Applicability of the AOP for Assessing Causality of Observations in Epidemiological Studies

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Outline

- Background on Adverse Outcome Pathways (AOPs)
  - Objective
  - Distinction from Chemical Specific Mode of Action (MOA)
- Evolution of WOE/Confidence Considerations in MOA/AOP Analysis
  - Lessons learned
- Implications for Assessment of Causality in Epidemiological Studies for Regulatory Application
  - Biological plausibility based on mechanistic data

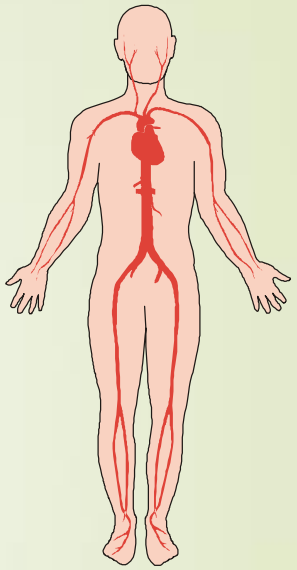
The Dilemma: Limitations of Current Approaches/Data on Toxicity

Epidemiological Studies: Ask the ***right*** question

- Examine the ***right*** species at the ***right*** doses

Answer it ***badly***

- Many factors which complicate interpretation (confounders)
- not very sensitive



Toxicological Studies: Ask the ***wrong*** question

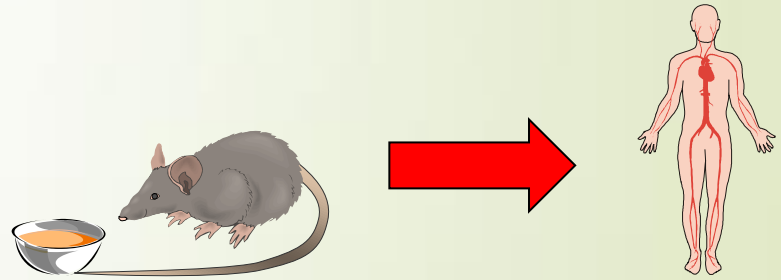
- Examine the ***wrong*** species at ***high*** doses,

Answer it ***well***

- Control of Variables

So What Helps?

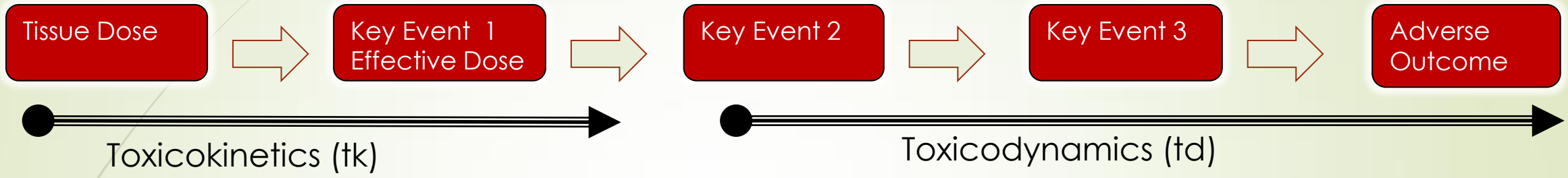
- ***Mechanistic*** data assist in interpretation of relevance and risk – to better integrate human & animal data
- What is it??
  - Data that informs us about ***how*** a chemical induces adverse effects
    - Kinetics
      - "Biologically effective dose"
    - Dynamics



To address:

- Are the effects in animals ***relevant*** to humans
- Are there ***groups at special risk*** (e.g., elderly)?
- What is the risk at the ***much lower doses*** to which humans are exposed?

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
- Recently updated

Objectives

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

Review Article

Journal of Applied Toxicology

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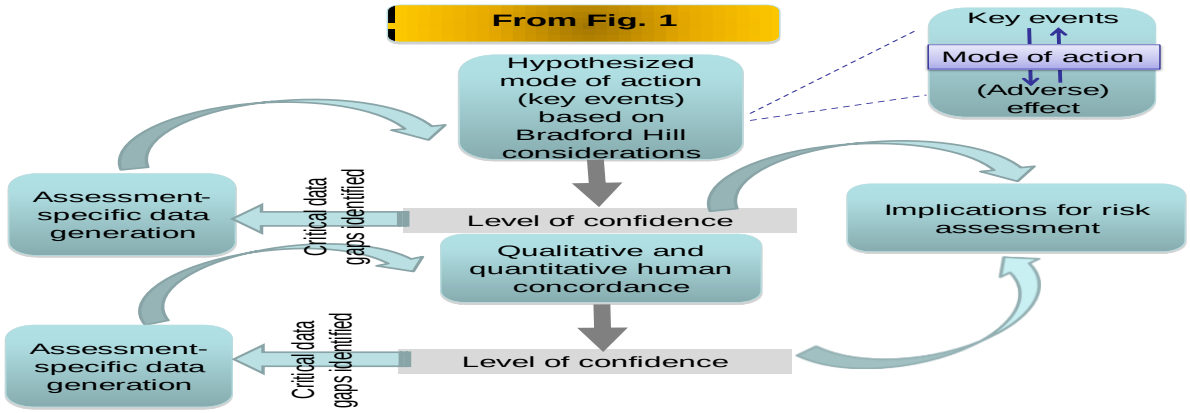
(wileyonlinelibrary.com) DOI 10.1002/jat.2949

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

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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

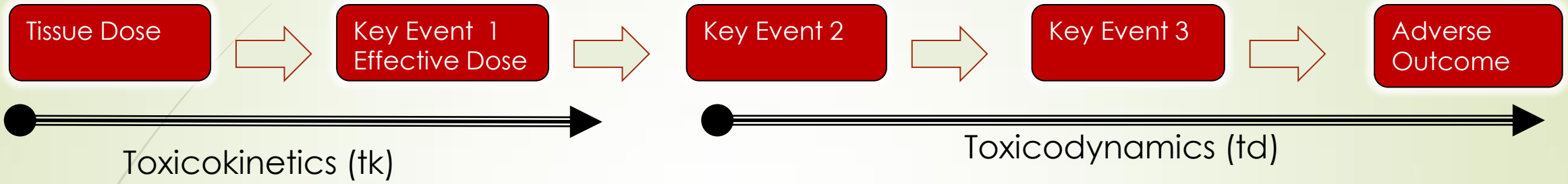
B/H	Def.	H	M	L
B.P.				
Essentiality				
Empirical				

Guidance for WOE Analysis – Mode of Action

Evolved BH Considerations	Stronger	Weaker
Biological Concordance	Well established	Novel biological processes
Essentiality of Key events	***Direct*** experimental evidence	Data on reversibility only or indirect data only
Concordance of Empirical Observations	***Expected*** Pattern	***Inconsistent*** or ***limited*** data.
Consistency	Pattern of effects are what you would expect across species, strains, organs, and/or test systems	Significantly inconsistent or limited data available to assess (*e.g.,* observed in single test system)
Analogy	Observations are consistent with those for other (related) chemicals having well defined MOA	Pattern of effects for other (related) chemicals is distinctly different. Insufficient data to evaluate whether chemical behaves like related chemicals with similar proposed MOA

Meek et al., 2014b

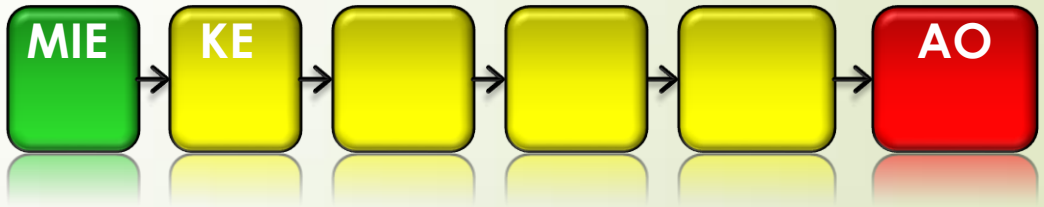
Mode of Action/Adverse Outcome Pathways



Chemical specific
absorption, distribution, metabolism, excretion

Chemical agnostic biological pathway

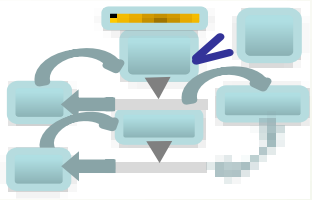
Adverse Outcome Pathway (AOP)



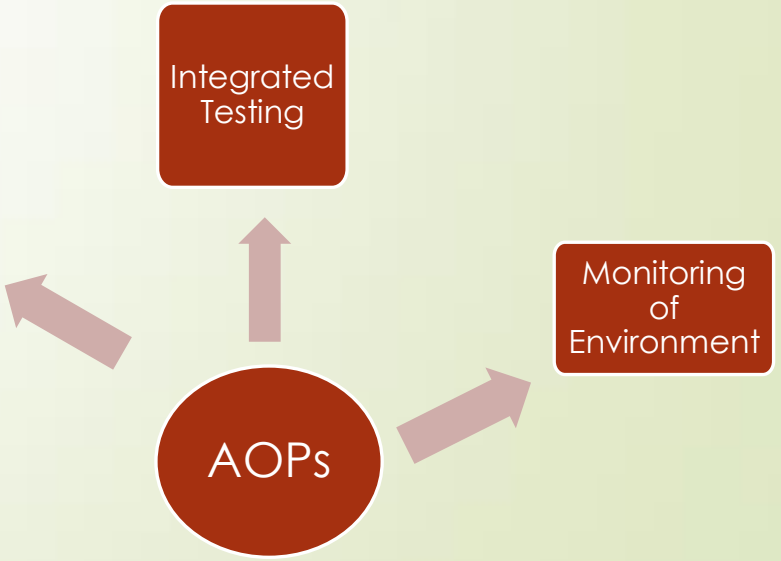
KERs

Why Distinguish MOA Analysis from AOPs?

- To move us from the observational adverse effect realm to more predictive approaches
- To provide repositories of descriptions of biological pathways for a number of different purposes (many qualitative), including in MOA analysis
  - E.g., development of testing strategies
  - considering biological plausibility in epidemiological studies
  - building networks
    - systems biology
  - environmental monitoring

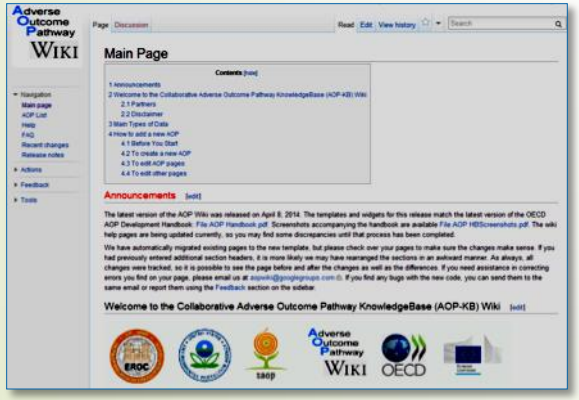


MOA Analysis; Biological Plausibility in Epi Studies

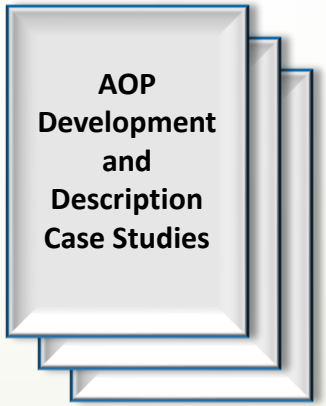


Formalizing AOP Descriptions and Assessment to Support Regulatory Application

- 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

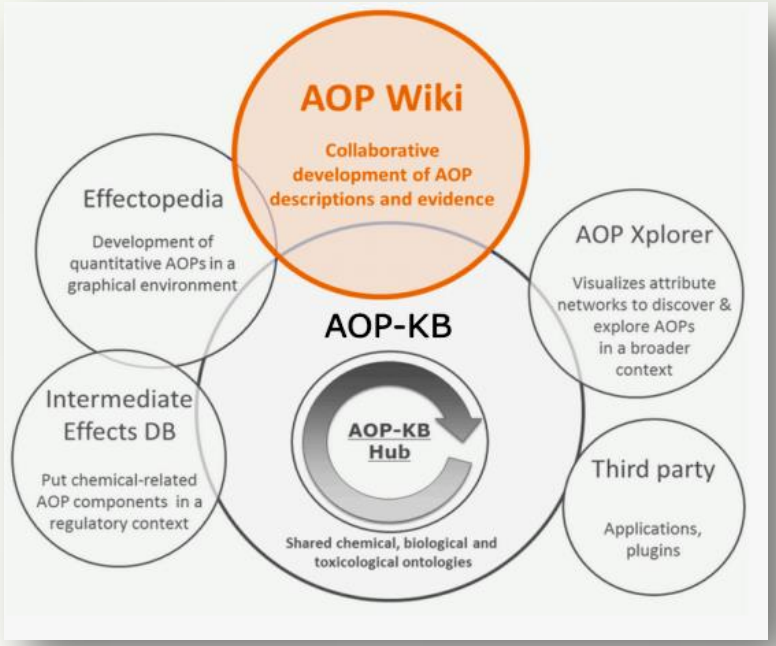


Users' handbook supplement to OECD guidance document for developing and assessing AOPs.

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

What is Weight of Evidence (in an 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 Draft

AOP Wiki

Section 5b – MIE, KE, and AO descriptions

Annex 1

AOP Pa

Section 1 - Title
Section 2 - Authors
Section 3 – Status and Date Modified
Section 4A – Abstract
Section 4B – Background (optional)
Section 5A – Summary of the AOP
- MIE
- KEs
- AO

Linkage table
- Key Event Relationships/Associations

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

Section 7 – Assembly of Evidence - Essentiality

Section 8 – Overall Assessment of the AOP

Section 9 – Potential Applications of the AOP (Optional)

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.)				

MIE Page

Chemical initiator(s)

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

AO Page

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

Section 6 – KER descriptions

KER Pages (section 6)
- Title
- Biological plausibility
- Empirical support
- Quantitative understanding
- Uncertainties and inconsistencies

Focus/Consistent Terminology – WOE for AOPs

- Biological Plausibility – ***KERs***
  - Biology of the pathway

More important

- Essentiality – ***KEs within AOP***
  - Necessity of Key Events
  - Experimental support normally from specialized studies to block or modify key events, stop/recovery studies

- Empirical Support – ***KERs***
  - Pattern of Quantitative Associations among Key Events often considered through application of stressors

Less important

Biological Plausibility of KERs

- Strength of our hypothesis about ***normal biology***, (structural/functional relationships)
  - The extent to which the relationships in a pathway are known, documented and accepted
    - Potential Measures?
- The extent to which we understand the pathway
  - Enables "prediction" or "testing" of the impact of disturbing it

Best Practice - Weight of Evidence/Confidence Analysis

- Distinguishing data supporting the various modified B/H considerations
- Characterizing nature of support for each of these considerations based on defining questions
- ***Identifying inconsistencies/uncertainties*** in supporting data
  - Templates/tables help
- Delineating consistent rationales for high, moderate and low confidence based on examples
- Identifying critical data gaps relevant to increasing confidence for regulatory application

Facilitating Regulatory Engagement

Meek, M.E. & Lipscomb,J.
Toxicology 332 (2015) 112–123

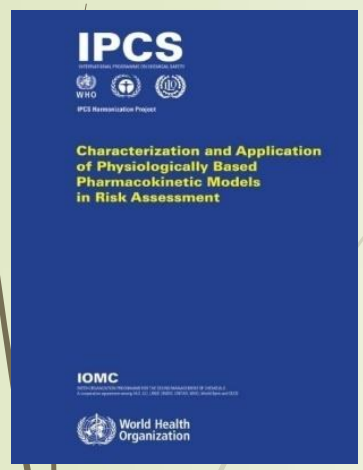
Principles:

- 1. transitioning in a familiar context
- 2. tiering to acquire experience and increase confidence
- 3. contextual knowledge transfer to facilitate interpretation and communication in application
- 4. coordination and development of expertise and
- 5. the importance of continuing challenge

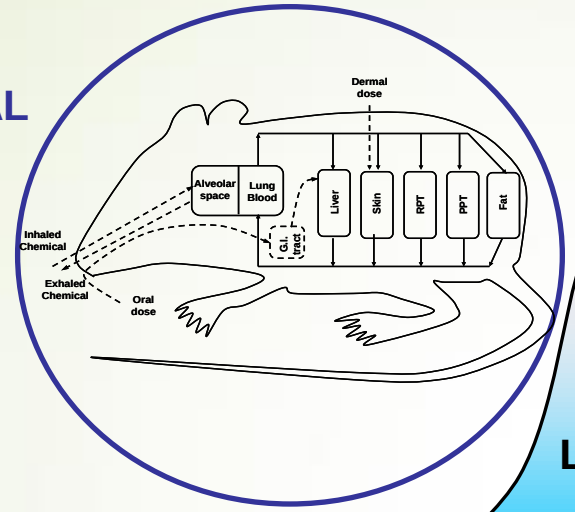
Requires:

- Collaboration between the research and regulatory communities to increase understanding and tailor objectives, design and documentation
- Transparency and consistency in documentation/public repositories

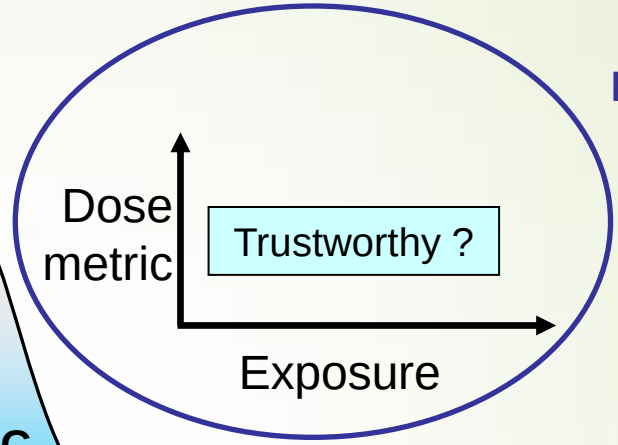
Physiologically Based Pharmacokinetic Models (PBPK) – Evaluation for Regulatory Application



BIOLOGICAL BASIS



RELIABILITY

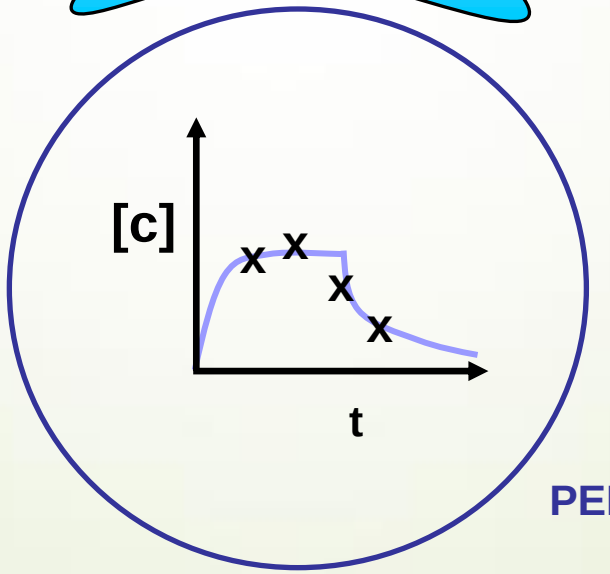


UNCERTAINTY

SENSITIVITY	H	M	L
H			
M			
L			

LOC in PBPK models

WHO Guidance on Characterization and Application of PBPK Models in Risk Assessment (2010) & Case Study Update
Reg. Tox. & Pharmacol. 66:116–129 (2013)



PERFORMANCE

Regulatory Uptake of PBPK Models

- Recent project of the WHO Chemical Risk Assessment Network
- Considered extent of regulatory uptake of PBPK models for development of chemical specific adjustment factors since release of CSAF Guidance (2005)
  - Literature review and data call
- Over 100 CSAF identified; 50% were based on PBPK models (50/100)
- Approximately 50% of the PBPK-based values were those adopted by regulatory Agencies (23/50)
- The confidence considerations as per the IPCS PBPK Guidance were well addressed in the regulatory Agency adopted values
  - in the non-regulatory values, inconsistent reporting, lack of transparency and confidence often unaddressed

Bhat, V., Meek, M.E. et al. (2017) Crit. Rev. Toxicol. 47:9, 729-749.

Potential Contribution of AOPs to the Assessment of Causality in Epidemiological Studies

- AOPs well suited to consideration of biological plausibility for causation in epidemiological studies
- Considerations for confidence in experimental support for AOPs well developed and applied
  - build on considerable regulatory experience (MOA analysis)
- Importance of the distinction of confidence in a mechanistic pathway (AOPs) vs. replication of a similar effect in animal studies as support for biological plausibility for causation in epidemiological studies
  - Mechanistic support far more convincing and predictive
- Importance of considering chemical case studies building on AOPs as examples to address current disconnects
  - Examples to include epidemiological data and collaboration of epidemiologists/toxicologists?

Implications – Planning, Conduct and Assessment of Epidemiological Studies for Regulatory Application

- Need for common "metrics" for assessment to facilitate purpose specific regulatory application
  - Precise definition of elements
    - Biological plausibility
  - "categories of confidence" based on acquired experience
- Integration of assessment by investigators based on "metrics" in templates for descriptions of study design
  - Prerequisite for public funding of studies?
  - Increases understanding by investigators of aspects important for consideration and documentation to facilitate regulatory application
- Need for basic epidemiological training of assessors in the regulatory environment

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