



Interagency Coordinating Committee on the Validation of Alternative Methods

EPA Update

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Agency for Toxic Substances and Disease Registry • Consumer Product Safety Commission • Department of Agriculture
Department of Defense • Department of Energy • Department of the Interior • Department of Transportation
Environmental Protection Agency • Food and Drug Administration • National Institute for Occupational Safety and Health
National Institutes of Health • National Cancer Institute • National Institute of Environmental Health Sciences
National Library of Medicine • Occupational Safety and Health Administration

Replace: Incorporation of Alternative Assays

- Alternate testing framework for classifying eye irritation potential for labeling antimicrobial pesticide products with cleaning claims
 - <http://www.epa.gov/pesticides/science/eye-irritation.html>

EPA OPP Guiding Principles for Data Needs

- *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.
 - “...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....”
 - <http://www.epa.gov/pesticides/regulating/data-require-guide-principle.pdf>
- *Part 158 Toxicology Data Requirements: Guidance for Neurotoxicity Battery, Subchronic Inhalation, Subchronic Dermal and Immunotoxicity Studies*
 - Purpose: use a weight of evidence evaluation to determine data needs or to review a waiver justification
 - <http://www.epa.gov/pesticides/regulating/part158-tox-data-requirement.pdf>

Data Waivers for Pesticides

- Hazard and Science Policy Council (HASPOC) is the EPA-OPP forum for implementing the waiver guidance document
- Although not specifically covered by the guidance, we still consider other guideline studies using the same principles.....
 - Reduce: Waivers for developmental, reproductive, DNT, chronic/carcinogenicity toxicity
 - Refine: Special protocol studies (e.g., acute inhalation for fumigants, CCA studies, shorter duration) instead of standard guideline protocols
 - Refine: Pharmacokinetic studies in lieu of toxicity study

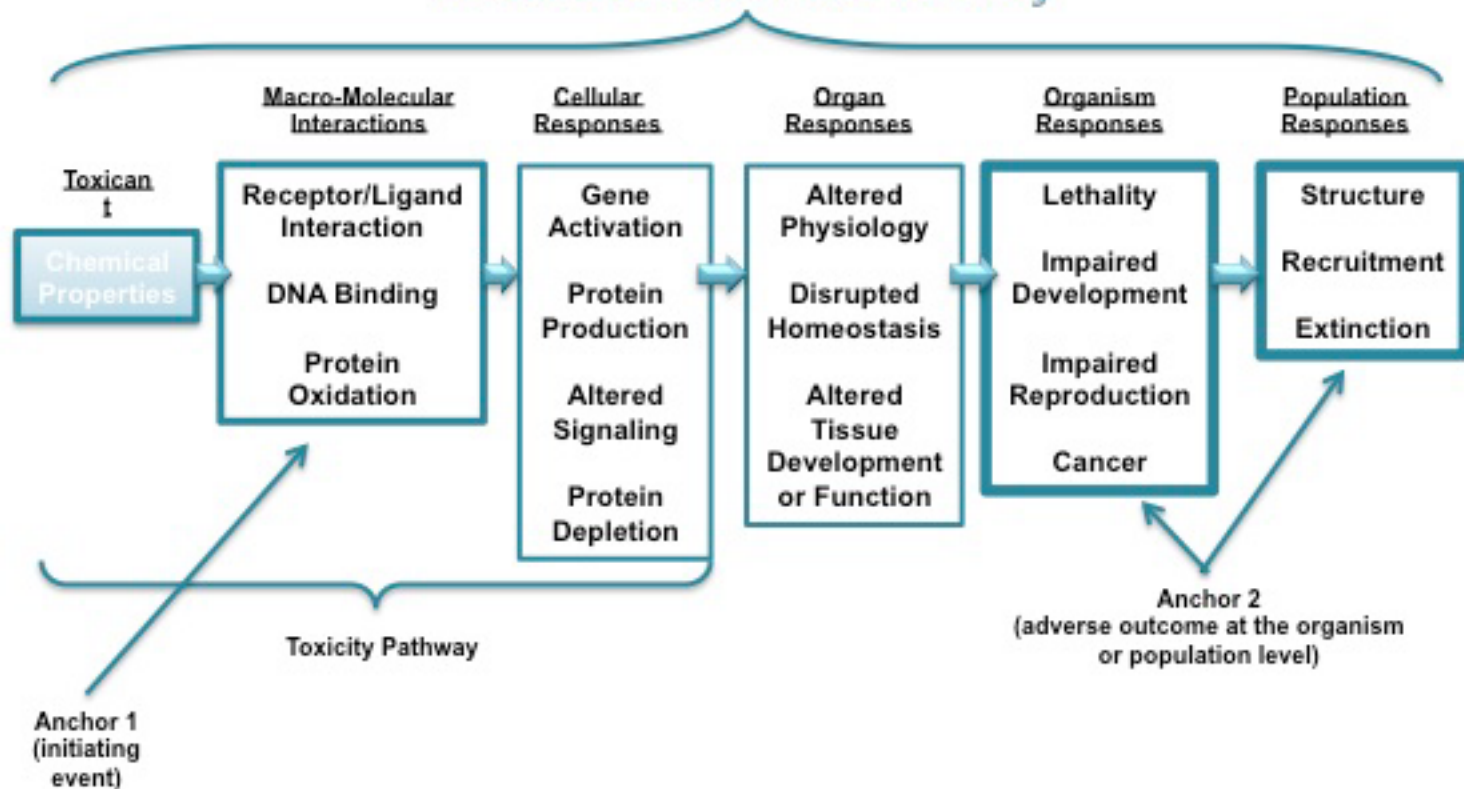
From December 8, 2011 to April 11, 2014, HASPOC has:

- Discussed 285 chemicals
- Reviewed 540 study waivers
- Required 81 studies
- Waived 459 studies
 - 363 for inhalation, neurotoxicity batteries, immunotoxicity
 - >60,000 animals not used
 - >\$40 million savings to industry

Alternative Assays

- EPA-OPP is in the early stages of collaborative project with multiple stakeholders & NICEATM
 - Alternative batteries for skin sensitization, dermal irritation, skin irritation
 - Canada PMRA, animal welfare groups, & industry
 - Meeting held on May 20

Adverse Outcome Pathway



AOP Applications:

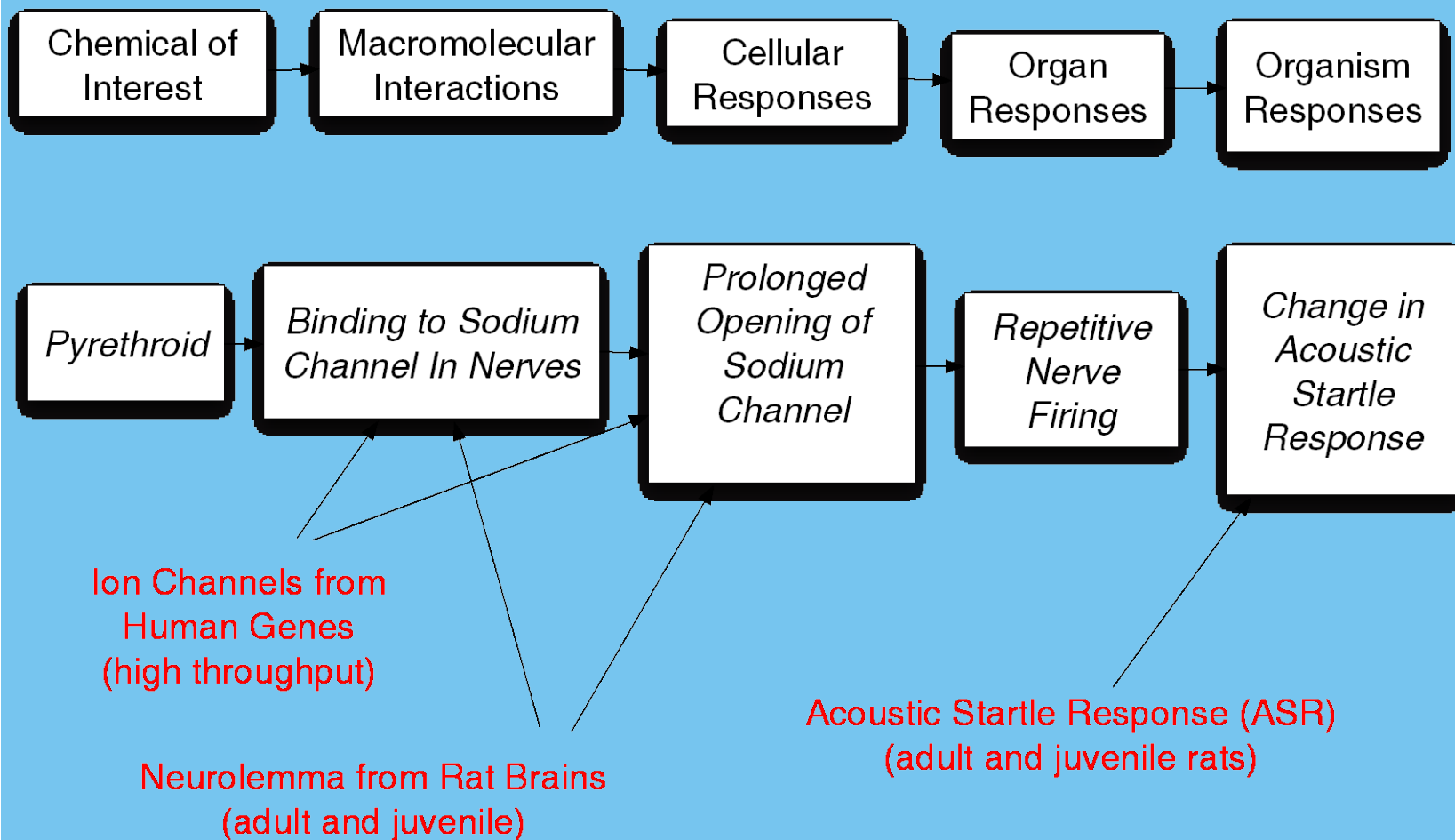
- Developing and applying lower tiered tests & non-animal models (e.g., QSAR, *in vitro* HTS)
- Forming Chemical Categories & Read Across methods
- Better dosimetry and biomarkers in experimental studies, epidemiology, population monitoring
- Species extrapolation

Example: Utility of AOP Knowledge

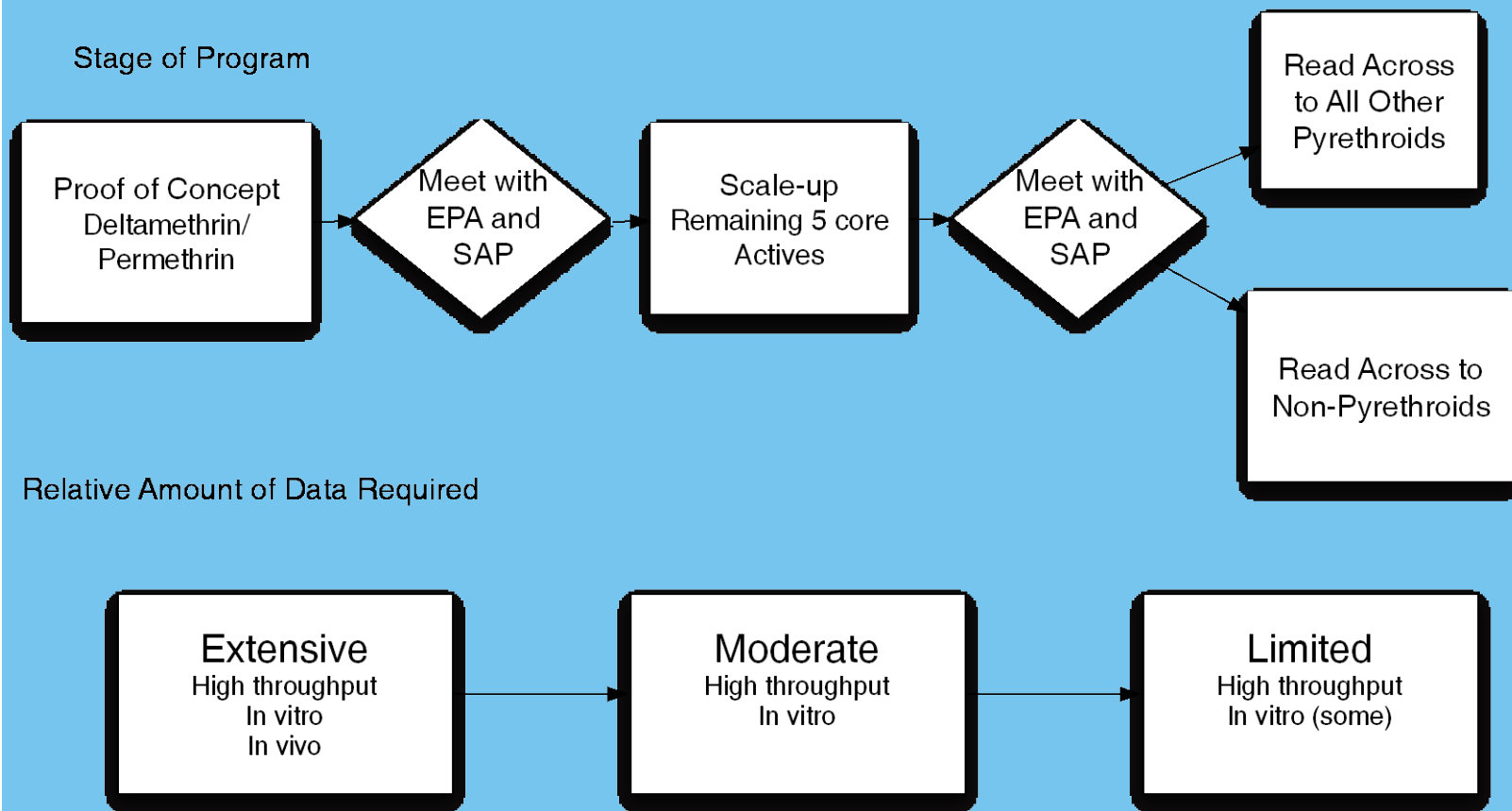
Synthetic Pyrethroids & Naturally Occurring Pyrethrins:

- Until 2009, OPP had been routinely requiring DNTs for all pyrethroids.
- In September 2009, EPA-OPP issued a letter to all pyrethroid companies noting that the DNT was not providing the type of data needed to assess comparative lifestage sensitivity.
- An initial, draft protocol in July, 2010 was reviewed by the FIFRA Scientific Advisory Panel
- In December, 2010, pyrethroid registrants, OPP & ORD achieved a verbal agreement on the three major components of the work:
 - *in vitro* studies: high-throughput human Na channels & neurolemma
 - *in vivo* acute, behavioral studies
 - PBPK modeling

Adverse Outcome Pathway - Targeted Testing



Data Development to Support Read Across for Pyrethroids and Non-pyrethroids



Application of AOPs for Endocrine Disruption Screening

- EDSP21 is focused on developing high throughput, risk-based AOP methods to prioritize targeted testing
- Utilize AOPs for prioritizing and screening chemicals for their potential to interact with certain endocrine pathways leading to adverse effects
 - Draft AOPs are being generated for Estrogen (E), androgen (A), and Thyroid (T) pathways
- Integrative approach
 - Key measurement endpoints are considered in relation to the assessment tools (i.e., assays, computer models and test guidelines) relevant to the US EDSP
 - Measurement endpoints include molecular initiating event (MIEs) as well as intermediate and terminal events along the recognized pathways
 - AOP linkage of relevant measures and tools assists in the interpretation and assessment of chemicals for potential interaction and adverse consequence



Office of Research & Development

- EPA's Office of Research has multiple research programs related to developing, conducting, interpreting, and using *in vitro*, *in silico*, or lower taxa assays.
 - <http://www2.epa.gov/epa-research>
 - <http://www2.epa.gov/sites/production/files/2014-06/documents/strap-overview.pdf>



What is ToxCast?

- A major part of EPA's CompTox research is the Toxicity Forecaster (ToxCast™).
 - <http://www.epa.gov/ncct/toxcast/>
 - ToxCast is a multi-year effort launched in 2007 that uses automated chemical screening technologies (called "high-throughput screening assays") to expose living cells or isolated proteins to chemicals.
 - The cells or proteins are then screened for changes in biological activity that may suggest potential toxic effects and eventually potential adverse health effects.
 - These innovative methods have the potential to limit the number of required laboratory animal-based toxicity tests while quickly and efficiently screening large numbers of chemicals.



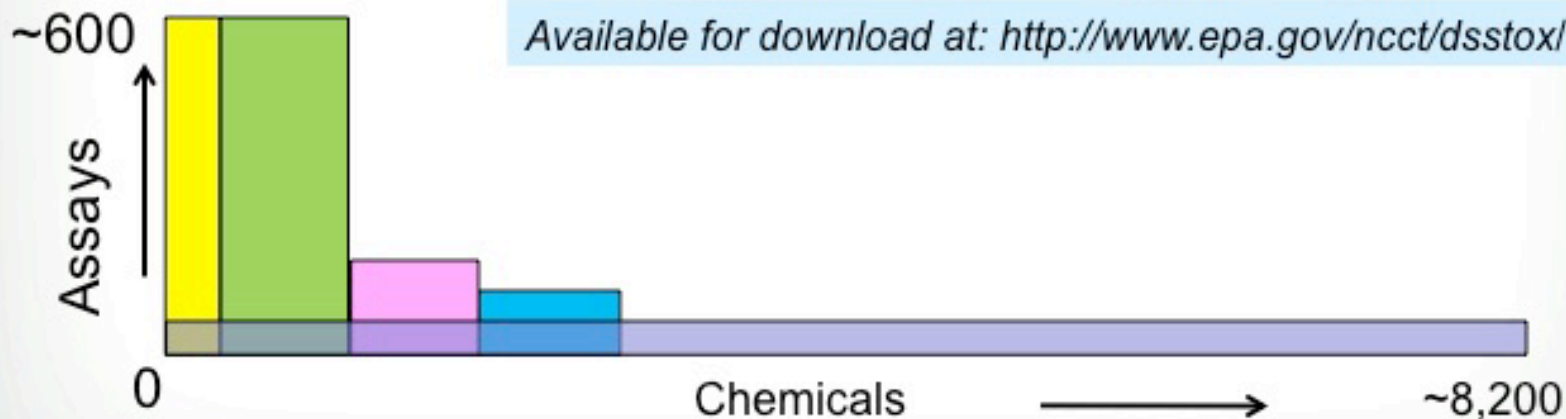
What is ToxCast?

- ToxCast results are contributed to the federal agency collaboration called Toxicity Testing in the 21st Century (Tox21).



ToxCast and Tox21 Chemicals, Assays and Timelines

Set	Chemicals	Assays	Endpoints	Completion	Available
ToxCast Phase I	293	~600	~700	2011	Now
ToxCast Phase II	767	~600	~700	03/2013	Now
ToxCast Phase III	1001	~100	~100	Just starting	2014
E1K (endocrine)	880	~50	~120	03/2013	12/2013
Tox21	8,193	~25	~50	Ongoing	Ongoing



Pesticides, antimicrobials, food additives, green alternatives, HPV, MPV, endocrine reference cmpds, other tox reference cmpds, failed drugs, NTP in vivo, EPA high interest compounds, industrial, marketed drugs, fragrances, ...

Summary

- Rapid advances to implementing the 3R's into regulatory testing and alternative approaches but there is more work to do.
- Lessons learned so far...
 - Mining existing data provides a robust source of information for assessing data which are needed.
 - Collaborative approaches working with investigators across sectors is most effective approach
 - Harmonization and coordination across state, federal, and international regulatory agencies is important