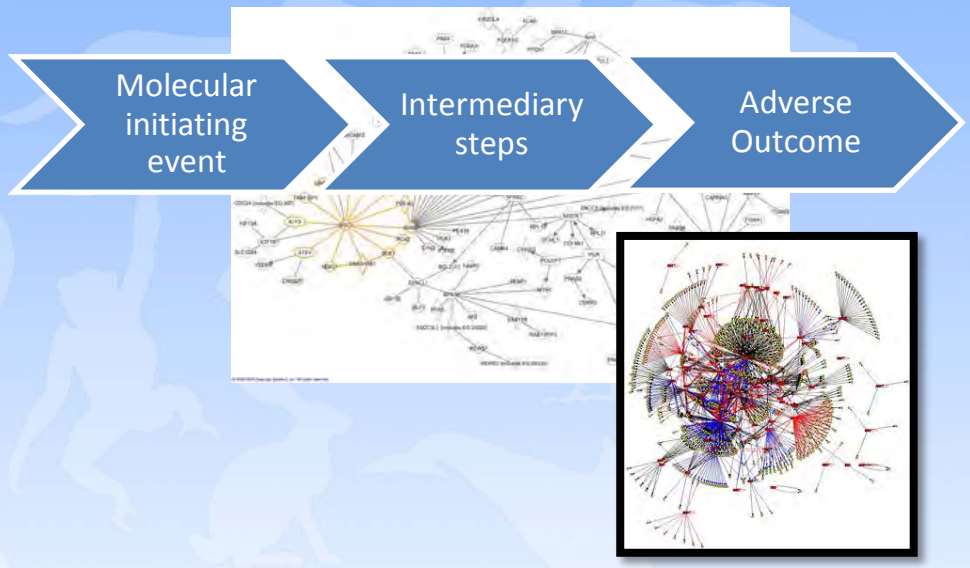
The Shift from Empirical (mostly animal-based) to Predictive (pathway-based) Approaches to Safety Assessment: benefits and applicability



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EPA OPP Stakeholder workshop: Where Vision Meets Action: Practical Application of 21st Century Methods
July 9, 2013 | Arlington, VA

Outline

- The need for a new approach to toxicology
- Precedents and projects
- How to build a pathway
  - OECD guidance
  - Workshop(s) conclusions
- Requirements for different uses
- What's needed for the future

The argument for a new approach

Pharmaceuticals:

- 92% of drug candidates fail in clinical studies
- "The average drug developed by a major pharmaceutical company costs at least $4 billion, and it can be as much as $11 billion" (Forbes 2012)
- Need to assess novel chemistries (i.e. nanomaterials)

Industrial chemicals:

- Growing concern over lack of data (> 10K chemicals worldwide)
- Large-scale regulatory programs: REACH (EU, China, S.Korea)

Pesticides:

- Registration requires the use of approximately 10,000 animals, millions of USD, and many years (decades)
- Need to identify "greener" chemistries

Cosmetics:

- European (and now Indian) ban on animal testing
- Consumer concern over safety and animal testing worldwide

The opportunity for a new approach

- Capitalize on advances in chemistry, biology, and engineering (since ~1970)
- Fully utilize all existing knowledge
- Increase relevance to humans (and other species)
- Increase assessment capacity (“throughput”)
- Increase efficiency (benefit/cost)
- Increase *predictivity*

Decrease uncertainty in hazard and risk assessment

Precedents for pathway-based toxicology

1. Dose-response modeling
   - Using pharmacokinetic and mechanistic information
2. IPCS/WHO mode of action frameworks
   - Human relevance of rodent cancer findings
   - Extrapolated to non-cancer endpoints
3. Mode of action pathways in drug development
   - Drug and target-specific
4. 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**"*

Pathway projects and workshops

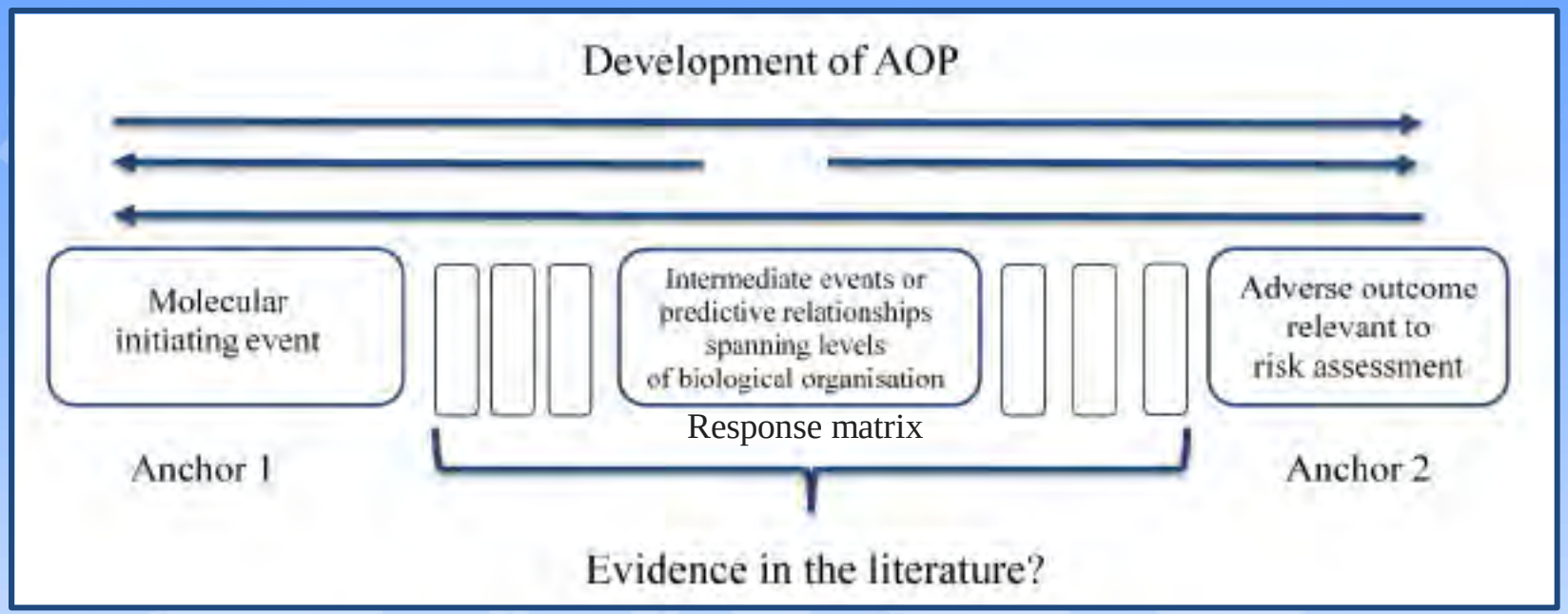
1. OECD Test Guidelines Programme
   - 2010 Workshop on using mechanistic information in forming chemical categories
   - Extended Advisory Group on Molecular Screening and Toxicogenomics,
   - VMG-non-animal under the EDTA-AG
2. JRC-SEURAT 2012 workshop: Describing mode-of-action in liver toxicity using adverse outcome pathways
   - Fibrosis and steatosis as prototypes
   - Way to organize and integrate SEURAT data
3. CAAT 2012 Workshop: Concept and Tools for Pathways of Toxicity
   - Combination of toxicity pathway and 'omics approaches
   - Estrogen signaling as prototype
4. The Hamner Institutes: "Tier 1 and Done"
   - Estrogen signaling pathway as prototype
   - Including dose-response extrapolation modeling
5. HTPC 2013 workshop: Building Shared Experience to Advance Practical Application of Pathway-Based Toxicity: Liver Toxicity Mode-of-Action

Building a Pathway

1. What basic elements are needed for pathway development?
2. Where do you start?
   - How do you determine which MIEs, pathways to focus on?
   - E.g. do you start with one MIE and develop pathways for each AO?
3. How and where to limit the pathway
   - Must every pathway begin at the MIE and end with an AO
     - at the individual or population level?
   - When is it appropriate to include branching?
4. How to evaluate and assess the completeness and confidence of a pathway?
5. How to identify which uses would be appropriate?

OECD AOP project

http://www.oecd.org/env/ehs/testing/molecularscreeningandtoxicogenomics.htm



Guidance

- Template for building
- Criteria for evaluating
- Glossary of terms

OECD Series on Testing and Assessment No. 184. 2013. Guidance Document on Developing and Assessing Adverse Outcome Pathways (available online)

OECD AOP development template

1. Three basic elements:
    a. MIE ←→ intermediate events ←→ Adverse Outcome
2. Begin from any of these elements
    1. MIE: molecular description of how the chemical interacts with the initial biomolecule
    2. AO: specific and well-defined outcome, associated with OECD TG endpoint
3. An AO results from a finite number of MIEs, and conversely an MIE results in a finite number of AOs, but an AOP is limited to a single MIE → a single AO
4. Information from different levels of biological organization are integrated into a single description

OECD AOP reporting

Data summation:

- Assays that are fit for purpose, repeatable, reproducible, and directly or indirectly linked to AO
- WoE supports the evidence used

AOP assessment:

- Reliability and robustness
- Strength of qualitative and quantitative understanding (Bradford-Hill criteria):
  - strength of association
  - consistency of the evidence
  - specificity of the relationship
  - consistent temporal relationships
  - dose-response relationships
  - biological plausibility
  - coherence of the evidence
  - and consideration of alternative explanations

Other practical considerations

1. Annotation of pathway should include
   a. Well-defined terminology
   b. Diagram(s)
   c. Language for representing multi-dimensions including temporal
   d. Explanation of how the each step was deduced
2. Quality assessment of input data
   a. Evidence Based Toxicology?
   b. Klimisch score?
3. Quality of and confidence in causal linkages
   a. Bradford-Hill criteria
   b. Human relevance
4. Consideration of Scope
   a. species, developmental stage, sex, chemical space limitations
5. Temporal hierarchy
   a. E.g. gene expression changes that precede cellular changes
6. Quantitative linkages
   a. Threshold and scale

Uses of AOPs

Near-term use:

- Inform chemical categories and structure activity relationships
- Hazard identification
- Prioritization of chemicals for further assessment
- Increase certainty of interpretation of both existing and new information
- Develop integrated testing strategies that maximize useful information gained from minimal testing

Longer-term use:

- Identify key events for which non-animal tests can be developed, thereby facilitating mechanism-based, non-animal chemical assessment
- Create predictive toxicological assessments with low uncertainty and high human relevance
- Eventually without the use of animals

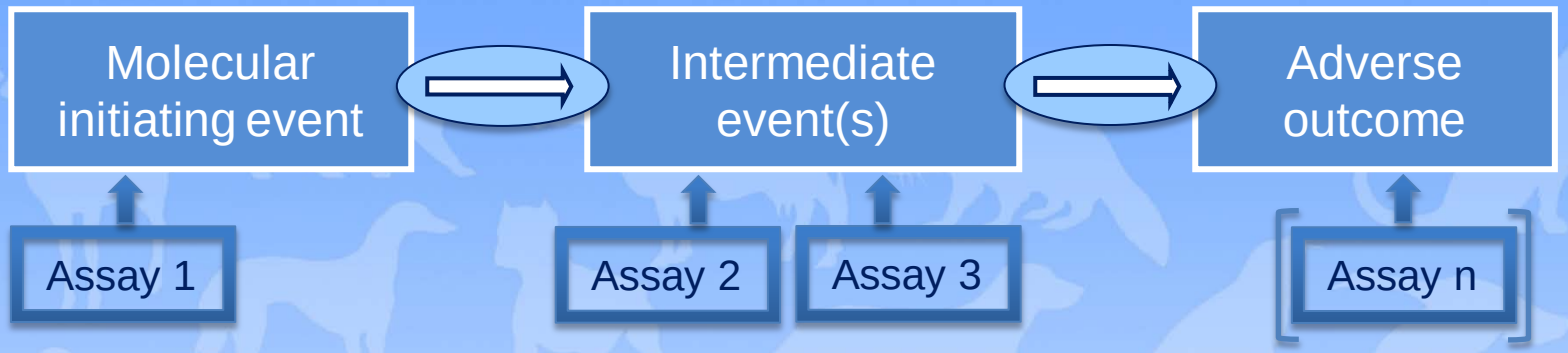
Use ∝ strength/type of information

Chemical categories

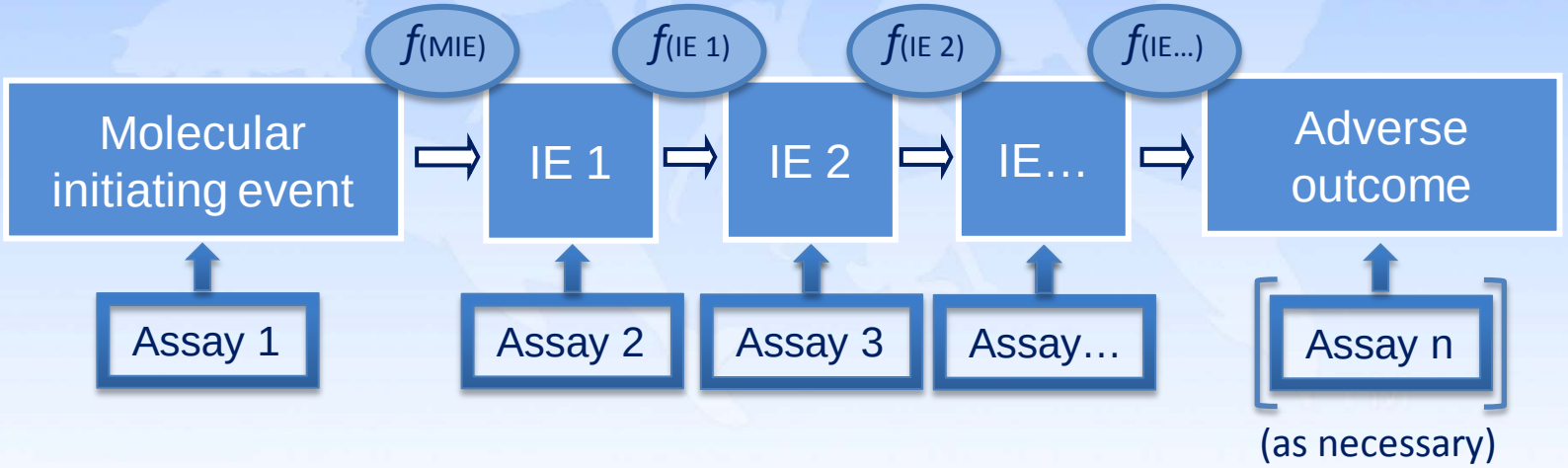
Hazard identification
Prioritization

Use ∝ strength/type of information

Integrated strategy design

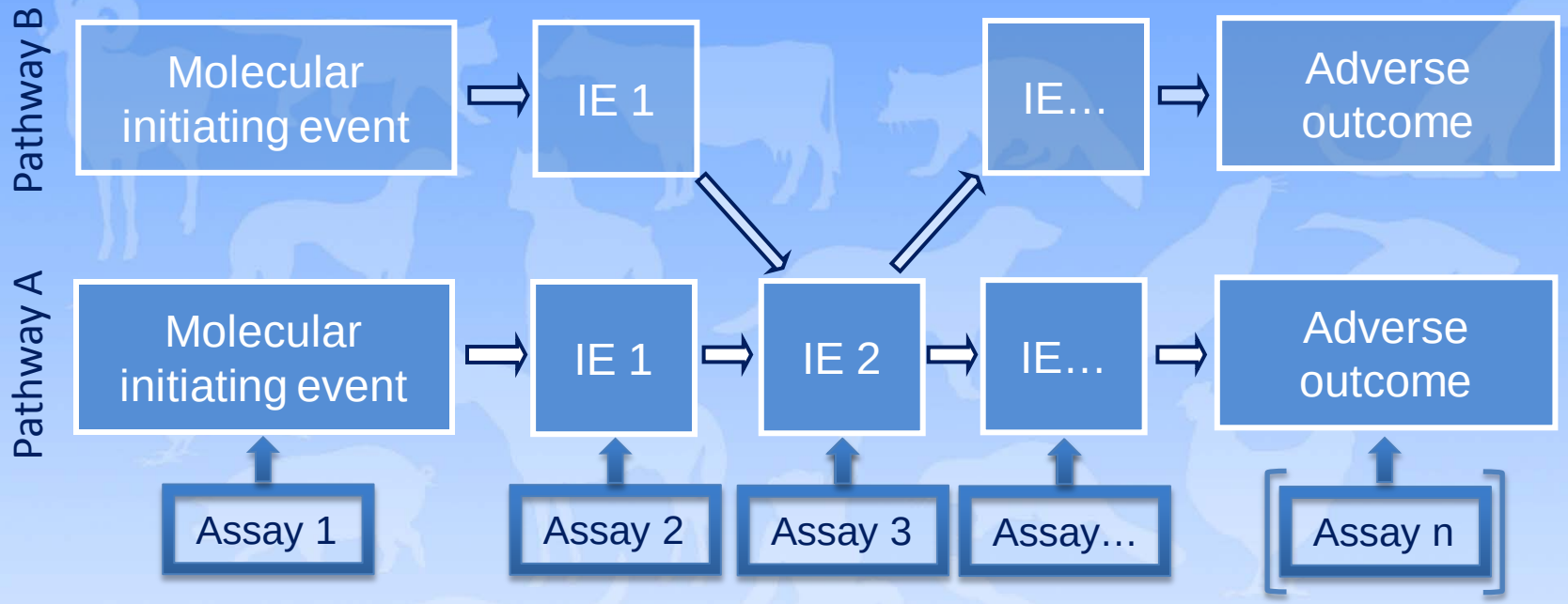


Risk Assessment



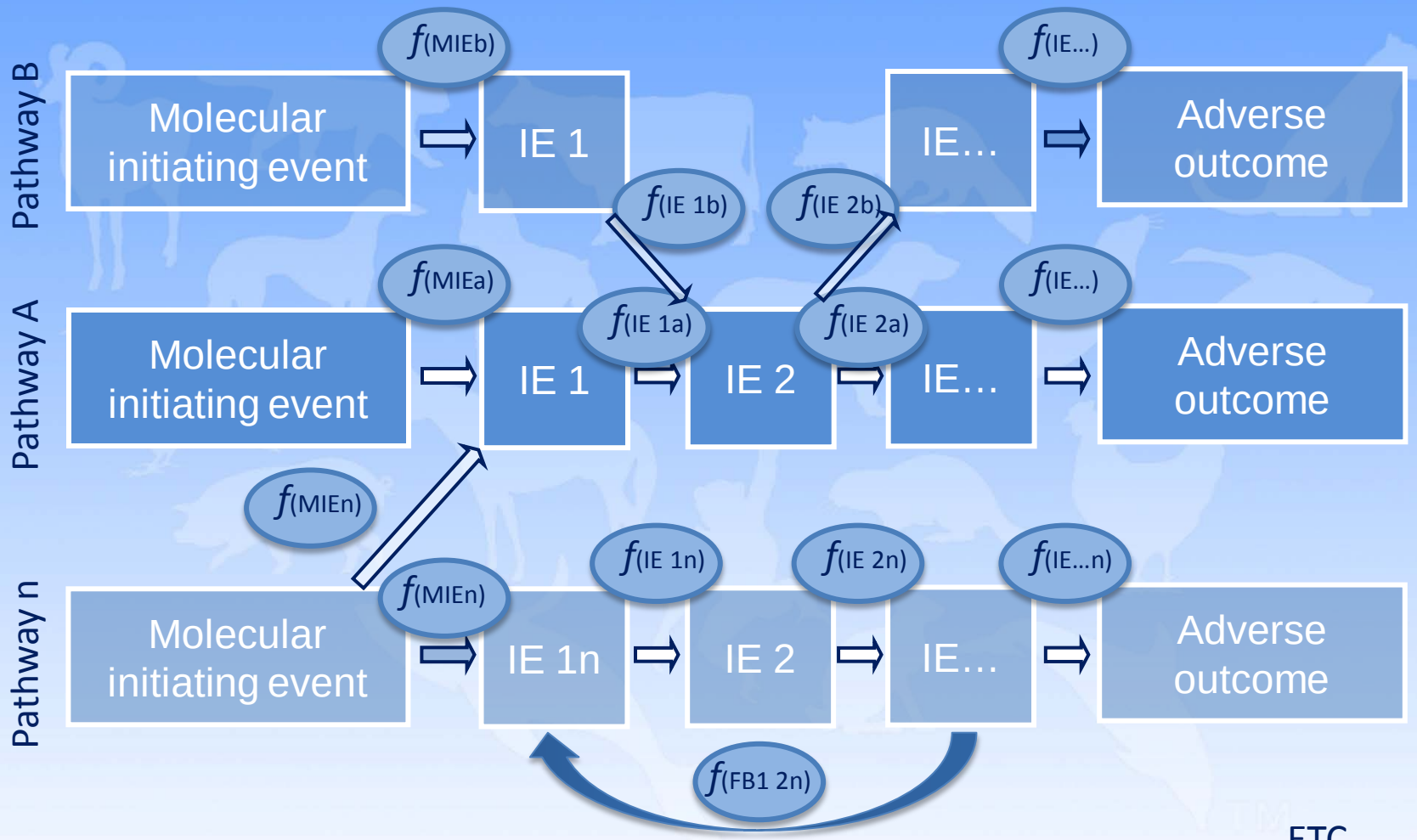
Use ∝ strength/type of information

ID key events that link pathways



Use ∝ strength/type of information

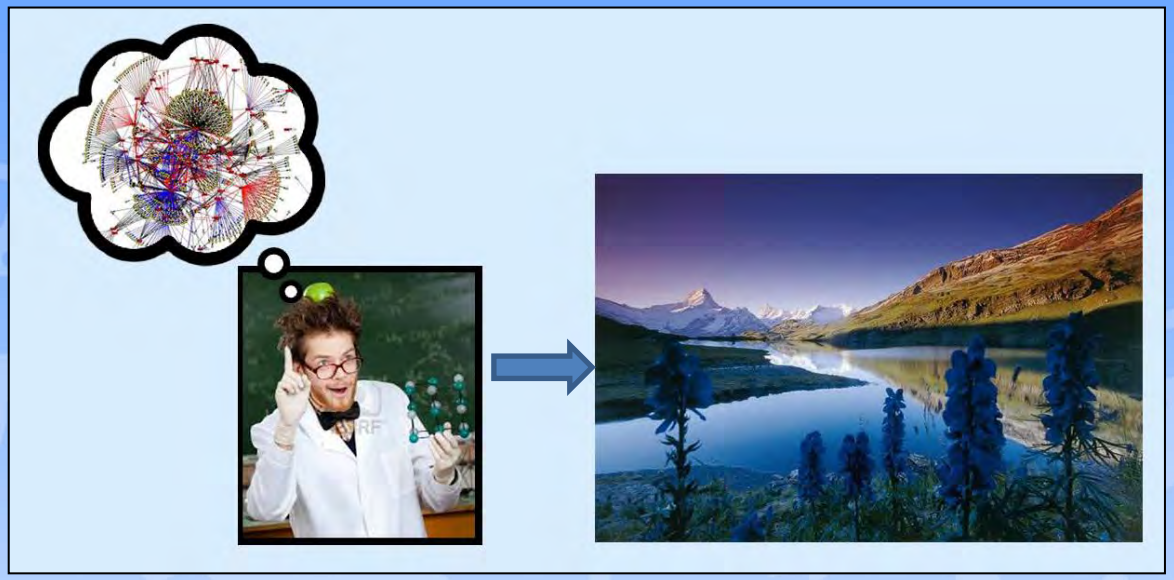
Predictive system for toxicology



What's needed for the future

- **Build a series of prototype pathways**
  - OECD / EPA / FDA / industry / academia
  - OECD Guidance
- **Improve predictive tools**
  - NIH National Center for Advancing Translational Sciences
  - EPA's Computational Toxicology Research
  - OECD QSAR tool box
  - The Hamner Institutes
- **Develop assessment systems for complex endpoints**
  - Reconstructed tissues and organ systems
- **Integrate absorption, metabolism and distribution information**
  - QSAR
  - Liver cells, tissues, extracts, reconstructed tissues
- **Integrated databases and "knowledge bases"**
  - **OpenTox / AOP Wiki (JRC/EPA/OECD) -** open knowledge aggregation and collaboration tools that provide a means of describing adverse outcome pathways in an encyclopedic manner
- **Engage stakeholders**
  - Informational resources and outreach (EPA website, HTPC)
  - Opportunities for conversations
    - Workshops (like this)
    - Webinars

Thank You



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OECD AOPs in development

Extended Advisory Group on Molecular Screening and Toxicogenomics

- Mitochondrial toxicity – OECD
- Cell proliferation/differentiation – OECD
- Fish reproductive toxicity – US EPA
- Thyroid hormone pathways – US EPA
- PPARα – OEDC, Hamner
- Cancer epigenetics – S.Korea
- Germ cell mutagenicity – Canada
- Neurotoxicity and inflammation – Switzerland
- Liver Steatosis and Fibrosis – JRC
- AhR – BIAC
- Aquatic toxicity: UK and Japan
- Mutagenic MOA: US
- PPARa/CAR: US
- Embryonic vascular development: US