ingredients List;
  - Long-term approach proposed an approach to review chemicals in the TSCA active list (about 40K chemicals) based upon risk-related scoring and information availability
- On March 20, 2019, EPA initiated the prioritization process by issues a list of 40 chemical substances and began effort to designate 20 as high-priority and 20 low-priority substances.

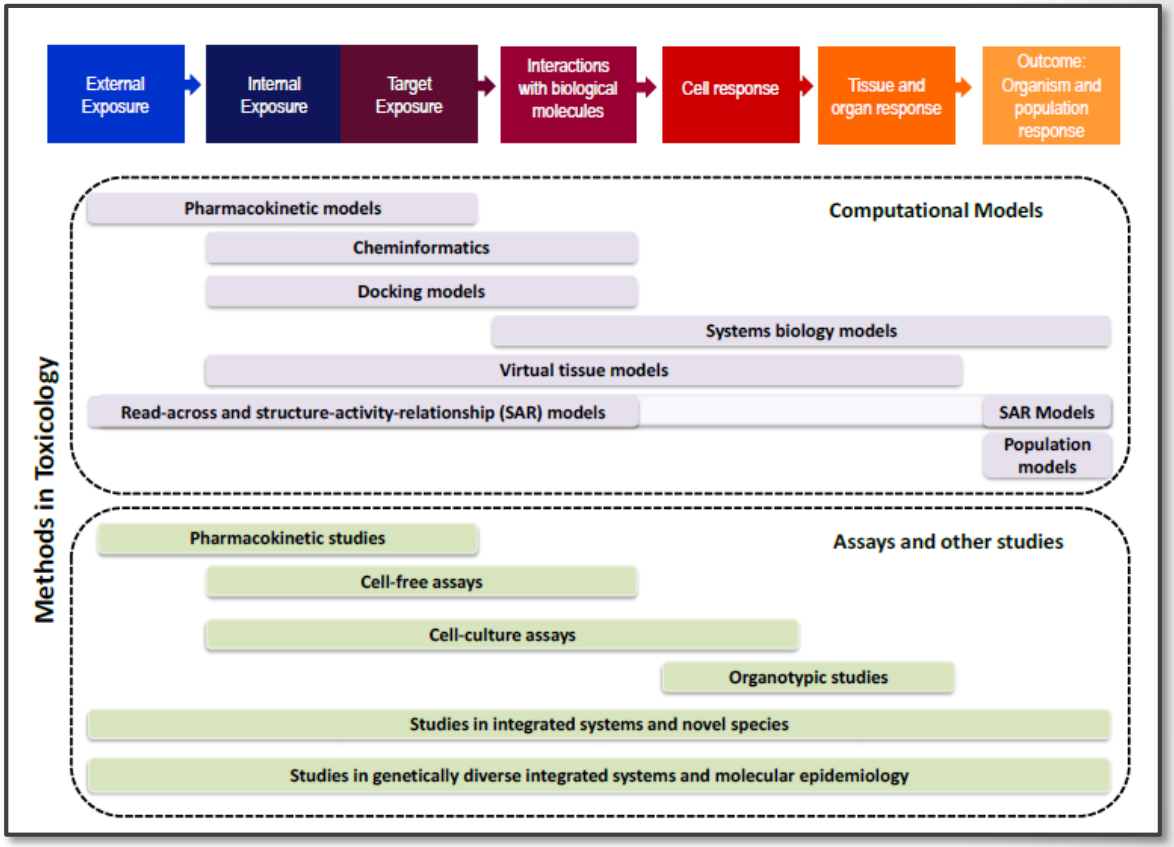
Advancing Risk Assessment





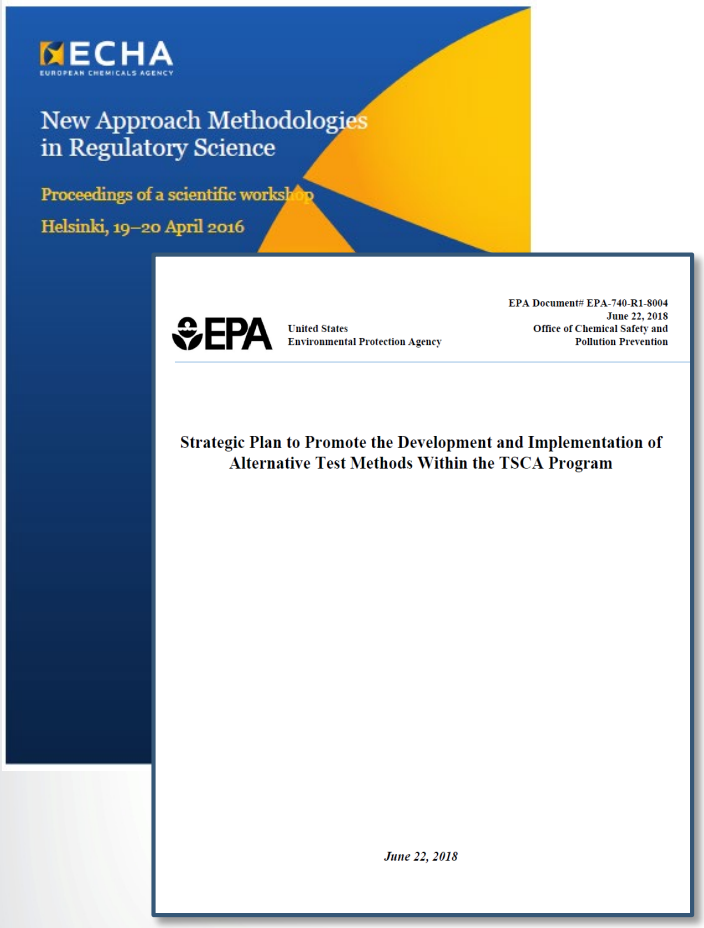


Toxicology Moving to Embrace 21st Century Methods



https://www.nap.edu/catalog/24635/using-21st-century-science-to-improve-risk-related-evaluations

New Approach Methodologies (NAMs)



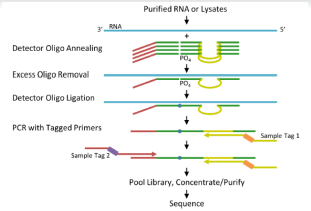
- Commonly defined to include *in silico* approaches, *in chemico* and *in vitro* assays, as well as the inclusion of information from the exposure of chemicals in the context of hazard assessment.

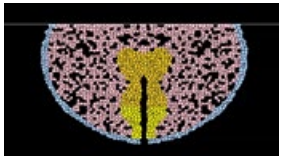
- Recently defined in the EPA's TSCA Alternative Toxicity Strategy as:
  - a broadly descriptive reference to any technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment that avoids the use of intact animals.

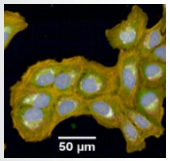
https://echa.europa.eu/documents/10162/22816069/scientific_ws_proceedings_en.pdf

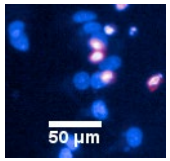
https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/alternative-test-methods-and-strategies-reduce

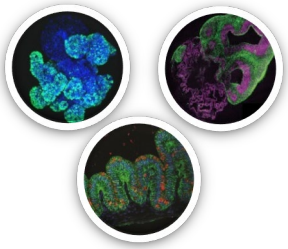
New Approach Methodologies (NAMs)

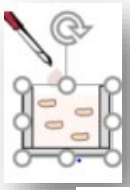


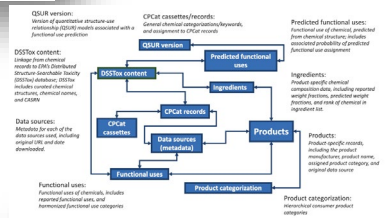


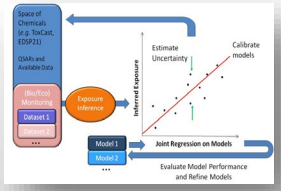






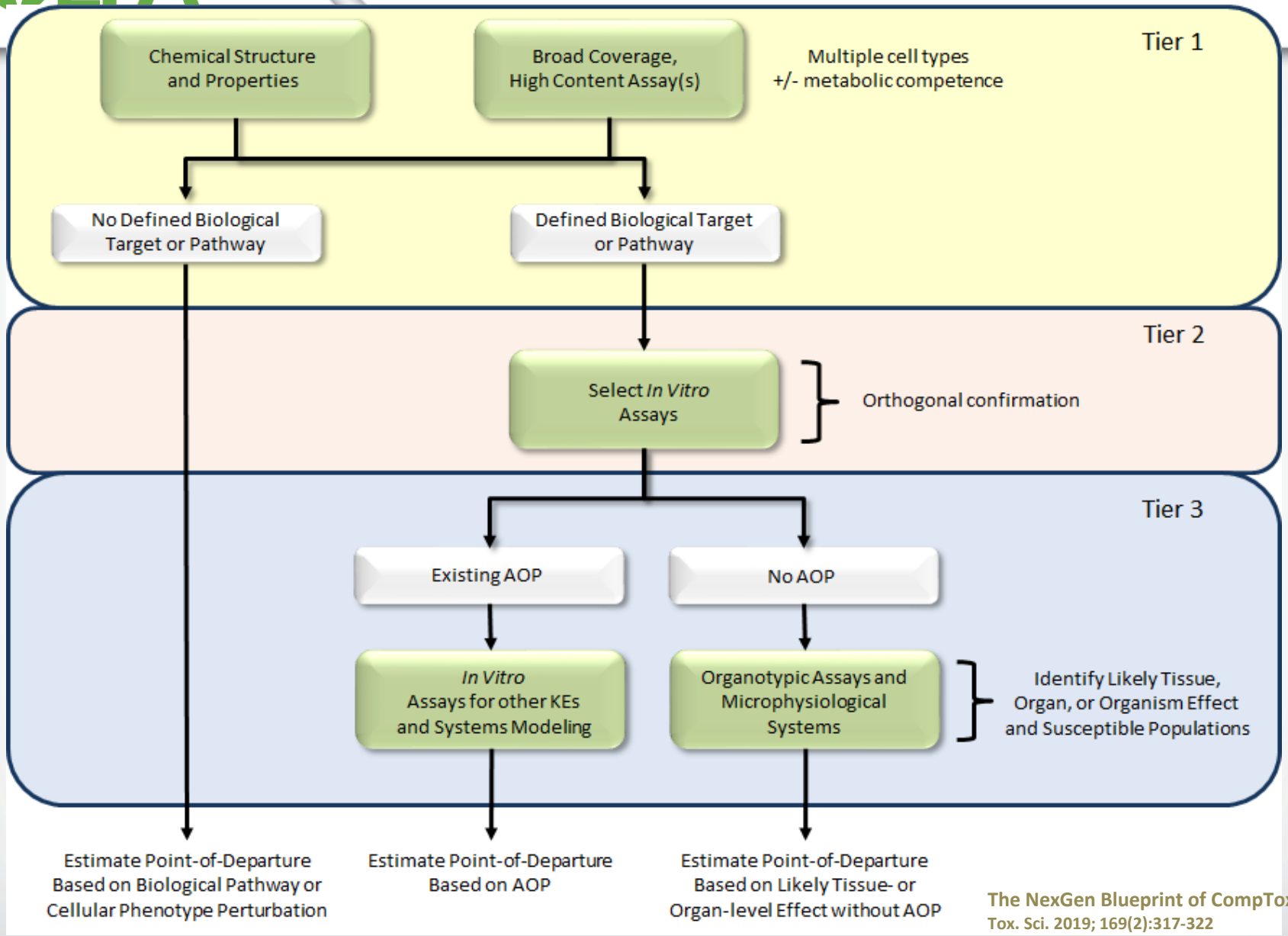






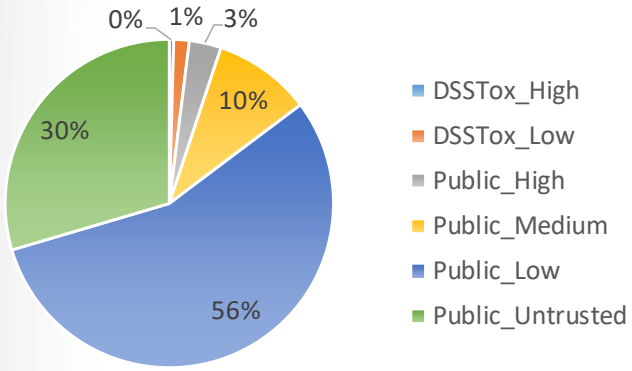
- In silico (e.g. QSAR and Read-across)
  - Estimate effects and doses
- In vitro assays
  - Broad / screening (transcriptomics, cell painting)
  - Targeted (receptors, enzymes)
  - In vitro PODs, modes / mechanisms of action
- In vitro Toxicokinetics
  - Allow conversion of an in vitro POD to in vivo (IVIVE)
- Computer models
  - Integrate multiple in silico and in vitro data streams
- Databases of existing traditional toxicology data
  - Enables training and validation of NMA models

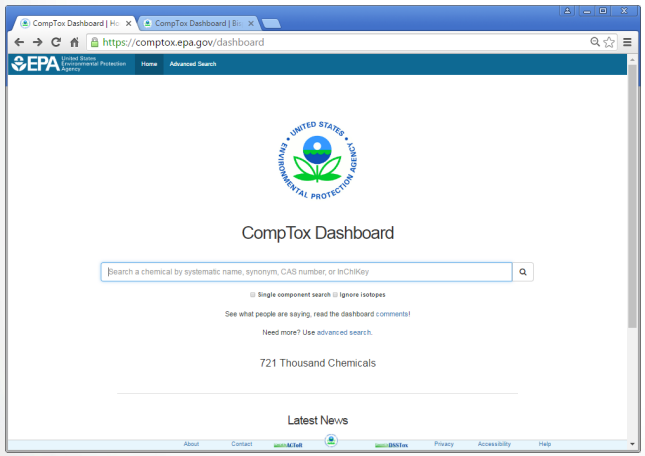
Tiered Hazard Evaluation Approach



The NexGen Blueprint of CompTox at USEPA
Tox. Sci. 2019; 169(2):317-322

Computational Chemistry

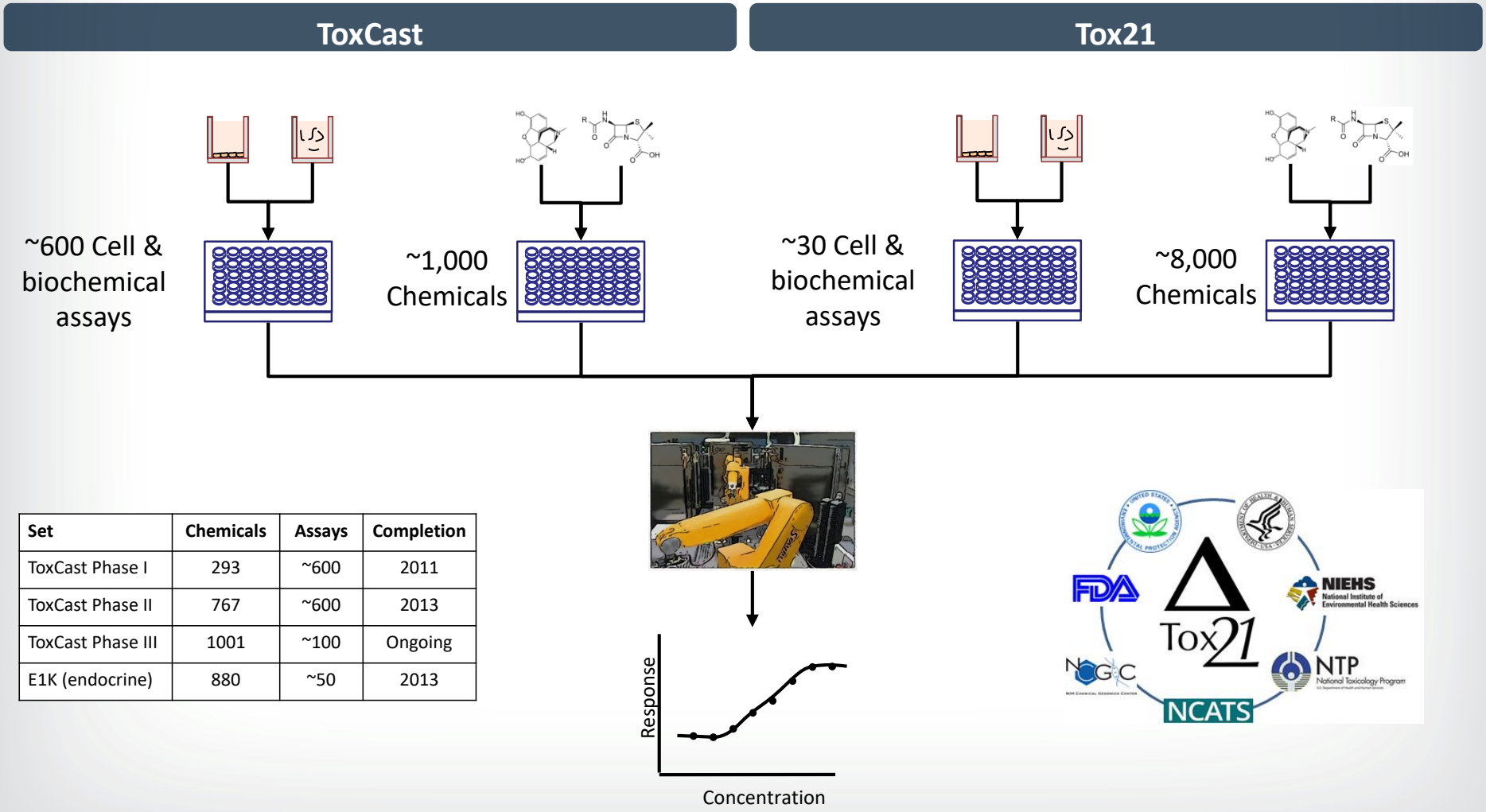




https://comptox.epa.gov/

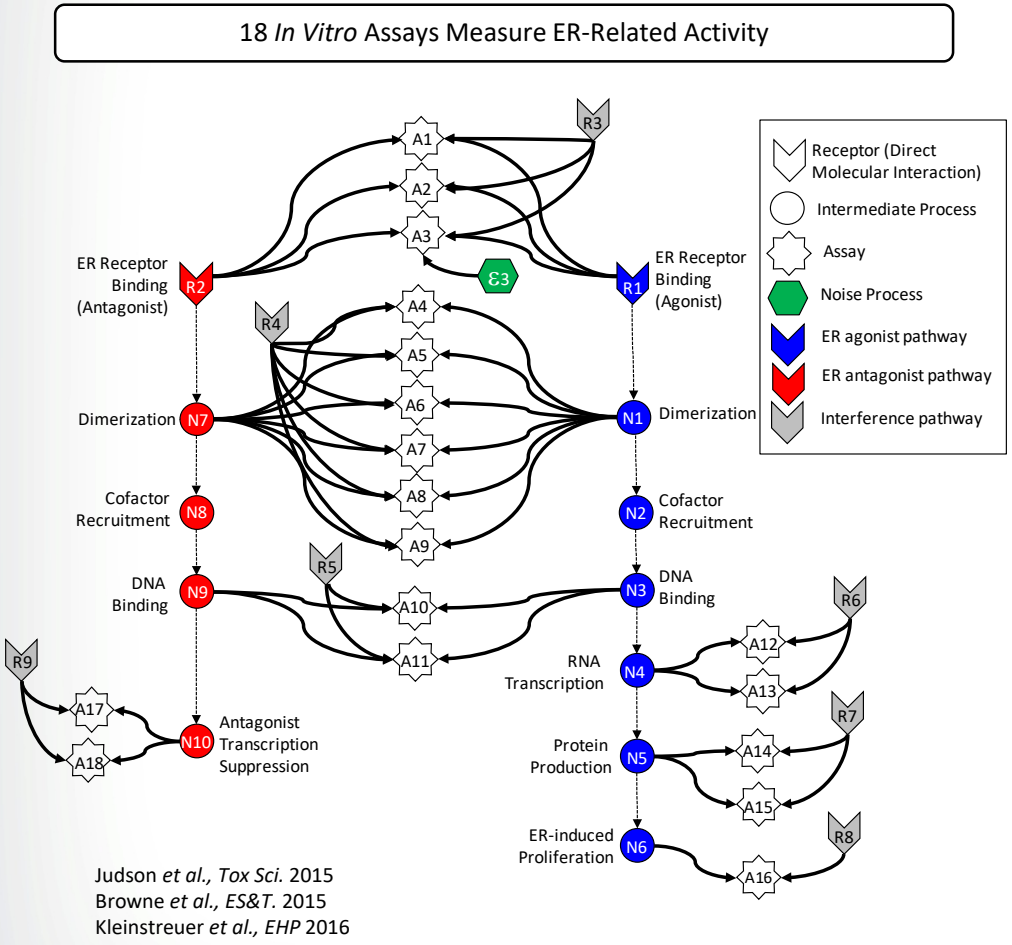
- Curated chemical structure database of >800,000 unique substances with QC flags to link chemical structure with names and identifiers
- Comprehensive physical-chemical property database (experimental and predicted) to harmonize properties across the Agency
- Consensus QSAR models for a range of physical chemical properties, environmental fate, and hazard characteristics
- Curation of reference chemical lists

ToxCast and Tox21: Adding the High-Throughput Hazard Screening Component



Set	Chemicals	Assays	Completion
ToxCast Phase I	293	~600	2011
ToxCast Phase II	767	~600	2013
ToxCast Phase III	1001	~100	Ongoing
E1K (endocrine)	880	~50	2013

Application of High-Throughput Assays to Identify Potential Endocrine Disrupting Chemicals

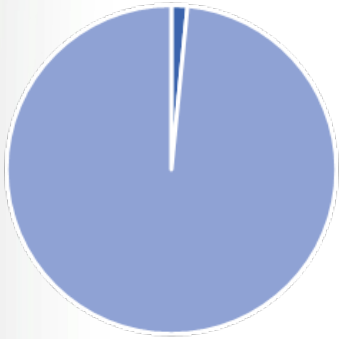


Judson *et al., Tox Sci.* 2015
Browne *et al., ES&T.* 2015
Kleinstreuer *et al., EHP* 2016

- Use multiple assays per pathway
  - Different technologies
  - Different points in pathway
- No assay is perfect
  - Assay Interference
  - Noise
- Use model to integrate assays
- Model creates a composite dose-response curve for each chemical to summarize results from all assays

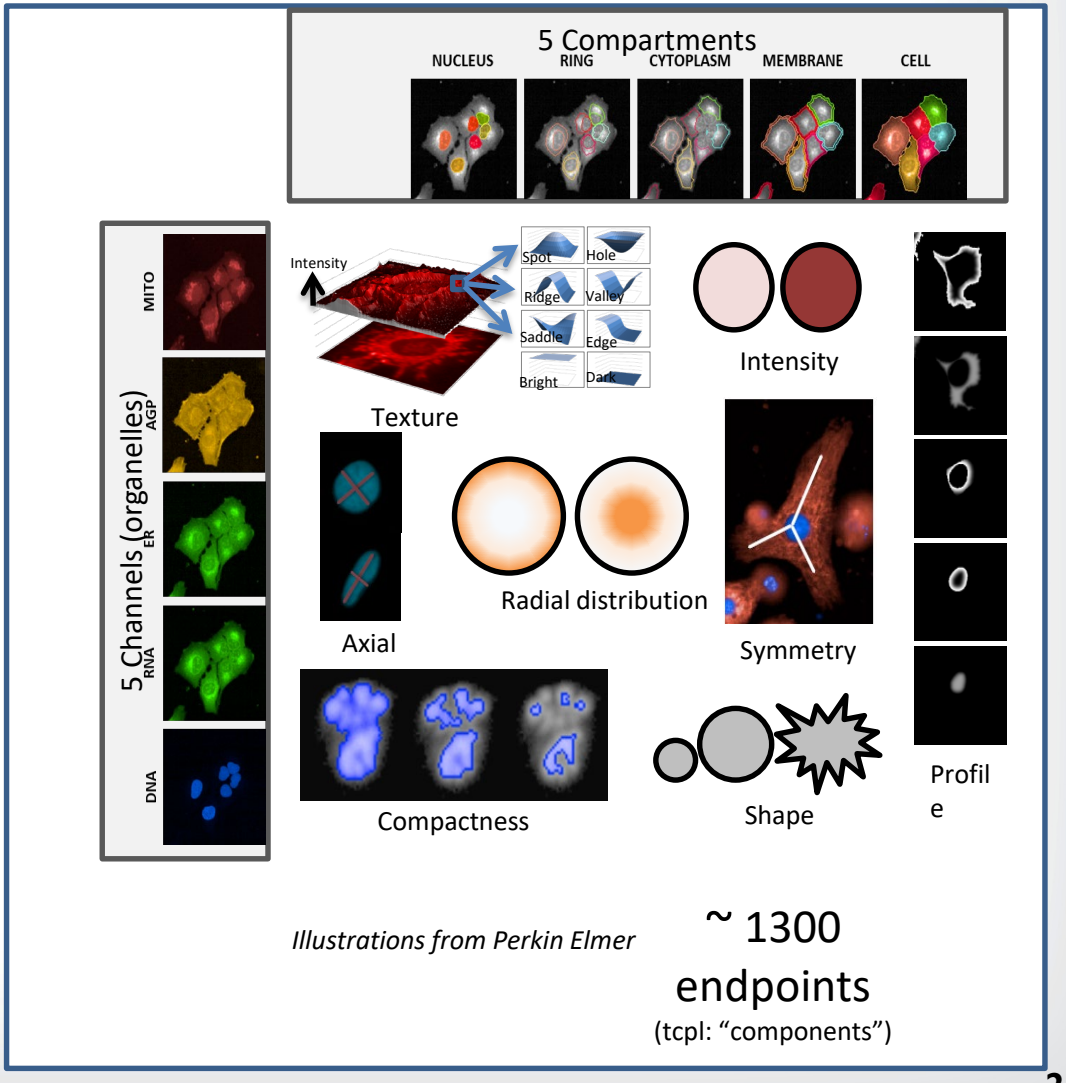
Beginning to Address Concerns for Increased Biological Coverage

Gene Coverage



Pathway Coverage*

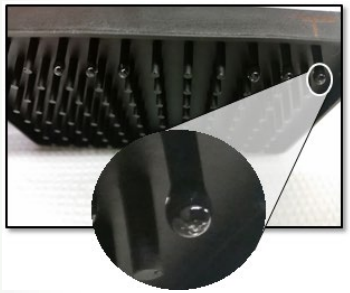
*At least one gene from pathway represented

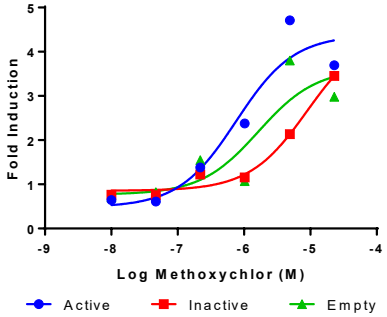


Beginning to Address Metabolic Competence

"Extracellular" Approach

Chemicals metabolism in the media or buffer of cell-based and cell-free assays

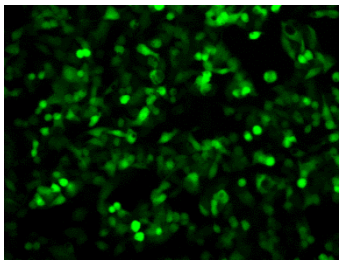


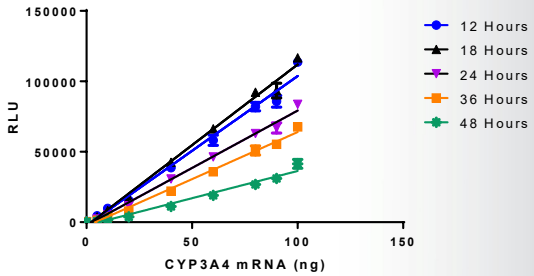


More closely models effects of hepatic metabolism and generation of circulating metabolites

"Intracellular" Approach

Capable of metabolizing chemicals inside the cell in cell-based assays





More closely models effects of target tissue metabolism

Integrated approach to model *in vivo* metabolic bioactivation and detoxification

Collaboration with Unilever

Adding the High-Throughput Toxicokinetic Component

EPA ToxCast Phase I and II Chemicals

Human Liver Metabolism

Human Plasma Protein Binding

Population-Based IVIVE Model

Upper 95th Percentile Css Among 100 Healthy Individuals of Both Sexes from 20 to 50 Yrs Old

- Currently evaluated ~700 ToxCast Phase I and II chemicals
- Models available through ‘“httk” R package (https://cran.r-project.org/web/packages/httk/)

In Vitro Potency Value

Plasma Concentration

Exposure Route

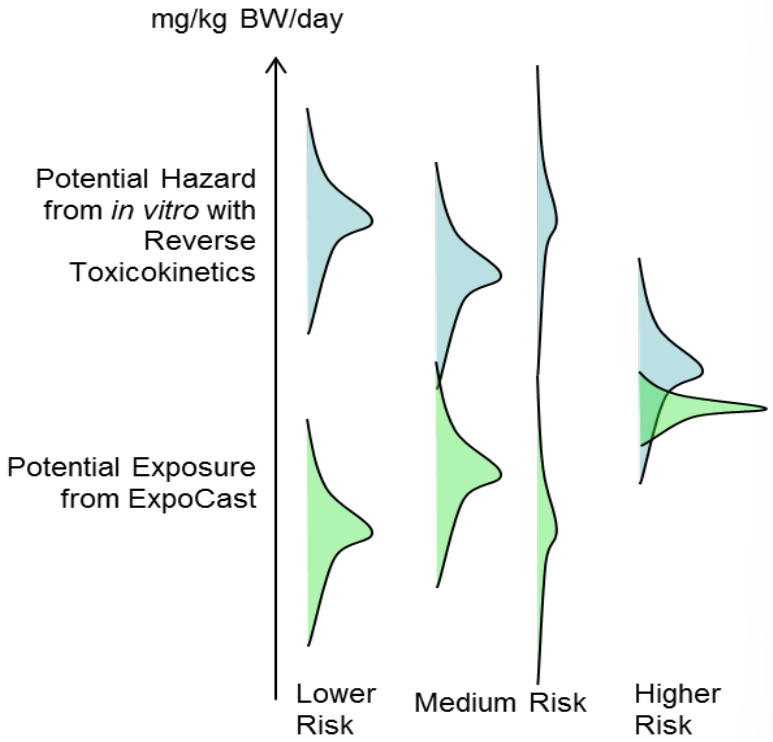
Reverse Dosimetry

Administered Dose Required to Achieve Steady State Plasma Concentrations Equivalent to *In Vitro* Bioactivity

Rotroff *et al., Tox Sci.*, 2010
Wetmore *et al., Tox Sci.*, 2012
Wetmore *et al., Tox Sci.*, 2015

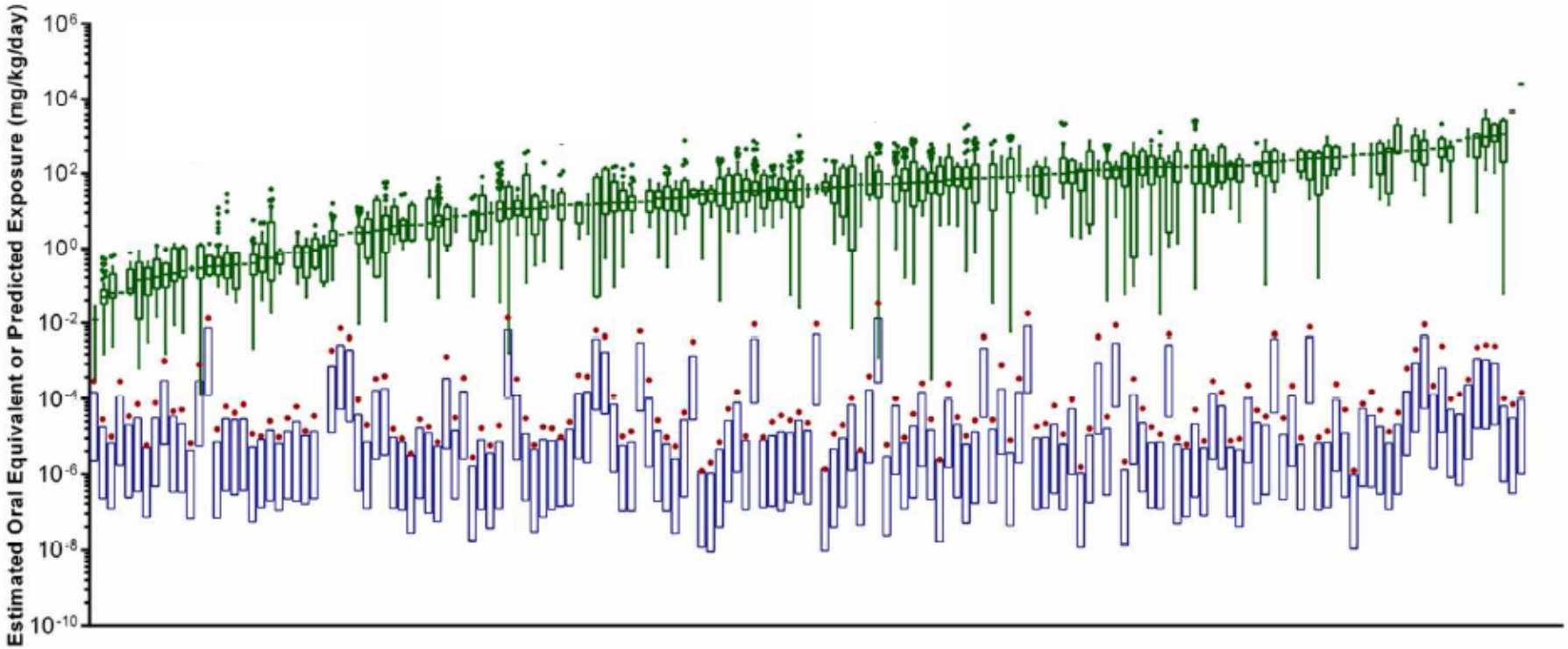
Linking Bioactivity and Exposure (*i.e.* Risk)

- **High throughput risk characterization** relies on three components:
  1. High throughput **hazard** (*i.e.* bioactivity) characterization
  2. High throughput **exposure** forecasts
  3. High throughput **toxicocokinetics** (*i.e.* dosimetry)



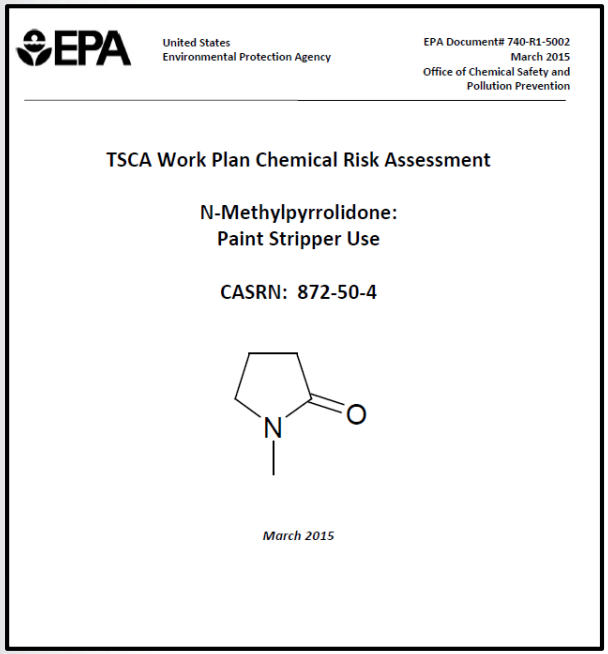
SAP Dec 2014: http://www2.epa.gov/sap/meeting-materials-december-2-4-2014-scientific-advisory-panel
ExpoCast: http://www2.epa.gov/chemical-research/rapid-chemical-exposure-and-dose-research
Wambaugh 2015. "A Systems Approach to Exposure Modeling (ExpoCast)"

Enabling Risk-Based Prioritization



Wetmore *et al., Tox Sci.,* 2015

Covering All the Components of a 21st Century Risk Assessment



United States Environmental Protection Agency

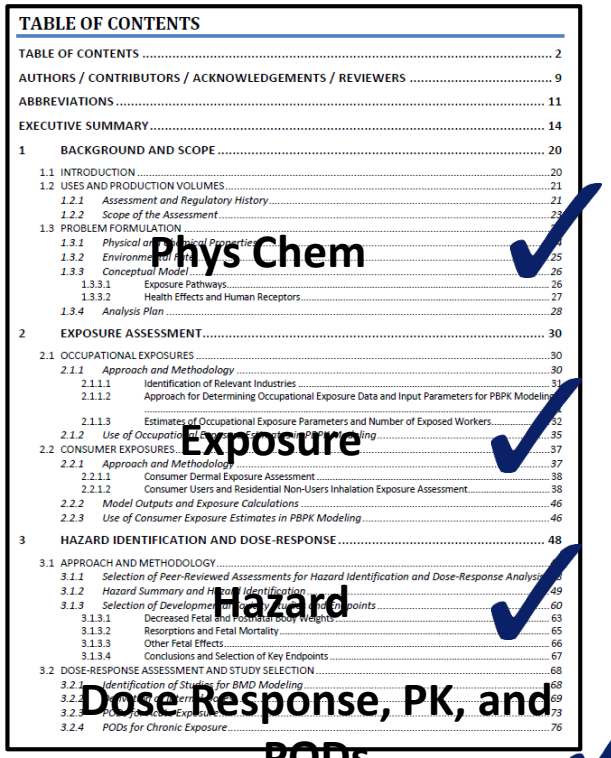
EPA Document# 740-R1-5002
March 2015
Office of Chemical Safety and Pollution Prevention

TSCA Work Plan Chemical Risk Assessment

N-Methylpyrrolidone: Paint Stripper Use

CASRN: 872-50-4

March 2015



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What is needed to expand translation and implementation of NAMs?

- Integration of NAM data with traditional data
- Fit-for-purpose applications
- Build confidence and understanding
- Engage stakeholders

Closing

- Incorporating new technologies and innovations in toxicology can more rapidly and inexpensively screen chemicals for potential adverse biological effects.
- EPA has made great advances in the development of NAMs for filling information gaps for decision-making and integrating those tools and data streams into chemical risk assessment.
- EPA has worked with other stakeholders to leverage resources and develop NAMs that can support different regulatory contexts.
- Building confidence in the use of NAMs for regulatory decision-making is key to the increased implementation of these methods.

Questions?