EPA United States Environmental Protection Agency

EU-ToxRisk Project and NCCT Capabilities

EU-ToxRisk – Tox21 Joint Meeting

19-21 September 2016, Mainz, Germany

Office of Research and Development

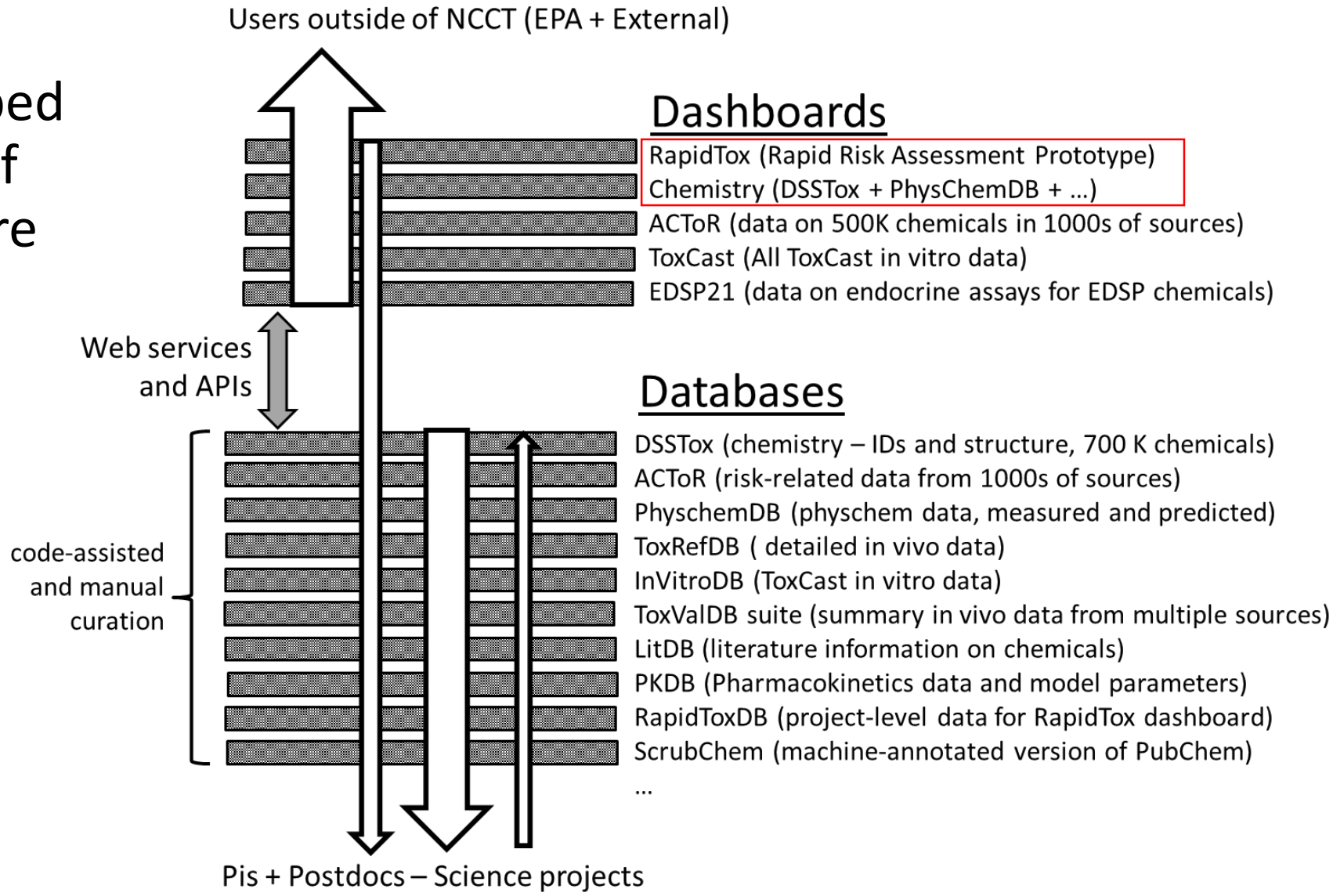
EU-ToxRisk Project and NCCT Capabilities

Highlighting today *(very briefly)* NCCT capabilities and projects that could be useful in collaborations with EU-ToxRisk

- Software and Database Development
- Two New Dashboards – Cheminformatics & RapidTox
- Ongoing and New Modeling Efforts
  - Read Across with Uncertainties
  - Biological dynamics and Tipping Points
  - HTTK
  - Transcriptomics
  - In vitro metabolism retrofits

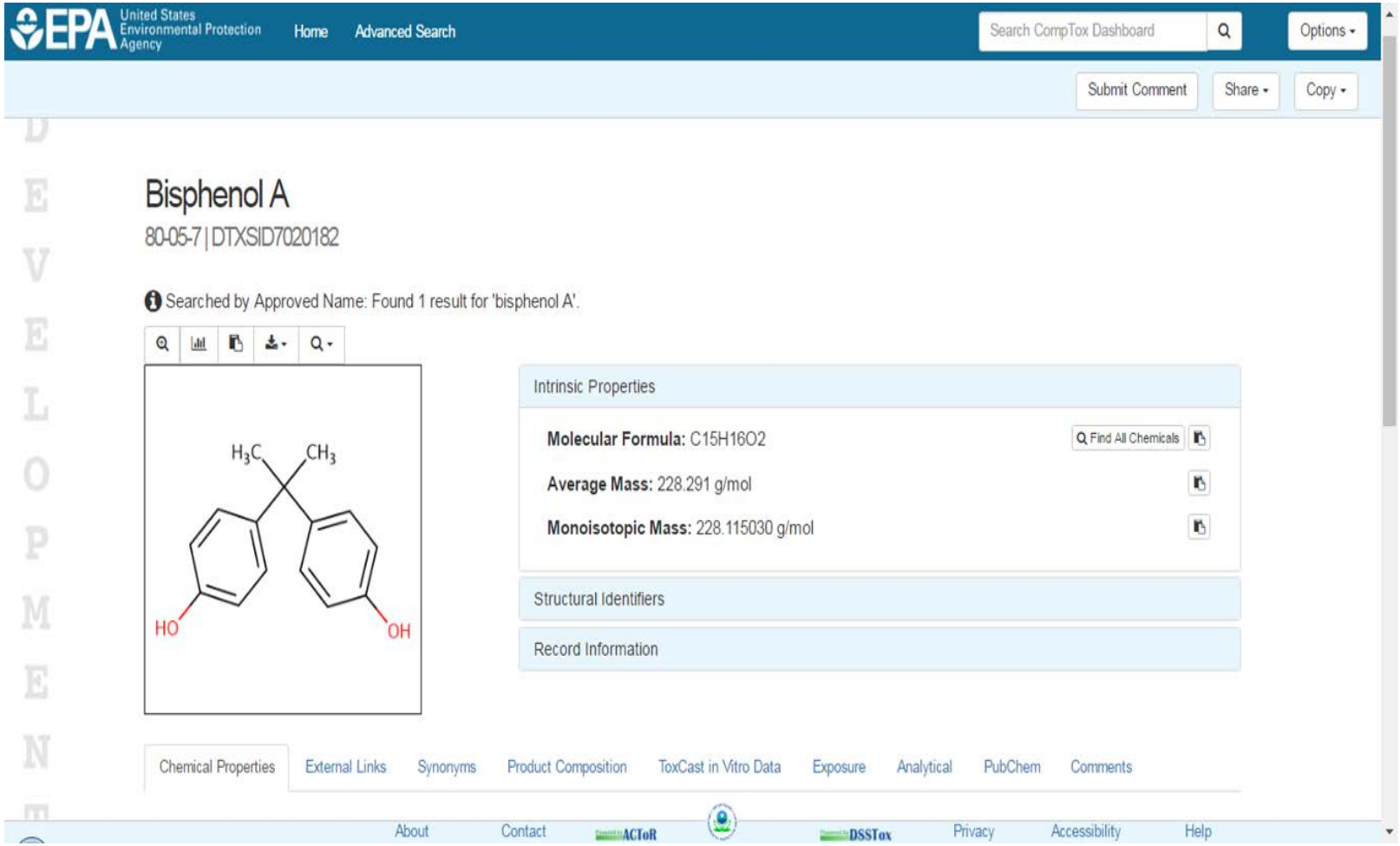
Database and Software Development

- We have developed a wide number of databases that are use to drive Dashboard Tools



Cheminformatics – The New Comptox Dashboard

- **~720,000 chemicals**
  - With quality metric scores
- >10 years assembling data
- Physchem properties
- Use and composition information
- Mass spec data
- Structural, formula, mass spec searching
- Downloading search outputs



https://comptox.epa.gov

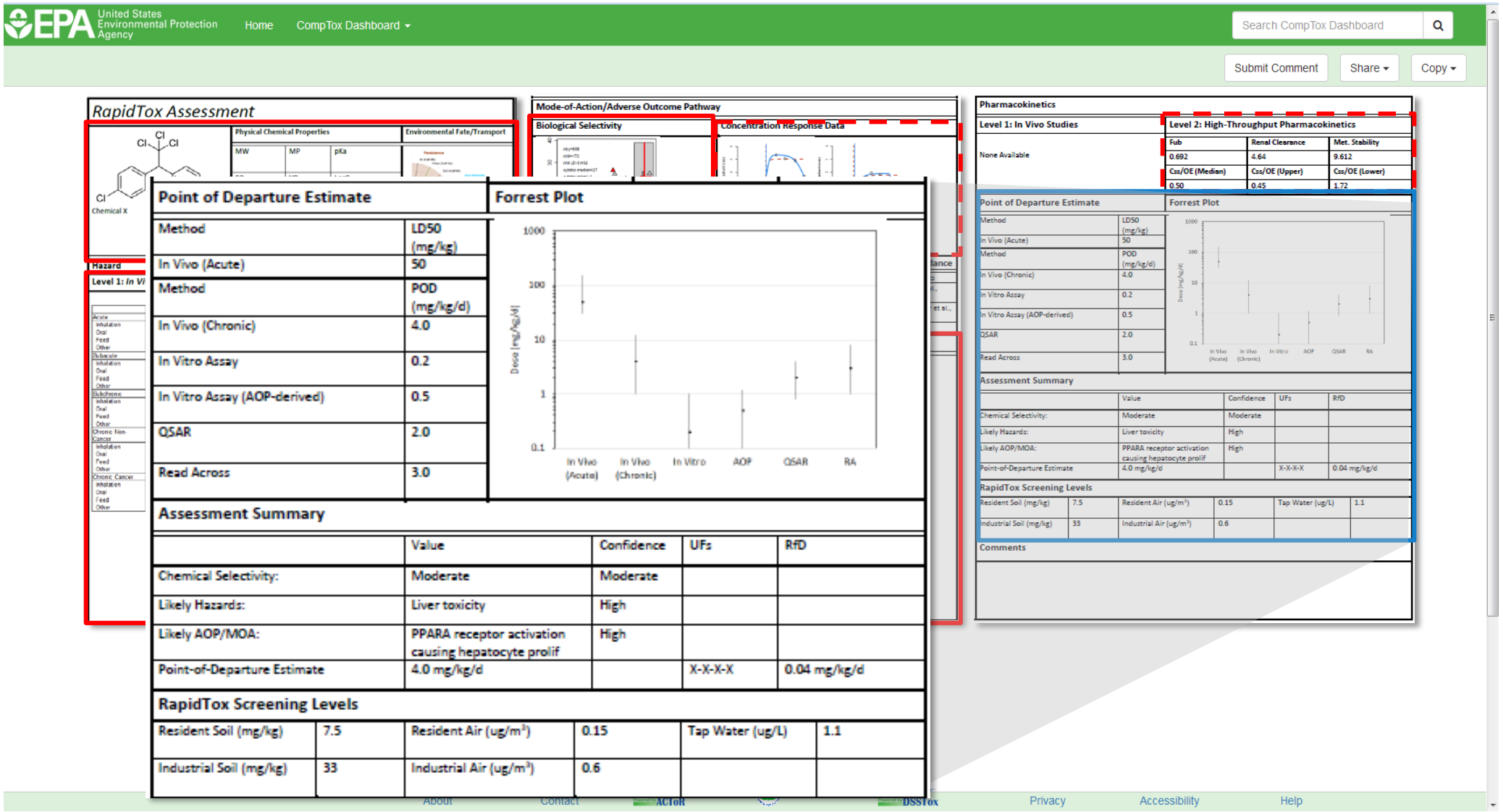
RapidTox Dashboard

- Goal: Enable *screening-level assessments* to be performed for hundreds to thousands of chemicals as part of a tiered approach
- Integrates data on chemical properties, fate and transport, hazard, and exposure through an interactive on-line dashboard

Tiered approach

- High Tier - Access to high-quality data as inputs to risk assessments, when available (e.g., IRIS, RfDs)
- Lower-Tier – access lower-tier data when higher-tier is not available (e.g., PPRTVs, in vivo and in vitro data)
- Develop and provide modeled inputs when lower-tier data in not available

RapidTox Dashboard

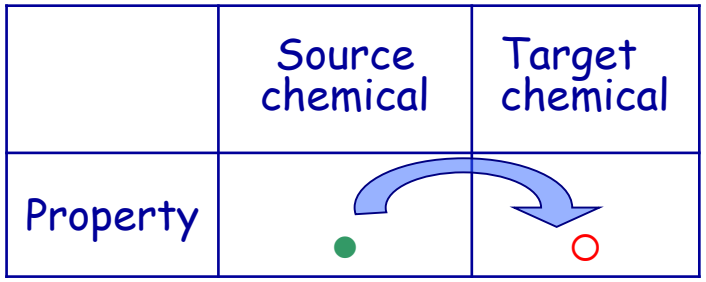


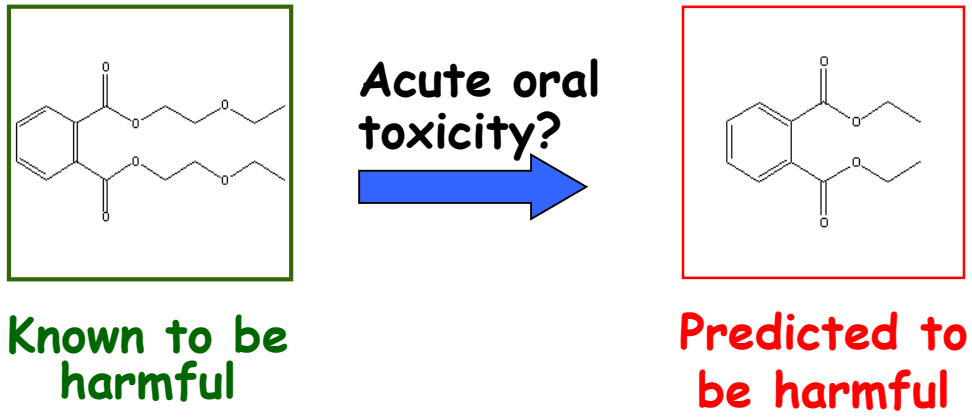
Not yet publically released

Uncertainty and Read-Across

- A major uncertainty in Read-Across models is that *development and acceptance* is very context dependent and based on subjective expert judgement.
- There is no harmonized approach to ensure er reproducible decisions

Critical need is an objective measure of uncertainty in a read-across prediction



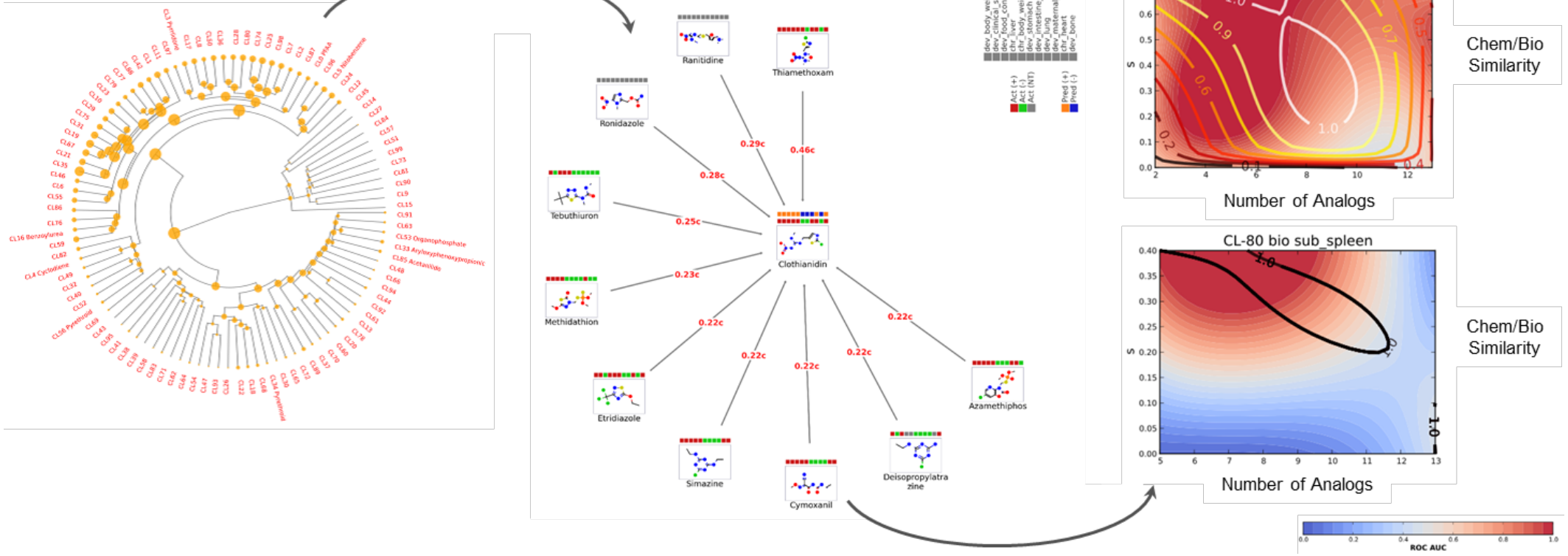


Quantitatively Evaluating Read-Across Uncertainty

Chemicals Clustered Based on Chemotype, Structure, or Biological Descriptors

Read-across Analysis Based on Similarity-Weighted Activity of Nearest Neighbors

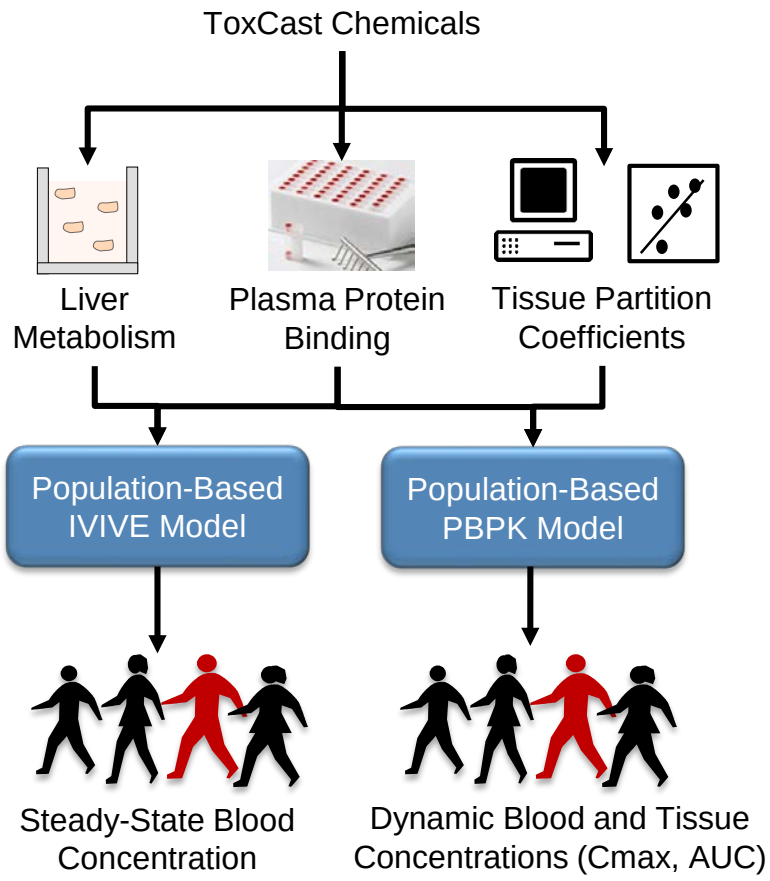
Uncertainty Analysis



Read-across approach will allow users to define similarity and analog cut-offs while trading off uncertainty

Patlewicz *et al.*, In Review

Evolution of High-Throughput Toxicokinetics



Present

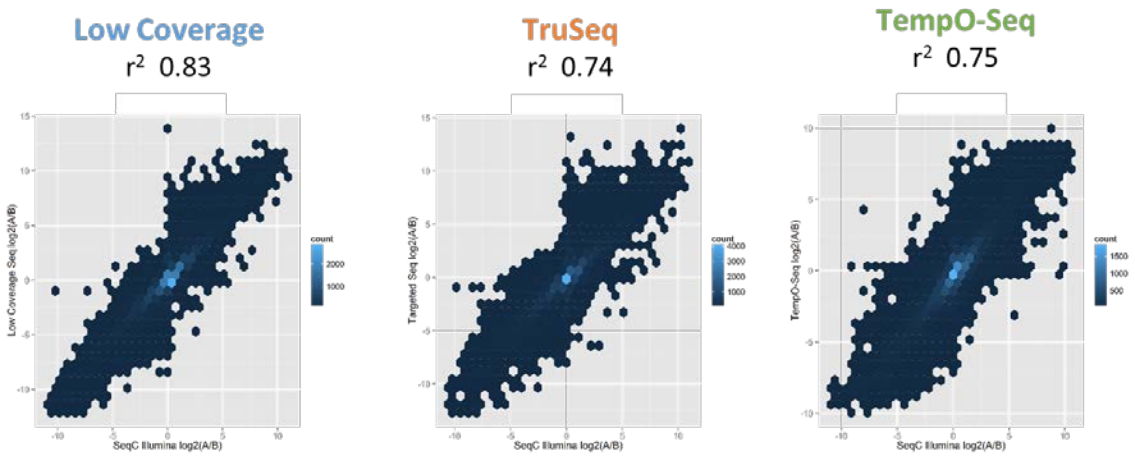
- Steady-state IVIVE models for hundreds of chemicals based on limited high-throughput *in vitro* assays
- Monte carlo methods incorporate inter-individual variability
- Structure-based methods to estimate tissue partitioning
- HT-Physiologically-Based Pharmacokinetic (HT-PBPK) models for hundreds of chemicals

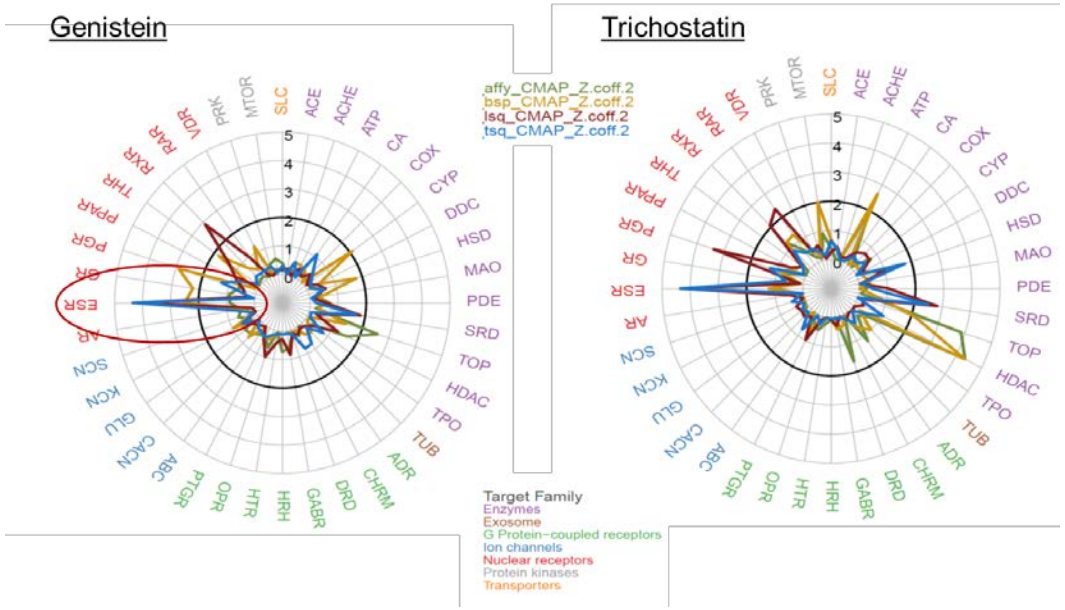
Planned

- Computational framework to compare IVIVE with *in vivo* data and allow explicit estimates of uncertainty
- Distinguish chemical classes where we do good and poor job of predicting pharmacokinetics

Ongoing Transcriptomics @ USEPA

- Technical & contractual evaluation of 3 technologies providing whole genome transcriptomics (Omega Low Coverage and Targeted & BioSpyder Temp-O-Seq)





Technical Performance Equal

Functional Performance Not Equal for Positive Controls

- BioSpyder awarded contract – based on functional performance and cost
- Currently engaged in pilot study to validate workflow and refine experimental design

Transcriptomics @ USEPA

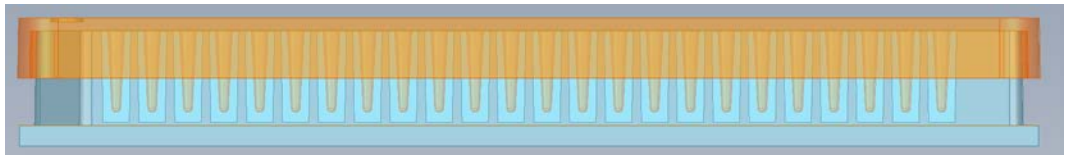
- **High-throughput transcriptomics will fundamentally change the way we evaluate chemicals for safety**
  - Greater coverage of biological space
  - Reduced cost
  - Ability to leverage large existing databases of gene expression data
  - Fits logically in a tiered testing approach
  - Allows dose- and time-response characterization

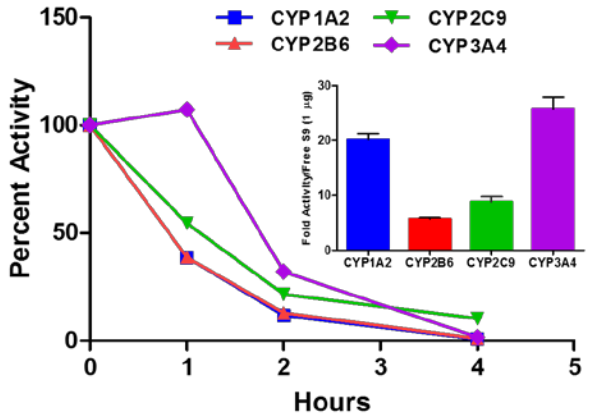
- **Optimization & operationalization underway - pilot study to validate workflow and refine experimental design**

- **Challenges remain:**
  - Cell type/line selection
  - Data handling and processing
  - Optimal data analysis procedures

Retrofitting Assays for Metabolic Competence – Extracellular Approach

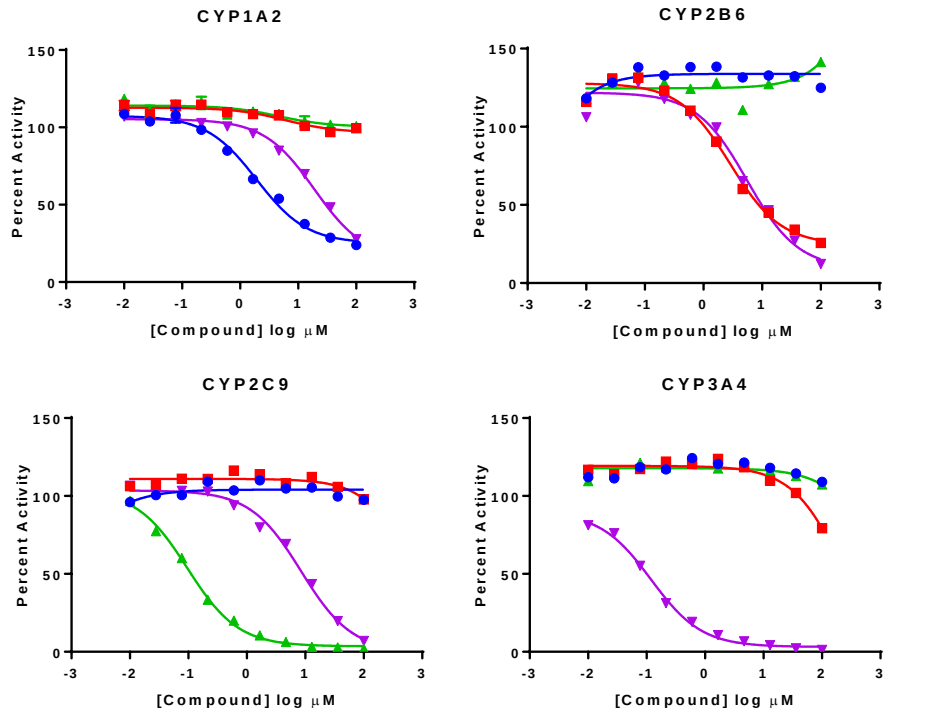
Alginate Immobilization of Metabolic Enzymes (AIME)





XME Activity in Microspheres

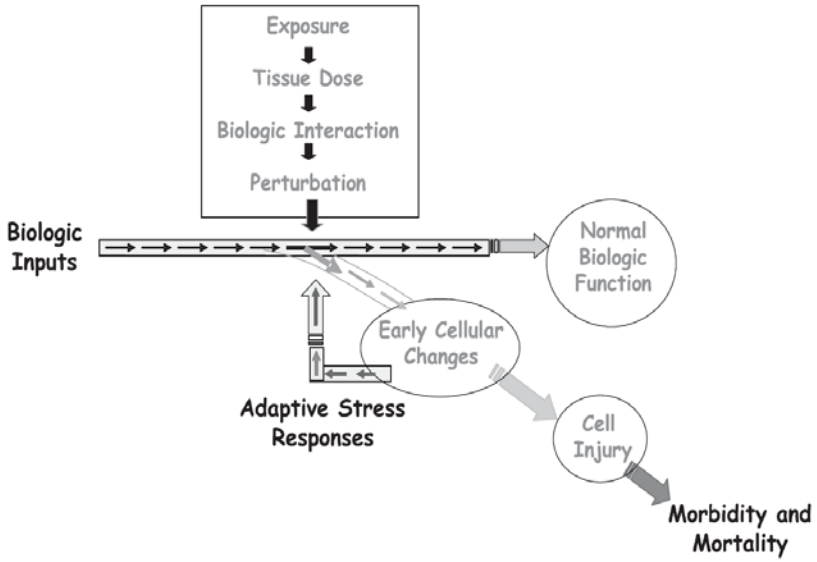
Small Molecule Inhibition of XME Activity



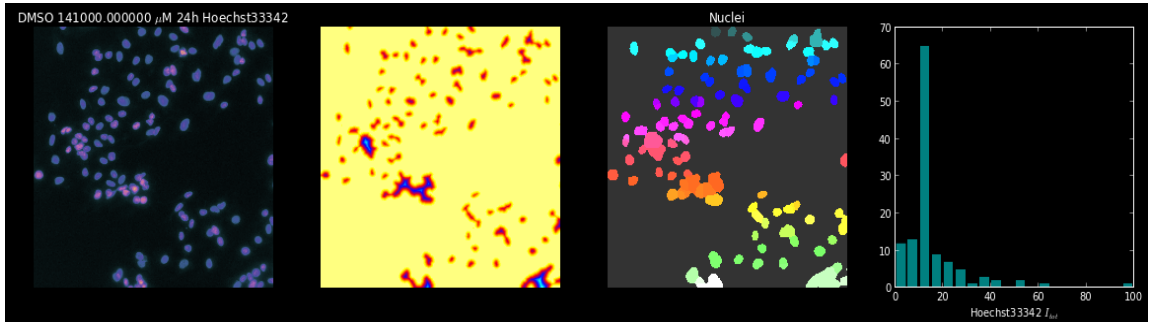
In Vitro Data – What is Adverse?

- What data from in vitro assays do we use as the point of departure for hazard assessments?
- How to discriminate between compensatory changes from changes that will (might) lead to adverse outcomes?

❑ **Tipping Point**: Threshold between adaptation and adversity



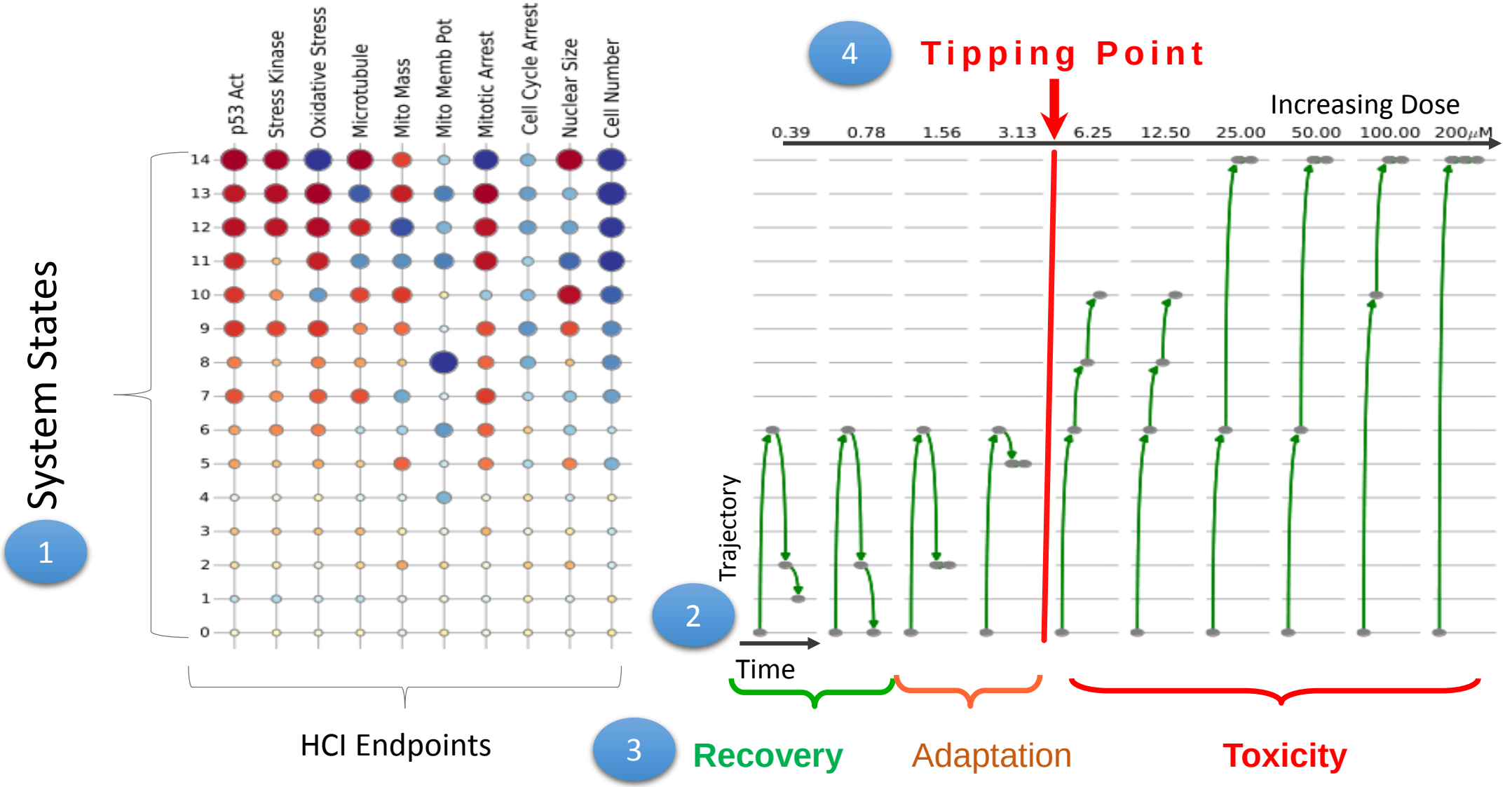
❑ Use ToxCast High Content Imaging (HCI) data to identify Tipping Points



- 967 chemicals (ToxCast)
- HepG2 cells culture
- 10 concentrations
- 3 Time points
- 10 HCI Assays
- 400 plates
- 100,000 wells
- 2,400,000 images

❑ Can we use **Tipping Point** to define a point of departure (PoD) for risk assessment ?

Tipping Point Analysis



Shah et al Environ Health Perspect 124:910–919; http://dx.doi.org/10.1289/ehp.1409029

EPA United States Environmental Protection Agency

EU-ToxRisk – Tox21
NCCT Team

Grace

Matt

We look forward to productive discussions and generating some great ideas for collaborative case studies

Kevin

Richard