

Can AOPs Save the World?

Physicians
Committee
for Responsible Medicine

Kristie Sullivan, MPH
VP for Research Policy



What is an Adverse Outcome Pathway?

- First described by US EPA ecotoxicologists in 2010
- OECD AOP Programme formed
 - Crowd-sourced database called AOP Wiki
 - Trainings conducted at dozens of fora
 - Review and publication process established
- Since 2010, there have been 4000 publications
- SAAOP formed to host AOP Wiki and facilitate training
- Lush black box prize awarded in 2015
- All major regulatory agencies incorporating AOP concepts

AOP: A knowledge bridge



Regulatory Toxicology (or, safety evaluations)

Organizational Framework for Information

Combines information from multiple fields of inquiry to illuminate knowledge of biological pathways, highlight species differences or similarities, identify research needs, and support regulatory decisions.

Molecular Interactions

- Receptor interaction
- Covalent binding

Organelle/Cellular Effects

- Gene activation
- Oxidative stress
- Immune cell activation

Organ Effects

- Tissue proliferation
- Altered function

Individual Effects

- Altered reproduction
- Disease
- Lethality

Population Effects

- Population reduction
- Extinction

Effort to catalog AOPs is bringing toxicity information into a usable, accessible format

Regulatory Context for Nonanimal Test Methods

Link molecular events to events of regulatory interest, provide mechanistic support for computational tools, ID assay development needs, & inform IATA

Molecular Interactions

Organelle/Cellular Effects

Organ Effects

Individual Effects

Population Effects

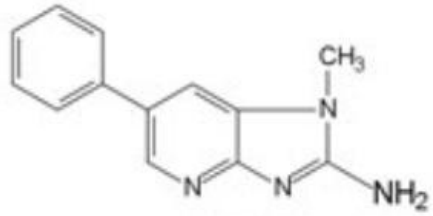
High-throughput assays

In vitro 2D cell lines / iPS / primary cells

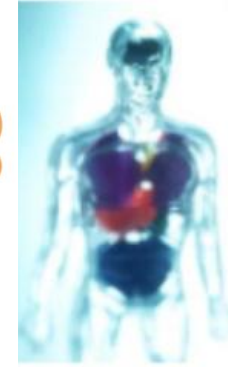
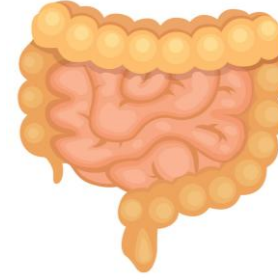
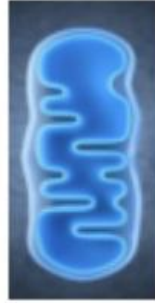
In vitro 3D reconstructed tissues

Microphysiological systems

Computational Modeling



Heterocyclic Amines



Chemical Exposure

Molecular Interactions

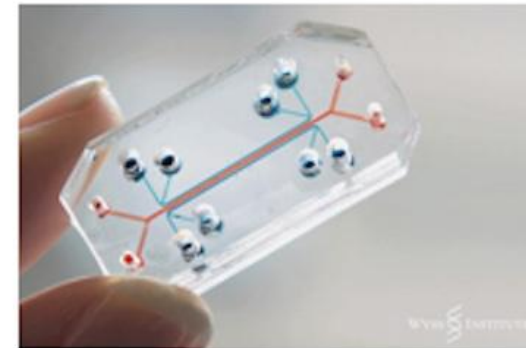
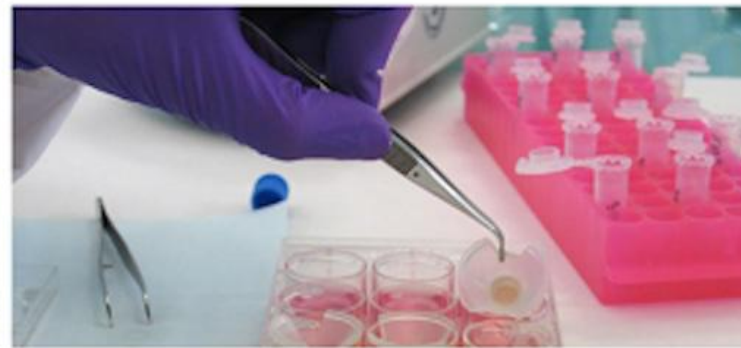
Organelle Effects

Cellular Effects

Organ Effects

Individual Effects

Population Effects



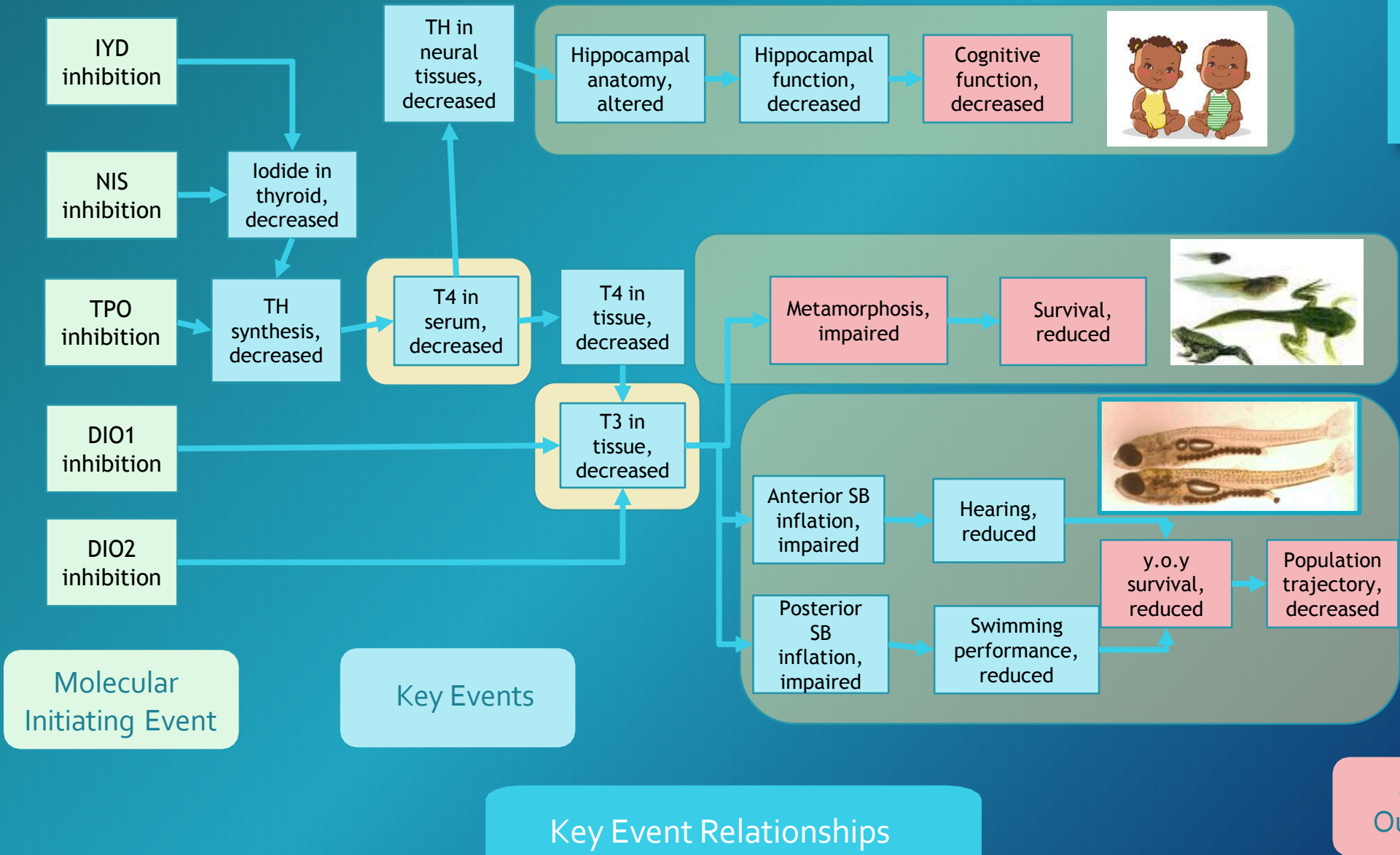
OECD's AOP Programme: A success story

- 8 Published AOPs
- Global AOP Network
 - 230 AOPs
 - 1125 Key Events
 - >1300 KE Relationships
 - >380 Stressors
 - ~3500 Pathways

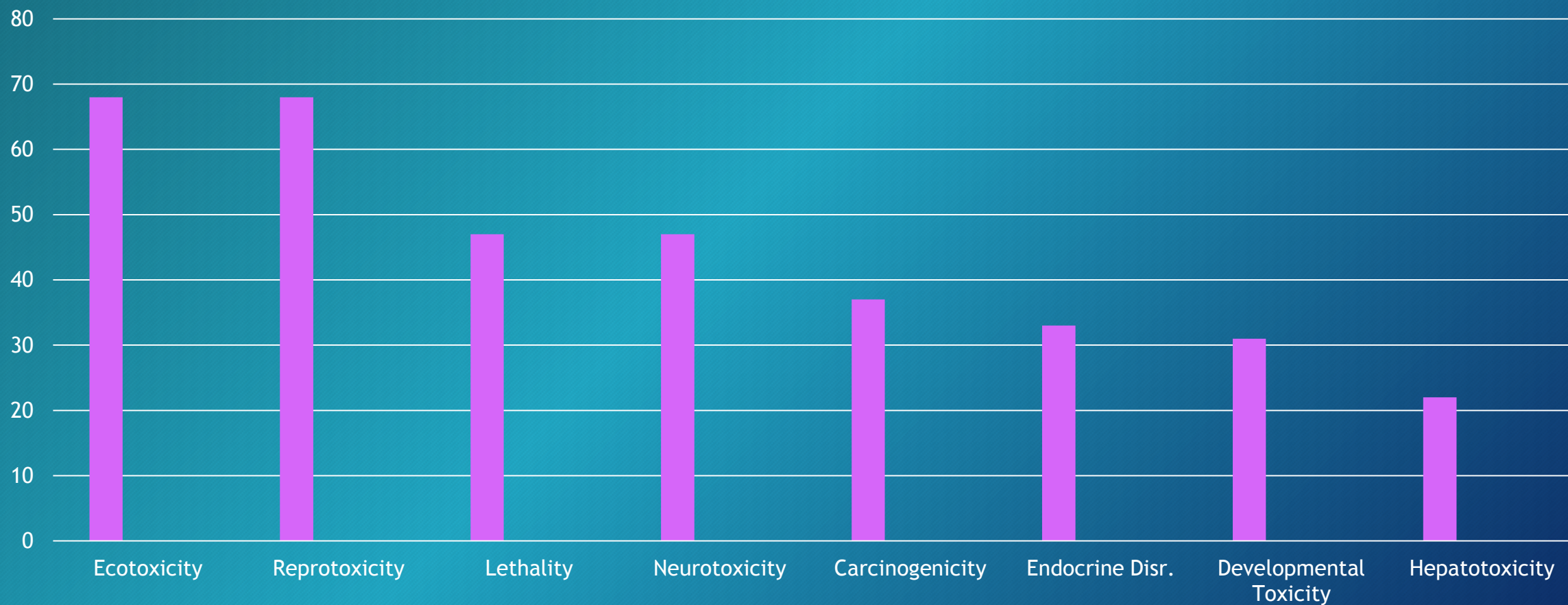
<https://aopkb.oecd.org>
<https://aopwiki.org>



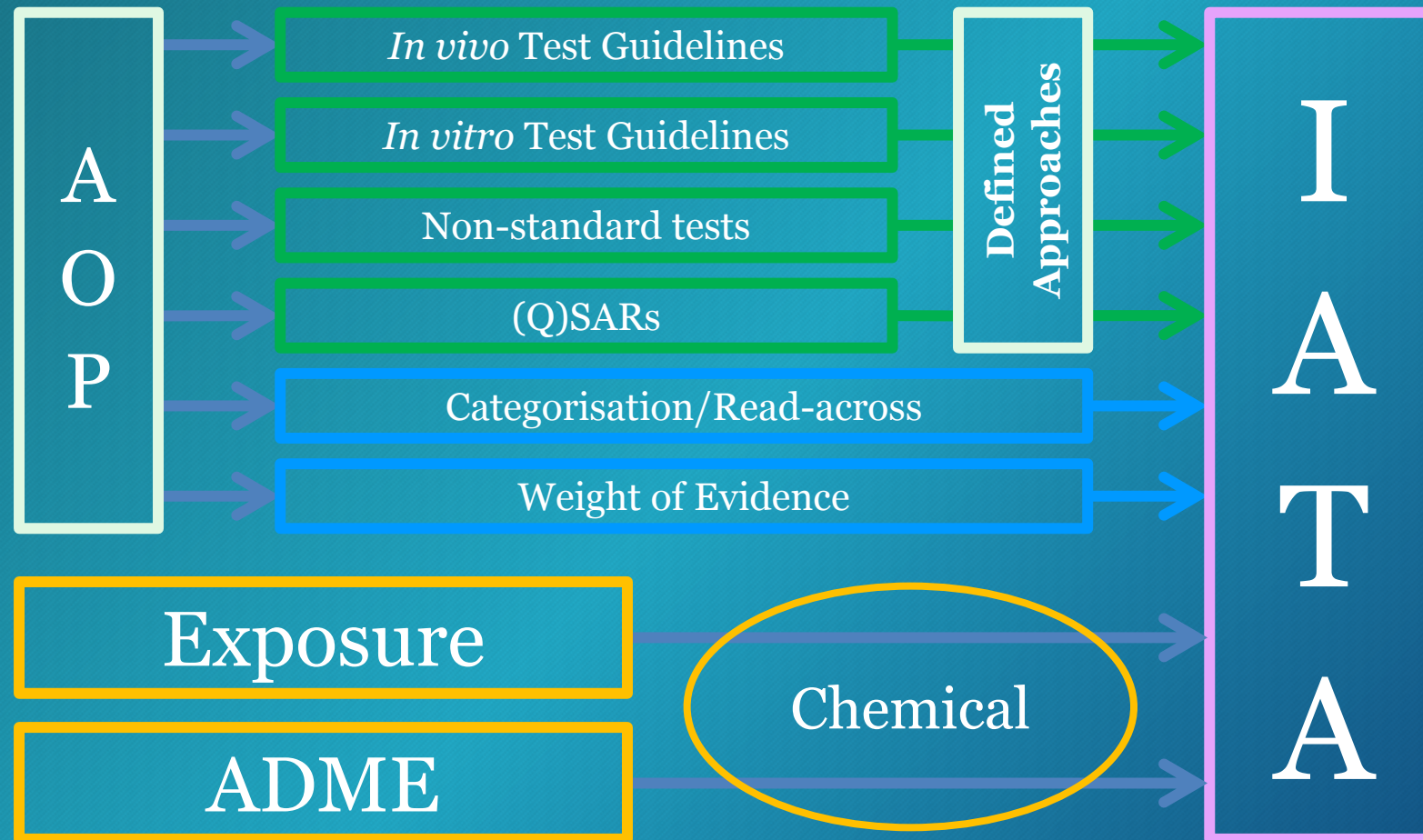
AOP ELEMENTS: THYROID AOP NETWORK



AOP Wiki endpoint coverage



IATA is the New OECD Test Guideline



What about medical research?

- Atherosclerosis as a Model Workshop, April 2018 (NIEHS)
 - Using AOP framework to combine chemical and non-chemical stressors related to biological pathways for atherosclerosis
- Parkinsonism
 - Adverse outcome pathways: Application to enhance mechanistic understanding of neurotoxicity (Bal-Price and Meek 2017, doi: [[10.1016/j.pharmthera.2017.05.006](https://doi.org/10.1016/j.pharmthera.2017.05.006)])
 - Suggest mechanism-based reclassification of disease
- Alzheimer's, Asthma, and others
 - Recommendations toward a human pathway-based approach to disease research (Marshall et al 2018, doi: [[10.1016/j.drudis.2018.05.038](https://doi.org/10.1016/j.drudis.2018.05.038)])
 - BioMed21: A Human Pathways Approach to Disease Research, June 2017

Reality Check

- It's taken decades to replace tests using few animals
- So far AOPs have only led to one animal test replacement
- Tests using thousands of animals each are still conducted every year
- Nonanimal methods are increasingly being used to trigger animal tests
- Aquatic toxicology is exploding
- Toxicology represents small percentage of animals used in science

What is Needed

- Financial investment by regulatory agencies/governments
- Quantitation of AOP elements
- More directed AOP network development
- Training and outreach to scientific community
- Incentives and requirements from
 - Funding bodies
 - Journals



marthymousehouse.com

Kristie Sullivan
ksullivan@pcrm.org

Thank you for your attention!