SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

Toxicogenomics and Its Relevance to Support Hazard Assessment

May 4, 2022

Toxicogenomics to Support Hazard Assessment

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Conflict of Interest Statement

- No conflicts of interest to declare.
- The views expressed in this presentation are those of the presenter and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency, nor does mention of trade names or products represent endorsement for use.

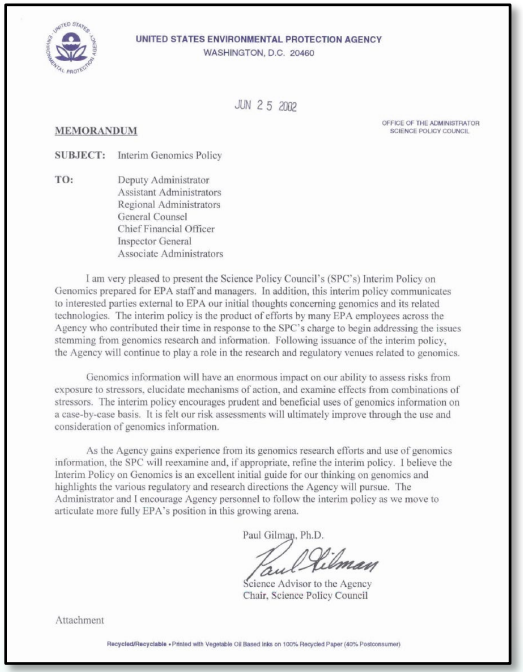
Objective and Outline

Objective: Provide a high-level overview of the application of toxicogenomics at EPA

- Evolution in the application of toxicogenomics at EPA
- More recent frameworks for applying toxicogenomics
- Examples of ongoing EPA research for toxicogenomics application
- Building confidence in toxicogenomic methods and approaches

Evolution in Application of Toxicogenomics at EPA

- EPA released interim policy on genomics in 2002
- Expressed interest in using toxicogenomics data to enhance assessments and priority setting
- Consider toxicogenomics data on case-by-case basis in a weight of evidence approach
- Conveyed that toxicogenomics data alone not sufficient as basis for decisions



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

JUN 25 2002

OFFICE OF THE ADMINISTRATOR
SCIENCE POLICY COUNCIL

MEMORANDUM

SUBJECT: Interim Genomics Policy

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

I am very pleased to present the Science Policy Council's (SPC's) Interim Policy on Genomics prepared for EPA staff and managers. In addition, this interim policy communicates to interested parties external to EPA our initial thoughts concerning genomics and its related technologies. The interim policy is the product of efforts by many EPA employees across the Agency who contributed their time in response to the SPC's charge to begin addressing the issues stemming from genomics research and information. Following issuance of the interim policy, the Agency will continue to play a role in the research and regulatory venues related to genomics.

Genomics information will have an enormous impact on our ability to assess risks from exposure to stressors, elucidate mechanisms of action, and examine effects from combinations of stressors. The interim policy encourages prudent and beneficial uses of genomics information on a case-by-case basis. It is felt our risk assessments will ultimately improve through the use and consideration of genomics information.

As the Agency gains experience from its genomics research efforts and use of genomics information, the SPC will reexamine and, if appropriate, refine the interim policy. I believe the Interim Policy on Genomics is an excellent initial guide for our thinking on genomics and highlights the various regulatory and research directions the Agency will pursue. The Administrator and I encourage Agency personnel to follow the interim policy as we move to articulate more fully EPA's position in this growing arena.

Paul Gilman, Ph.D.
Science Advisor to the Agency
Chair, Science Policy Council

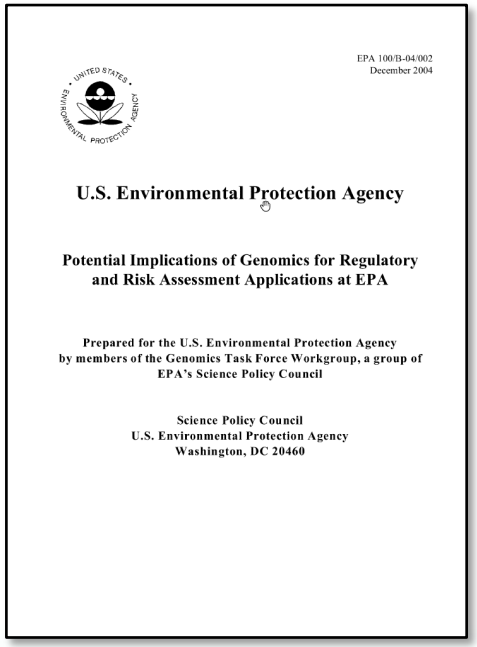
Attachment

Recycled/Recyclable • Printed with Vegetable Oil Based Inks on 100% Recycled Paper (40% Postconsumer)

U.S. EPA, Science Policy Council, 2002.

Evolution in Application of Toxicogenomics at EPA

- EPA published first report on potential applications of genomics in chemical risk assessment in 2004
- Emphasized potential applications in prioritization, monitoring, reporting provisions, mode of action, identifying sensitive populations, and addressing mixtures
- Noted challenges in linking genomics information to adverse outcomes, interpreting information for risk assessment, development of a framework for regulatory acceptance, and training of risk assessors/managers



EPA 100/B-04/002
December 2004

U.S. Environmental Protection Agency

Potential Implications of Genomics for Regulatory and Risk Assessment Applications at EPA

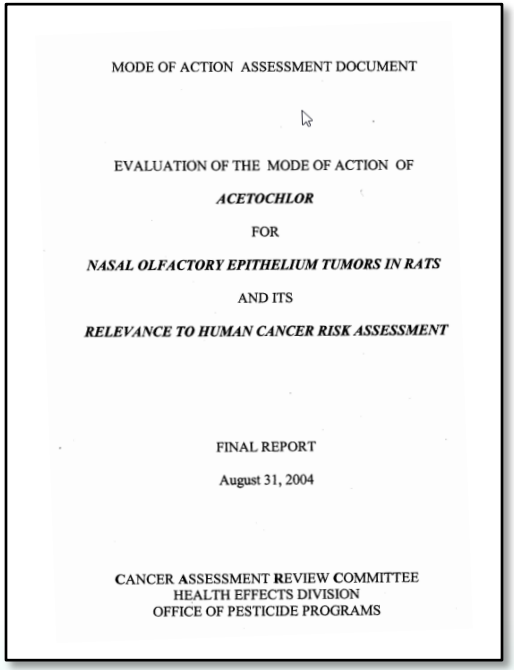
Prepared for the U.S. Environmental Protection Agency by members of the Genomics Task Force Workgroup, a group of EPA's Science Policy Council

Science Policy Council
U.S. Environmental Protection Agency
Washington, DC 20460

U.S. EPA, Science Policy Council, 2004.

Evolution in Application of Toxicogenomics at EPA

- EPA used toxicogenomics information in a mode-of-action weight of evidence cancer risk assessment in 2004
- Time course toxicogenomics data was derived from rat olfactory mucosa at a single dose
- Early gene expression changes interpreted to be consistent with oxidative damage to DNA followed by cell proliferation
- Late gene expression changes interpreted to be consistent with tumorigenic progression



MODE OF ACTION ASSESSMENT DOCUMENT

EVALUATION OF THE MODE OF ACTION OF

ACETOCHLOR

FOR

NASAL OLFACTORY EPITHELIUM TUMORS IN RATS

AND ITS

RELEVANCE TO HUMAN CANCER RISK ASSESSMENT

FINAL REPORT

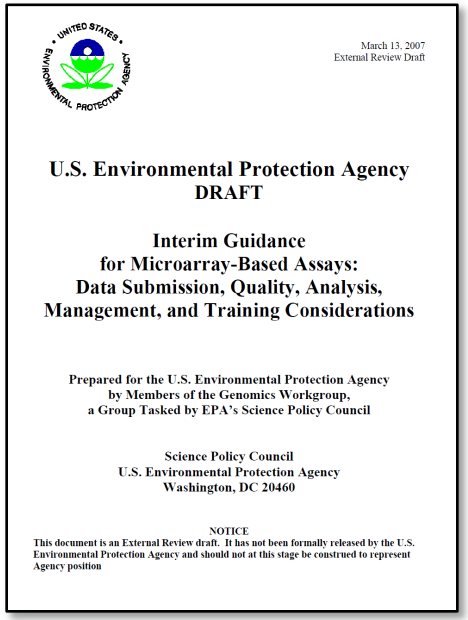
August 31, 2004

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

U.S. EPA, Office of Pesticides Programs, 2004.

Evolution in Application of Toxicogenomics at EPA

- EPA released interim guidance for microarray data submissions, quality, and analysis in 2007
- Draft guidance was never finalized
- Provided recommendations on performance approaches for quality assessment parameters, data analysis approaches, Agency data submissions, and data management practices
- Issued a draft Genomics Data Evaluation Record template
- Recommended development of training modules and materials for risk assessors, cross-Agency collaboration, and case study application



March 13, 2007
External Review Draft

U.S. Environmental Protection Agency
DRAFT

Interim Guidance
for Microarray-Based Assays:
Data Submission, Quality, Analysis,
Management, and Training Considerations

Prepared for the U.S. Environmental Protection Agency
by Members of the Genomics Workgroup,
a Group Tasked by EPA's Science Policy Council

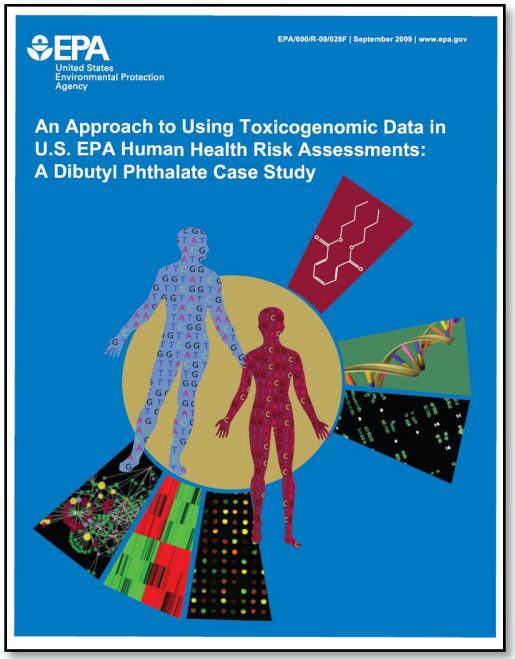
Science Policy Council
U.S. Environmental Protection Agency
Washington, DC 20460

NOTICE
This document is an External Review draft. It has not been formally released by the U.S. Environmental Protection Agency and should not at this stage be construed to represent Agency position

U.S. EPA, Science Policy Council, 2007.

Evolution in Application of Toxicogenomics at EPA

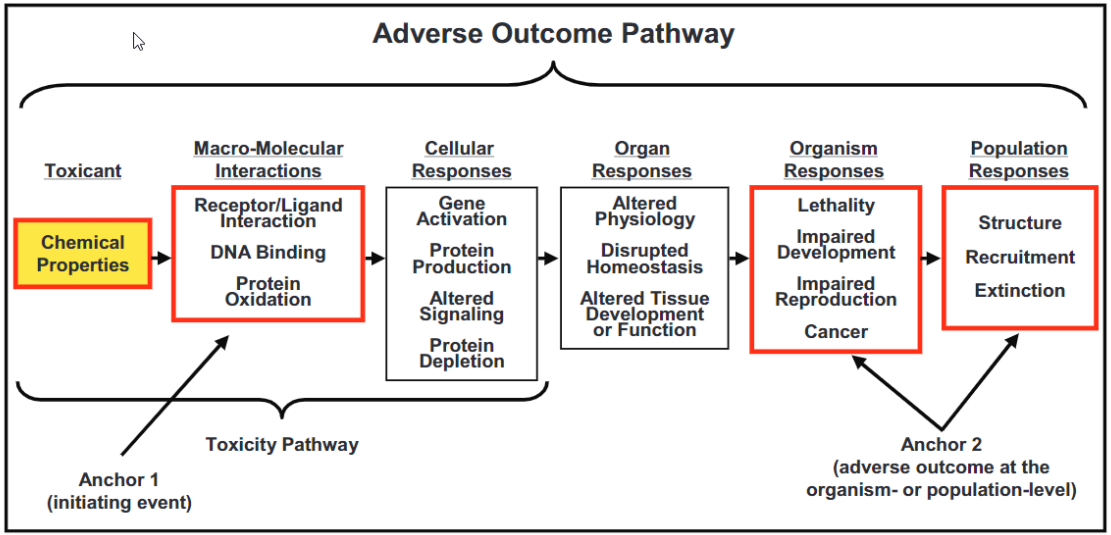
- EPA released a case study for application of toxicogenomic data to human health risk assessment in 2009
- Outlined a systematic and flexible approach to accommodate different health and risk assessment practices
- Focused primarily on informing mode-of-action as part of a weight-of-evidence
- Provided some recommendations on best practices and highlighted current limitations
- Many of the limitations were noted in previous reports (e.g., linkage to adverse effects, consistency in interpretation/analysis methods)



U.S. EPA, Office of Research and Development, 2009.

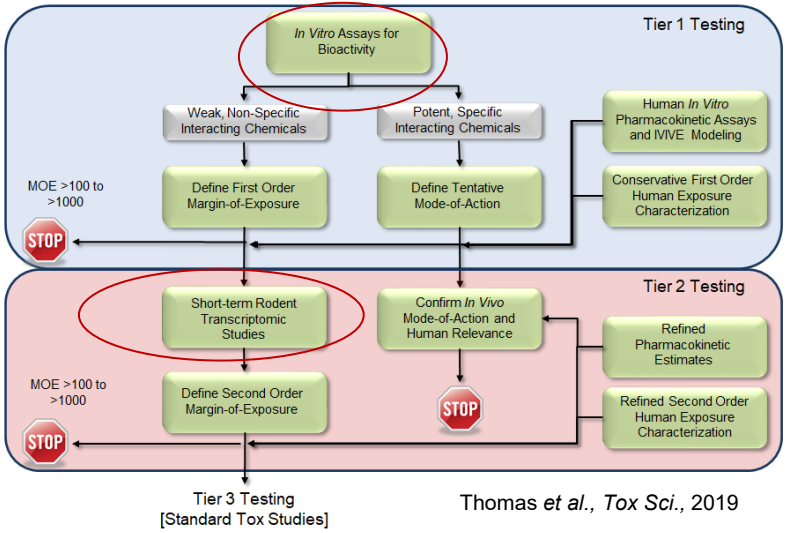
Adverse Outcome Pathway Framework

- The Adverse Outcome Pathway (AOP) framework introduced in 2010
- Organizes existing knowledge linking direct molecular initiating events and adverse outcomes, at a level of biological organization relevant to risk assessment
- Facilitates interpretation of pathway and biological process gene expression changes in adverse outcome context
- Review and acceptance of AOPs by OECD provides confidence for application



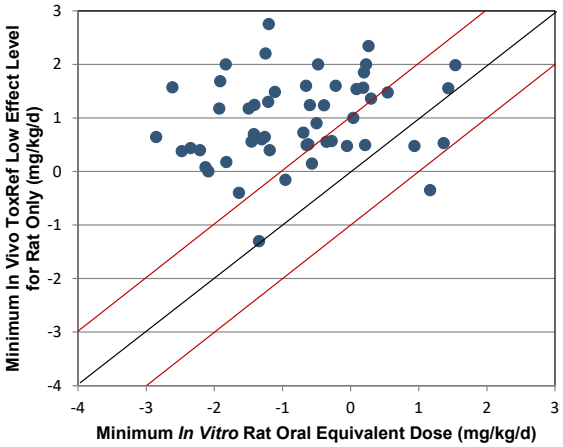
Ankley et al. Environ. Toxicol. Chem., 2010

In Vitro and *In Vivo* Focused Tiered Toxicity Testing Framework



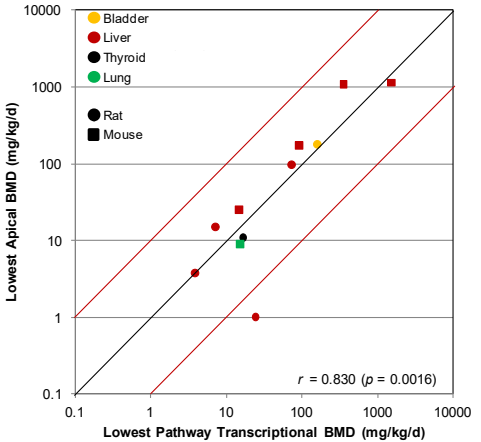
Thomas *et al., Tox Sci.*, 2019

Tier 1
Protective *In Vitro* Screening
Points of Departures



Wetmore *et al., Tox Sci.*, 2013

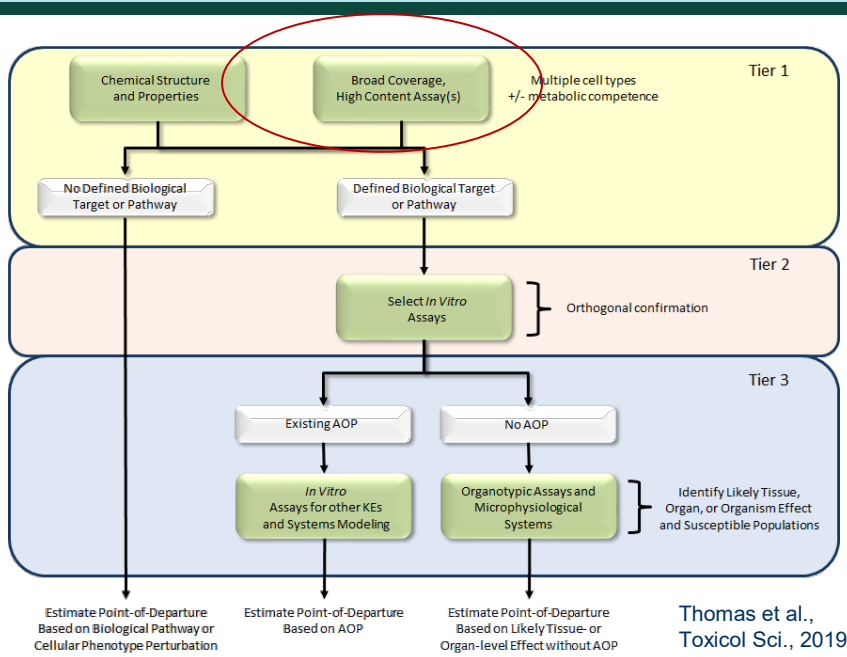
Tier 2
Predictive *In Vivo* Screening
Points of Departure



Thomas *et al., Tox Sci.*, 2013

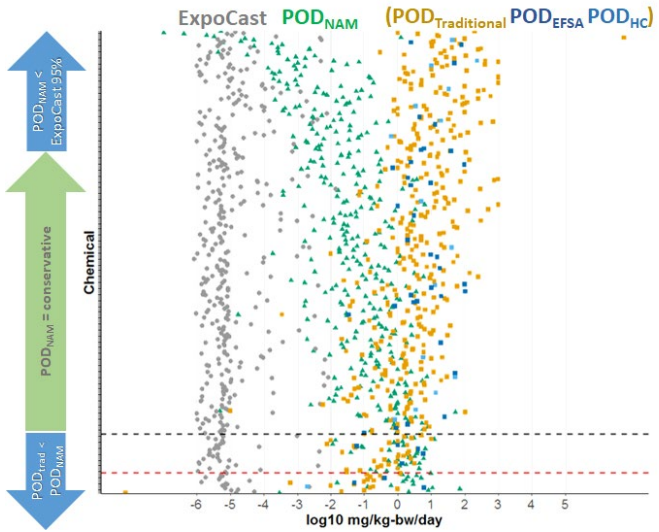
An initial tiered toxicity testing framework outlined application of *in vitro* and *in vivo* toxicogenomic methods in a quantitative, risk-based context

In Vitro and *In Silico* Focused Tiered Toxicity Testing Framework



Thomas et al., Toxicol Sci., 2019

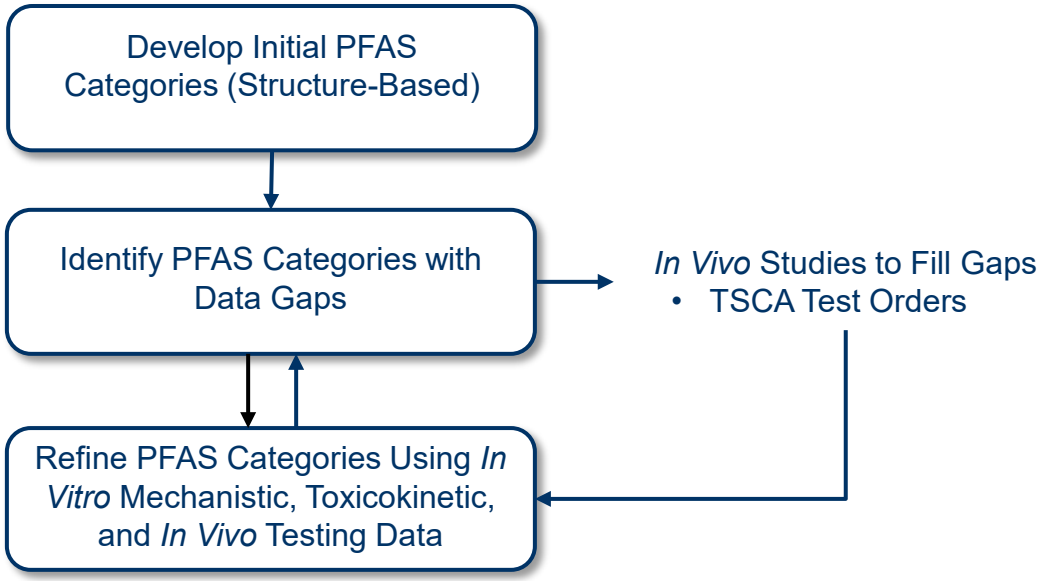
Tier 1
Protective *In Vitro* Screening PODs

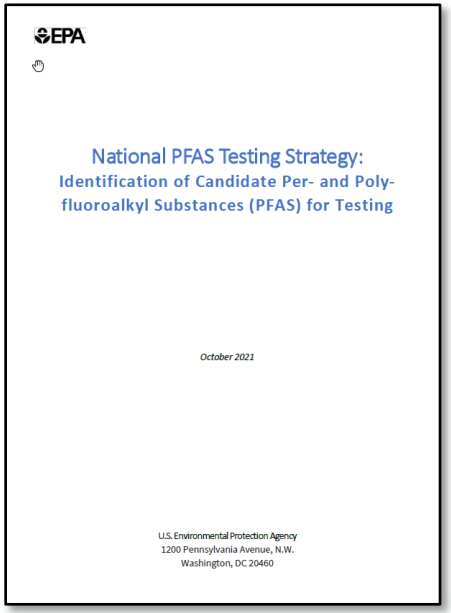


Paul-Friedman et al., Toxicol Sci., 2020

An initial tiered toxicity testing framework outlined application of *in vitro* toxicogenomic methods in a quantitative risk assessment context

Examples of Ongoing EPA Research for Toxicogenomics Application – PFAS Testing




EPA

National PFAS Testing Strategy:
Identification of Candidate Per- and Poly-fluoroalkyl Substances (PFAS) for Testing

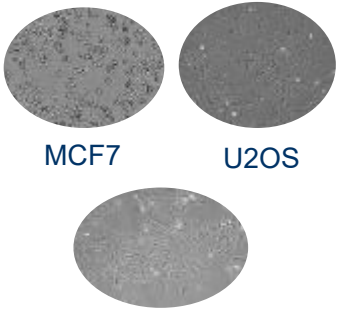
October 2021

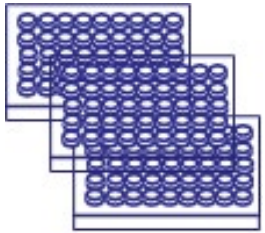
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, DC 20460

In vitro mechanistic data includes toxicogenomic dose response studies for 150 PFAS in two cell types

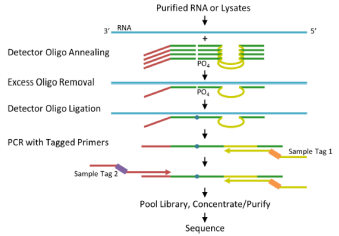
U.S. EPA, 2021.

Examples of Ongoing EPA Research for Toxicogenomics Application – Screening PODs

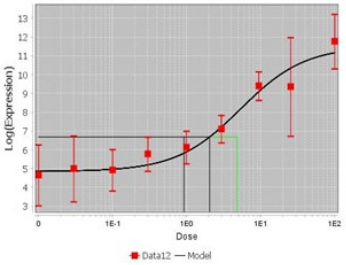




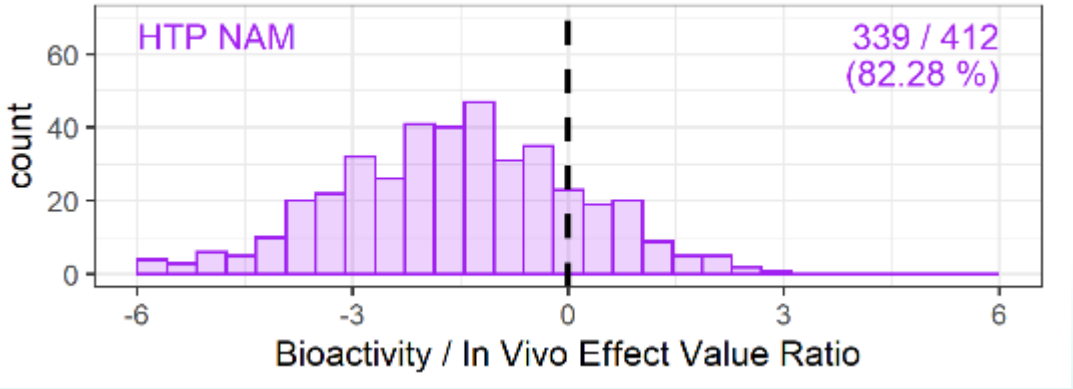
>1000 chemicals
Conc response
6, 24 hr exposure



Whole Genome
Transcriptomics (HTTr)

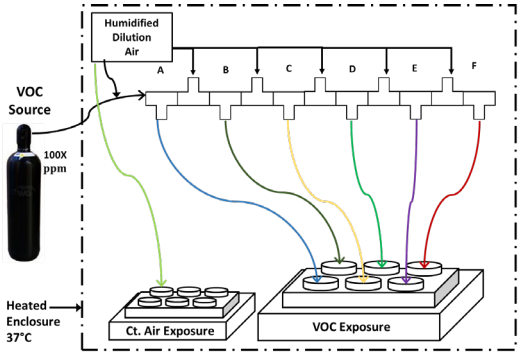


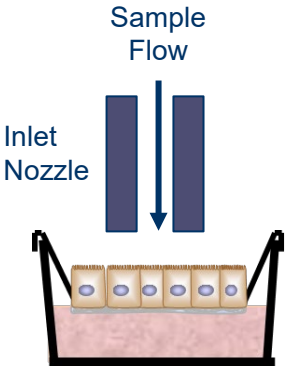
Concentration Response
Modeling



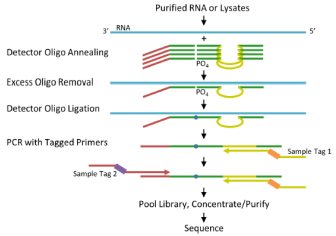
- HTTr-based bioactivity PODs across 3 cell types provide a protective POD ~82% of the time
- Average fold-difference was ~30
- Many of the non-protective PODs were from neuroactive chemicals

Examples of Ongoing EPA Research for Toxicogenomics Application – VOC Screening PODs

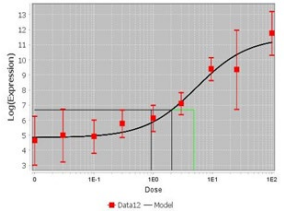




Whole Genome Transcriptomics (HTTr)



Concentration Response Modeling



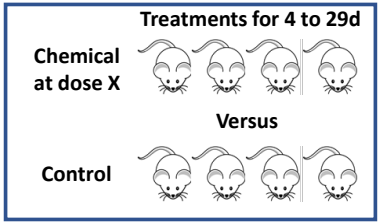
Speen et al. Toxicol. Sci., 2022

	ACGIH TLV-TWA (ppm)	BEAS-2B HTTr POD (ppm)	HBEC HTTr POD (ppm)
Acrolein	0.1	0.58	--
Formaldehyde	0.3	NA	--
1,3-Butadiene	10	13.98	--
Acetaldehyde	25	NA	--
1-Bromopropane	0.1 (10)*	2.25	NA
Carbon Tetrachloride	10	9.56	NA
Trichloroethylene	50	44.8	28.1
Dichloromethane	100	142.13	266.7

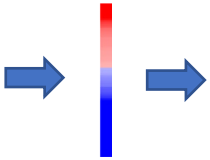
* The ACGIH TLV TWA for 1-bromopropane was updated to 0.1 ppm in 2012. Prior to that the TLV-TWA for 1-bromopropane was 10 ppm.

- HTTr-based bioactivity PODs were generally concordant with TLV values

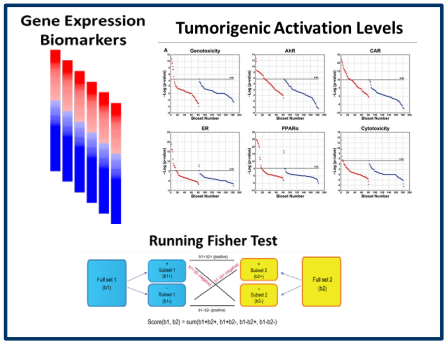
Examples of Ongoing EPA Research for Toxicogenomics Application – Pesticide MOA



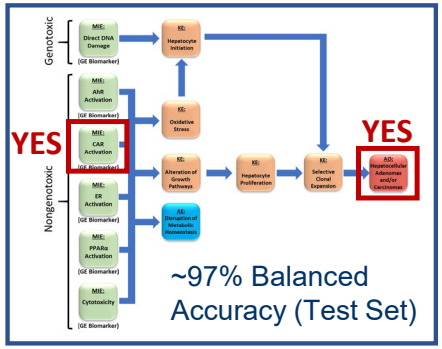
List of DEGs and fold-changes



Computational Model



Network of Liver Cancer AOPs



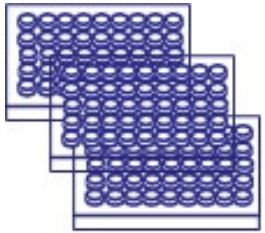
Hill et al. Toxicol. Sci., 2020

Study in Progress to Apply Signatures to Evaluate Liver Tumor MOA for Pesticides

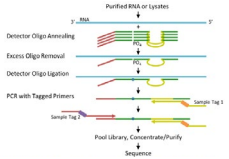
Pesticide	Nontumorigenic Dose (mg/kg/d)	Tumorigenic Dose (mg/kg/d)
Alachlor	63	189
Amitrole	15	75
Cyhalofop-butyl	1.23	5.16
Lactofen	28.5	114
Thiabendazole	15	135
Fluxapyroxad	16.5	217.5
Etofenprox	39	280.5
Benalaxyl-M	28.5	189
Metofluthrin	12.3	116.7
Imazalil	65.8	134.8

Examples of Ongoing EPA Research for Toxicogenomics Application – Eco Screening PODs

Fathead Minnow



Conc response
24 hr exposure



Whole Genome
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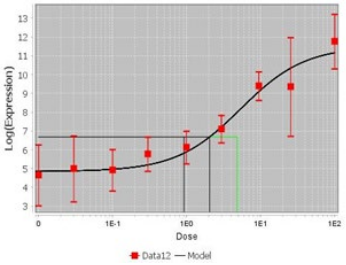
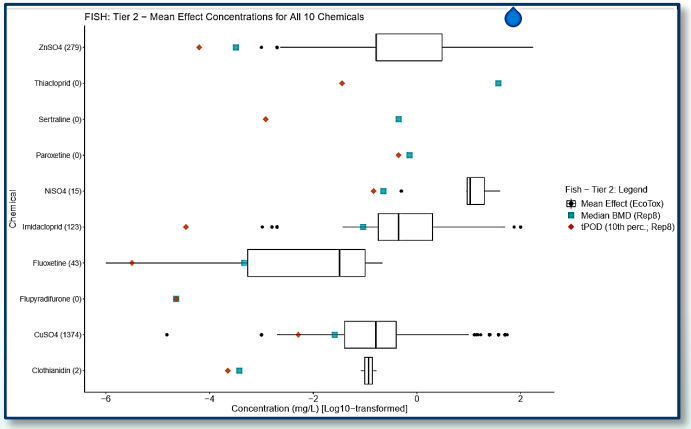


Concentration Response
Modeling

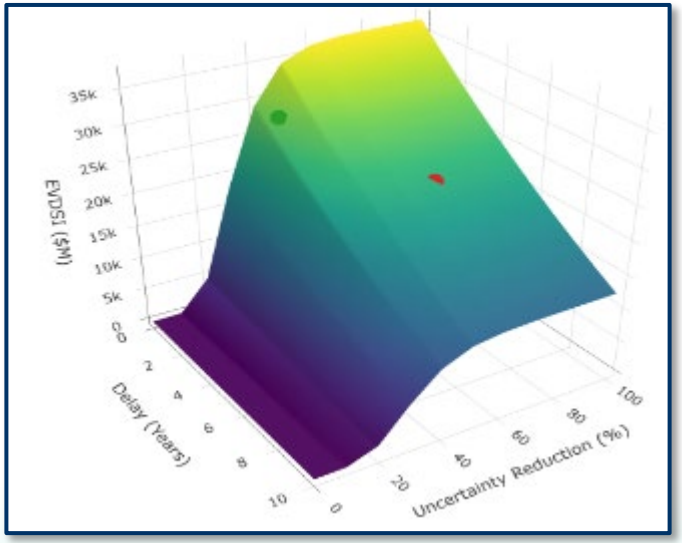


- HTTr-based bioactivity PODs in fathead minnow provide a protective POD compared with 25th centile of ECOTOX effect concentrations
- HTTr-based bioactivity PODs in fathead minnow were not always protective of effect concentrations in crustaceans

Examples of Ongoing EPA Research for Toxicogenomics Application – Health Impacts

- Value of Information (VOI) method developed to evaluate the trade-offs between timeliness, uncertainty, and costs of toxicity testing methods
- The trade-offs are evaluated on overall economic and human health costs associated with chemical exposure and control
- Different decision makers (benefit-cost, target risk) and health impacts can be incorporated
- Timeliness has a significant positive impact on the VOI of toxicity tests, even in the presence of smaller reductions in uncertainty
- The positive impact of the shorter tests may be multiplicatively amplified by the ability to test more chemicals
- Future research are applying this to evaluate the benefits of rapid toxicogenomic toxicity tests

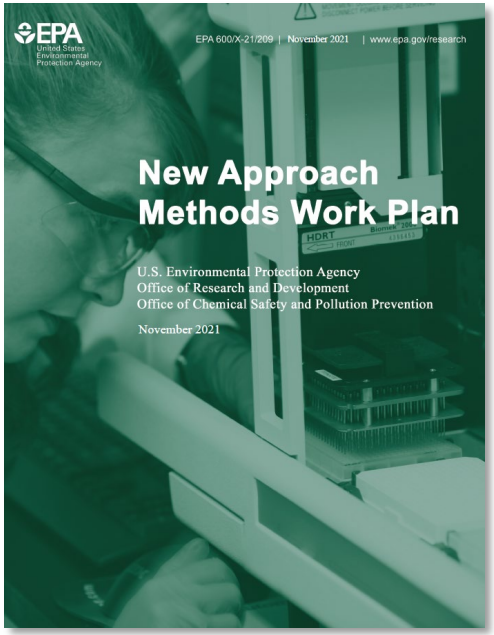
Trade-Offs of Uncertainty and Time of Toxicity Testing Methods
(Chronic Effect, Target Risk Decision Maker)



Hagiwara et al. Risk Anal., 2022

Building Scientific Confidence in Toxicogenomic Methods and Approaches – EPA NAMs Work Plan

- The EPA NAMs Work Plan provides multiple objectives and deliverables that aim to build scientific confidence
  - Evaluating the variability and relevance of existing methods to set a baseline for new methods
  - Developing case studies to evaluate application to regulatory decision making (some current case studies use toxicogenomics)
  - Developing an Agency-wide scientific confidence framework to evaluate the quality, reliability, and relevance of new methods



U.S. EPA, 2021.

Building Scientific Confidence in Toxicogenomic Methods and Approaches – OECD Activities

- The Organization for Economic Cooperation and Development (OECD) introduced an internationally accepted toxicogenomics reporting framework in 2021
  - Provides guidance on reporting of toxicogenomic information that fosters transparency and reproducibility
  - Currently captures experimental information, data acquisition/processing, and data analysis
  - Ensures sufficient information is available to enable evaluation of experimental data and interpretation
- Extension of the OECD efforts may pursue development of application reporting modules and additional case studies
  - Grouping and read across
  - Screening level risk assessment
  - Mode-of-action/adverse effect biomarkers

Regulatory Toxicology and Pharmacology 125 (2021) 105020

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Commentary

Progress towards an OECD reporting framework for transcriptomics and metabolomics in regulatory toxicology

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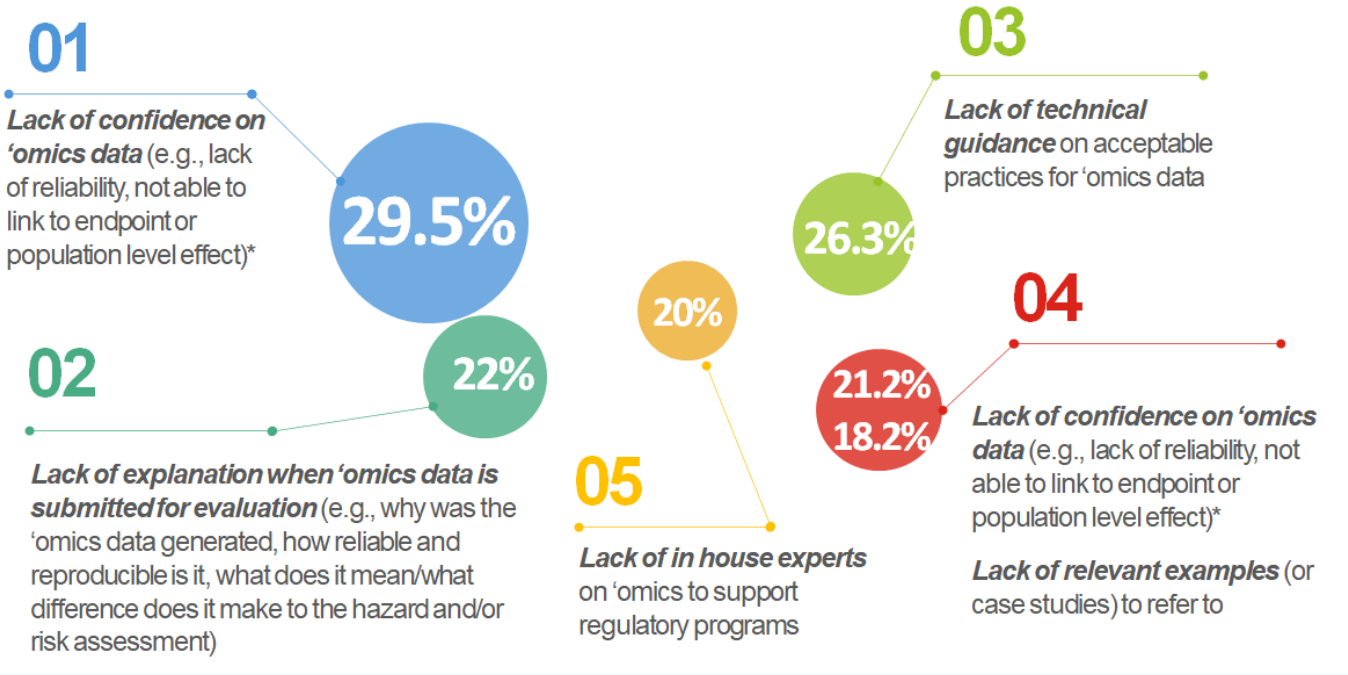
Building Scientific Confidence in Toxicogenomic Methods and Approaches – OECD Activities

What are the challenges of using omics data in chemical risk assessment?



Results from an OECD member survey - *Acknowledgements to Magda Sachana*

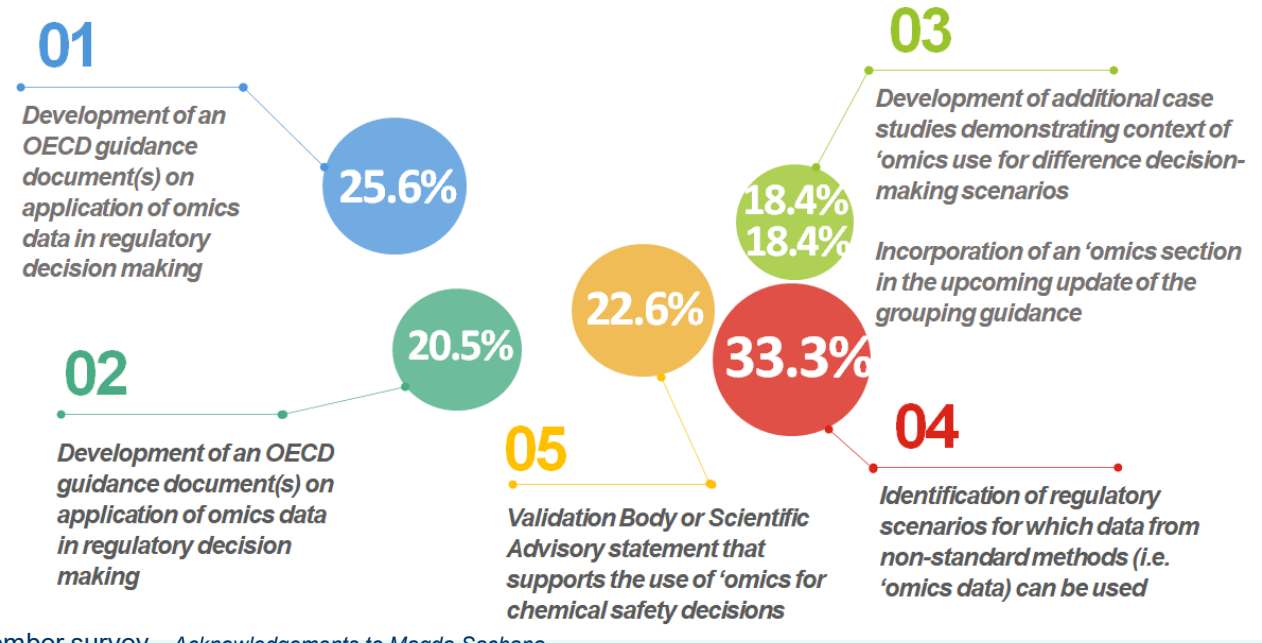
Building Scientific Confidence in Toxicogenomic Methods and Approaches – OECD Activities

Which of the following would increase your confidence on technical aspects of the use of 'omics data in chemical risk assessment?

Results from an OECD member survey - *Acknowledgements to Magda Sachana*

Building Scientific Confidence in Toxicogenomic Methods and Approaches – OECD Activities

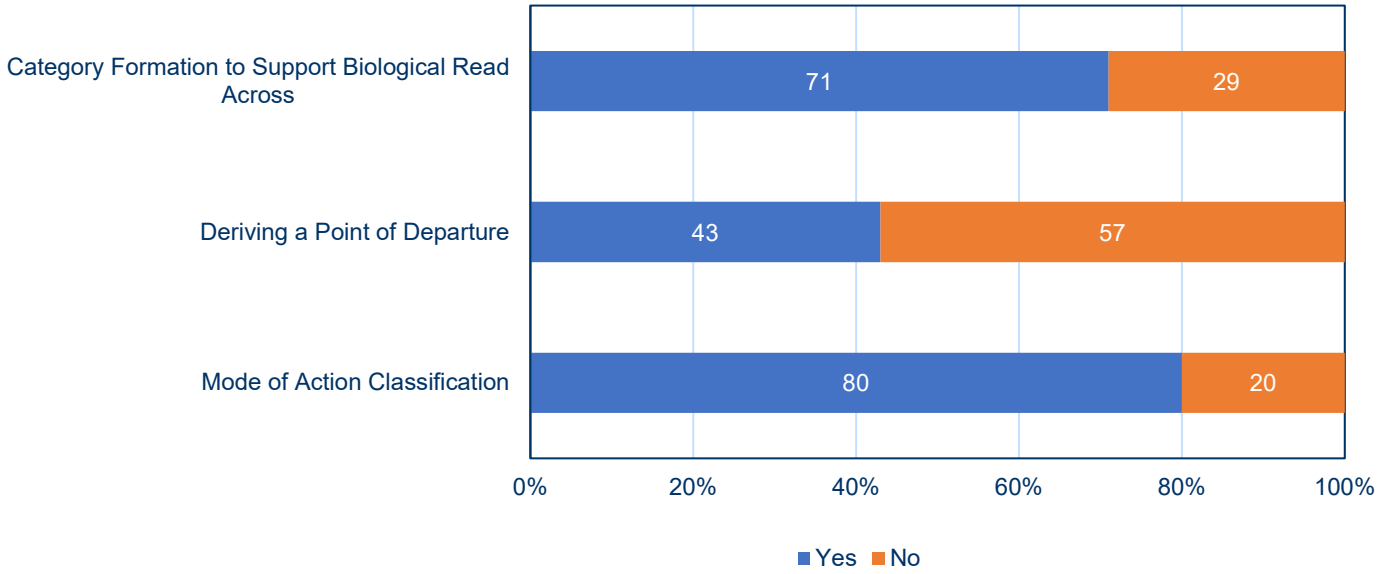
Which of the following would increase confidence on aspects related to application of the use of 'omics data in chemical risk assessment (beyond the reporting frameworks)?



Results from an OECD member survey - *Acknowledgements to Magda Sachana*

Building Scientific Confidence in Toxicogenomic Methods and Approaches – OECD Activities

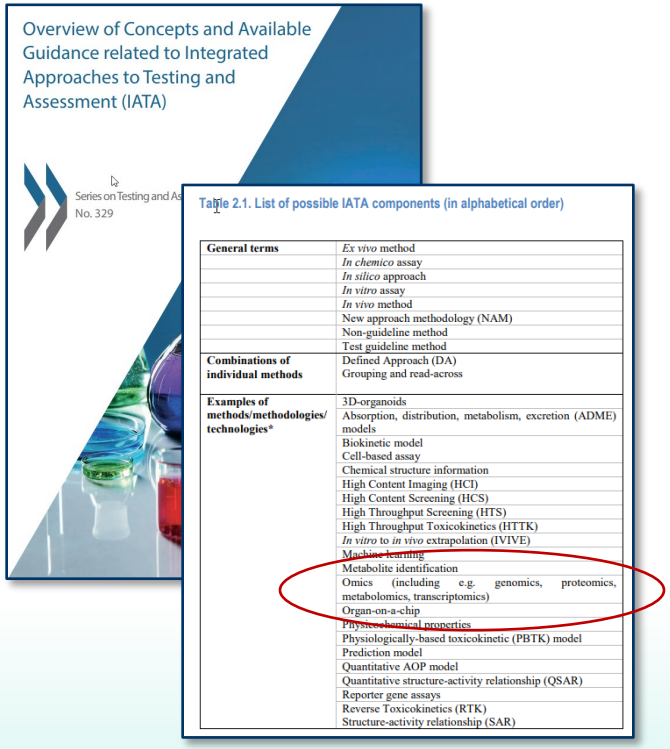
Identify for which of the following risk assessment applications the use of 'omics data might be beneficial in your regulatory jurisdiction over the next 5 years



Results from an OECD member survey - *Acknowledgements to Magda Sachana*

Building Scientific Confidence in Toxicogenomic Methods and Approaches – OECD Activities

- *In vivo* and *in vitro* toxicogenomics data can be readily incorporated into Integrated Approaches to Testing and Assessment (IATA)
- Provides integrated information about biological changes in a single assay and evaluated in an AOP framework
- Builds on previous work incorporating NAMs into IATA
- OECD IATA case studies project launched in 2015 to gain experience and build confidence in the application of new methods



Building Scientific Confidence in Toxicogenomic Methods and Approaches – OECD Activities

- OECD IATA case study for repeat dose toxicity of phenolic benzotriazoles evaluated the use of *in vivo* transcriptomics to support a read across assessment
  - *In vivo* transcriptomic profiles were used to support similar modes of action
- OECD IATA case study for systemic toxicity of phenoxyethanol evaluated the use of *in vitro* transcriptomics to support a quantitative safety assessment
  - *In vitro* transcriptomic profiles in 3 cell types used to derive a molecular point of departure (NOTEL) together with a battery of safety pharmacology assays

Two OECD IATA Case Studies Utilized Transcriptomic Data

OECD, 2017

OECD,2021

Summary

- Development and potential application of toxicogenomics for chemical safety decisions at EPA has been ongoing for more than twenty years
- New frameworks and research intends to address many of the perceived and real gaps in applying the technology
- EPA and international efforts to build scientific confidence in toxicogenomics are continuing
- A shift towards applying toxicogenomics more broadly in chemical risk assessment beyond its use in an overall weight-of-evidence remains elusive

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