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Existing efforts and roadmaps: North American perspective

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Precedents for pathway-based toxicology

Dose-response modeling

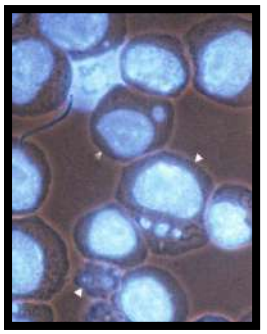
- Using pharmacokinetic and mechanistic information

IPCS/WHO mode of action frameworks

- Human relevance of rodent cancer findings
- Extrapolated to non-cancer endpoints

Mode of action pathways in drug and product development

- Drug and target-specific



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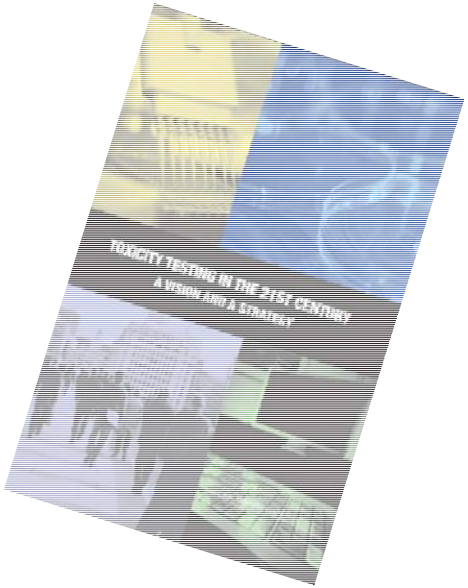
National Research Council in 2007 Report, Toxicity testing in the 21st century: A vision and a strategy

*"envisions a new toxicity-testing system that evaluates **biologically significant perturbations** in **key toxicity pathways** by using new methods in computational biology and a comprehensive array of in vitro tests **based on human biology**"*



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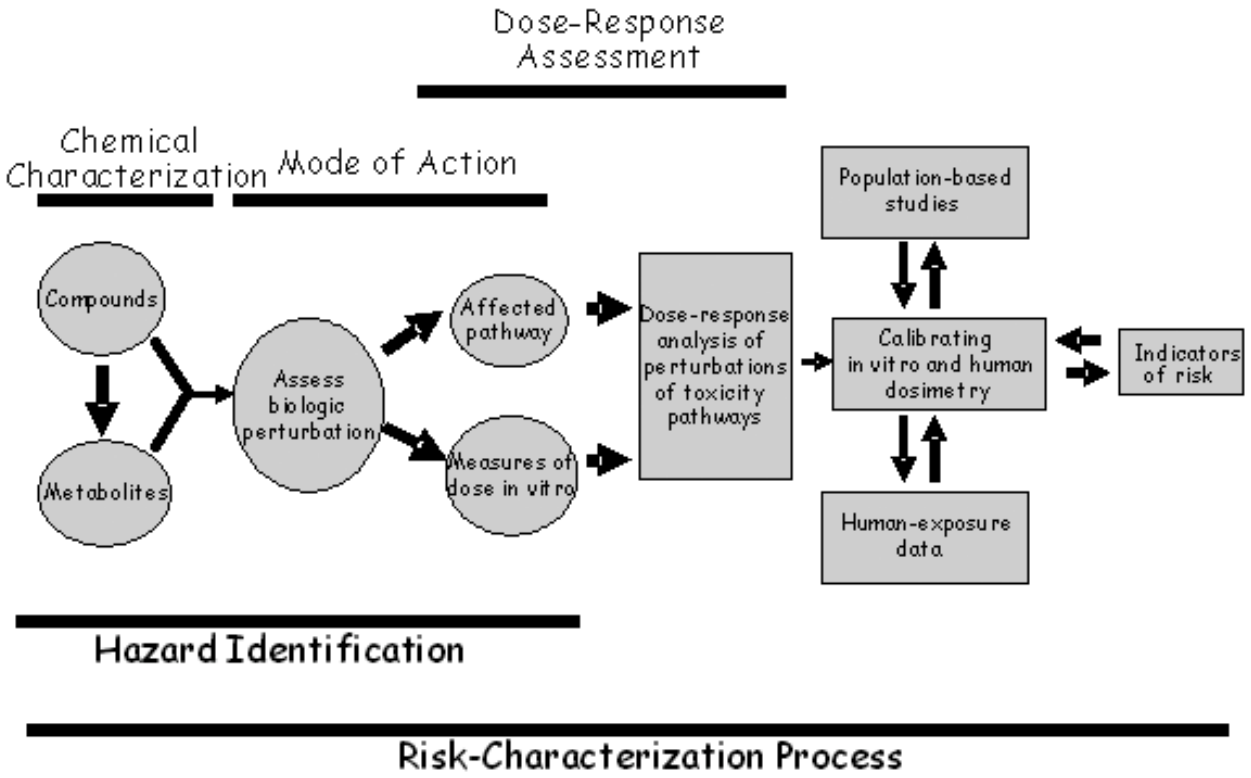
NRC 2007 Report



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NRC 2007 Report recommendations

- The realization of the vision will entail considerable research over many years and require substantial funding—hundreds of millions of dollars
- Much of the research will be interdisciplinary and consequently, to be most effective, should not be dispersed among discipline-specific laboratories
- The research will need high-level coordination to tackle the challenges presented in the vision efficiently
- The research should be informed by the needs of the regulatory agencies that would adapt and use the emerging testing procedures, but the research program should be insulated from the short-term orientation and varied mandates of the agencies

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Related US Roadmaps

EPA Strategic Plan for Evaluating the Toxicity of Chemicals, 2009

	Pathway-based screening	Pathway-based risk assessment	Institutional transition
Issue	Need to assess 10.000's of chemicals for all toxicities	Current approach is slow, expensive, limited Lack of biological understanding needs addressing	Requires significant institution investment, organizational transition, public outreach
Drivers	Lower costs, improve speed, decrease uncertainty	New scientific understanding and tools: molecular, computation, informatics	EPA lacks appropriate resources, knowledge and training.
New Approach	Elucidation of toxicity pathways, combine all types of in silico, in vitro information linked to existing animal data	Reliance on increased understanding of pathways, perturbations at concentrations relevant to exposure	Proof-of-concept, verification studies. Staff training.
Impact	Focus limited resources on chemicals with greatest potential risk, reduce cost and testing.	Provide scientifically relevant data for risk decisions.	Well-informed public will have greater confidence in hazard and risk decisions.

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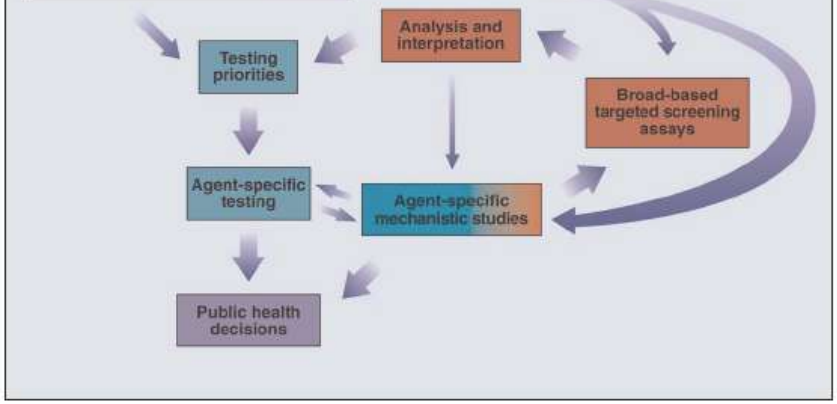
Related US Roadmaps

National Toxicology Program

A National Toxicology Program for the 21st Century, 2004

Figure 1. Use of Mechanistic Toxicology Studies in Public Health Decision-Making



Roadmap Activities: High-Throughput Screening (HTS)

Short-term Activities

- Catalogue available assays
- Convene working groups to provide advice on selection of assays
- Develop assays
- Identify initial set of chemicals for testing

Mid-term Activities

- Continue assay development
- Validate individual assays
- Develop methods for analysis of data
- Develop HTS database
- Review effectiveness

Long-term Activities

- Develop mechanisms to make chemical sets and tissue banks available for external researchers
- Evaluate HTS data for predictability of toxicity
- Develop a communication plan
- Review effectiveness

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Related US Roadmaps

Department of Defense: Application of Modern Toxicology Approaches for Predicting Acute for Military Assessments of Acute Exposures


PREPUBLICATION COPY

APPLICATION OF MODERN TOXICOLOGY APPROACHES FOR PREDICTING ACUTE TOXICITY FOR CHEMICAL DEFENSE

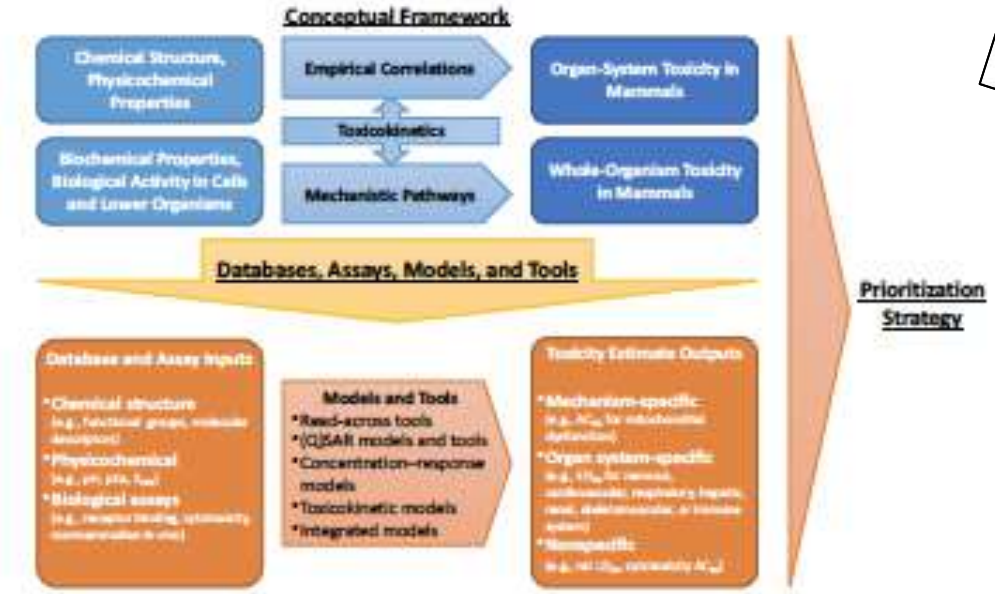
Committee on Predictive-Toxicology Approaches for Military Assessments of Acute Exposures

Board on Environmental Studies and Toxicology

Board on Life Sciences

Division on Earth and Life Studies

The National Academies of SCIENCES · ENGINEERING · MEDICINE



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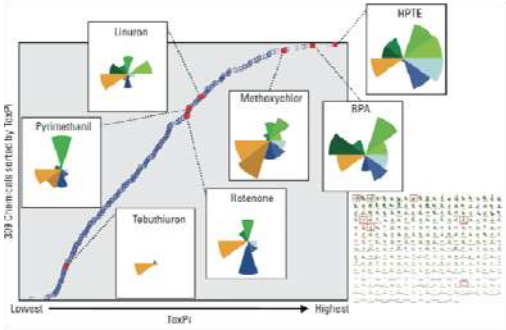
Related US projects

US Government



EPA: ToxCast

- High-throughput data generation
- With industry partners
- ~ 800 in vitro assays, thousands of endpoints
- ~300 pathways
- ~3000 chemicals at ~10 concentrations
- All data publically available
- Application to US EDSP: E, A and T pathways

Tox21: NIH/EPA/FDA

- Screening 10,000 chemicals, including drugs
- At the NIH Center for Advancing Translational Science using innovative robotic technology

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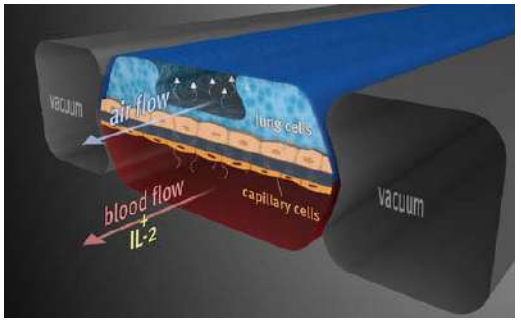
Pathway-related projects



US Government, cont.

“Human on a Chip”: DARPA/NIH/FDA

- $132 million over 5 years to universities
- lung, liver, intestine, heart, brain
- Goal is 10 organs in 5 years

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods

- Endocrine and developmental pathway development
- Assay development and evaluation

EPA: Mid-Atlantic division

- QSARs, AOPs for aquatic toxicity
- Estrogen receptor-mediated reproductive impairment
- Aromatase inhibition-mediated reproductive impairment

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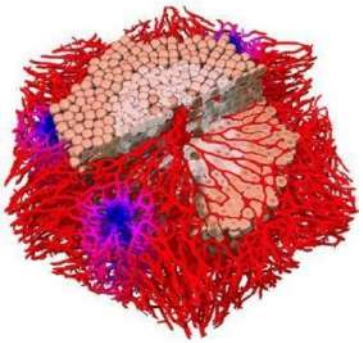
Pathway-related projects

US Government, cont.

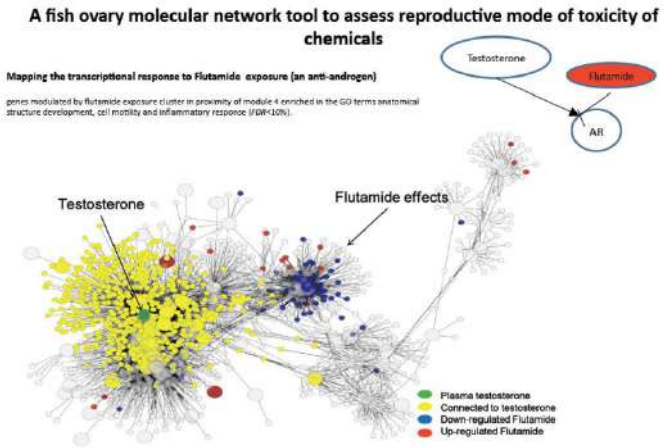


EPA Office of Research and Development

- Virtual liver
- Virtual embryo

US Army Corps of Engineers

- AOPs for ecotoxicology
- Aromatase inhibition
- androgen agonism
- HTG axis
- Chemical-specific case studies



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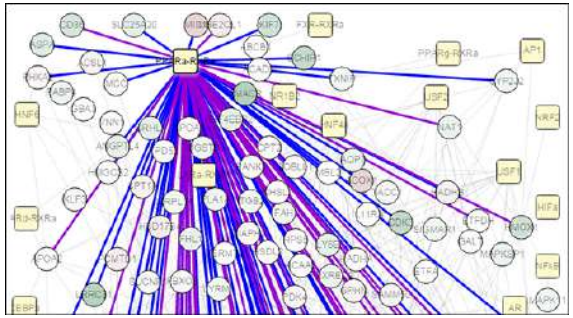
Pathway-related projects

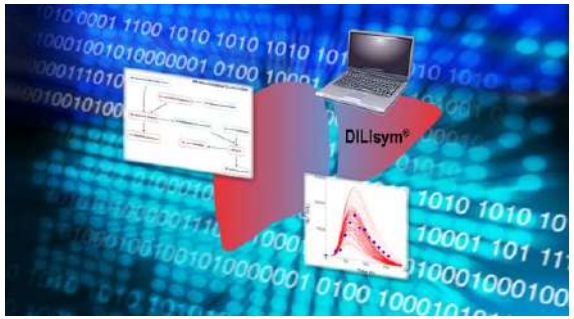
The Hamner Institutes

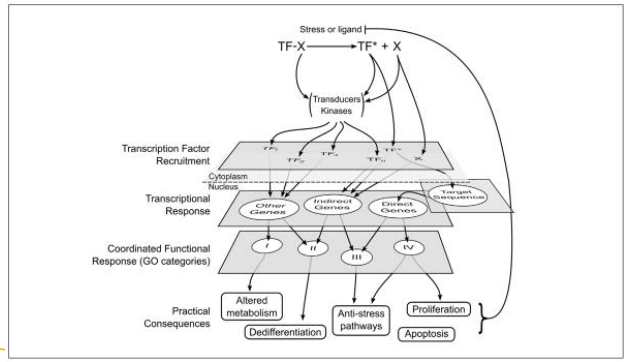
- "Tier 1 and done"
  - Complete estrogen receptor pathways
- PPARα network
  - Systems biology approach to complex network interactions
- DiliSym:
  - computer model for drug-induced liver injury

Johns Hopkins School for Public Health Center for Alternatives to Animal Testing

- Pathways of Toxicity
  - "omics" approaches to mapping all pathways
  - Goal of establishing the "Human Toxome"
- Evidence-based toxicology







Pathway-related projects

Organization for Economic Cooperation and Development

Advisory Group on Molecular Screening and Toxicogenomics

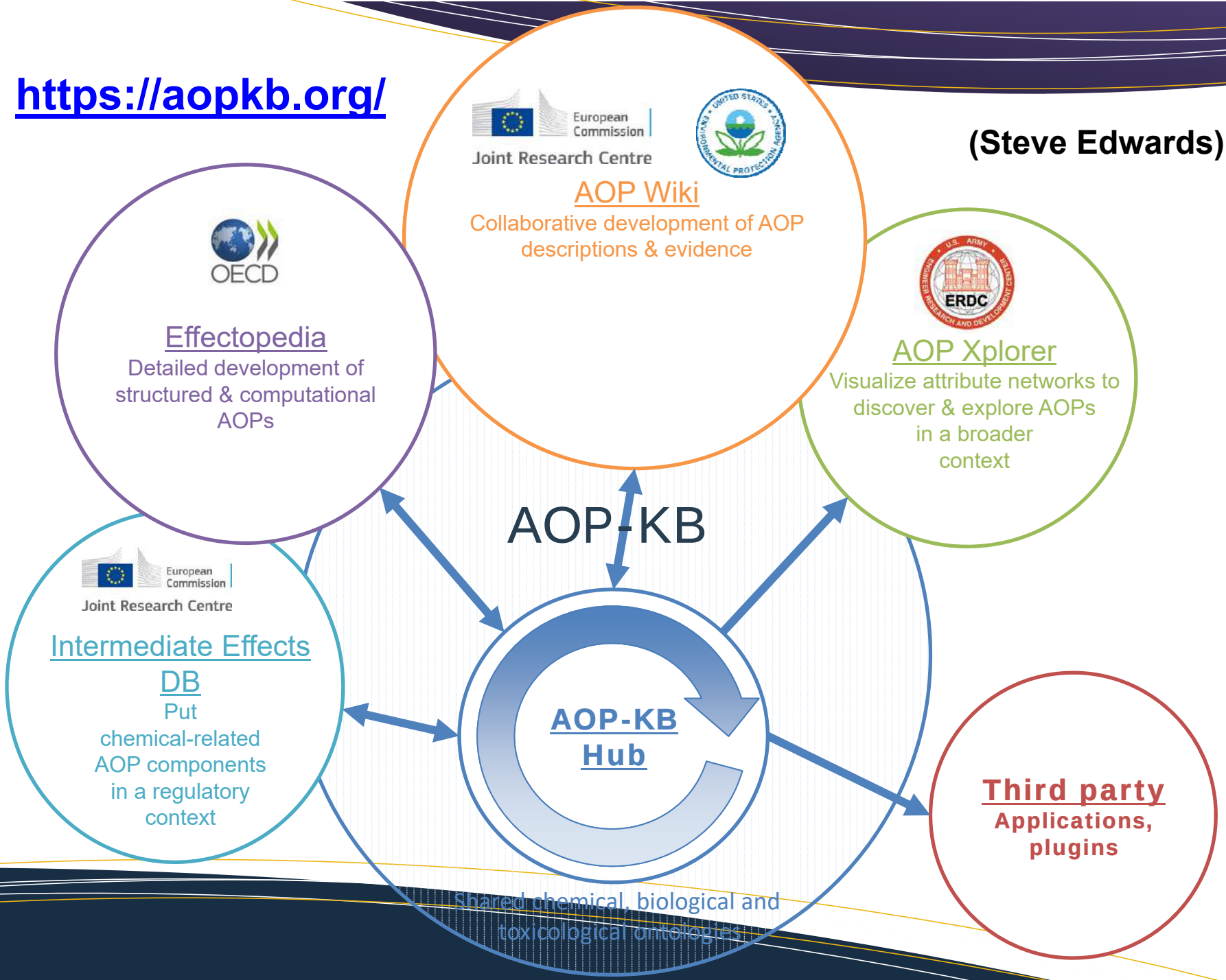
- Template for building AOPs, organizing information
- Guidance document on developing and assessing AOP (2013), No. 184 Series Testing and Assessment

OECD QSAR toolbox

- Large collection of QSAR and SAR models
- databases
- Guidance

https://aopkb.org/

(Steve Edwards)



AOP Wiki

Collaborative development of AOP descriptions & evidence

- Qualitative, **text-based descriptions** of an AOP in a structured environment
- Focus is on documenting the weight of **evidence** in support of the AOP
- **Synchronized** with the **OECD** guidance and **handbook** documents
- Online only access to encourage **crowd-sourcing** of AOP development
- Interfaces with the **AOP Xplorer** to provide AOP information in a **network** context

Effec

Detailed
structured

Joint Research Centre

Intermed
Effects D

Put chemical-related AOP components in a regulatory context

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Third party

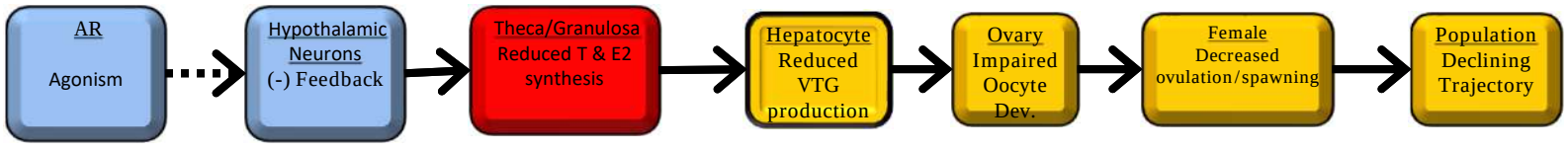
Applications, plugins

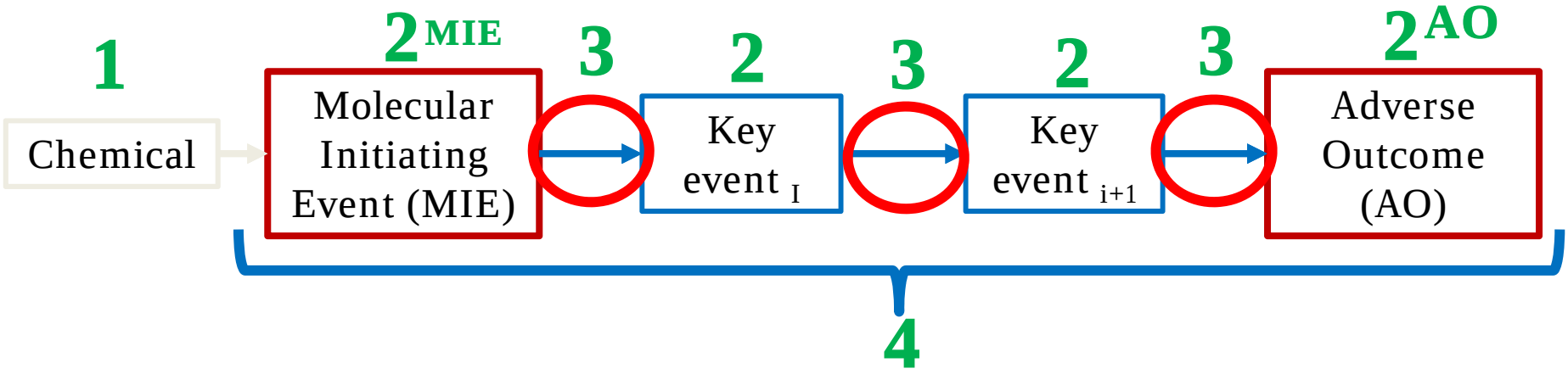
System Size

Shared chemical, biological and toxicological ontologies

http://aopwiki.org

Structuring and Storing AOP Information





AOP Components are mapped to specific entities in the KB

1. Chemical initiator
2. Key event (nodes)
   MIE & AO are special cases of KEs
3. KE Relationship (linkage; edge)
4. AOP

Wiki Matches OECD Guidance & Handbook

https://aopkb.org/common/AOP_Handbook.pdf

AOP Page

Section 1 – Title

Section 2 – Authors

Section 3 - Status

Section 4 – Abstract
Background (Optional)

Section 5a – Summary of the AOP
- MIE
- KEs
- AO

Linkage table
- Key Event Relationships

Applicability domain(s) of the AOP
- Life-stage
- Taxonomic
- Sex

Section 7 – Overall Assessment of the AOP
- Modified Bradford Hill Considerations

Section 8 – Considerations for Potential Applications of the AOP

Section 5b – MIE, KE, and AO descriptions

MIE Page
Chemical initiator(s)
- Description
- Measurement/ detection
- Taxonomic applicability
- *Evidence for chemical initiation*

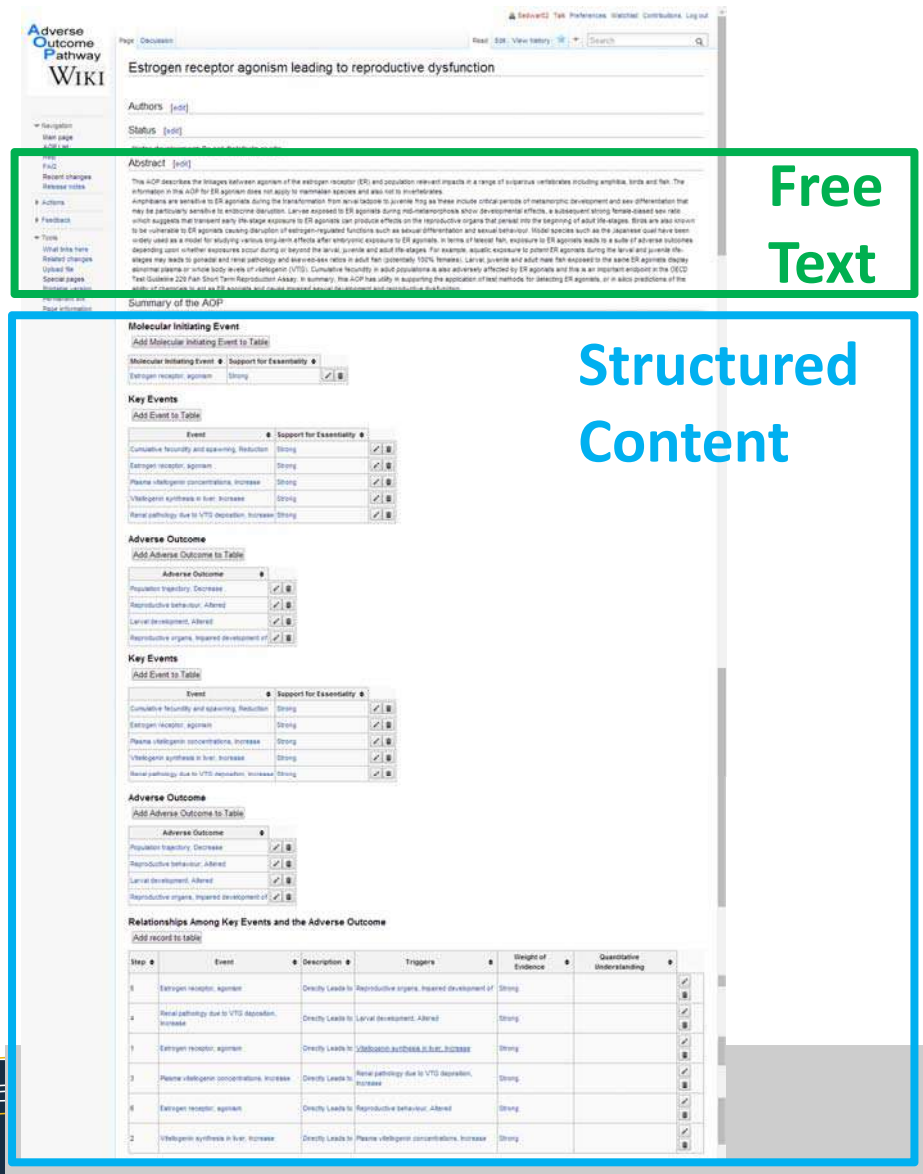
KE Pages
- Description
- Measurement/ detection
- Taxonomic applicability

AO Page
- Description
- Measurement/ detection
- Taxonomic applicability
- *Regulatory relevance*

Section 6 – Scientific evidence supporting the linkages in the AOP

KER Pages
- Title
- Description
- Biological plausibility
- Empirical support
- Inconsistencies and uncertainties
- Quantitative understanding

AOP Page in Wiki



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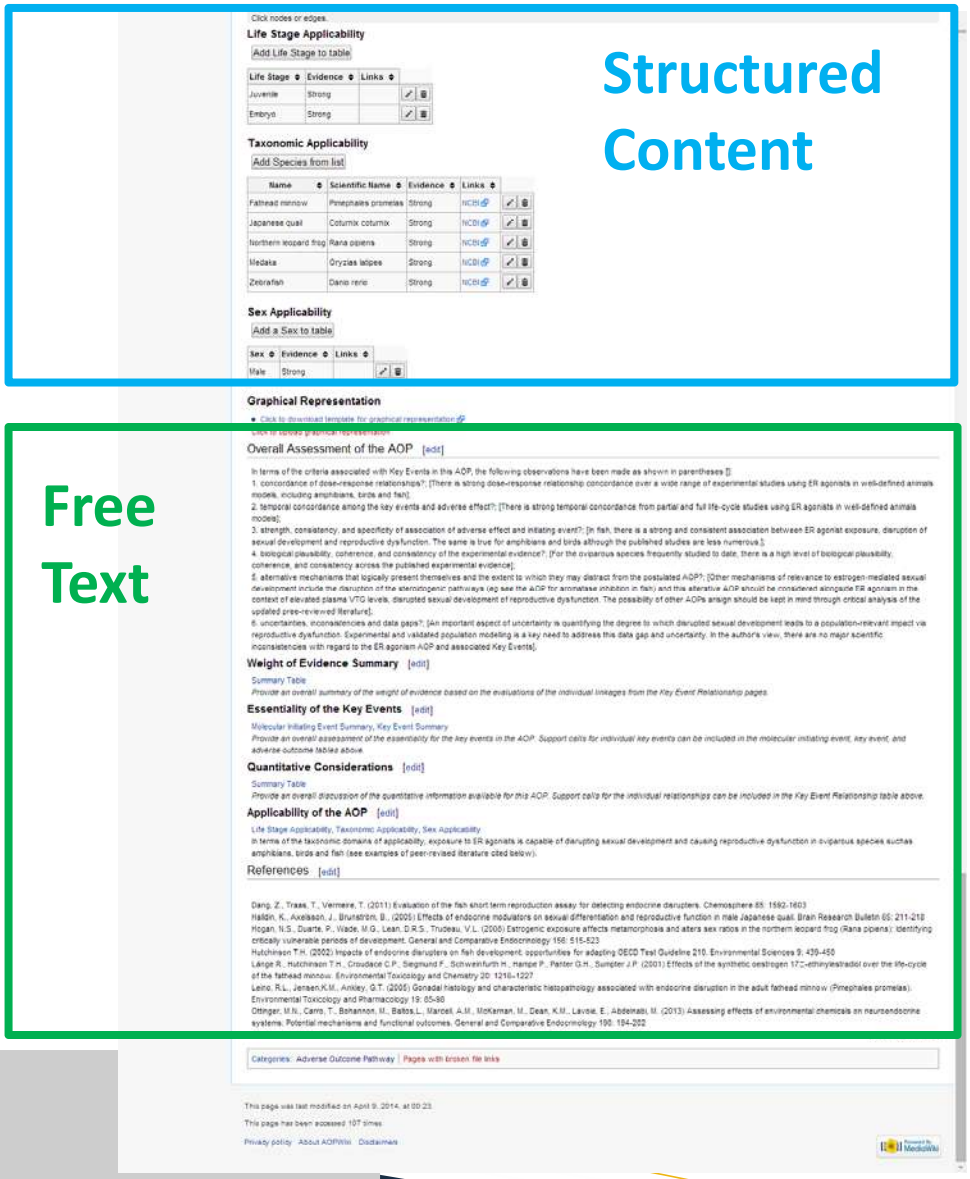

Structured Content

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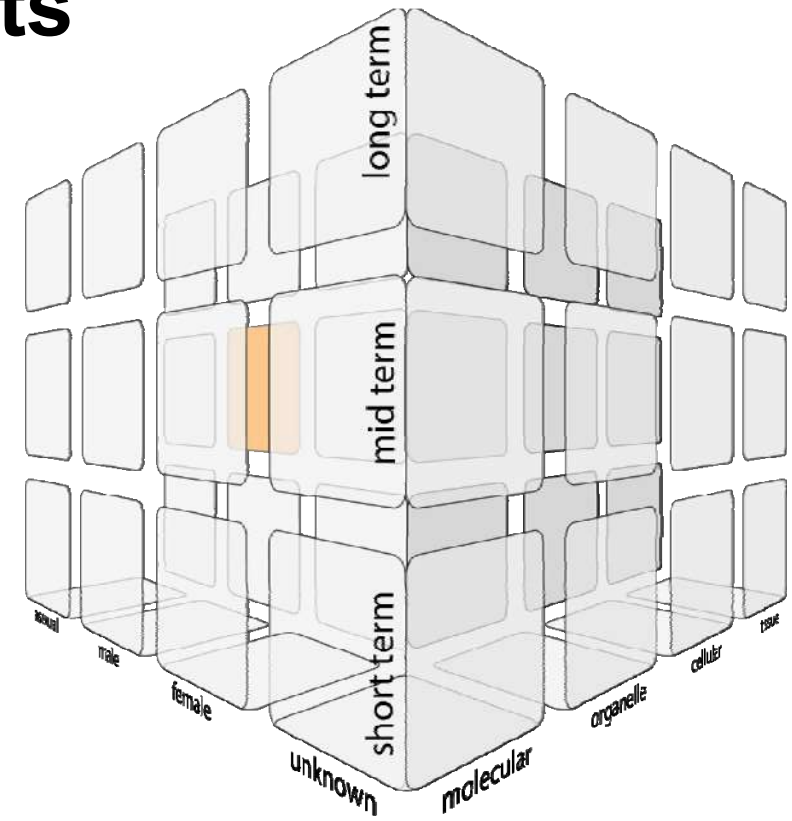
Pathway-related projects

Effectopedia

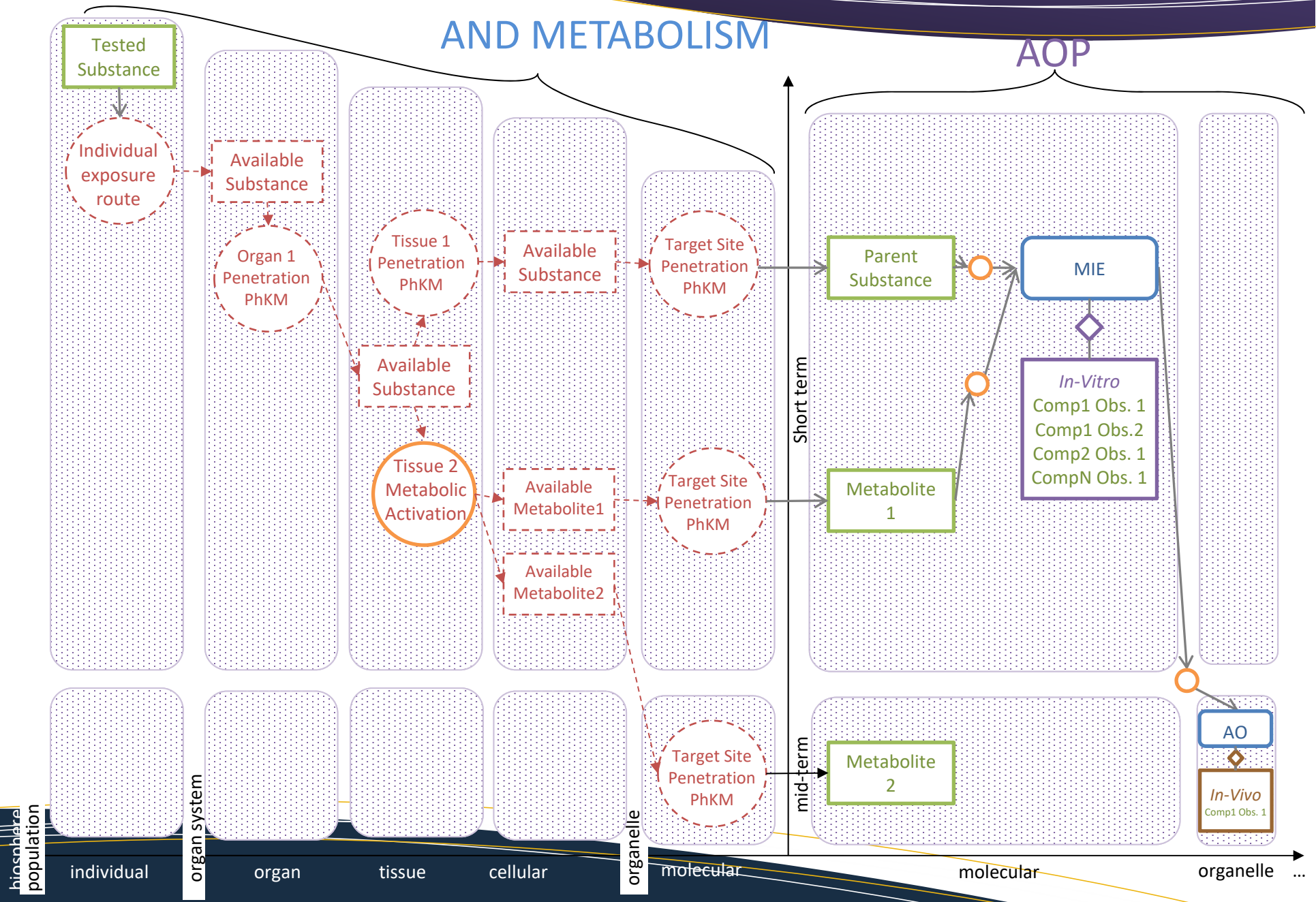
- Life stage
- Taxonomy
- Gender
- Generation
- Time to effect
- Level of biological organization
- …



User expandable set of biological context dimensions

Interface allows easy switching between pathway space 2D projections

FUTURE PENETRATION MODELS AND METABOLISM



US Funding

NIH: worlds largest medical research institution

"mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability."

- 30.1 billion USD annually
  - 27 institutes and centers
  - 80% to fund 50,000 competitive grants
- NCATS: $635,710,000 FY 15
- NIEHS: $665,080,000 FY 15
  - Small number of competitive grants to fund non-animal method development and validation (new)

US Funding

US EPA: 7.89 billion USD (FY2015)

- Science and Technology: 7.64 billion
- Chemical safety: $672,918,000 FY 15
- Chemical Safety and Sustainability, Human Health Risk Assessment, and Homeland Security Research programs: $162,600,000 FY 15
  - ToxCast
  - Research into non-animal methods, mechanisms of action, QSAR, modeling

HSI/HSUS Efforts through the Humane Society Legislative Fund

Focus has been on shifting appropriations within existing programs to prioritize funding for non-animal approaches to toxicological assessment:

- Senate and House FY15 Labor HHS Appropriations Report Language:
  - To Office of the Director - Supporting High Throughput Screening, Toxicity Pathway Profiling, and Biological Interpretation of Findings National Institutes of Health
- House FY15 Department of the Interior, Environment and Related Agencies Report Language
  - Research: Chemical Safety and Sustainability — rejecting decreases in funding new methods
- Endocrine Disruptor Research — supporting implementing the toxicity testing agenda that the 2007 National Academy of Sciences (NAS) report on Toxicity Testing in the 21st Century puts forth

Conclusions

The US has aligned strategic plans within:

- NIH, EPA, DARPA
- Based on 2007 NRC report

International collaboration is essential:

- To tackle the magnitude of the project
- For sharing/harmonized use of information

Potential funding is only partially tapped for the transition

Potential funding for a similar approach to disease and medicine is available through NIH's 17 institutes

Public/private partnerships, so successful in the EU, are underutilized in the US