Integrating and Weighting Mechanistic Evidence in Hazard and Risk Assessment

Break-Out Session, Managing Evidence
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Outline

- Background (Assimilating and Integrating Mechanistic Data)
  - Mode of Action (MOA) and Adverse Outcome Pathways (AOP) Analysis
- Weighted Integration/Confidence Considerations in MOA/AOP Analysis
  - Broader Context
- Implications for Managing Evidence

Current Developments/Challenges in Assessing Toxicity/Hazard of Chemicals

Evolving technologies which provide:

- Biological data at lower levels of organization
  - E.g., transcriptomics
  - in human tissues
- Increasing computational capacity for data assimilation and prediction

Legislative imperatives which require:

- Greater efficiency in chemicals assessment and management
- Less reliance on animal testing

Background: Assimilating Mechanistic Data Mode of Action/Adverse Outcome Pathways

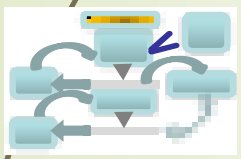
Chemical

Tissue Dose → Key Event 1 Effective Dose → Key Event 2 → Key Event 3 → Adverse Outcome

Toxicokinetics (tk) | Toxicodynamics (td)

Chemical specific absorption, distribution, metabolism, excretion

Chemical agnostic biological pathway



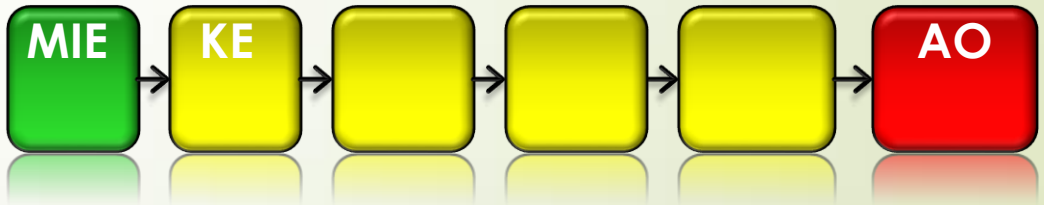
MOA Analysis;

Testing

Monitoring of Environment

AOPs

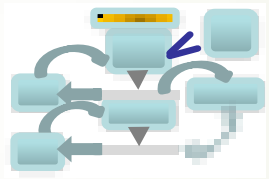
Adverse Outcome Pathway (AOP)



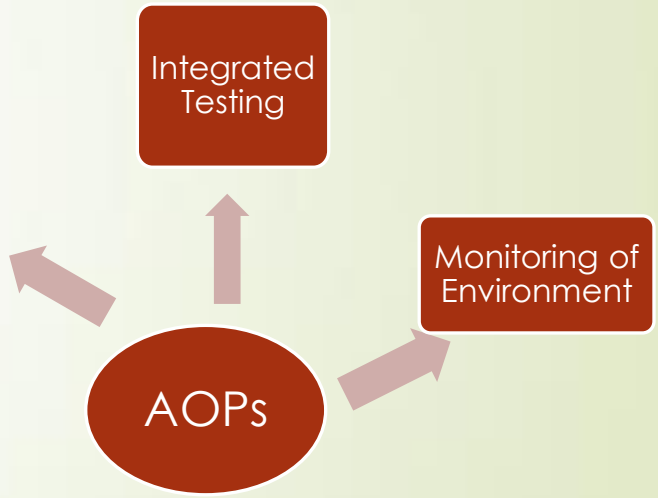
KERs

Why Distinguish MOA Analysis from AOPs?

- To move us from the observation in animal studies to more predictive approaches, by:
  - assimilating chemical agnostic mechanistic information on disease pathways at a broad range of biological levels of organization
    - *E.g., in vitro* and *in vivo* transcriptomics,
    - *in vivo* biochemical measures
    - *in vivo* histopathological measures
- For a range of regulatory applications
  - E.g., development of testing strategies
  - considering biological plausibility in epidemiological studies
  - Mode of action analysis for specific chemicals or groups
  - environmental monitoring

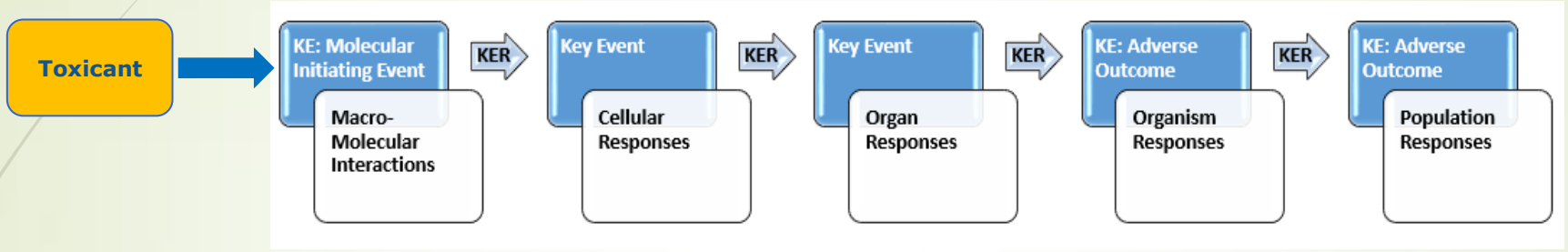


MOA Analysis; Biological Plausibility in Epi Studies



AOP/MOA – *Integrating Constructs*

Regulatory Endpoints



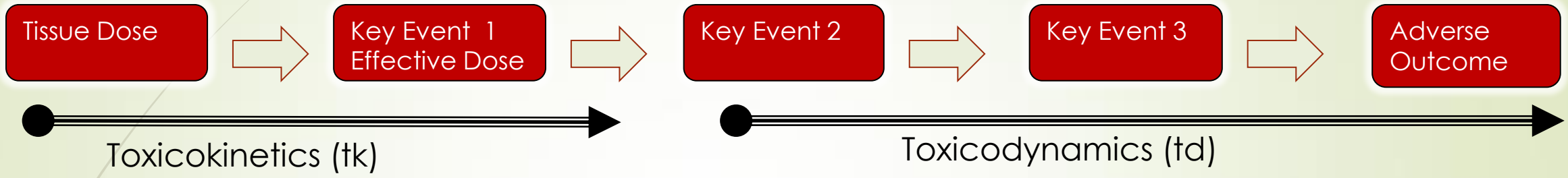
High Throughput Tox

Guideline Studies

Mechanistic Toxicology Data
Bioindicators

Epidemiology

World Health Organization (WHO)/International Programme on Chemical Safety (IPCS) Framework on Mode of Action/Human Relevance (MOA/HR)



- Developed in the late 1990's; 100s of experts engaged
  - Research/regulatory communities
- Widely incorporated in program guidance internationally
  - training
- Updated to incorporate technological advances (2014)

Objectives

- Drawing maximally and early on mechanistic data
- Transparency
- Bridging regulatory/research
  - Doing the right research/testing

Review Article

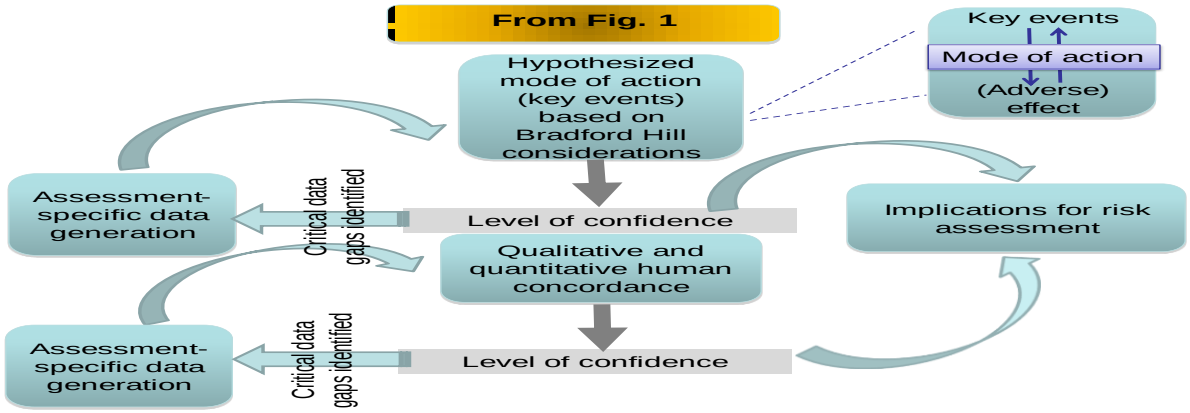
Journal of Applied Toxicology

Received: 18 September 2013, Accepted: 19 September 2013 Published online in Wiley Online Library: 25 October 2013

(wileyonlinelibrary.com) DOI 10.1002/jat.2949

New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis†

M. E. Meek[a], A. Boobis[b], I. Cote[c], V. Dellarco[d], G. Fotakis[e], S. Munn[f], J. Seed[g] and C. Vickers[h]*



Review Article

Journal of Applied Toxicology

Received: 2 November 2013, Revised: 28 November 2013, Accepted: 3 December 2013 Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI 10.1002/jat.2984

Mode of action human relevance (species concordance) framework: Evolution of the Bradford Hill considerations and comparative analysis of weight of evidence

M. E. (Bette) Meek*, Christine M. Palermo, Ammie N. Bachman, Colin M. North and R. Jeffrey Lewis

B/H	Support	Conflict	Gaps
1.			
2.			
3.			
4.			
5.			

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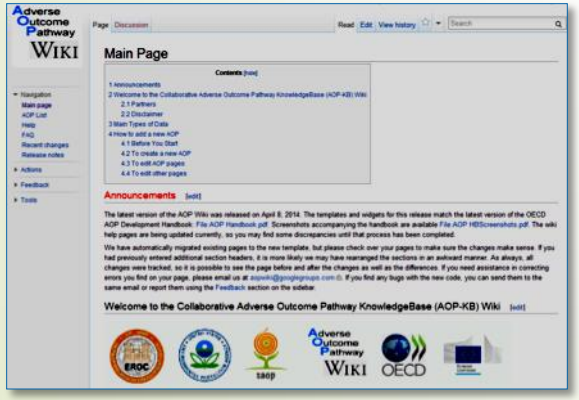
Users' handbook supplement to OECD guidance document for developing and assessing AOPs.

Early Examples: Becker et al., 2015 Regulatory Toxicology and Pharmacology 72 (2015) 514

B/H	Def.	H	M	L
B.P.				
Essentiality				
Empirical				

Formalizing AOP Descriptions and Assessment to Support Regulatory Application

- OECD Guidance on Developing and Assessing AOPs (2013, 2014)
  - Conventions and terminology
  - Information content of an AOP description
  - Weight of evidence (WOE)/confidence evaluation



AOPWIKI.org

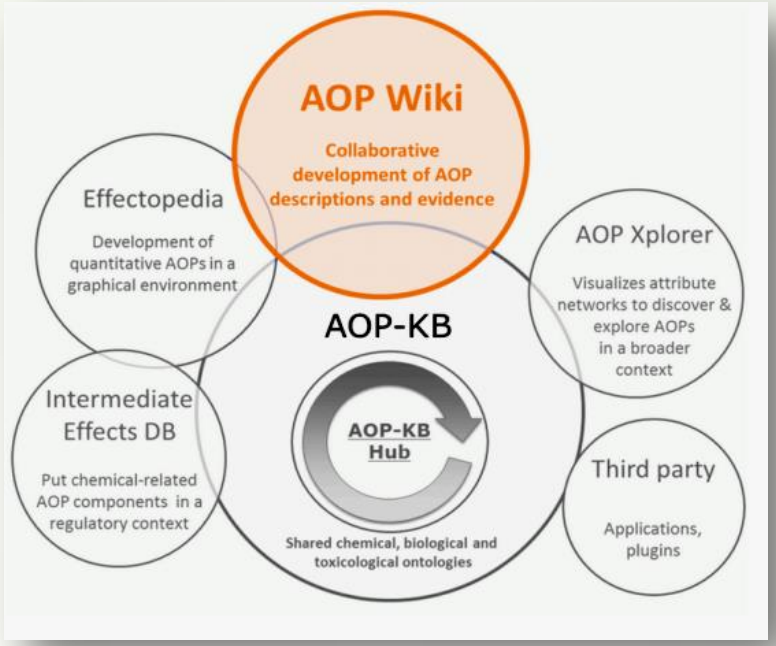
AOP Development and Description Case Studies

Users' handbook supplement to OECD guidance document for developing and assessing AOPs.

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

Addressing the Research-Regulatory Interface: The AOP Knowledge Base

OECD
AOP devt and assessment (2012)
Test Guidelines
Hazard Evaluation



AOPKB.org
AOPWIKI.org

> 200 AOPs

Facilitating research collaboration:

- Avoiding duplicative effort
- Integration and analysis
- Building networks
- Accessible and searchable

Addressing regulatory needs:

- Systematically organized
- Transparent, well documented
- Scientifically-defensible, credible

Identifying data gaps relevant to application

AOP Wiki

Annex 1

Section 5b – MIE, KE, and AO descriptions

Consideration	Defining Questions	High	Moderate	Low
Biological Plausibility of KERs (S. 6)				
Support for Essentiality of KEs (S.7)				
Empirical Support for KERs (S.6.)				

Section 1 - Title
Section 2 - Authors
Section 3 – Status and
Section 4A – Abstract
Section 4B – Backgrou
Section 5A – Summary

MIE

KEs

AO

Linkage table

Key Event Relationships/Associations

Applicability domain(s) of the AOP

Life stage

MIE Page

Chemical initiator(s)

- Description
- Measurement/ detection
- Taxonomic applicability
- *Evidence for*

Species	Chem	Conc.	KE1	KE2
FHM	A	1		
FHM	A	10		
FHM	A	100		
FHM	B	0.01		
FHM	B	0.1		
FHM	B	1		
RBT	B	0.05		
RBT	B	0.5		
RBT	B	2.5		

Section 6 – KER descrip

KER Page (section

- Title
- Biological plau
- Empirical supp
- Quantitative understanding
- Uncertainties inconsistencie

tiality

)P

AOP (Optional)

Event	Direct Evidence	Indirect Evidence	No or contradictory experimental evidence	None Contradictory
MIE				
KE1				
KE2				
KE3…… KEn				

The Templates Comparative Analysis

Mutagenic Mode of Action

Evolved B/H Consideration	Supporting Data	Inconsistent Data	Critical Datagaps
Biological Concordance	XXX		
Essentiality of KEs		XX	
Empirical Concordance	X	XXX	
Consistency		XXX	
Analogy			

Transparency and Consistency:

- explicit considerations & weighting

Meek et al., 2014a, 2014b

Cytotoxic Mode of Action

Evolved B/H Consideration	Supporting Data	Inconsistent Data	Critical Datagaps
Biological Concordance	XXX		
Essentiality of KEs	XXX		
Empirical Concordance	XXX	X	
Consistency	XX		
Analogy	XX		

Mutagenic MOA Pathway: Quantitative Scoring

	Assigned Weight	Score = (Weight X Rating) [10% evidentiary value for later, non-diagnostic KEs]				
		DNA Reactivity KE #1	Insufficient repair or misrepair KE#2	Perturbation of cell growth and survival KE#3	Clonal expansion of preneoplastic foci KE#4	Liver tumors KE#5
Biological Plausibility	Extensive documentation of scientific acceptance of the biological plausibility of this MOA					
Essentiality	0.4	0	0	0	0	0
Empirical Support	0.2	-0.6	-0.6	0.6	0.6	0.6
Empirical Support Temporal Concordance	0.2	-0.6	-0.6	0.6	0.6	0.6
Consistency	0.1	-0.3	-0.3	0.3	0.3	0.3
Analogy	0.1	-0.3	-0.3	0.3	0.3	0.3
∑SCORE: = -3.1/6.9 X 100 = -44 (Confidence Score)		-1.8	-1.8	1.8 (0.1) = 0.18	1.8 (0.1) = 0.18	1.8 (0.1) = 0.18

What is Weight of Evidence (in an MOA/AOP Context)?

- Comprehensive, integrated judgment of supporting evidence for an AOP:
  - Causal Question Definition and Data Selection*
  - Individual Study Review
  - systematic review of pertinent studies using pre-defined criteria and applying them uniformly
  - Data Synthesis and Evaluation
  - Application to Decision-Making

*Rhomberg et al., 2013; Crit. Rev. Toxicol. DOI: 10.3109/10408444.2013.832727

Assembling, weighting and ***integrating*** evidence – EFSA Scientific Opinion. Guidance on the Use of WOE doi: 10.2903/j.efsa.2017.4971

Review

A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP3067.

Weight of Evidence for Hazard Identification: A Critical Review of the Literature

Pierre Martin,[1,2] Claire Bladier,[3] Bette Meek,[4] Olivier Bruyere,[5] Eve Feinblatt,[3] Mathilde Touvier,[6] Laurence Watier,[7] and David Makowski[8]

So What's Important for Evaluation?

- Review of approaches to weight of evidence (WOE) evaluations of hazard:
  - published literature, and
  - directed requests to 63 international and national agencies
- WOE approaches considered based on their:
  - degree or extent of ***prescription***
  - their ***relevance***
    - for a wide range of ANSES assessments, and
  - ease of implementation (***feasibility***)
    - Time and material/human resources required,

Review

A Section 508-conformant HTML version of this article is available at https://doi.org/10.1289/EHP3067.

Weight of Evidence for Hazard Identification: A Critical Review of the Literature

So What's Important for Evaluation? (cont'd)

- Early (public) delineation of the protocol for assimilating, selecting, weighting and integrating evidence (template?)
  - rationale for selection of approaches/tools, taking into account:
    - 1.objectives, ***2.resourcing***, 3.level of acceptable uncertainty, and
    - 4.stages/steps that have ***greatest impact***
- Recognizing that:
    - preferred tools often most resource intensive but may ***not*** be ***required***
- What's most important?
  - ***transparency reproducibility/consistency***
- What contributes most?
  - level of prescription of an approach based on assimilated experience, balanced against feasibility
  - clearly delineated objectives in the ***context*** of intended application

So, What's Worked?
Critical Elements in Managing (Assimilating, Integrating and Weighting) Evidence in Hazard Assessment

- An integrating construct sufficient to assimilate an adequate level of detail
  - e.g., key events at different levels of biological organization for AOPs/MOA
  - relevant to application in regulatory context
    - Requires regulatory/research interface
- A limited number of expert informed most influential "determinants" for:
  - considering the extent of the supporting data (i.e., weight of evidence)
- A user friendly interface and platform for dissemination
  - Associated Development and Application Guide

What's been Challenging?

Balancing the scientific - regulatory interface

- the need for:
  - consistent terminology and documentation/description of construct and supporting evidence
    - Not the forte of the research community; essential for the regulatory community
- appropriate (not extensive) level of complexity
  - only as complex as it needs to be to address needs for regulatory application

    - i.e., focussed on critical (not all) aspects to facilitate communication and application within regulatory agencies (sensitivity – important or not?)
- sufficient experience and motivation/capacity to "codify" the important components of description and integration/weighting of evidence to enable incorporation in electronic tools