AOPs 101: THE HOW AND WHY OF DEVELOPMENT AND USE

10:00 Welcome
Why are AOPs important, and how can they be useful?  
  Catherine Willett, HSUS/HTPC

10:15: The OECD program on AOPs  
  Anne Gourmelon, OECD

10:45: Practical experience using the AOP Wiki  
  Kristie Sullivan, PCRM

11:00: Introduction to Effectopedia  
  Hristo Aladjov, OECD

11:10: Two example AOPs (15 min each)
  • Application of AOP in the Bayesian network ITS framework to assess skin sensitization  
    Joanna Jaworska, P&G
  • Constructing AOPs for Developmental Toxicities  
    Nicole Kleinstreuer, ILS/NICEATM

11:40: Additional questions and discussion
Why are AOPs important, and how can they be useful?

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Molecular initiating event → Intermediary steps → Adverse Outcome
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

   “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”
Adverse Outcome “Pathway”

• A chemical and biological description of what occurs when a substance interacts with a living organism and results in an adverse reaction

• A biological map from the molecular initiating event through the resulting adverse outcome that describes both mechanism and mode of action.

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

Hazard identification
Prioritization

Molecular initiating event

Intermediate event(s)

Assay 1

Assay 2

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

Integrated strategy design

Molecular initiating event
- Assay 1

Intermediate event(s)
- Assay 2
- Assay 3

Adverse outcome
- Assay n
Use $\infty$ 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 $\xrightarrow{f}$ Assay 2 $\xrightarrow{f}$ Assay 3 $\xrightarrow{f}$ Assay... $\xrightarrow{f}$ Assay n
Use $\propto$ strength/type of information

Risk assessment with increased certainty of a particular AO
Predictive toxicology

Pathway A
- Molecular initiating event
- $f(MIE)_A$
- $f(IE_1)_A$
- $f(IE_2)_A$
- $f(IE...)_A$

Pathway B
- Molecular initiating event
- $f(MIE)_B$
- $f(IE_1)_B$
- $f(IE_2)_B$
- $f(IE...)_B$

$Adverse \ outcome$

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

Predictive system for toxicology

Pathway B

- Molecular initiating event
  - $f(MIE)_B$
  - IE 1
  - $f(IE_1)_B$
  - IE...
  - $f(IE_\ldots)_B$
  - Adverse outcome

Pathway A

- Molecular initiating event
  - $f(MIE)_A$
  - IE 1
  - $f(IE_1)_A$
  - IE 2
  - $f(IE_2)_A$
  - IE...
  - $f(IE_\ldots)_A$
  - Adverse outcome

Pathway n

- Molecular initiating event
  - $f(MIE)_n$
  - IE 1n
  - $f(IE_1)_n$
  - IE 2
  - $f(IE_2)_n$
  - IE...
  - $f(IE_\ldots)_n$
  - Adverse outcome

ETC...
AOP Projects

Organization for Economic Cooperation and Development
- Guidance, Template, Handbook, Knowledge-bases (A. Gourmelon)

European Commission/OECD/US EPA
- Knowledge-bases (with EPA and OECD) (K Sullivan)
- Effectopedia (H Aladjov)

Case Studies:
Industry
- Safety assessment, e.g. skin sensitization (J Jaworska)

National Institutes of Health
- Constructing AOPs for Developmental Toxicities (N Kleinstreuer)
Thank You for Attending!

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