Why are AOPs important, and how can they be useful?

Catherine Willett, PhD
Director, Regulatory Testing
Risk Assessment and Alternatives
The Humane Society of the United States
kwillett@humanesociety.org
Outline

- Why do we need a new approach to toxicology?
- Precedents for pathway-based approaches
- Potential uses
- Requirements for different uses
- AOP projects
The need 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 Cosmetics Directives 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 assessment capacity ("throughput")
- Increase efficiency (benefit/cost)
- Increase relevance to humans/species of concern
- 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 and product development
   - Drug and target-specific

   
   "envision 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"
Uses of AOPs

Near-term use:

– Inform chemical categories and structure activity relationships
– Prioritization of chemicals for further assessment
– Hazard identification
– 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 $\propto$ strength/type of information

- Chemical categories
- Hazard identification
- Prioritization
- Integrated strategy design

- Molecular initiating event
  - Intermediate event(s)
  - Adverse outcome

- Risk assessment
- ID key events that link pathways
- Predictive system for toxicology
Use $\propto$ strength/type of information

**Structure Activity Relationships**

**Chemical categories**

- Molecular initiating event
- Intermediate event(s)
- Adverse outcome
Use $\propto$ strength/type of information

Hazard identification
Prioritization

Molecular initiating event

Assay 1

Intermediate event(s)

Assay 2

Adverse outcome
Use $\propto$ strength/type of information

Integrated strategy design

1. Molecular initiating event
   - Assay 1

2. Intermediate event(s)
   - Assay 2
   - Assay 3

3. Adverse outcome
   - Assay n
Use $\propto$ strength/type of information

Risk assessment

Molecular initiating event $\xrightarrow{f(MIE)}$ IE 1 $\xrightarrow{f(IE 1)}$ IE 2 $\xrightarrow{f(IE 2)}$ IE... $\xrightarrow{f(IE...)}$ Adverse outcome

Assay 1 $\xrightarrow{f(MIE)}$ Assay 2 $\xrightarrow{f(IE 1)}$ Assay 3 $\xrightarrow{f(IE 2)}$ Assay... $\xrightarrow{f(IE...)}$ Assay n
Use $\propto$ strength/type of information

Risk assessment with increased certainty of a particular AO
Predictive toxicology

Pathway A
Molecular initiating event $\rightarrow f(MIE)_A \rightarrow f(IE_{1A}) \rightarrow f(IE_{2A}) \rightarrow f(IE_{...A}) \rightarrow IE_{...} \rightarrow IE_{2} \rightarrow IE_{1} \rightarrow f(MIE)_B \rightarrow IE_{1} \rightarrow IE_{...} \rightarrow Adverse outcome$

Pathway B
Molecular initiating event $\rightarrow f(MIE)_B \rightarrow f(IE_{1B}) \rightarrow f(IE_{2B}) \rightarrow f(IE_{...B}) \rightarrow IE_{...} \rightarrow IE_{2} \rightarrow IE_{1} \rightarrow f(MIE)_A \rightarrow IE_{1} \rightarrow IE_{...} \rightarrow Adverse outcome$

ETC...
Use $\propto$ strength/type of information

Predictive system for toxicology

Pathway B
- Molecular initiating event
- $f_{(MIE)B}$
- $f_{(IE\,1)B}$
- $f_{(IE\,2)B}$
- $f_{(IE\,\ldots)B}$
- Adverse outcome

Pathway A
- Molecular initiating event
- $f_{(MIE)A}$
- $f_{(IE\,1)A}$
- $f_{(IE\,2)A}$
- $f_{(IE\,\ldots)A}$
- Adverse outcome

Pathway n
- Molecular initiating event
- $f_{(MIE)n}$
- $f_{(IE\,1)n}$
- $f_{(IE\,2)n}$
- $f_{(IE\,\ldots)n}$
- Adverse outcome

$\ldots$

ETC...
AOP Projects

Organization for Economic Cooperation and Development
- Guidance, Template, Criteria, Knowledge-bases (Dr. Schultz)

US Environmental Protection Agency
- Screening and prioritization (e.g. Endocrine Disruptor Screening Program)
- Prototype pathways, e.g. estrogen receptor-mediated reproductive impairment (Dr. Schmieder)

European Commission
- Knowledge-bases (with EPA and OECD)
- Framework programme project case studies (Dr. Vinken)

Industry
- Internal use
- Joint government projects for regulatory use (e.g. sensitization: Dr. Patlewicz)
Thank You

Catherine Willett, PhD
Director, Regulatory Testing
Risk Assessment and Alternatives
Humane Society of the United States

Coordinator, Human Toxicology Project
Consortium

kwillett@humanesociety.org