Supporting Regulatory Application of AOPs: The Pivotal Role of Weight of Evidence in Systematic Development and Quantitation

ECETOC Workshop on Quantitative Response-Response Relationships (AOPs)
October 18th – 19th, 2022
Brussels, Belgium

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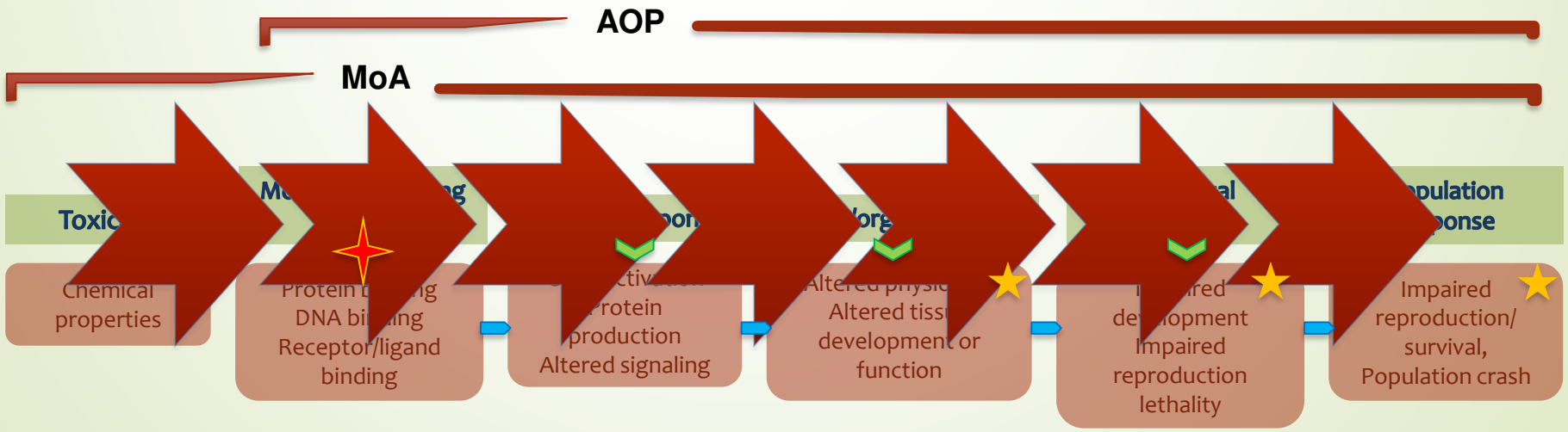
Outline

- Background/Objectives of Weight of Evidence (WOE) determinations in AOP Development
- The OECD Guidance on WOE for AOPs – Link to Quantitation
  - Moderate to High Confidence Empirical Support
  - Optimum Study Design to Support Quantitation of Key Event Relationships (KERs)
- What we've Learned from Regulatory Application of Quantitative Models
  - Implications for Documentation and Assessment of qAOP Models

Assessment of WOE/Confidence

Objective: Facilitating regulatory application through consistent consideration and communication of:

- weight of evidence (WOE)/confidence considerations in AOP development & documentation
- The "bridge" to testing/regulatory application
- Increasing knowledge in the development community of relevant aspects to tailor research



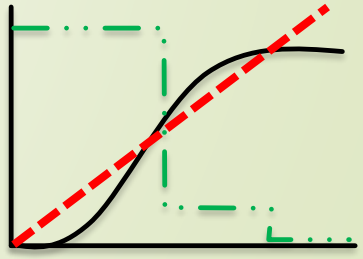
Distinguishing Weight of Evidence/Quantitation of KERs

Qualitative WOE

- To *simplify*, clarify and "codify" to the extent possible, qualitative WOE consideration addressing:
  - Focus (a limited no. of critical elements)
    - Including "patterns of empirical support"
  - Clarification of the nature of supporting data through:
    - defining questions (and nature of critical studies which support)
    - criteria & examples

Quantitation of KERs

- quantitation of the KERs, as a basis for developing predictive response-response models



How much change in KE_{up} is needed to evoke some unit of change in KE_{down}?

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 AOP Description

Section 2 KE Descriptions

- MIE
- KEs
- AO

Section 3 – KER Descriptions

- Key Event Relationships/Associations

Section 4 – Overall Assessment of the AOP

Event	Direct Evidence	Indirect Evidence	No or contradictory experimental evidence	
MIE				
KE1				
KE2				
KE3…… KEn				

MIE Page

Chemical initiator(s)

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

AO Page

- Description
- Measurement/

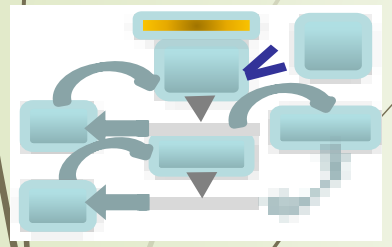
KER Pages

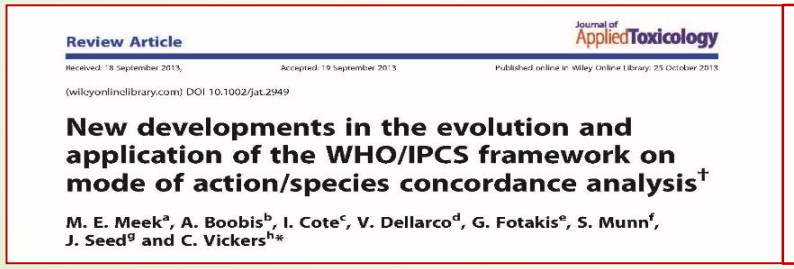
- Title
- Biological plausibility
- Empirical support
- Quantitative understanding
- Uncertainties and inconsistencies

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		

Systematically Considering Weight of Mechanistic Evidence

- Comprehensive, integrated judgment of the extent of supporting/conflicting evidence
- Based on modified Bradford Hill (B/H)considerations
  - International Frameworks to consider the extent or weight of evidence for hypothesized modes of action since the late '90's
- Continue to evolve, based on increasing experience in application





Review Article

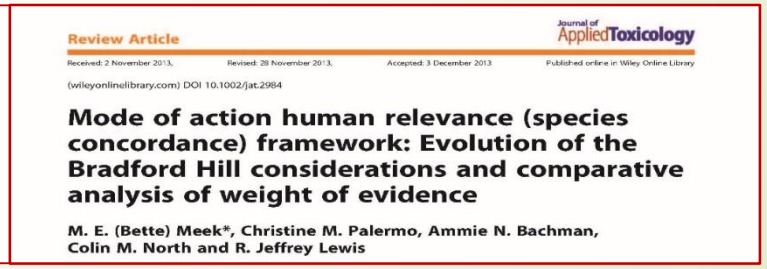
Journal of Applied Toxicology

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

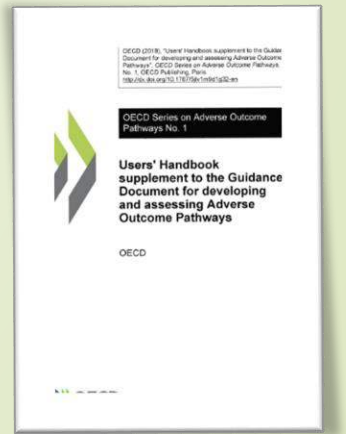
Journal of Applied Toxicology

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



OECD Series on Adverse Outcome Pathways No. 1

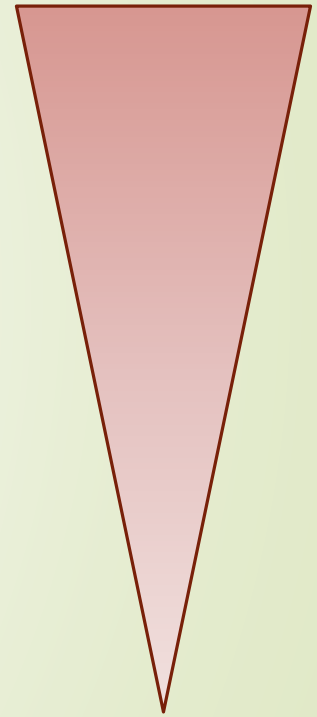
Users' Handbook supplement to the Guidance Document for developing and assessing Adverse Outcome Pathways

OECD

Weight/Extent of the Evidence - AOPs

- Biological Plausibility – *KERs*
  - Biology of the pathway
  - Knowledge of the structural-functional relationships
  - Consistency with prediction - experimental support from disrupting the pathway
- 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
  - The link to quantitation
  - Best supported by studies determining benchmark doses for hypothesized KEs at several levels of biological organization

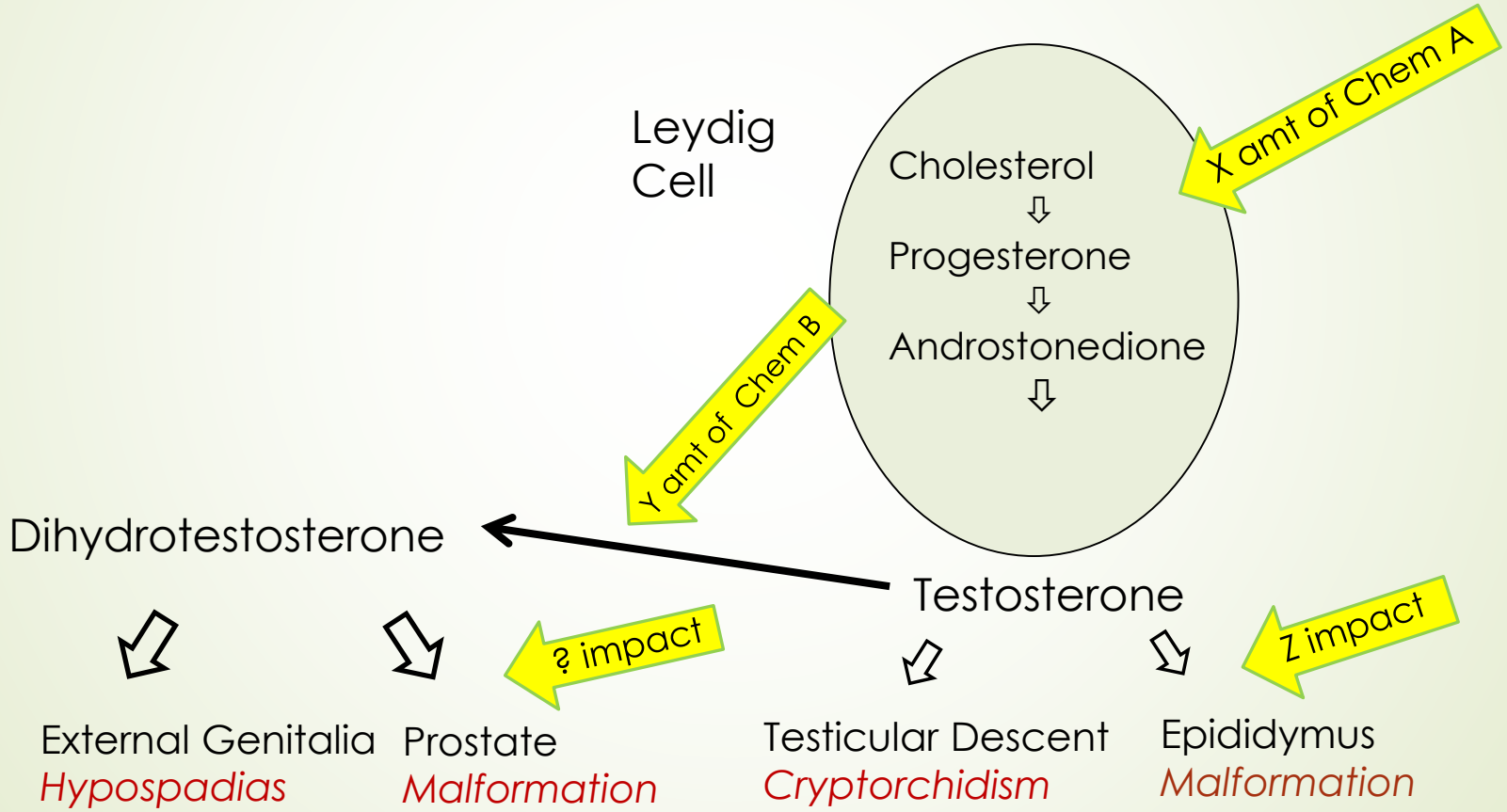
More important



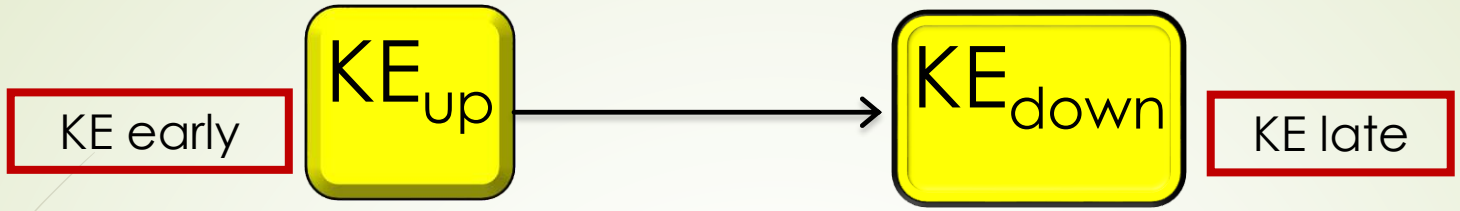
Less important

WOE: Empirical Support

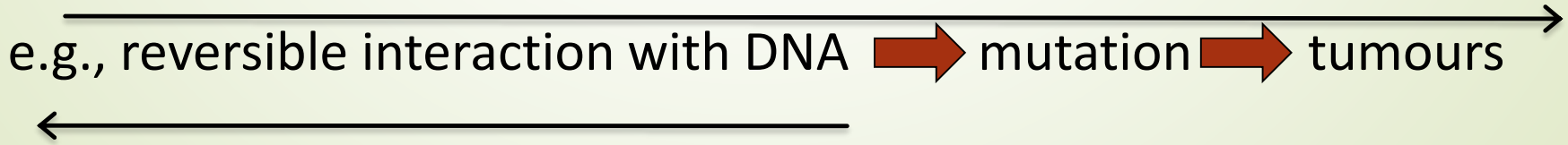
- Adding quantitative experimental support *for association* between key events to what we know about the biology
- Do the patterns of quantitative associations between and across key events support the proposed MOA, following administration of the chemical?



Empirical Support: Expected Patterns



- Temporal Association (Time)
  - Early key events precede hypothesized late key events
- Response-Response (often considered on the basis of dose-response for applied stressors, as a surrogate)
  - The impact of early KEs is less than that for late KEs (severity↑)
    - Impact at increasing levels of biological organization to compromise normal function e.g., impact on cells vs. organs
  - Early key events occur at lower doses than late key events
  - For a given dose, the *incidence* (relative abundance/proportion impacted/frequency) of early key events is greater than or equal to that of later key events



Summary: Weight of Evidence

More important

Biological Plausibility:

- How well documented is the pathway?

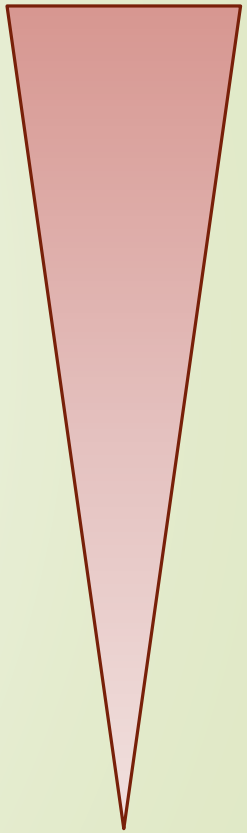
Essentiality

- What happens if we block or reverse a key event?

Empirical Support:

- Are the patterns of quantitative associations between and across key events what we expect?
- Less influential than biological plausibility, essentiality
- Ranked below other considerations
  - Correlation ≠ causation

- Rather, contributes in combination
  - In general, if high confidence in biological plausibility and essentiality, a small amount of empirical support can provide high confidence.
  - If weak support for plausibility, essentiality – need much empirical support to have predictive confidence



Less important

Confidence Ratings for Biological Plausibility and Essentiality

Biological Plausibility:

- *Level of understanding of the biology - structural or functional relationships*
  - Well understood H
  - Plausible but understanding incomplete M
  - Previously undocumented L

Essentiality:

- *whether the experimental evidence is direct, indirect or contradictory for how many key events*
  - Direct evidence for AOP H
  - Indirect evidence for some KEs M
  - No or contradictory experimental evidence L

Confidence Ratings for Empirical Support

Empirical Support:

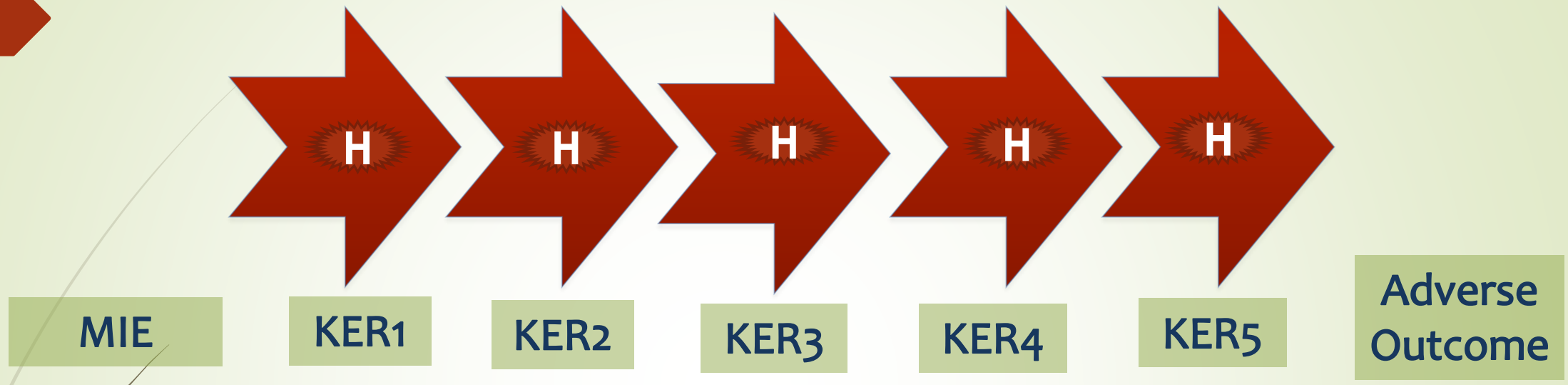
Extent of data supporting expected patterns of empirical relationships following application of stressors

- As expected based on application of a wide range of stressors with no or few data gaps or inconsistencies — H
- data with smaller number of stressors; some explainable inconsistencies — M
- limited or no relevant studies; unexplainable inconsistencies — L

WOE - Link to Quantitation of KERs

- For KERs for which confidence in qualitative empirical support is *moderate* to *high*, data are likely sufficient to support quantitation
- The data identified for empirical support are those relevant to quantitation of KERs
- WOE focuses early attention on data critical for quantitation of KERs based on *qualitative patterns* of quantitative support as part of assessing the extent of supporting data for causality
  - To guide regulatory application
- It also indicates the types of studies that best inform quantitation of the KERs
  - i.e., determination of benchmark doses/concentrations at a range of relevant dose levels for hypothesized KEs in the same study, if possible

Confidence Rating for Empirical Support – KERs – AOP 3 (cont'd)



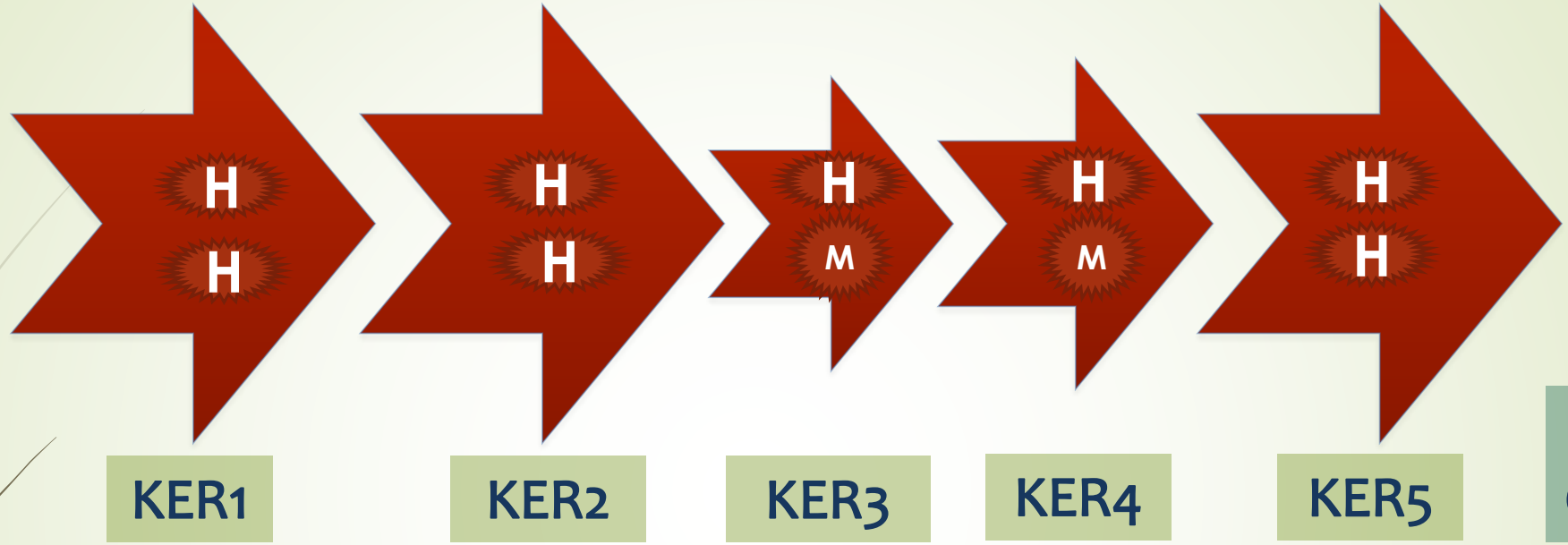
Moving from Qualitative (Empirical Support) to Quantitative

KE1 Inhibition of C I	KE2 Mitochondrial dysfunction	KE3 Impaired proteostasis	KE4 Degeneration of DA neurons of nigrostriatal pathway	AO Parkinsonian motor symptoms
Approx. 53% (Rotenone) [4-5]	Approx. 20-53% ↓ in respiration rate) [1-2]	Approx. 20-60% (decrease in UPS (26S) activity) [3]	Neuronal loss (50% of animal affected)[2]	Motor impairment (100% of animals with neuronal loss) [2]
Approx. 50-75% (MPP+) [5]	Approx. 38% ↓ in phosphorylating respiration [5]	Approx. 60% ↓ in UPS activity [4]	Approx. 50% of neuronal loss [4-5]	Motor impairment [4]

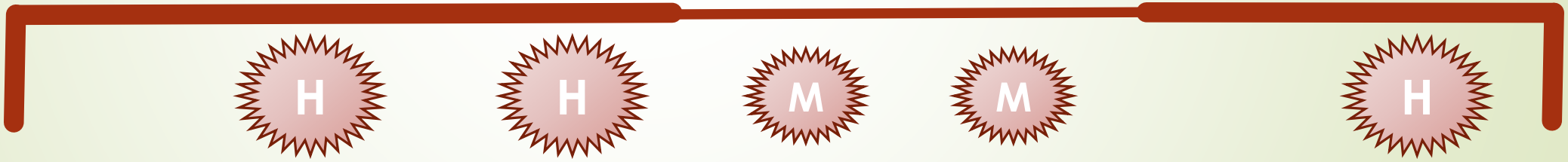
Data from: Okun et al. 1999 [1]; Barrientos and Moraes 1999 [2]; Borland et al.2008 [3]; Thomas et al 2012 [4]; Betarbet et al 2000 [5]

WOE/Confidence and Quantitation of KERs – AOP 3

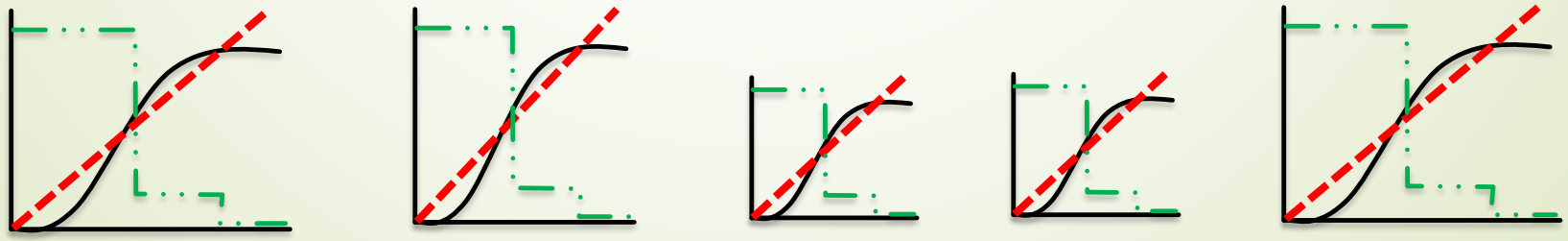
B.P. & Empirical Support - KERS



Essentiality of KEs - AOP



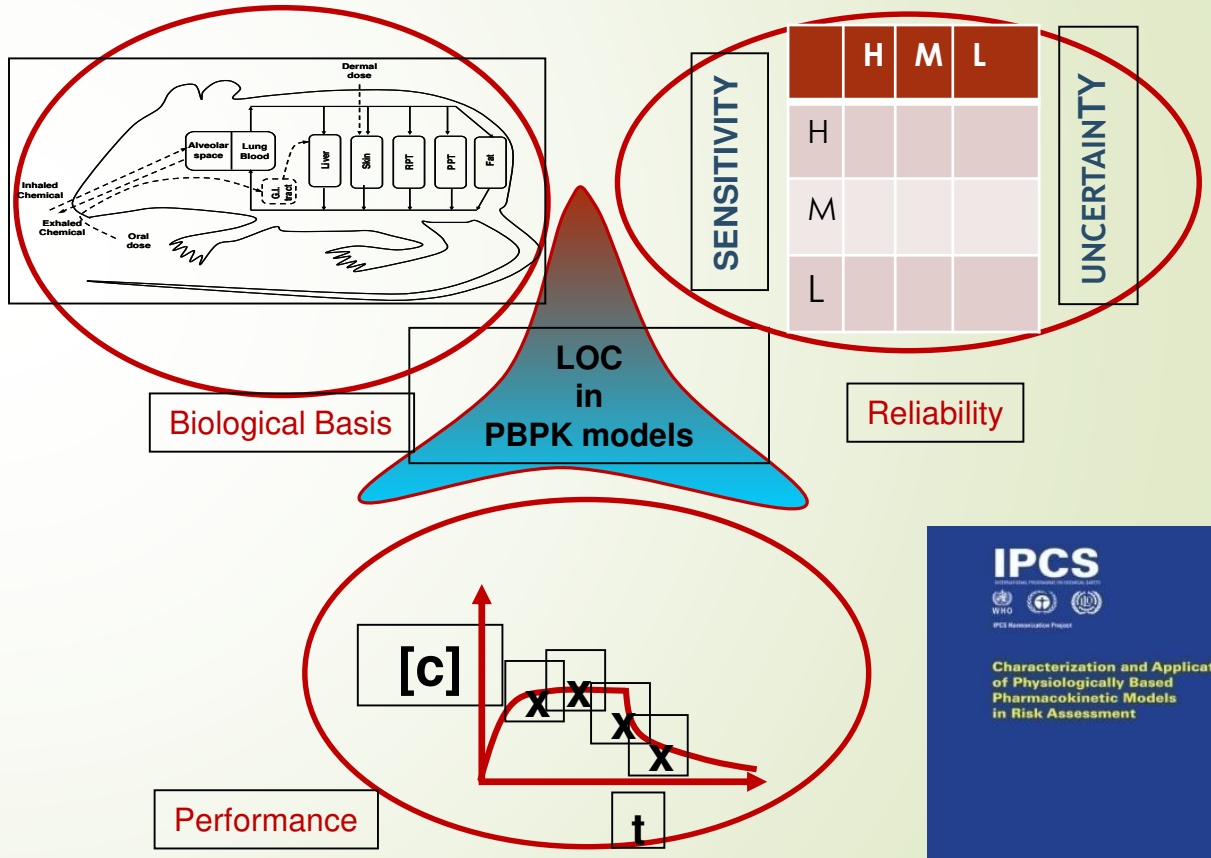
Quantitation of KERs

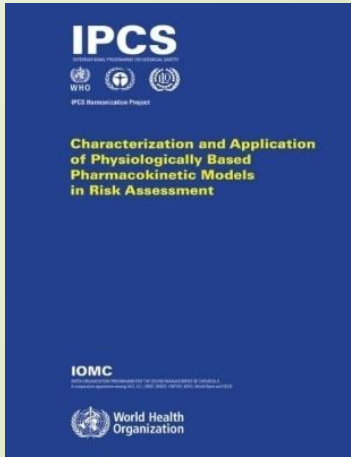


What We've Learned – Regulatory Uptake of Quantitative Models

- The importance of templates for description to facilitate regulatory uptake
- The value of common, consistent, simple "metrics" concerning *relative* confidence in the extent of the evidence which supports the model
- Critical in the regulatory acceptance and uptake of models (Bhat et al., 2016 – WHO IPCS Risk Assessment Network)

Metrics for Confidence in Supporting Data Existing International Guidance





The Need for Assessment Frameworks for Quantitative Models

Context & Implementation

- Regulatory purpose
- Model applications
- Software implementation
- Peer input / review
- Documentation

Model validity

- *Biological basis (model structure and parameters)*
- *Theoretical basis of model equations*
- *Reliability and relevance of input parameters*
- *Sensitivity of output to parameters*
- ***Goodness-of-fit and predictivity***

Reporting template

Evaluation checklist

In vivo data NOT required

In vivo data required

Confidence Matrix

Regulatory Applications Vary	**Low**		**High**
Degree of confidence			
Biological Basis	Model inconsistent with biology or the state of knowledge of kinetics of the chemical	Questionable basis of some model parameters, structural elements or assumptions.	Reasonable biological basis for model parameters and structure, supporting kinetic data
Model simulations of data	Unable to reproduce shape of the kinetic time course curves, for chemical or analogue.	Model reproduces the shape of part of the kinetic time course curves, for chemical or analogue	Model consistently reproduces kinetic data, including the shape of time course profiles for chemical or analogue
Uncertainty *Sensitivity*	No uncertainty and sensitivity analyses	Local Sensitivity Analysis supports the robustness of the model.	Global Sensitivity Analysis supports the robustness of the model.

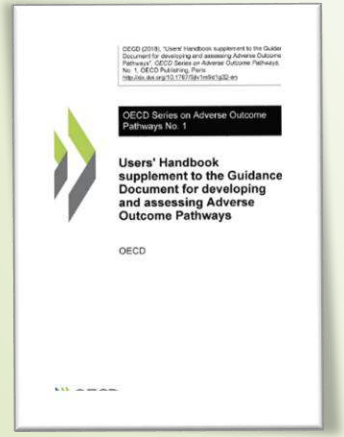
The OECD AOP Development Program – Supporting Regulatory Application

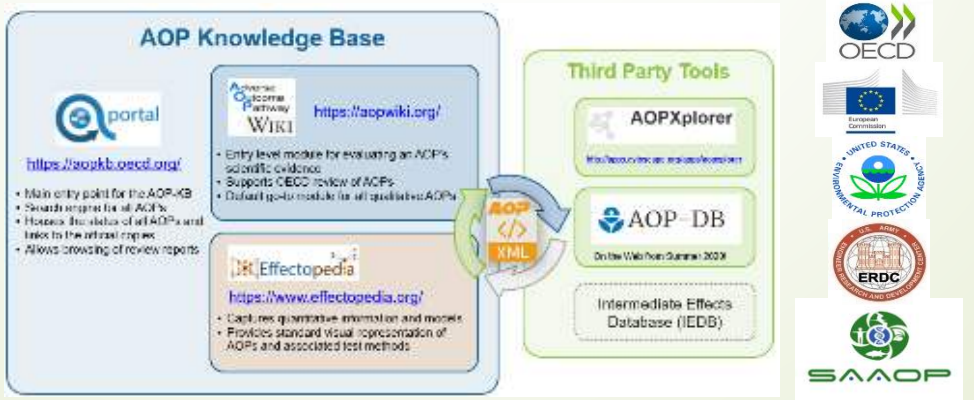
Convene Expert Team

Data Assimilation and Evaluation

AOP Development and Description (incl. WOE)

Internal/External Review and Approval





Compliance Check

Content/structure review

External Technical review

Process review

OECD Publication

Systematic Methods in the OECD AOP Development Program

Background:

- WOE considerations systematically address patterns of supporting evidence across KEs and KERs
  - appropriate for an integrating construct
  - identifies the types of studies and test methods that contribute to confidence for regulatory application
- Looking to address additionally:
  - systematic documentation of the identification and evaluation of relevant sources of information for AOP development and
  - management and accessibility of the supporting information

Challenges:

- Potential benefits/resource impact in an integrating mechanistic construct such as AOPs unclear
  - the *extremely broad and often longstanding* evidence base
- Interface with the focus on integration
  - efficiency - most relevant/critical data

Appropriate Focus of the Application of Systematic Review Methods for Efficient AOP Development – the Importance of Quantitation

- The important balance of:

Transparently identifying the right (most informative) information to meet the objectives:

- Documenting the broadest range of biology possible to support:
  - Regulatory application (*confidence and applicability*)
    - *empirical support and quantitation critical*

vs.

Identifying *all* (often previously *well documented* canonical) information

It's not about *describing and quantitating individual KERs,* but rather focusing on quantitation of the appropriate parts of the pathway *("trip points")* to support *application*

World Health Organization

Thank You!!!!!

OECD

Questions??