# Computational Toxicology and High-Throughput Risk Assessment

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# ToxCast / Tox21 Context
# EDSP as case study

- Congress has mandated that EPA test 4000-8000 chemicals for their potential to be endocrine disruptors
  - Through interaction with estrogen and other pathways
  - US testing labs and EPA reviewers have a capacity to test ~100 chemicals per year in guideline studies (Tier 1)
  - 40-80 year backlog
- Prioritization is a logical approach
  - Test chemicals for ability to interact with E, A, T, S *in vitro*
  - "Validate" *in vitro* assays against expert-derived reference chemicals
  - Estimate **dose** at which activity can occur
  - Compare with estimated human exposure levels
  - Suggest testing those with an overlap **first** in science-based, standard, GLP, guideline studies

# High-Throughput Risk Assessment (HTRA)

- Uses HTS data for initial, rough risk assessment of data poor chemicals

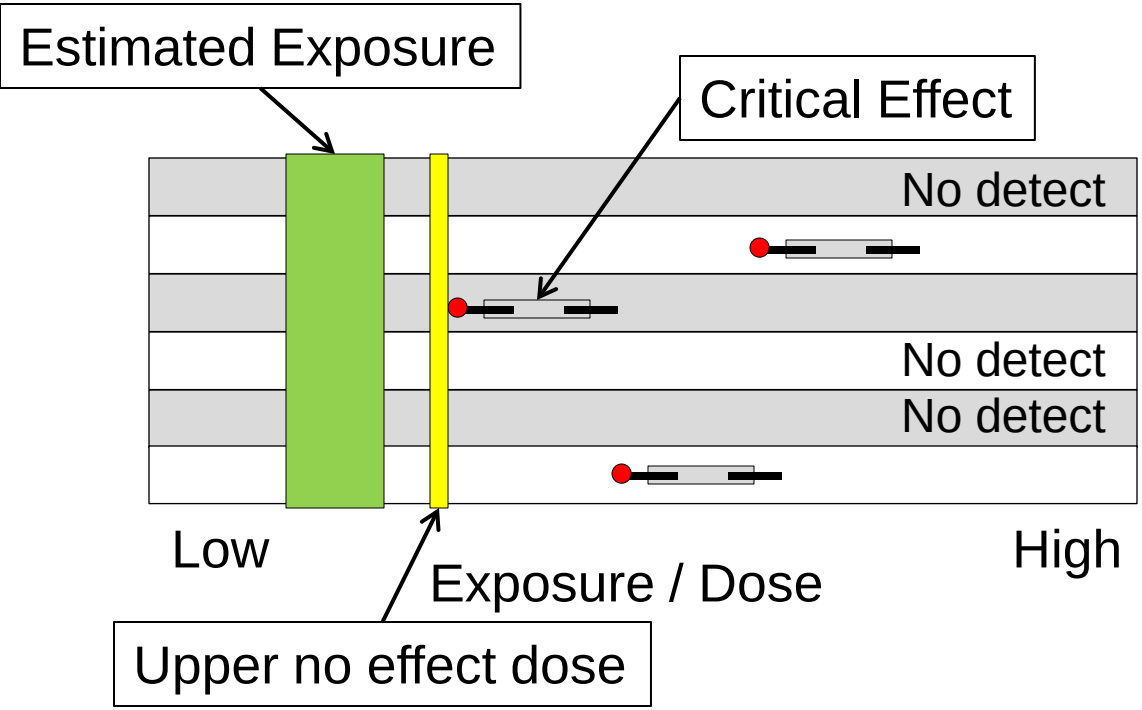
- Risk assessment  approach
  - Estimate upper dose that is still protective (~ RfD, BMD)
  - BPAD (Biological Pathway Altering Dose)
  - Compare to estimated steady state exposure levels

- Contributions of high-throughput methods
  - Focus on molecular pathways whose perturbation can lead to adversity
  - Screen 100s to 1000s of chemicals in HTS assays for those pathways
  - Estimate oral dose using High-Throughput PK modeling (R. Thomas talk)

- Incorporate population variability and uncertainty

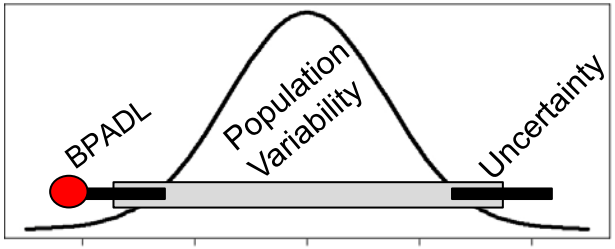
# High Throughput Risk Assessment (HTRA)

**HTRA Report Card For Chemical: ABC**



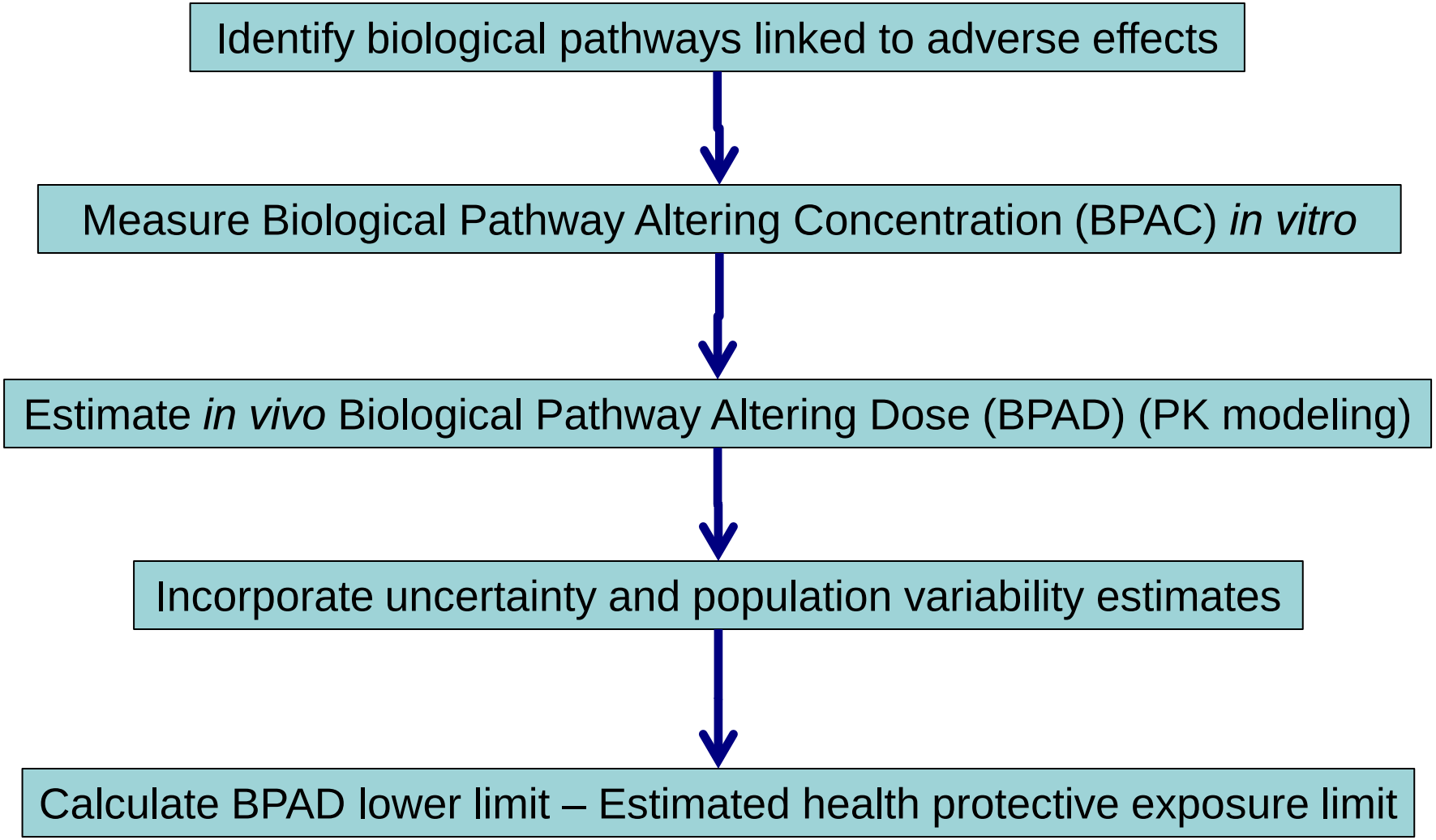

Pathway / Target / Model

CAR/PXR Pathway
ER / AR / Endocrine Targets
ReproTox Signature
DevTox Signature
Vascular Disruption Signature
Thyroid Cancer Signature




**BPAD Distribution**

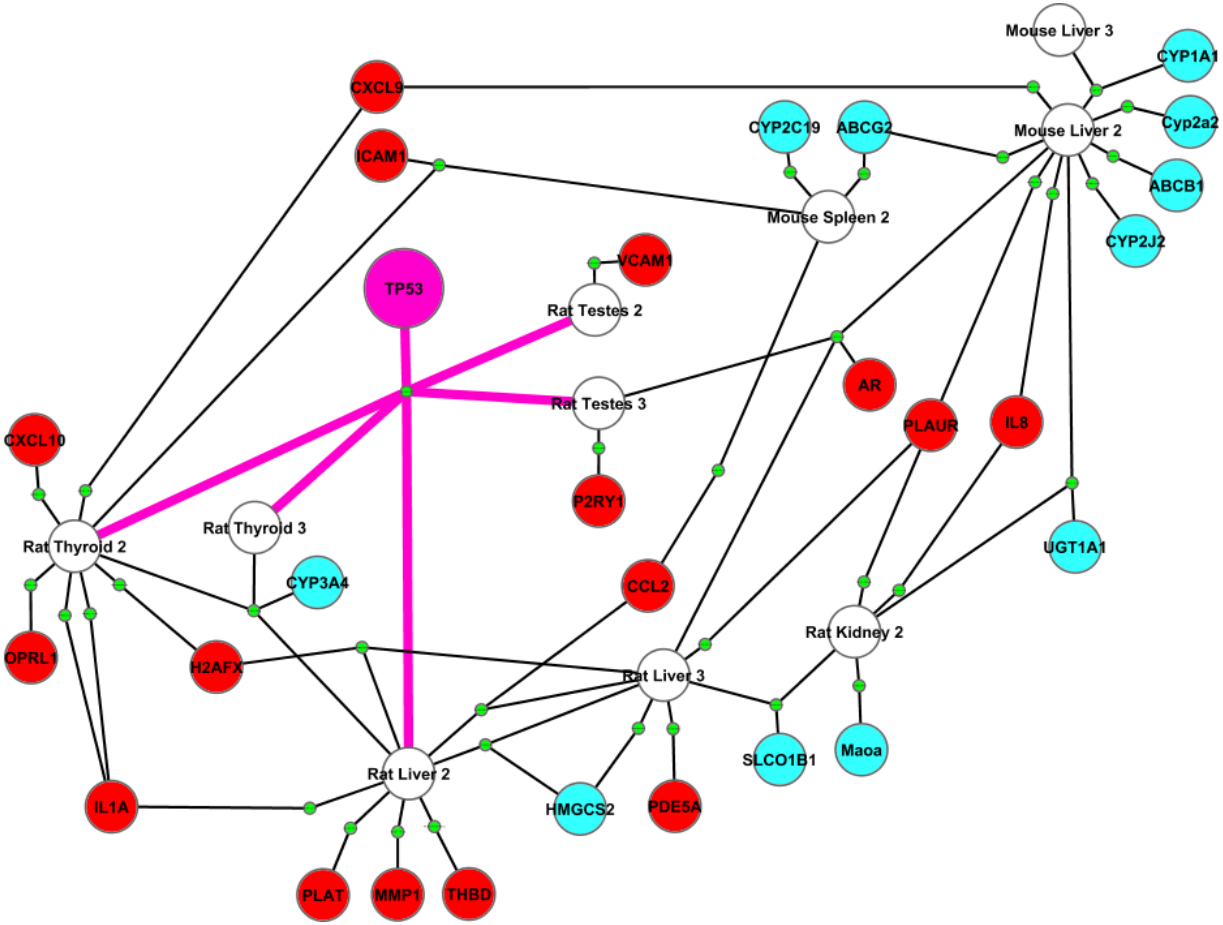
# HTRA Outline



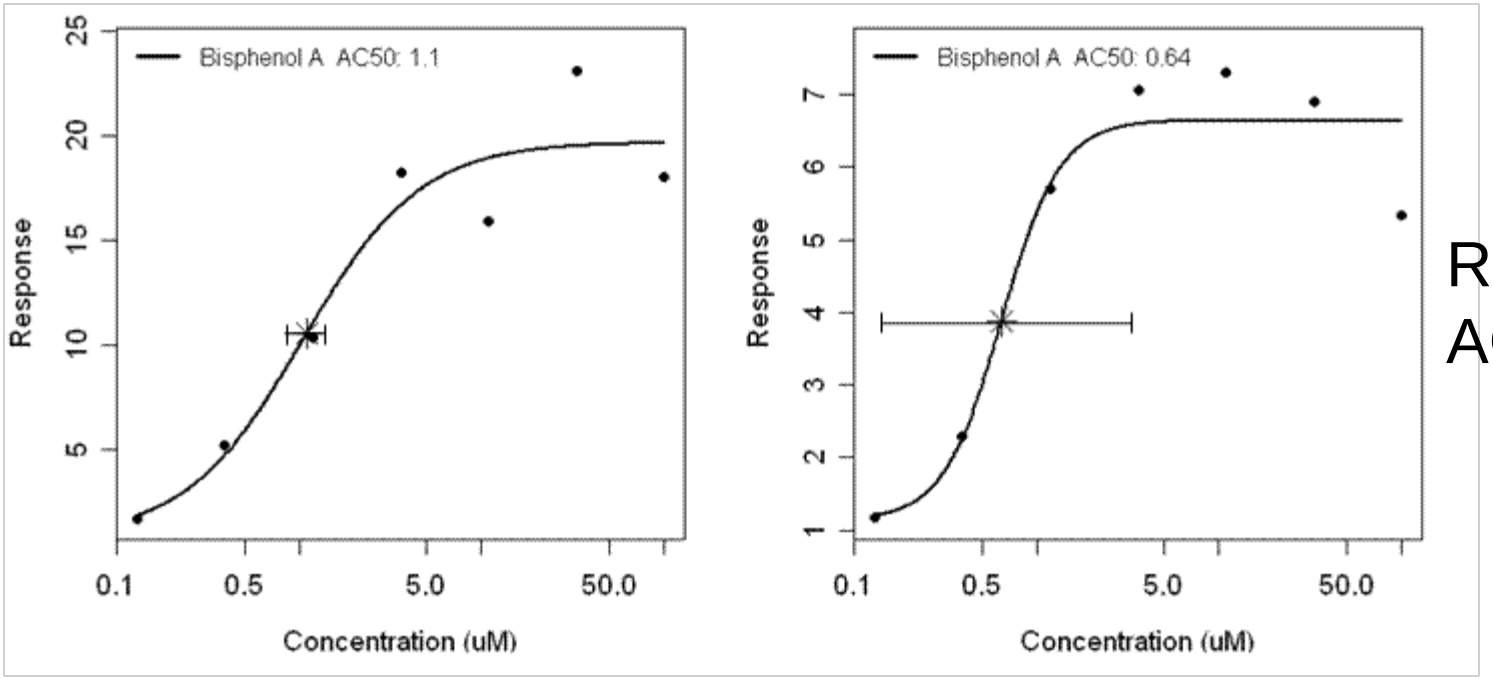
# Assay targets linked to rodent cancer

Out of hundreds of assays and targets, only a few are statistically associated with adversity and therefore useful for toxicity testing prioritization

All of these target-cancer links are backed up by the broader biomedical literature



# HTS – Pharmacodynamics (PD)

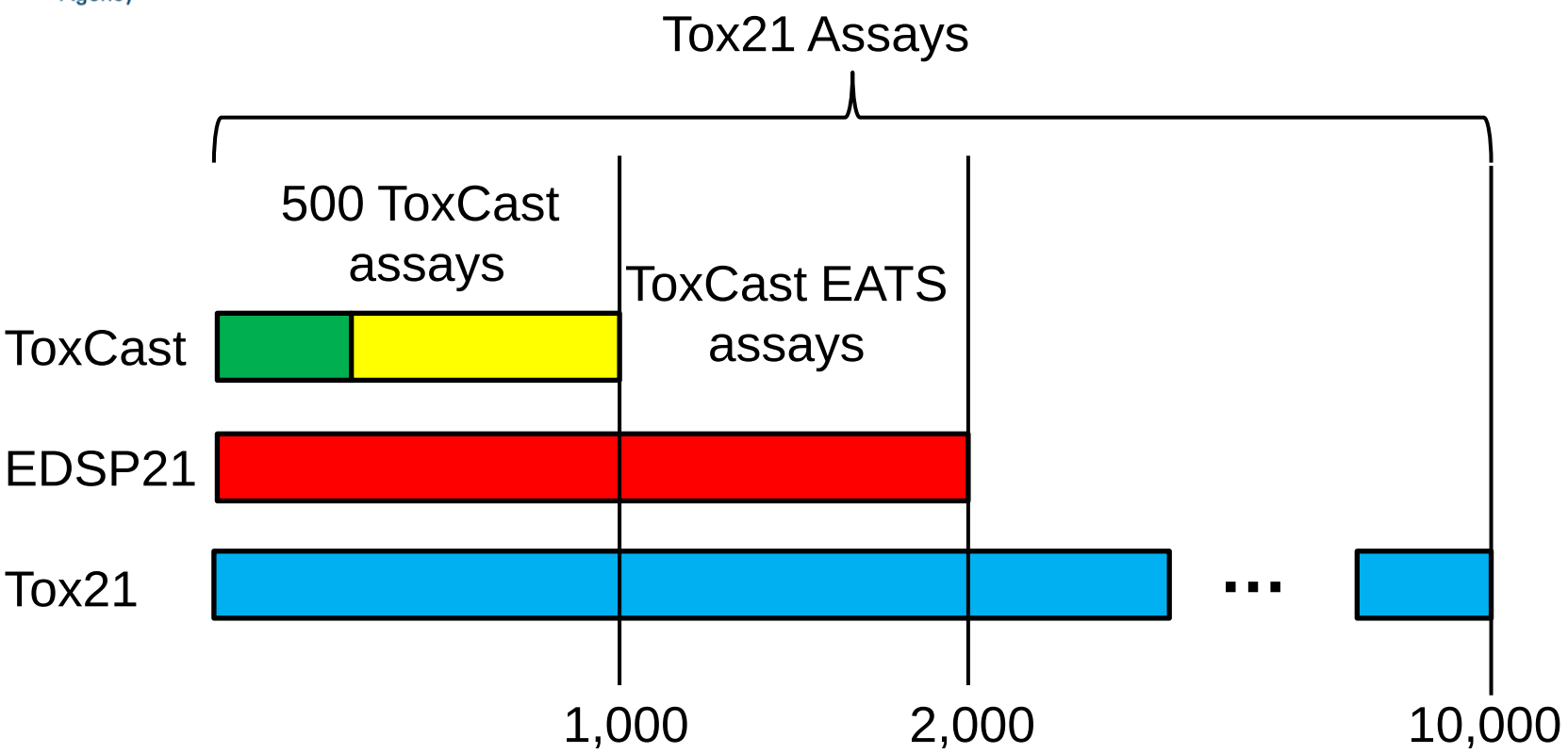



Result:
AC20, AC50

Sample curves for BPA in two ER assays

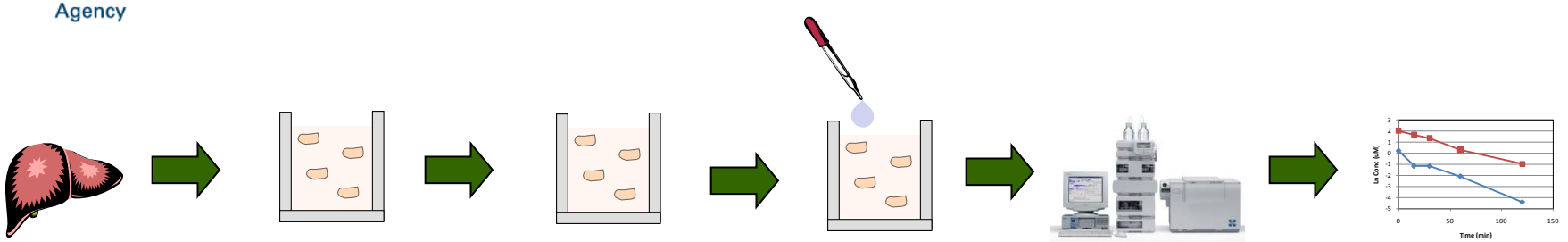
Full concentration-response profiles can be measured, at arbitrary spacing and to arbitrarily low concentrations

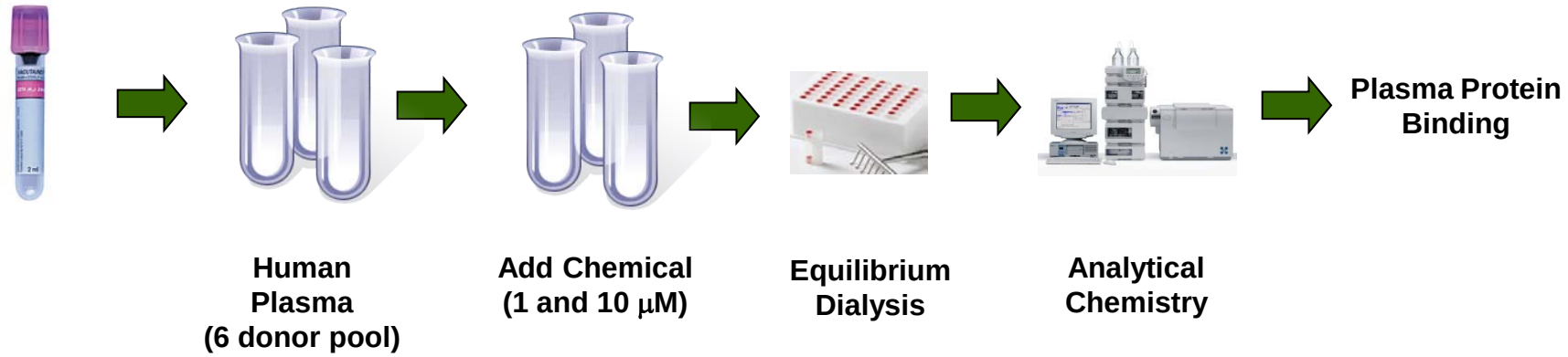
# HTRA HTS Chemical Space




Pesticides (active and inert), industrial chemicals, consumer products, marketed and failed pharmaceuticals, food additives, water contaminants, natural human metabolites

# Reverse Toxicokinetics



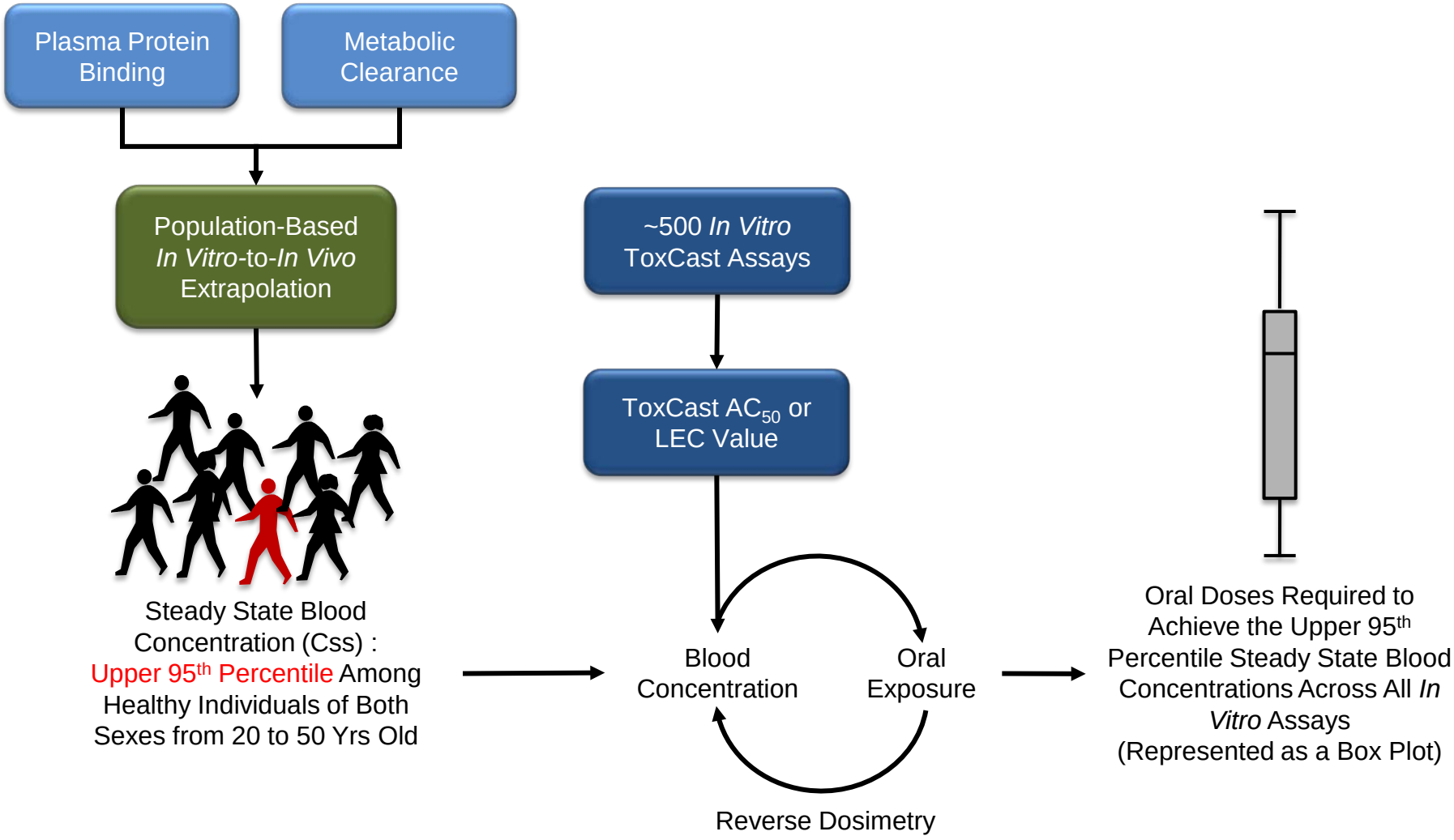

Combine experimental data with PK Model to estimate dose-to-concentration scaling

"Reverse Toxicokinetics"

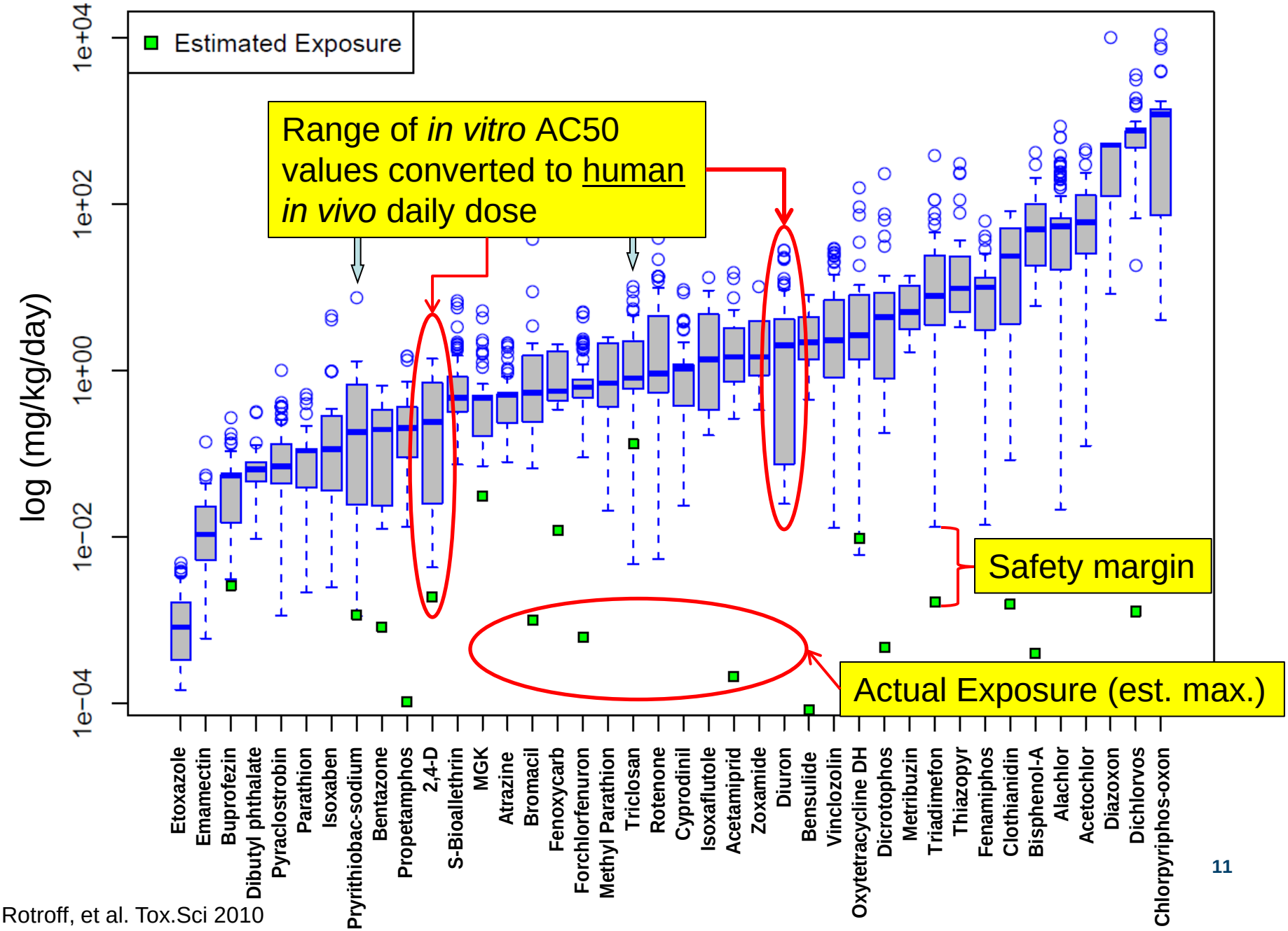


In collaboration with Hamner Institutes / Rusty Thomas, et al.

# Oral Equivalent Distributions

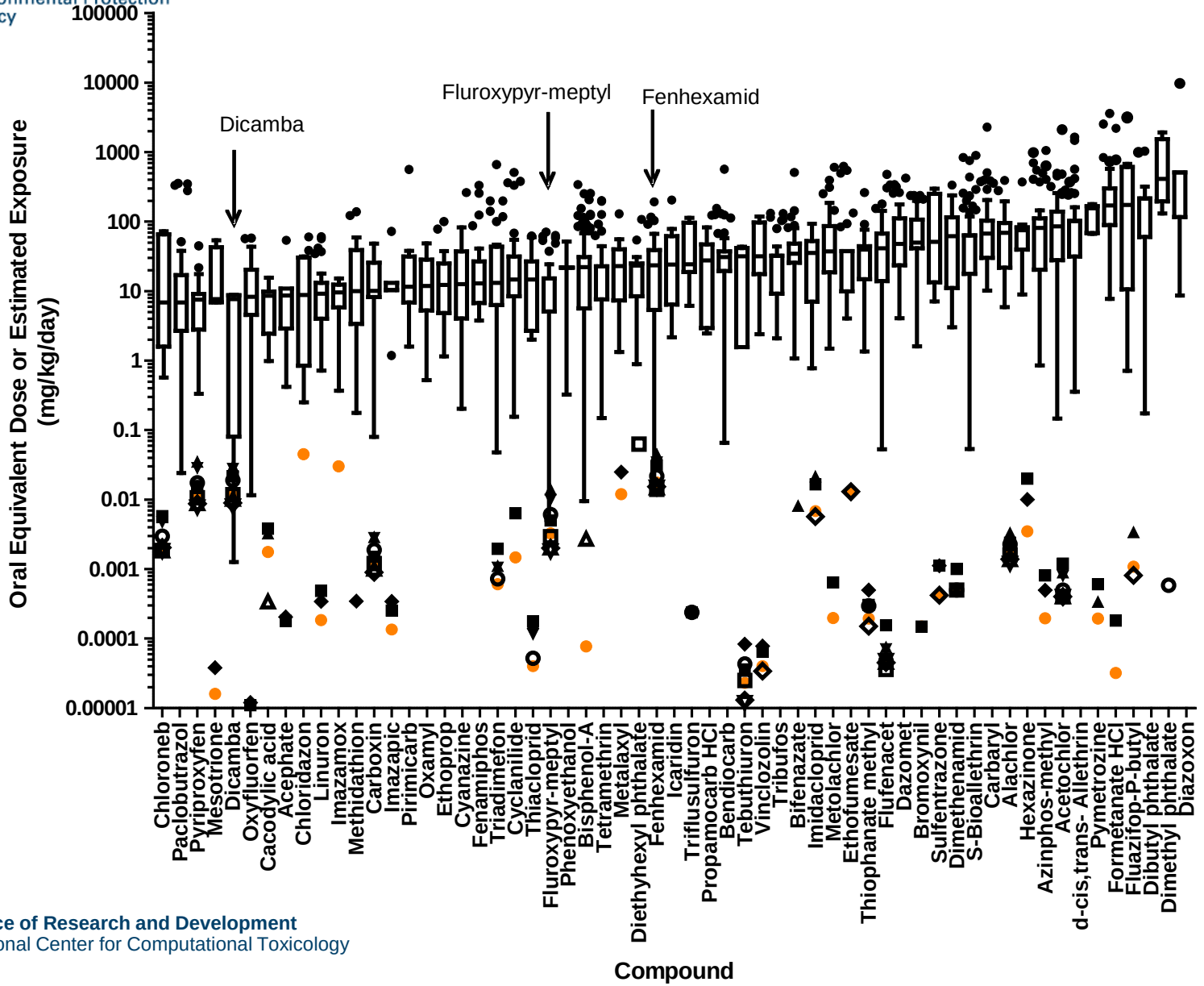


# Combining *in vitro* activity and dosimetry



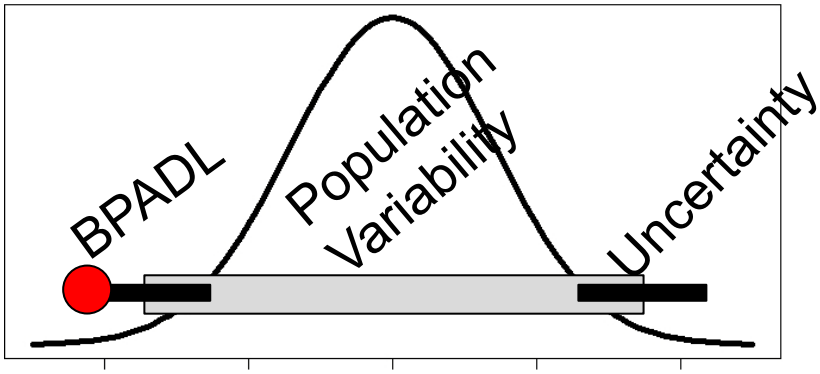

Rotroff, et al. Tox.Sci 2010

United States Environmental Protection Agency



# BPAD Probability Distribution

- "Biological Pathway Altering Dose"
- BPAD = BPAC / $C_{ss}$ / DR




**BPAD Distribution**

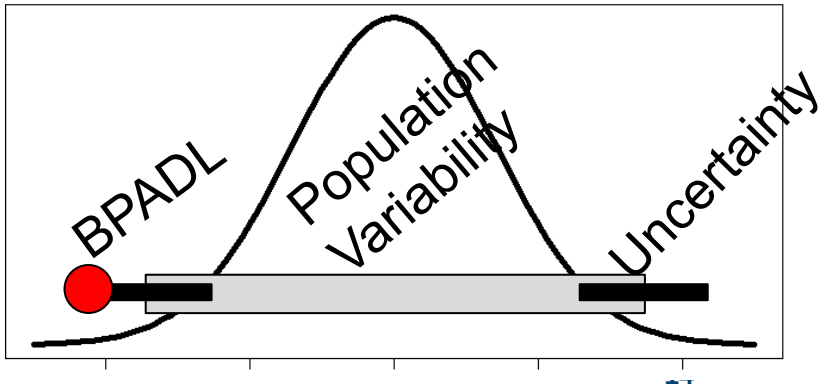
- Add in uncertainty and population variability
- Take low dose end of distribution (BPADL) as health-protective estimate of allowable safe exposure level

This is being used where no animal data is available!

# BPAD Variability and Uncertainty

- Variability
  - PK – models are available (CYPs, liver mass, age, populations)
  - PD – HapMap vs. chemicals vs. assays (UNC, NCGC)

- Uncertainty
  - PK – model uncertainty, experimental measurement
  - PD – assay background, experimental noise

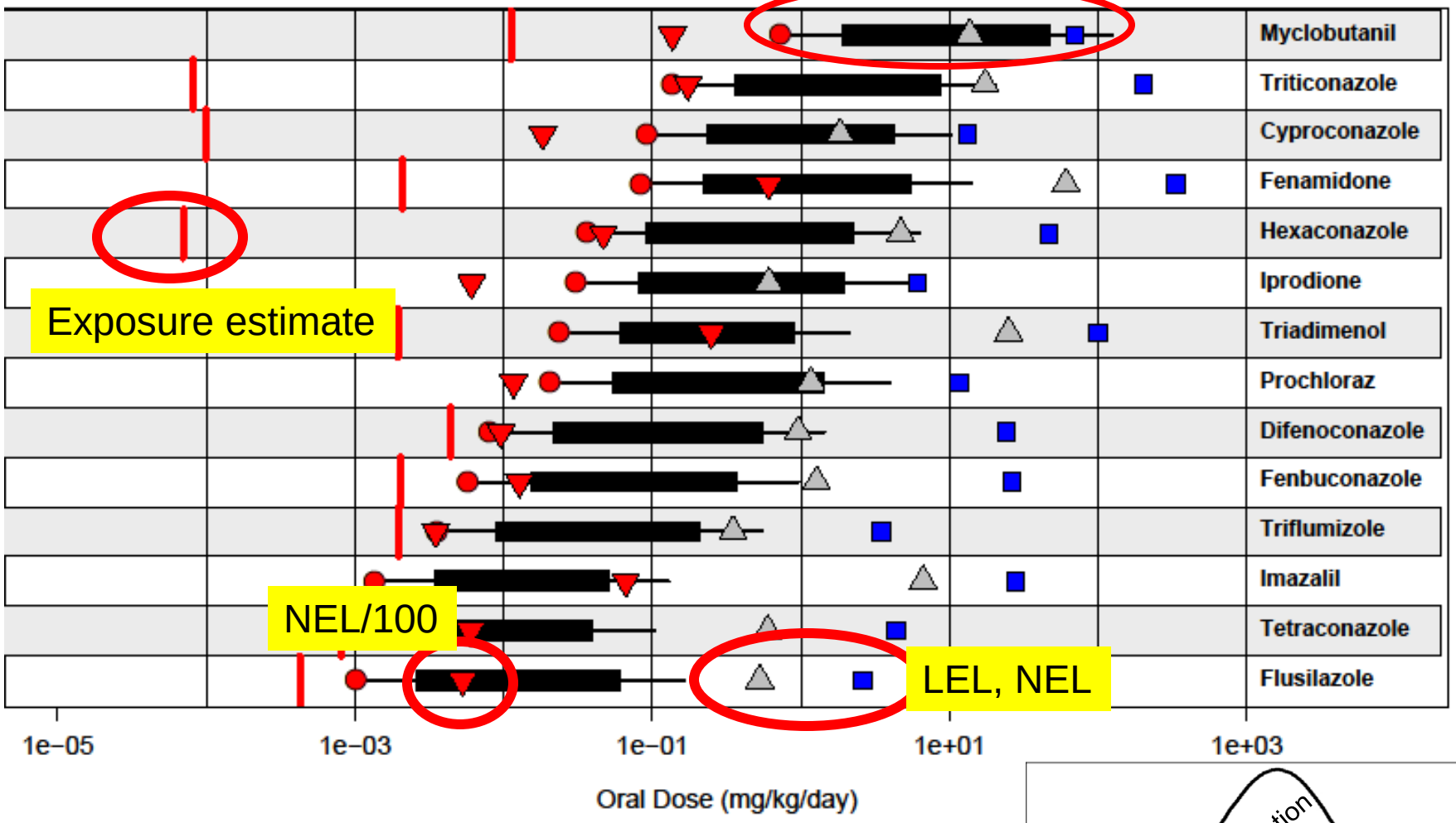


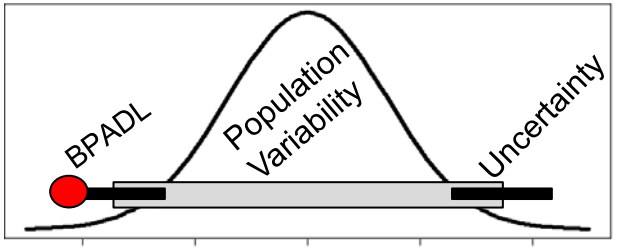

**BPAD Distribution**

# Conazoles and Liver Hypertrophy

- Conazoles are known to cause liver hypertrophy and other liver pathologies
- Believed to be due (at least in part) to interactions with the CAR/PXR pathway
- ToxCast has measured many relevant assays
- Calculate BPADL for 14 conazoles
  - Compare with liver hypertrophy NEL/100

# Conazole / CAR/PXR results




**BPAD Distribution**

# Conazole Summary

- Rough quantitative agreement
  - Significant BPADL vs. NEL/100 rank correlation (p=0.025)
  - 12 of 14 chemicals have BPADL within 10 of NEL/100
  - For only 3 is BPADL significantly less protective than NEL/100
  - All BPADL > Exposure estimate

- Some apples to oranges: human BPADL, rat NEL
  - Rat RTK underway for some of these chemicals

# BPADL vs. Exposure

- "Allowable exposure levels" (RfD, BPADL, etc.) are only relevant compared to exposure

- HTRA looks at many chemicals simultaneously in a prioritization context
  - Prioritize further testing if BPADL < estimated exposure

- Drives ExpoCast program (exposure parallel to ToxCast)
  - Hard to measure exposure in HT
  - Need to model

# HTRA Summary

1. Select toxicity-related pathways
2. Develop assays to probe them
3. Estimate concentration at which pathway is “altered” (PD)
4. Estimate *in vitro* to *in vivo* PK scaling
5. Estimate PK and PD uncertainty and variability
6. Combine to get BPAD distribution and health protective exposure limit estimate (BPADL)

- Many (better) variants can be developed for each step (1-6)
- Use for analysis and prioritization of data-poor chemicals

# ExpoCast

Environment

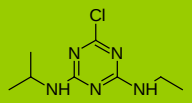
Human

Sources

Distribution/Fate

Products

Contact




Chemicals

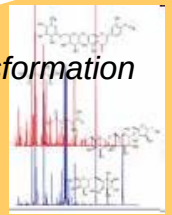
Exposure

Exposure Media

Uptake

Background Exposure

Biotransformation



Biomonitoring

Population

Host Susceptibility

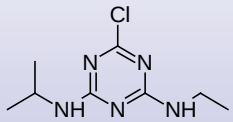
Rapid Prioritization

Relate real-world exposures with toxicity pathway perturbations

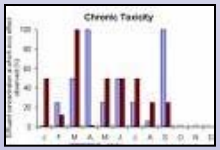
Select doses for toxicity testing

Translate in vitro results for risk assessment

HTS assays




Toxicity endpoints




In vivo bioassays

Data Repositories

Mechanistic Models

Informatics Approaches

Knowledge Systems

Network Models

Exposome

# High-throughput Exposure Estimates

- Hard, because most chemicals are not BPA, dioxin-like in their data-richness
- Data
  - Use class, products
  - Measured data
    - Pesticide residues
    - Water / air / monitoring
  - Captured in ACToR (http://actor.epa.gov)
- Models
  - USEtox
  - RAIDAR
  - MENTOR
  - GxE FRAMES

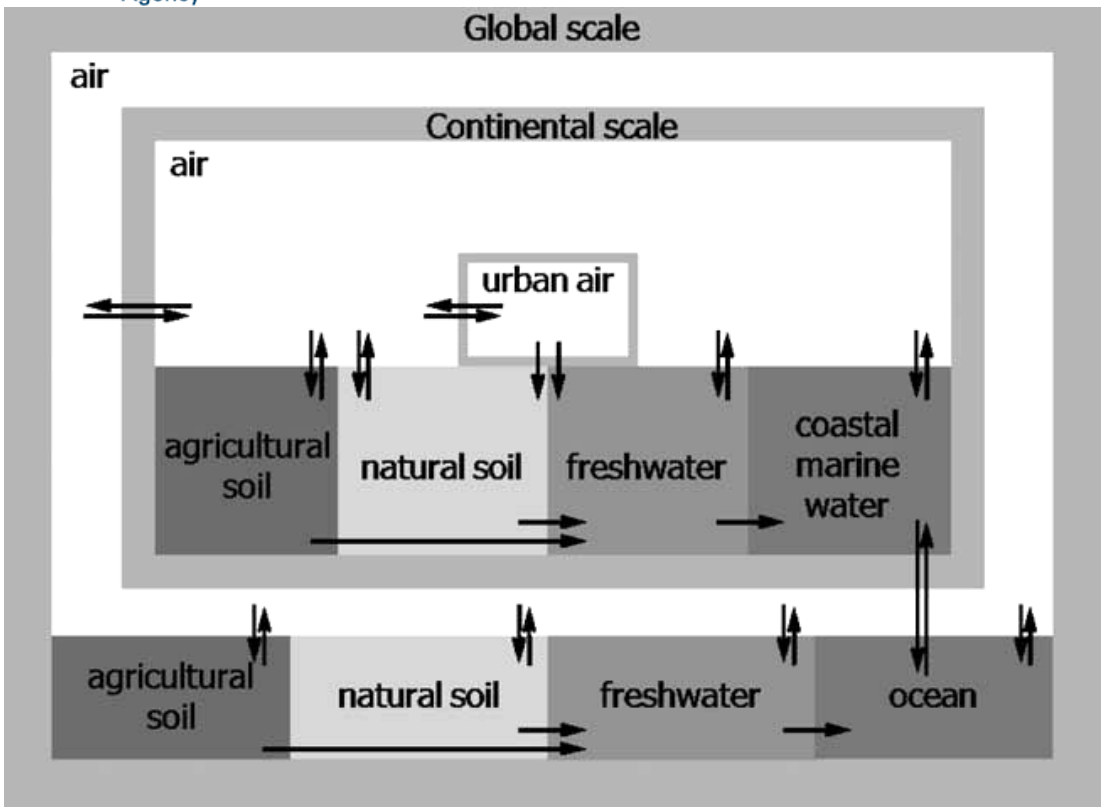
# Exposure-Based Prioritization Model Challenge

- Improve understanding of existing prioritization schemes or models for evaluating potential exposures.

- Participating teams/models
  - USEtox
  - RAIDAR
  - MENTOR
  - GxE FRAMES

- Models are being applied to evaluate common list of 52 chemicals
  - High interest to EPA
  - Relatively data rich
  - Do not span the full range of potential exposure

# Far Field Exposure (Fate and Tranport) Models: USEtox




http://www.usetox.org/

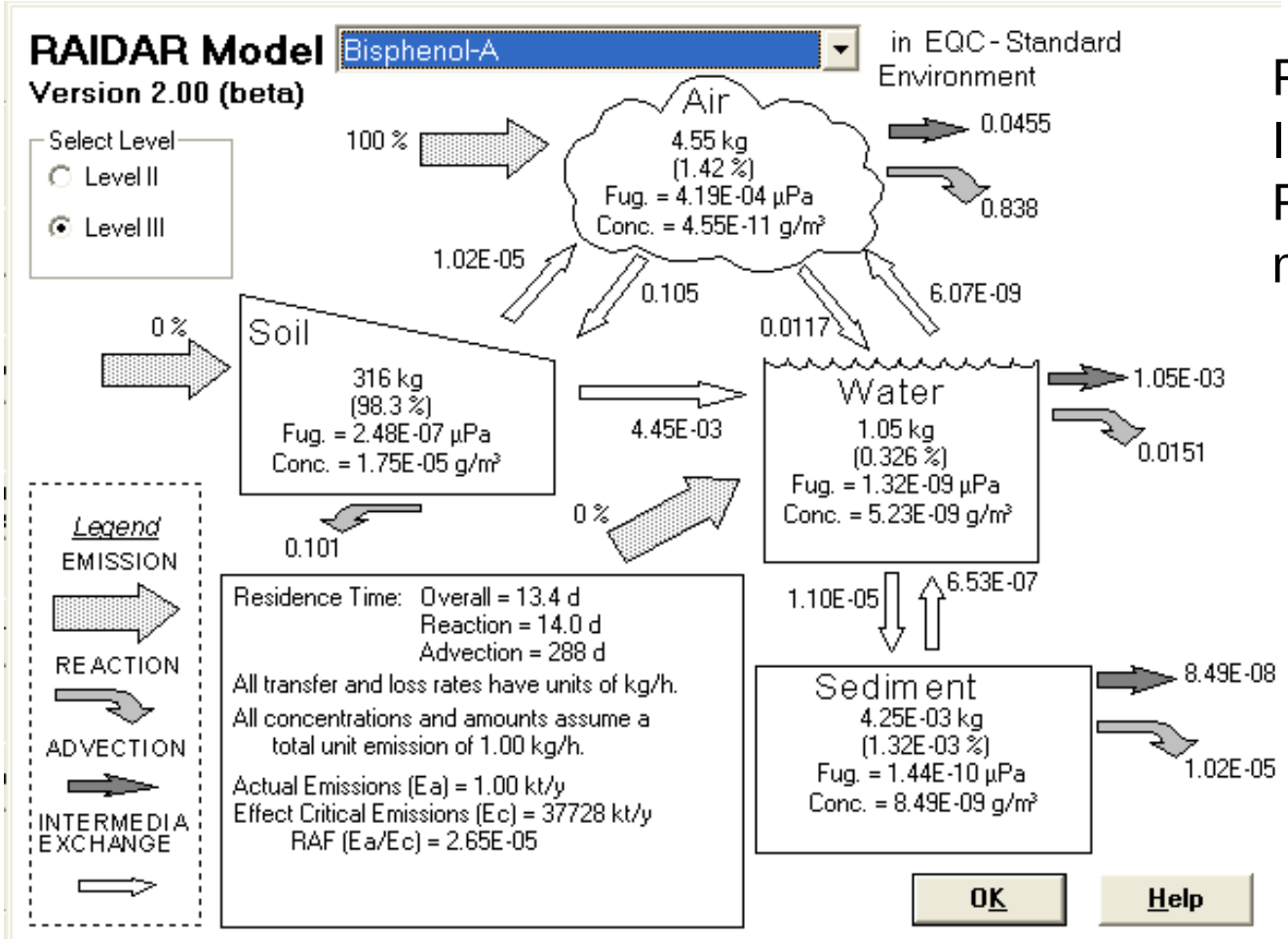
"The USEtox™ model is an environmental model for characterization of human and ecotoxic impacts in Life Cycle Impact Assessment and for comparative assessment and ranking of chemicals according to their inherent hazard characteristics."

*Rosenbaum, R.K. et al., (2008)* Int J Life Cycle Assess DOI 10.1007/s11367-008-0038-4

Predicts increase in eleven compartments (five global, five continental, and urban air) due to additional 1 kg/day emitted

Steady-state model

# Far Field Exposure (Fate and Transport) Models: RAIDAR




Risk Assessment, IDentification, And Ranking (RAIDAR) model

*Arnot, J.A., Mackay, D., and Webster, E. Environ. Sci. Technol.* (2006) 40 (7), pp 2316–2323

Steady-state model

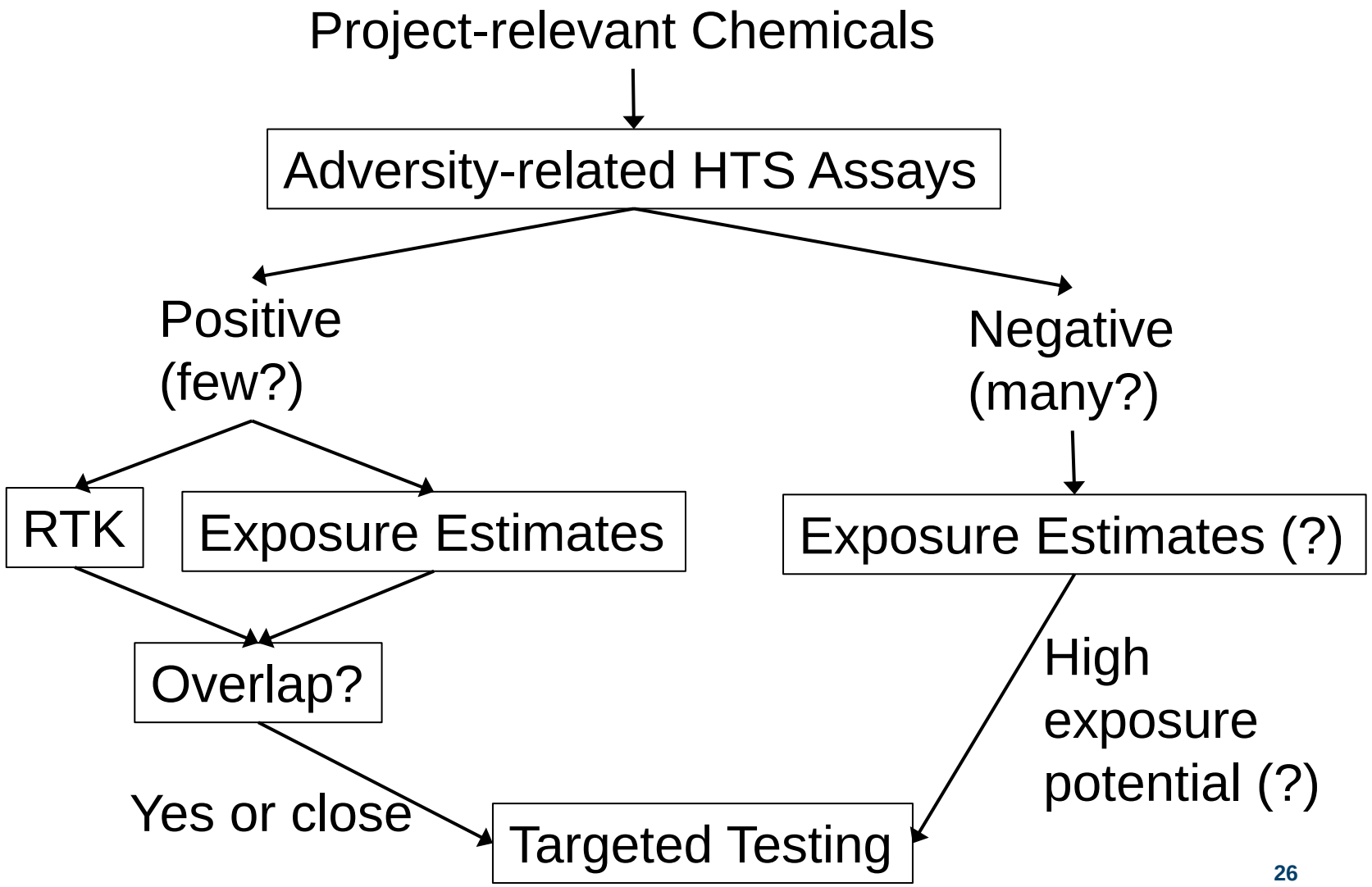
# LRI RfP: Developing Exposure Indices for Rapid Prioritization of Chemicals in Consumer Products:

- Leverage the best existing exposure models
  - Derive exposure classification indices

- Consider multiple metrics to cover important aspects of exposure space and product lifecycle:
  - Physical -Chemical properties
  - Product characteristics (manufacture, formulation, use, lifecycle)
  - Emission characteristics (indoor/outdoor, media of release, amount available for release/contact)
  - Pathways (media, routes)
  - Scale (far-field, near-field)
  - Target characteristics (individual, population, lifestage, lifestyle, susceptibility)
  - Dosimetry (ADME)

- Demonstrate application ~100-1000 chemicals

# HTRA Prioritization Scheme

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