From Data to Decisions:
21st Century Understanding of Chemical Mixtures

Prepared for EFSA/RIVM Symposium on Chemical Mixtures
May 18-19, 2016
Utrecht, The Netherlands

Tina Bahadori, ScD
National Program Director, Chemical Safety for Sustainability
US EPA Office of Research and Development

21st Century Environmental Challenges

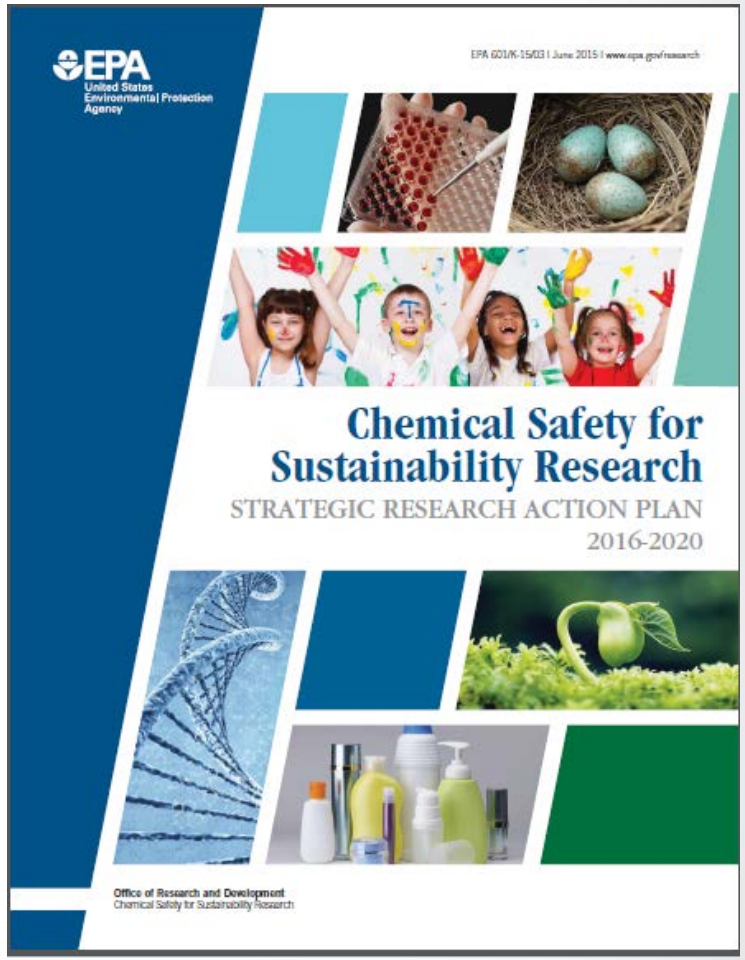
- Climate change
- Changing energy landscape
- Multi-pollutant exposure
- Increasing nitrogen and phosphorus impair water quality
- Susceptibility & environmental justice
- Thousands of new industrial chemicals and pesticides each year
- Chemical, biological, radiological-based terrorism

Connections: ORD National Research Programs and Cross Cutting Roadmaps

NOTE: Final StRAPs and 2 Roadmaps (Nitrogen & Co-pollutants, Children's Environmental Health) are completed and available at http://www2.epa.gov/research/strategic-research-action-plans-2016-2019. Revised draft roadmaps for Climate Change and EJ being reviewed at Dec. 2015 BOSC review meeting.

CSS 2016-2019 Strategic Research Action Plan (StRAP)

- **Build Knowledge Infrastructure**
  - Make information publicly accessible.
  - Combine different types of data in new ways to characterize impacts of chemicals across their life cycle to human health and the environment
- **Develop Tools for Chemical Evaluation**
  - Develop and apply rapid, efficient, and effective chemical safety evaluation methods
- **Promote Complex Systems Understanding**
  - Investigate emergent properties in complex chemical-biological systems by probing how disturbances and changes in one part affect the others and the system as a whole
- **Translate and Actively Deliver**
  - Demonstrate application of CSS science and tools to anticipate, minimize, and solve environmental health problems



https://www.epa.gov/research/chemical-safety-sustainability-strategic-research-action-plan-2016-2019

Mixtures: Why Here and Why Now?

Advances in Exposure Science

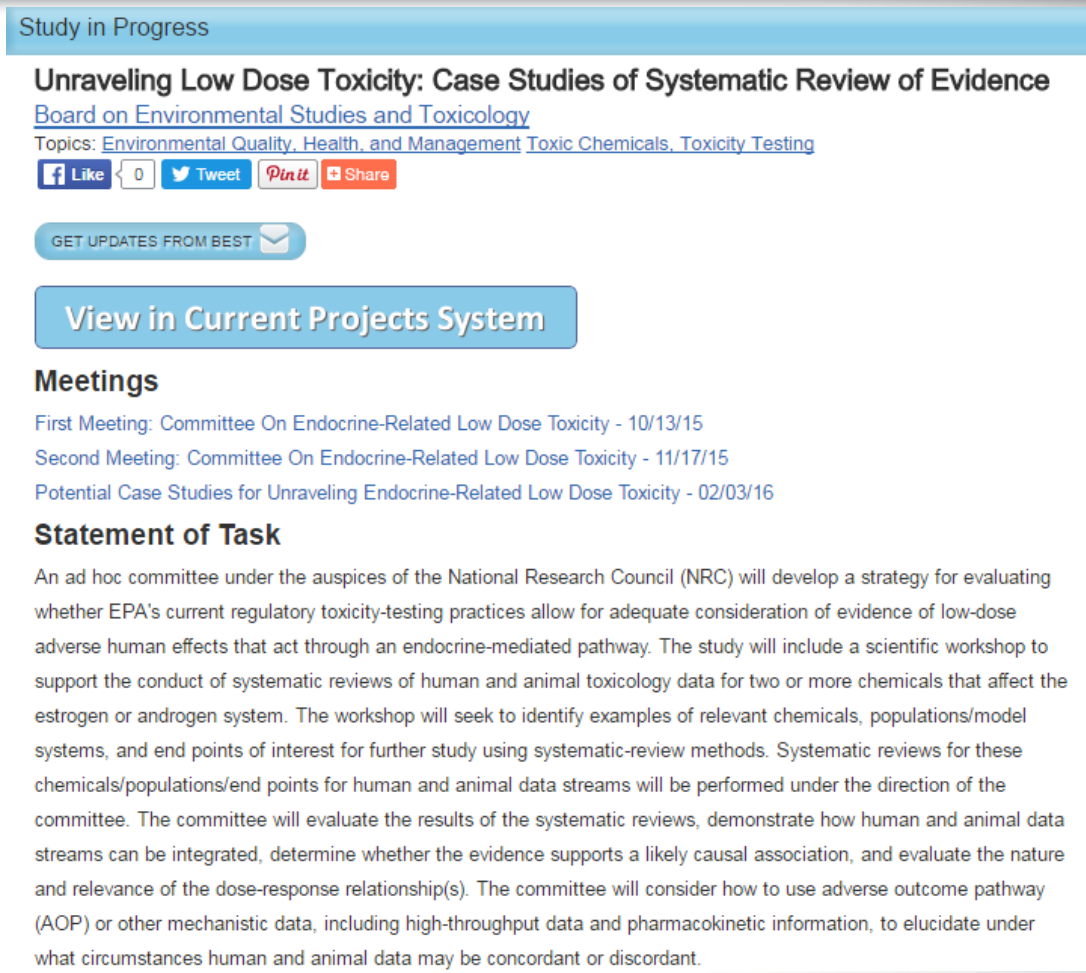
- Flow of exposure information (monitoring, modeling, sensors, non-targeted analyses, product information, informatic approaches, better reporting)
- Data need to be organized
  - To understand the impact of exposures
  - To identify gaps
  - To mitigate adverse exposures and enhance beneficial ones.

Advances in Biology

- Adverse Outcome Pathways and networks of pathways
  - Chemical/Stressor agnostic approaches
  - Deconstruct biology
  - Present putative and plausible models to evaluate impact of exposures
  - Lay the groundwork for predictive approaches

Incidental Exposures

- Important question for public health – we are all exposed every day to multiple chemicals at very low doses. What does this mean for risk and human health?
- There is evidence that chemicals can also interact synergistically, not just simultaneously
  - Co-occurrence is important, but it may just be the low hanging fruit
  - Other pathways of synergistic exposures need to be considered.
- Chemical and non-chemical stressors



Study in Progress

Unraveling Low Dose Toxicity: Case Studies of Systematic Review of Evidence

Board on Environmental Studies and Toxicology

Topics: Environmental Quality, Health, and Management Toxic Chemicals, Toxicity Testing

Like 0 Tweet Pin it Share

GET UPDATES FROM BEST

View in Current Projects System

Meetings

First Meeting: Committee On Endocrine-Related Low Dose Toxicity - 10/13/15

Second Meeting: Committee On Endocrine-Related Low Dose Toxicity - 11/17/15

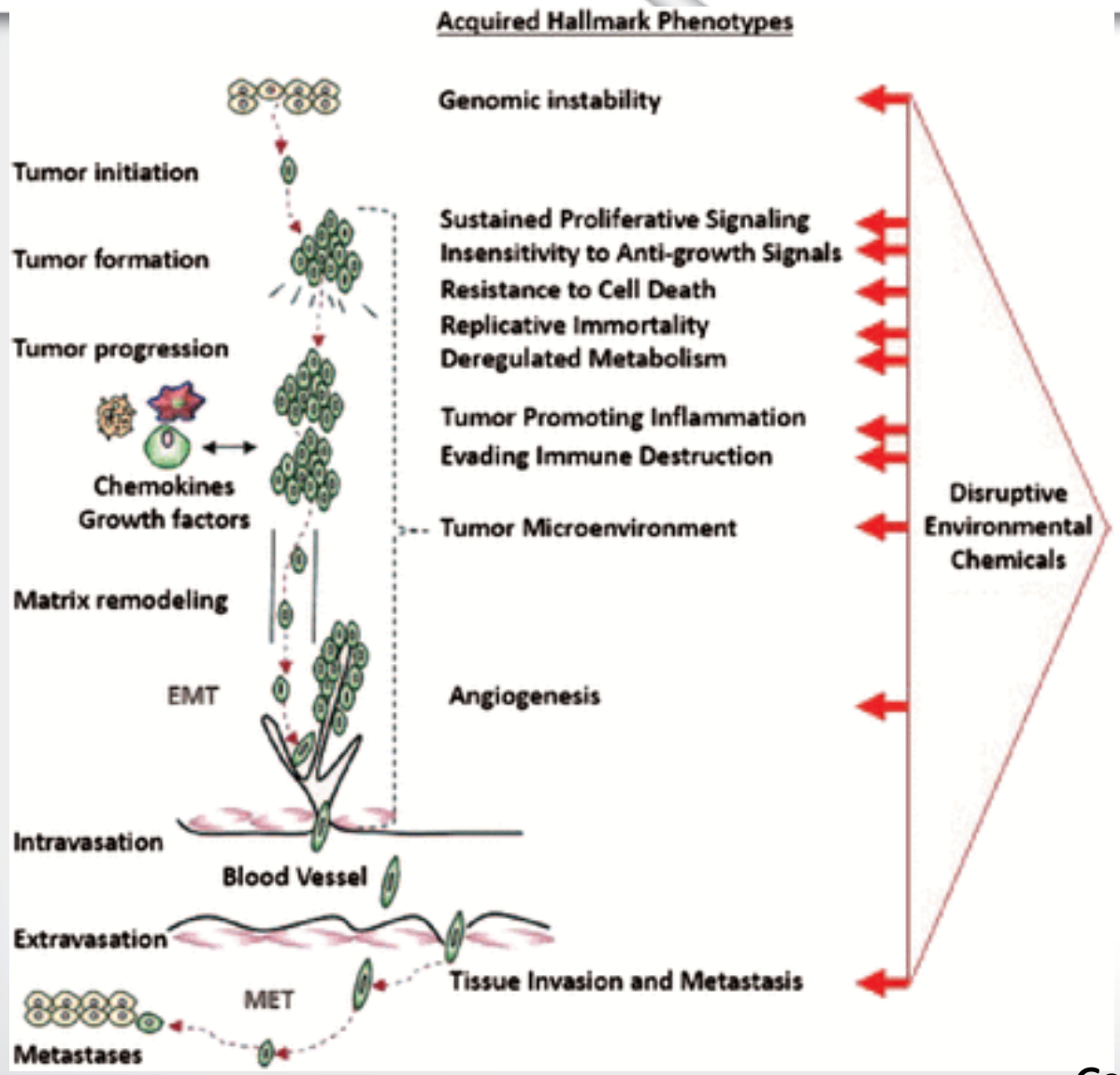
Potential Case Studies for Unraveling Endocrine-Related Low Dose Toxicity - 02/03/16

Statement of Task

An ad hoc committee under the auspices of the National Research Council (NRC) will develop a strategy for evaluating whether EPA's current regulatory toxicity-testing practices allow for adequate consideration of evidence of low-dose adverse human effects that act through an endocrine-mediated pathway. The study will include a scientific workshop to support the conduct of systematic reviews of human and animal toxicology data for two or more chemicals that affect the estrogen or androgen system. The workshop will seek to identify examples of relevant chemicals, populations/model systems, and end points of interest for further study using systematic-review methods. Systematic reviews for these chemicals/populations/end points for human and animal data streams will be performed under the direction of the committee. The committee will evaluate the results of the systematic reviews, demonstrate how human and animal data streams can be integrated, determine whether the evidence supports a likely causal association, and evaluate the nature and relevance of the dose-response relationship(s). The committee will consider how to use adverse outcome pathway (AOP) or other mechanistic data, including high-throughput data and pharmacokinetic information, to elucidate under what circumstances human and animal data may be concordant or discordant.

http://dels.nas.edu/Study-In-Progress/Unraveling-Dose-Toxicity-Case-Studies/DELS-BEST-14-07?bname=best

Disruptive Potential of Mixed Exposures



"Interacting contributors need not act simultaneously or continuously, they might act sequentially or discontinuously. So a sustained focus on the carcinogenicity of individual chemicals may miss the sorts of synergies that might reasonably be anticipated to occur when combinations of disruptive chemicals (i.e. those that can act in concert on the key mechanisms & pathways related to these hallmarks) are encountered."

Goodson et al. Carcinogenesis. 2015 Jun; 36(Suppl 1): S254–S296.

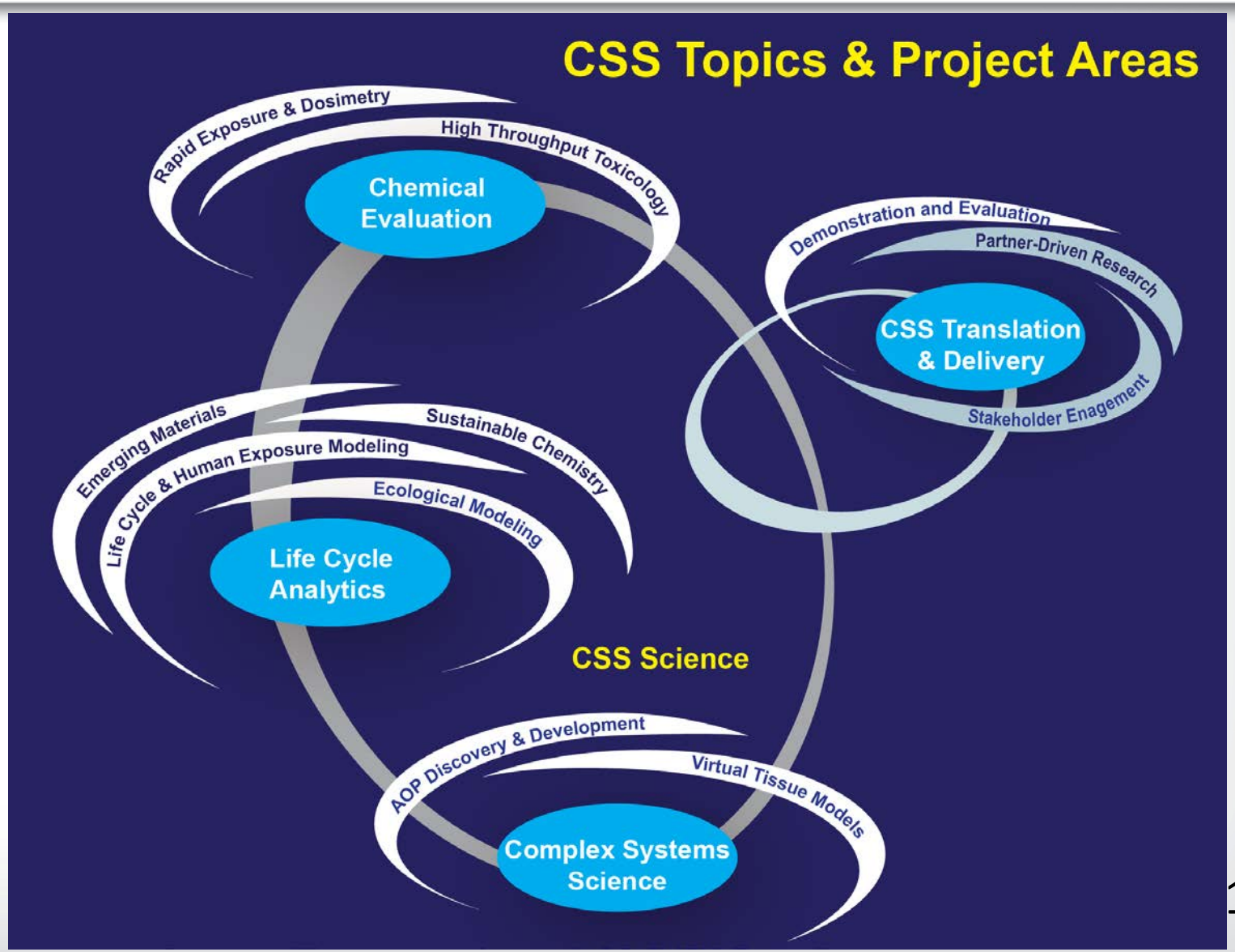
CSS Program Design

Three Research Topics

- Chemical evaluation
- Life cycle analytics
- Complex systems

One Translation Topic

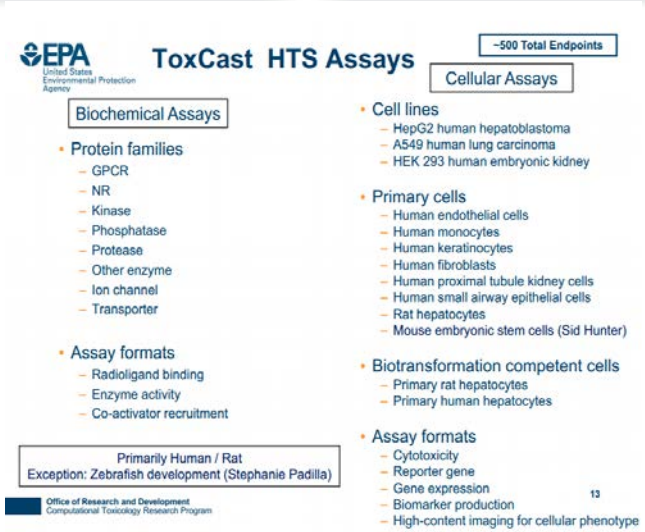
- Solutions-Based Translation and Knowledge Delivery



CSS Tools

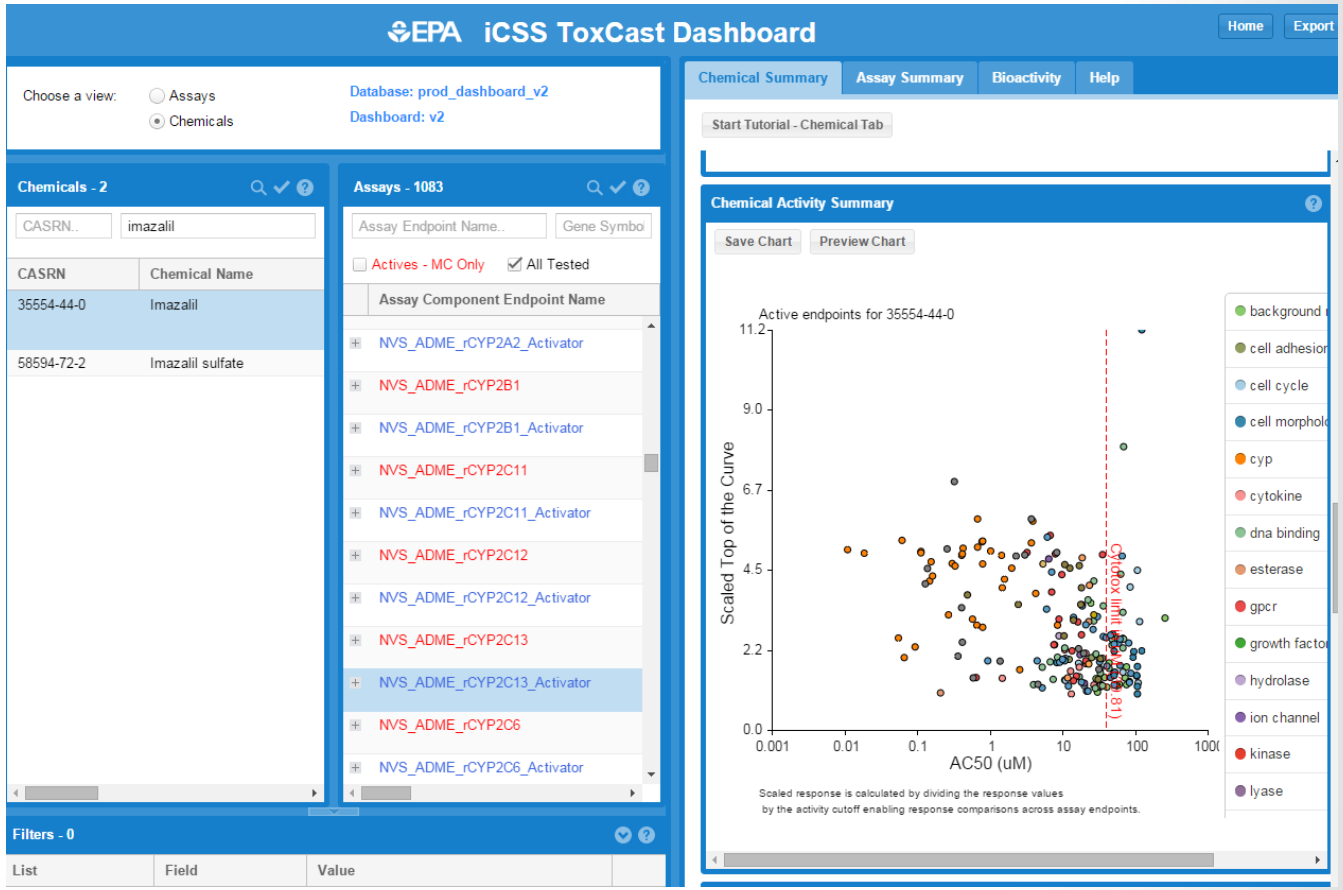
ToxCast

> 600 assays, >2000 chemicals,



- 1536 well HTS
- 10,000 chemicals
- 25 assays per year

Tox21



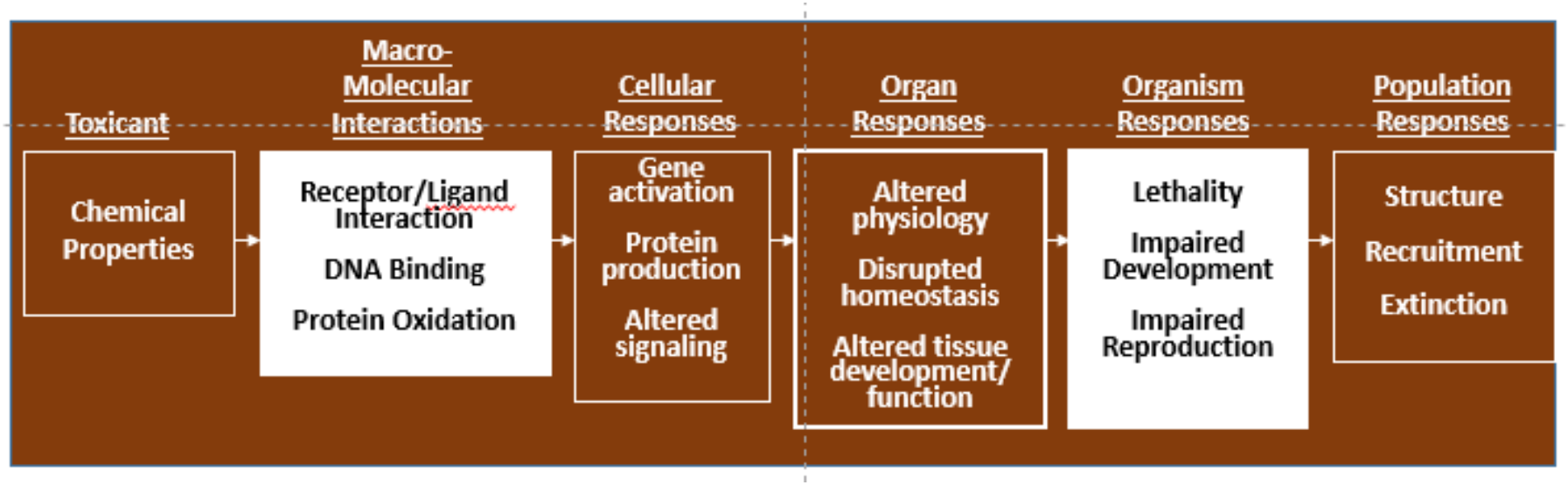
http://actor.epa.gov/dashboard/

CSS EFSA/RIVM Mixtures

Adverse Outcome Pathway

An Adverse Outcome Pathway (AOP) is a conceptual framework that portrays existing knowledge concerning the linkage between a direct molecular initiating event and an adverse outcome, at a level of biological organization relevant to risk assessment.

(Ankley et al. 2010, Environ. Toxicol. Chem., 29(3): 730-741.)



- Helps us organize what we know
- And make more effective use of pathway-based data in risk-based decision-making

Aggregate Exposure Pathway

"Completing the Link between Exposure Science and Toxicology for Improved Environmental Health Decision Making"

- Capturing the complex nature of human and ecological exposure to stressors is a major challenge for environmental health decision making.
- The Aggregate Exposure Pathway (AEP) concept offers an intuitive framework to organize exposure data, setting the stage for more meaningful collection and use of exposure data.

Teeguarden, Tan, et al. (2016) *Completing the Link between Exposure Science and Toxicology for Improved Environmental Health Decision Making: The Aggregate Exposure Pathway Framework*. Environ Sci Technol, 50(9): 4579-4892.

Real-World Exposures

Under the Lamppost - NOT

Environmental Science & Technology

Article

pubs.acs.org/est

Identification of Novel Perfluoroalkyl Ether Carboxylic Acids (PFECAs) and Sulfonic Acids (PFESAs) in Natural Waters Using Accurate Mass Time-of-Flight Mass Spectrometry (TOFMS)

Mark Strynar,*[,†] Sonia Dagnino,[†,‡] Rebecca McMahen,[†,‡] Shuang Liang,[†,‡] Andrew Lindstrom,[†] Erik Andersen,[†] Larry McMillan,[§] Michael Thurman,[∥] Imma Ferrer,[∥] and Carol Ball[⊥]

[†]National Exposure Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolin United States

[‡]Oak Ridge Institute for Science and Education, Oak Ridge, Tennessee 37831 United States

[§]National Caucus and Center on Black Aged, Inc., Durham, North Carolina 27713, United States

[∥]Center for Environmental Mass Spectrometry, University of Colorado Boulder, Boulder, Colorado 80309, United State

[⊥]Agilent Technologies Inc., Wilmington, Delaware 19808, United States

Applying Non-Targeted Screening

- Water
- Dust
- Biological media
- Consumer products

ELSEVIER

Environment International

Volume 88, March 2016, Pages 269–280

Linking high resolution mass spectrometry data with exposure and toxicity forecasts to advance high-throughput environmental monitoring

Julia E. Rager[a], Mark J. Strynar[b], Shuang Liang[a], Rebecca L. McMahen[a], Ann M. Richard[c], Christopher M. Grulke[d], John F. Wambaugh[c], Kristin K. Isaacs[b], Richard Judson[c], Antony J. Williams[c], Jon R. Sobus[b,]

Show more

doi:10.1016/j.envint.2015.12.008

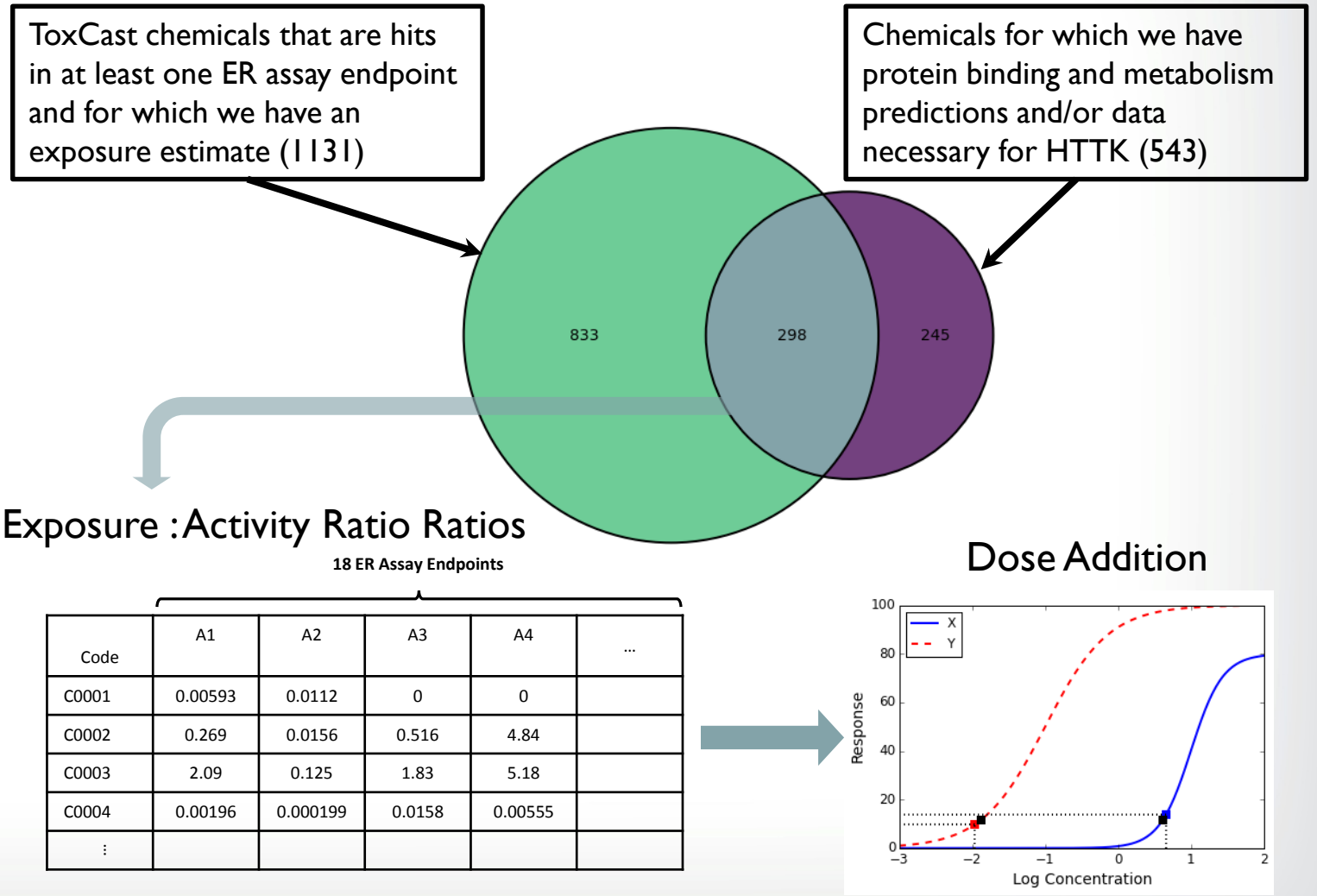
Get rights and content

Probing Mixtures

Mixture prioritization 1: based on ER-relevance of constituent chemicals

- Focus on estrogenicity by selecting ToxCast chemicals that are hits in 18 **ER-relevant** assay endpoints (Browne et al., 2015)
- Utilize exposure estimates (ExpoCast) and high throughput toxicokinetics (HTTK) to estimate **Exposure : Activity Ratio**
- Estimate effects of mixtures using **conservative dose addition**.
- Look for **mixtures** that **exceed a threshold** in some/all of the 18 ER-relevant assay endpoints.
  - Smallest mixture of chemicals where ExpoCast background exposures would hit all 18 contains 26 chemicals

Dustin Kapraun with Woody Setzer, John Wambaugh

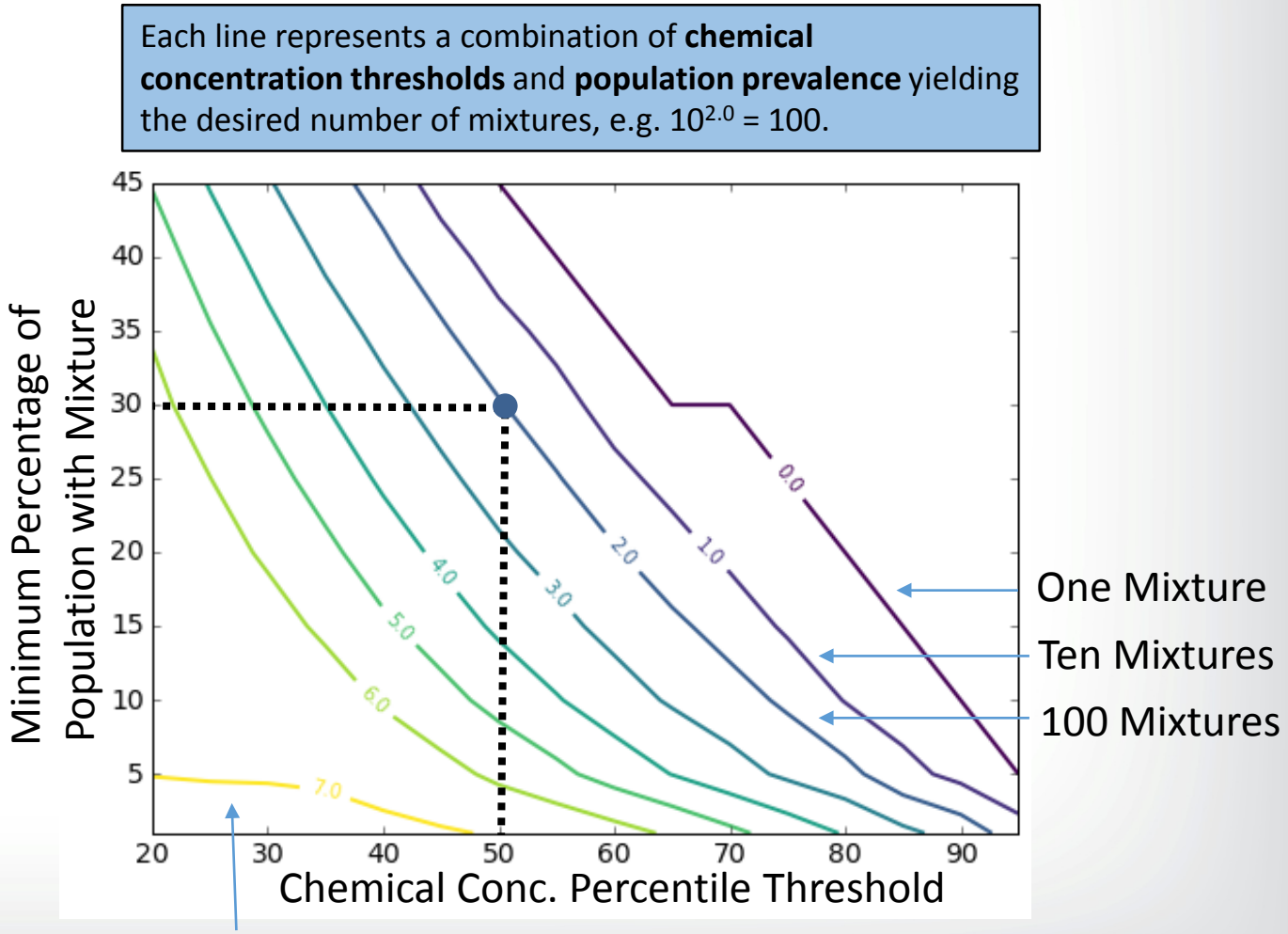


Mixtures Prioritization 2: Select mixtures based on prevalence of co-occurrence

- Examine **2009-2010 NHANES** data.
- Use **Big Data analytics** to **identify mixtures** that appear to co-occur in US residents.

  "How Target Figured Out A Teen Girl Was Pregnant Before Her Father Did" Forbes, Feb. 16, 2012
- Choose parameters to generate approximately **100 sets of chemicals** that occur together "frequently".

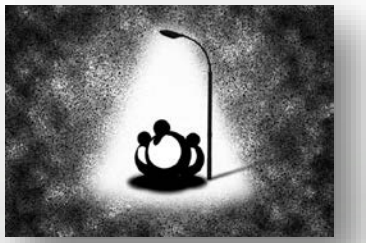
Dustin Kapraun with Woody Setzer, Mike Tornero-Velez, John Wambaugh



From the Vantage Point of Effects

Effect-Based Monitoring (EBM)

- **Different contaminant-oriented programs have successfully complemented chemical measurements with determination of biological effects**
  - **NPDES (effluent) program (e.g., cladoceran survival/reproduction, fish growth)**
  - **Dredged material assessment (e.g., amphipod, chironomid survival/growth)**
- **Variety of *in vitro* and/or *in vivo* biological systems used, but a limitation is coverage of the multitude of biological pathways/responses of concern**
  - **In vivo systems reflect integrated responses, but species/endpoints used may be insensitive to contaminants present (e.g., NPDES assays will not detect endocrine activity)**
  - **Targeted in vitro assays useful (e.g., for estrogenicity), but usually deployed "singly"**
- **Extensive pathway coverage afforded by different HTT platforms offers opportunity for broad pathway representation in context of affordable, rapid measurements**



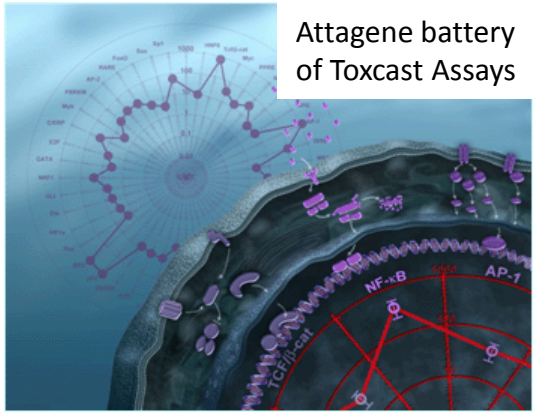
Bio-effects Surveillance

Ambient water sample

extract

"Unknown" Chemical Mixture

Complex mixture

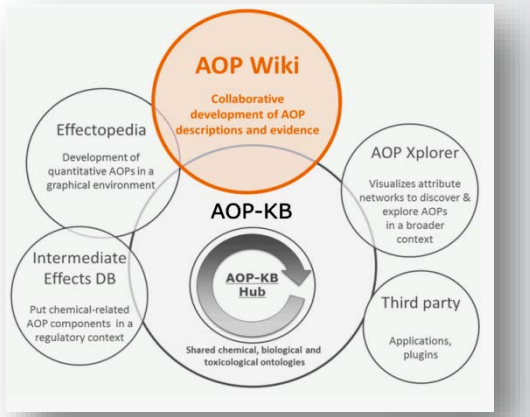


Attagene battery of Toxcast Assays

Factorial cellular biosensor system (HepG2 cell line)

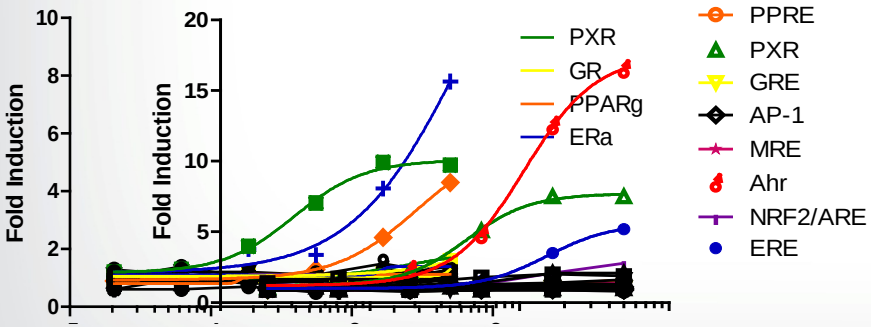
81 different assay features

AOP Knowledge-base (aopkb.org)



- Predicted hazards
- Taxonomic relevance
- Endpoints for targeted monitoring

cis- Assays



Relative Enrichment Factor (REF)

trans- Assays

Relative Enrichment Factor (REF)

‘Regulatory’ Applications

Pesticide Cumulative Risk Assessment

- Candidate Common Mechanism Groups (CMG)
- Application of CompTox for Screening Pesticide Chemical Groups for Cumulative Risk Assessment
- Re-clustering based on Z-score
- Leveraging high-throughput transcriptomic contract (in process) to perform whole transcriptome analysis on the pesticides
  - Concentration response format
  - Across multiple cell types/lines

Transformation Builds on Knowledge

- **Increase Predictive Capacity**
  - **Organize what we know and utilize that knowledge to support risk-based decision-making**
  - **Evaluate effects of cumulative exposures and cumulative risk**
- **Exploit complex systems modeling to advance mechanistic understanding**
  - **Integrate understanding of exposures-dose-effects across levels of biological organization**
  - **Predict early 'tipping-points'**
- **Consider exposures that matter: focus on developmental health, vulnerable and susceptible populations and lifestages**
- **Focus on Lifestage: Account for early life exposures with life long health implications**
- **Provide a new vantage point on Cumulative Exposure and Cumulative Risk Assessment**
- **Enable environmental (and public) health protection**

Acknowledgements

ORD Research Facilities