ICCVAM Public Forum: Update from EPA

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Background: Pesticides

- EPA's Office of Pesticide Programs has developed a *Strategic Direction for New Pesticide Testing and Assessment Approaches*
  - http://www.epa.gov/pesticides/science/testing-assessment.html.
  - A broader suite of computer-aided methods to better predict potential hazards and exposures, and to focus testing on likely risks of concern;
  - Improved approaches to more traditional toxicity tests to minimize the number of animals used while expanding the amount of information obtained;
  - Improved understanding of toxicity pathways to allow development of non-animal tests that better predict how exposures relate to adverse effects;

Guiding Principles for Data Needs for Pesticides

- *Guiding Principles for Data Requirements*
  - Purpose: provide consistency in the identification of data needs, promote and optimize full use of existing knowledge, and focus on the critical data needed for risk assessment.
  - http://www.epa.gov/pesticides/regulating/data-require-guide-principle.pdf
- "…ensure there is sufficient information to reliably support registration decisions that are protective of public health and the environment while avoiding the generation and evaluation of data that does not materially influence the scientific certainty of a regulatory decision…."
- "…avoid unnecessary use of time and resources, data generation costs, and animal testing."

From December 8, 2011 to March 20, 2015

Type of Study	Waivers Granted	Required Studies	Total # of Requests
Inhalation	173	42	215
Neurotoxicity	118	13	131
Dermal	35	2	37
Developmental	21	4	25
DNT	10	1*	11
Subchronic Dog	7	1	8
Reproductive	16	3	19
Immunotoxicity	165	11	176
Chronic/ Carcinogenicity	15	2	17
Subchronic Rat	5	1	6

Alternative Assays: Implementation

- *PROCESS FOR ESTABLISHING & IMPLEMENTING ALTERNATIVE APPROACHES TO TRADITIONAL IN VIVO ACUTE TOXICITY STUDIES*
  - USEPA OPP document: Draft for public comment will be available soon
- This draft document describes a transparent, stepwise process for evaluating and implementing alternative methods of testing for acute oral, dermal, inhalation toxicity, along with skin and eye irritation and skin sensitization (often referred to as the "six pack studies").
- Three phases of this process and the implications for reporting information under section 6(a)(2) of FIFRA.
  - Evaluation
  - Transition
  - Implementation

Alternative Assays: Implementation

- Collaborative project with multiple stakeholders & NICEATM
- Goal: Integrated testing strategies for skin sensitization, dermal irritation, eye irritation that apply to pesticides
  - EPA OPP, Canada PMRA, animal welfare groups, & industry
  - Eye irritation being evaluated first
- Science & policy issues for consideration:
  - single agents vs. mixtures (formulations)
  - GHS vs. US/Canada categorization schemes
  - Training of staff
  - Implications for labeling

Case Example: Synthetic pyrethroids & naturally occurring pyrethrins

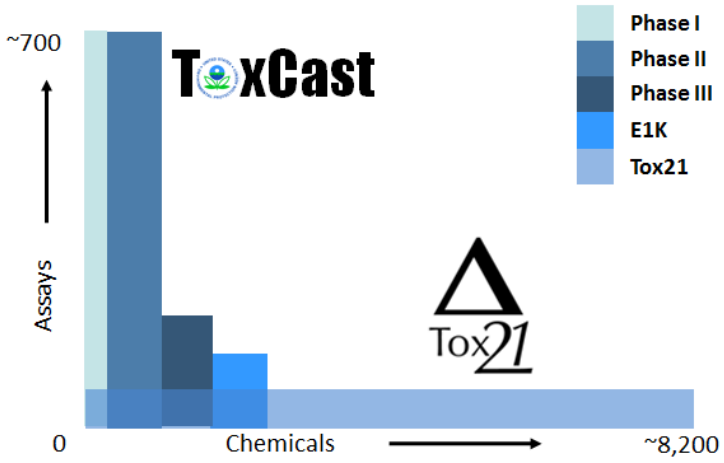
- Move away from apical endpoints towards hypothesis-based testing using
  - *in vitro* studies,
  - targeted *in vivo* studies,
  - Read across
    - Large dataset for 2, medium for several more, low for remaining
- Focus on toxicokinetics & internal dosimetry
  - predictive PBPK modeling (reliant largely on *in vitro* to *in vivo* extrapolation)
- Industry research effort using AOP.
  - Status of the research reviewed by the FIFRA SAP, May 19-22, 2015

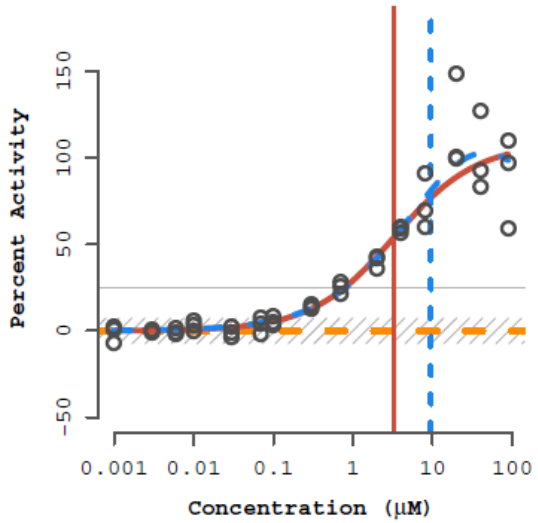
EPA EDSP Update

- EPA Program Offices working closely with ORD and NICEATM to evaluate high throughput data and computational models for regulatory decision making
- December 2014
  - Independent scientific review of high throughput bioactivity models (ToxCast/Tox21)
  - Integration of bioactivity and exposure models for prioritizing and screening chemicals

High-Throughput Screening

- ToxCast has screened ~2,000 chemicals across ~700 assay endpoints
- Tox21 has screened ~8,200 chemicals across ~50 endpoints
- ToxCast assay coverage represents over 327 genes and 293 pathways

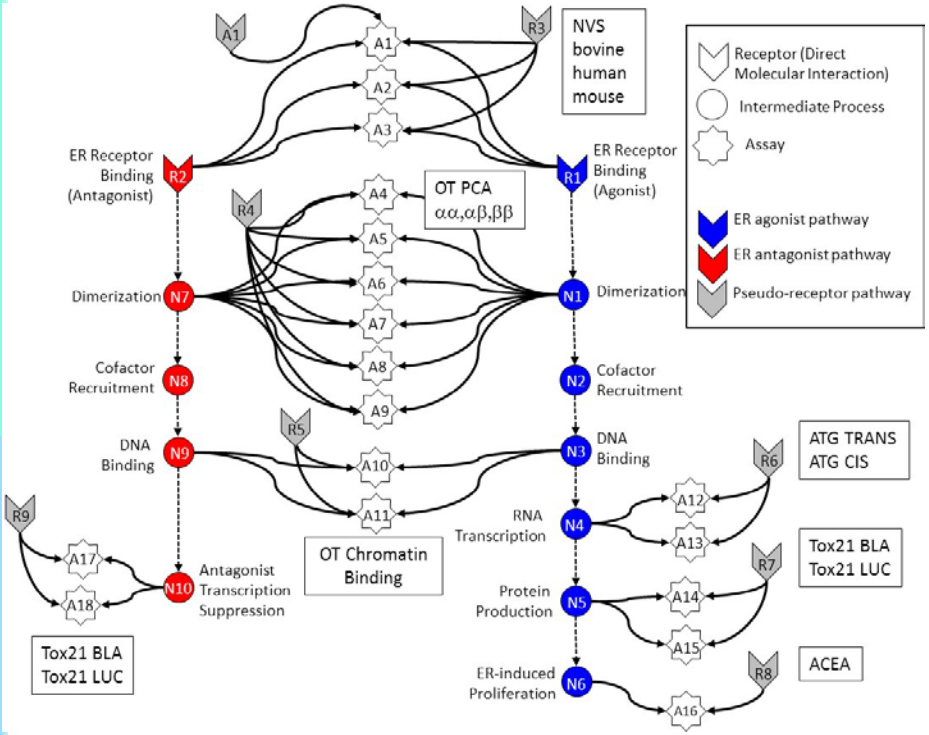




HTS Application to EDSP

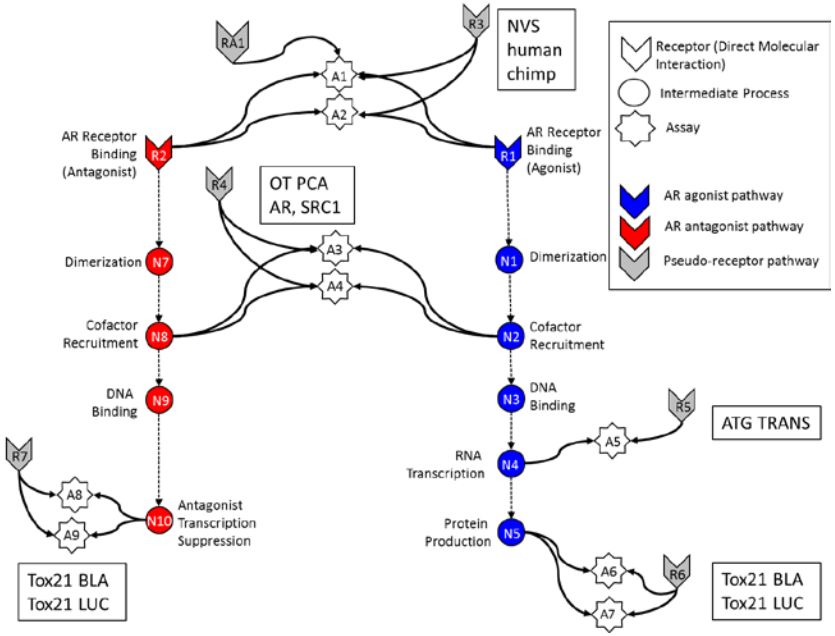
ER Network Model:

18 ER assays



AR Network Model:

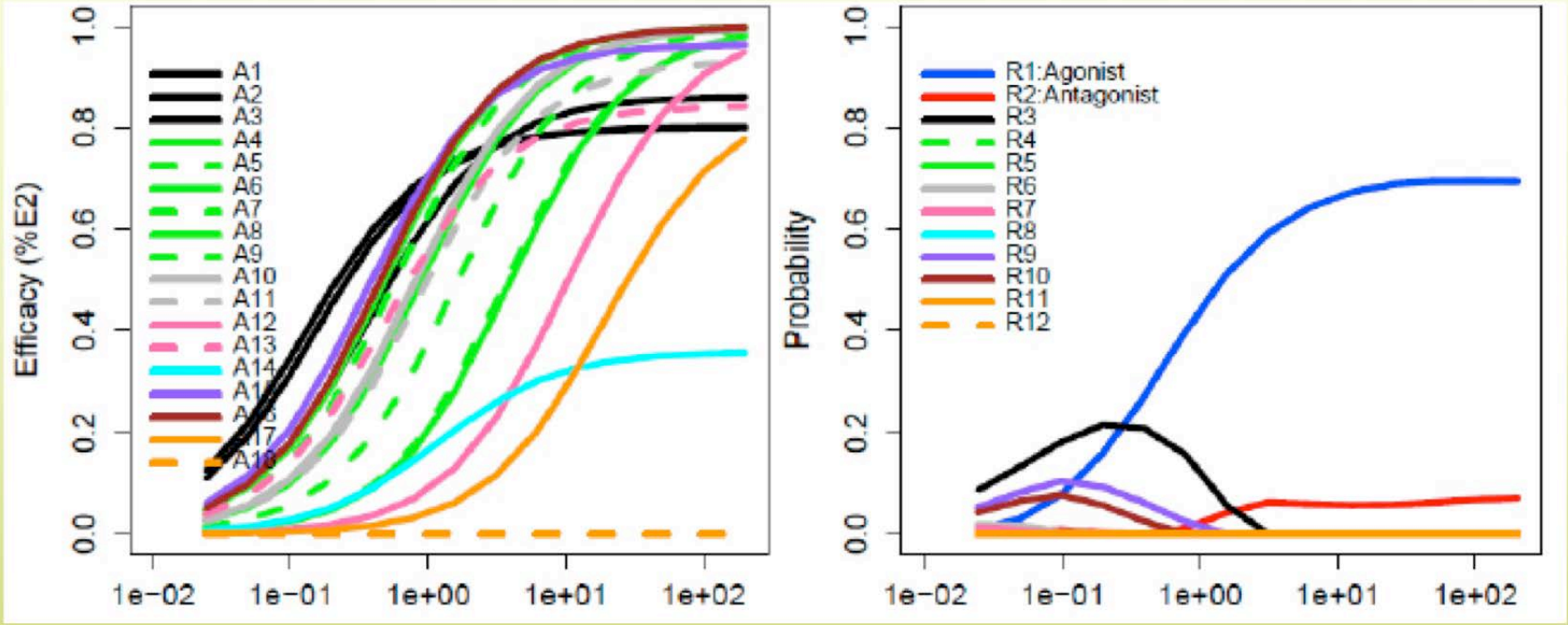
9 AR assays



High Throughput Model

- ER bioactivity model based on dose:response from 18 assays
- Detect receptor interaction at various points along signaling pathway
- Use a variety of technologies
  - Capable of distinguishing “true” activity from cytotoxicity
- Values range from 0 to 1
  - ER agonists

High throughput assays integrated into a pathway bioactivity model



Judson et al. 2015 *in review*

Performance-Based Validation Approach

- Reference chemical set includes range of structures and potencies accurately detected
  - *in vitro* reference chemicals
  - *In vivo* reference chemicals
- New methods compared with EDSP and OECD test guidelines
  - Bioactivity model versus EDSP Tier 1 guideline and "guideline-like" results

Model Performance

- **95% Accuracy** of ToxCast ER model compared to *in vitro* and *in vivo* reference chemicals
- Agency is considering accepting ER data for 1812 chemicals as alternative to EDSP Tier 1 ER binding, ERTA, and uterotrophic assays

EDSP Works in Progress

- Performance-based validation approach to evaluate alternative methods
  - Define in vitro and in vivo reference chemicals across a range of potencies for other bioactivities
    - e.g., AR, steroidogenesis, etc.
  - Develop network Biological Pathway models for estrogen, androgen, and thyroid pathways
    - Integrate more assays/models
    - Integrate more key events
- Reverse toxicokinetics to extrapolate *in vitro* concentration to *in vivo* dose
- High throughput exposure models to determine environmental exposures

Questions?