Recent International Developments in Mode of Action/Adverse Outcome Pathway Analysis

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Outline

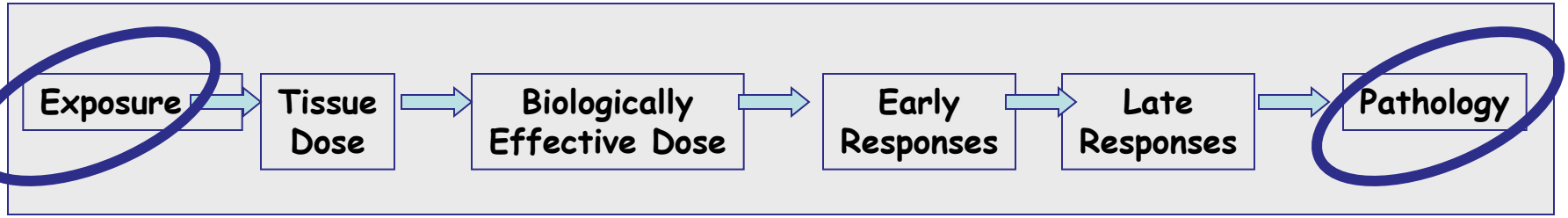
Update of WHO/IPCS Mode of Action Framework
- Objectives , Construct, Examples
- Moving to more MOA –based predictive approaches
- Engaging the regulatory risk assessment community

Coordination with OECD

Drawing from experience internationally to increase efficiency in testing, assessment and engagement – immediate term

Exposure-Response Continuum (Source to (Adverse) Outcome Pathway)

Mode of Action involves identification of several key events between exposure and effect



Physiologically Based Pharmacokinetic Models

Tissue Dose Metric

Mode of Action

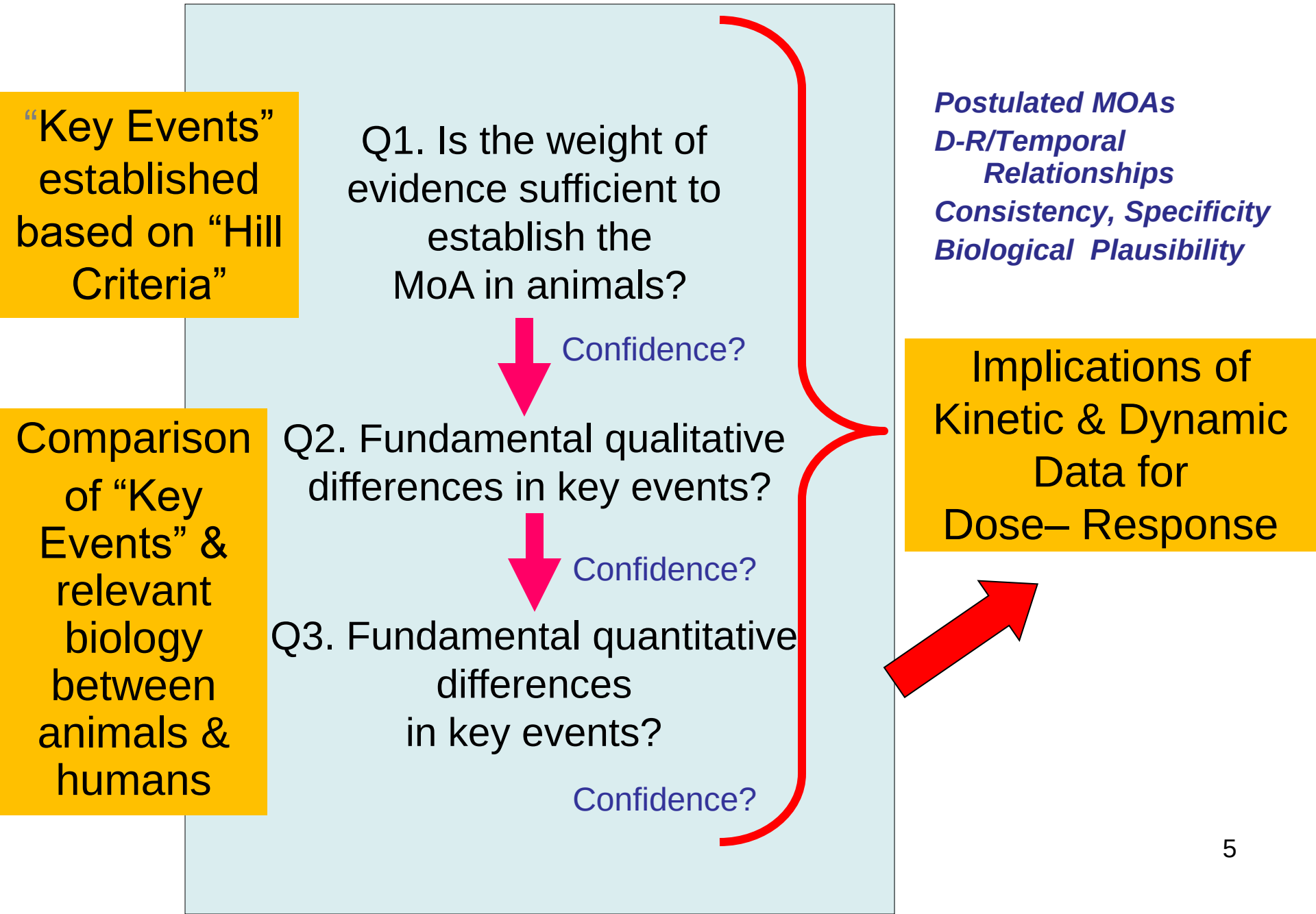
Toxicokinetics

Toxicodynamics

Evolution of "Key Event"

- An empirically **observable**, precursor step that is a **necessary** element of the mode of action, or is a **marker** for same
  - Key events are **necessary** but not always **sufficient**
- Early key events often chemical-related; later ones MOA-related ("tripped")
- Not linear, interdependent networks of events
- Originally considered in context of late stage cellular, biochemical and tissue events, e.g.,
  - metabolic transformation, direct and indirect reaction with genetic material (DNA),cytotoxicity, hormonal perturbations
- Evolving to incorporate data from lower levels of biological organization and non-test methods

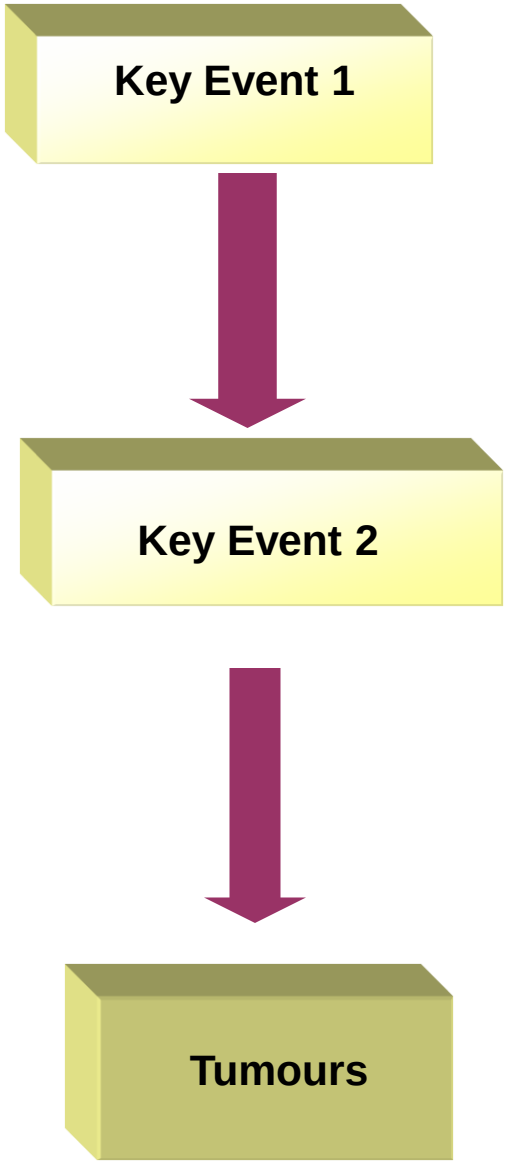
IPCS/ILSI MOA/HR (WOE) Framework

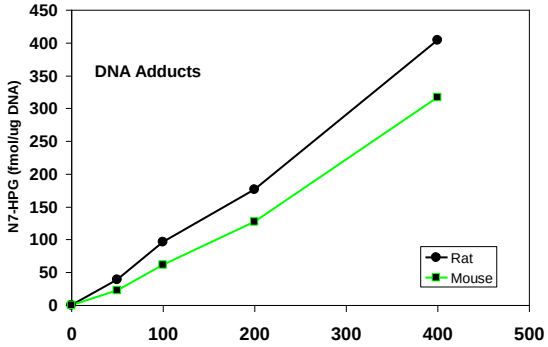


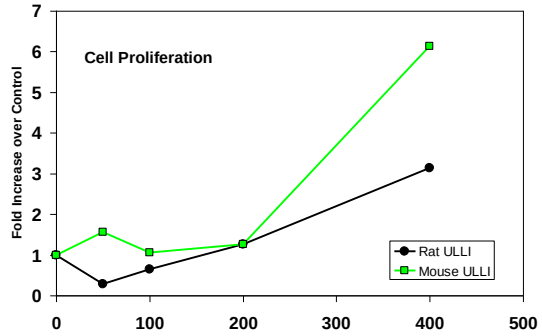
Implications for Dose-Response Analysis

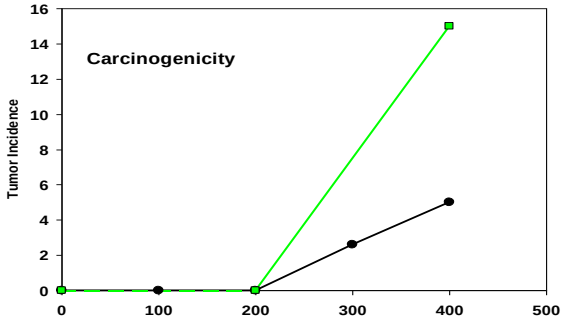
What is the shape of the dose-response curve in the range of both observation and inference for the rate limiting ***key events***, based on an understanding of MOA?

Key Event









Examining an Individual Key Event (KEDRF)

Considering impact on dose-response of factors that determine outcome of individual events:

- Dose (level, frequency and duration)
- Physiological mechanisms (e.g., homeostasis, repair, immune response, compensatory pathways)
- Host factors (life-stage, disease state, genetic makeup, nutritional status, co-exposure)

What data would demonstrate discontinuity?

Objectives – MOA/HR analysis

Transitioning the Risk Assessment Community

Increasing predictive capacity and utility of risk assessment

- Drawing maximally and early on the most relevant information (including patterns): not an "add on"
  - data on kinetics/dynamics and the broader biology base;
- Transparency
  - Rigor & consistency of documentation
  - Explicit separation of science judgment on weight of evidence from science (public) policy considerations
- Doing the right research/testing
  - Chemical Specific: Iterative dialogue between risk assessors/researchers
  - Developing more progressive testing strategies

Engagement – MOA/HR Analysis

- Derived from early EPA work
- >23 case studies for >10 MOA
- 100's of experts involved in its development
- international engagement (ILSI RSI; WHO-IPCS; more recently, OECD, ECETOC) (1999-present)
- widely incorporated in program guidance (EFSA, 2006; EC, 2003; IPCS, 2003, 2006; JMPR, 2006; OECD, 2002, 2012) & extensively adopted in risk assessments
- Training materials with well over 1000 students trained

Issues in MOA/HR WOE Analysis in Practice

- Perception that it is "labour intensive" add on
- Lack of early consultation to robustly define hypothesized MOAs
  - Research/regulatory risk assessment
- Inconsistent use of individual B/H Considerations
  - Application being interpreted by the evaluation program
- Lack of consistency in determinations of what constitutes "adequate" weight of evidence across evaluations
  - Lack of transparency in separating science policy/judgment
- Need for simplicity for broad applicability, including evolving technology

Status - WHO MOA Framework Update

- ECETOC workshop held in November, 2009 on use of MOA to improve regulatory decision making
- October, 2010 – WHO/IPCS convened a Steering Group on MOA/AOP
  - OECD, EU, US, etc.
  - Extending MOA and MOA/HR framework concepts as the coordinating construct between the ecological/health risk communities; QSAR modelling/risk assessment communities
  - Updating the framework was one of the work areas; knowledge base another
- October, 2010 to Present- Drafting Group to Update MOA Framework
- Updated Framework submitted for approval/publication
- Follow-up ECETOC-WHO/IPCS workshop – February, 2013

Members of the Drafting Group

- M.E. Meek, University of Ottawa (Chair)
- A. Boobis, Imperial College, London
- I. Cote, NCEA, US EPA
- V. Dellarco, OPP, US EPA
- G. Fotakis, ECHA, Helsinki
- S. Munn, EU JRC, Ispra
- J. Seed, OPPT,US EPA
- C. Vickers, WHO/IPCS

Objectives of the Update

- To clarify terminology (MOA = AOP)
- To reflect evolving experience in application
  - E.g., Additional articulation of the modified Bradford Hill considerations for weight of evidence and implications of kinetic and dynamic data for dose-response
- To extend utility to emerging areas in toxicity and non-toxicity testing
  - Framework can be used as originally intended where toxicological effects are known, or
  - in hypothesizing effects resulting from chemical exposure, based on putative key events

Contents of the WHO Guidance Update

- Roadmap for fit-for-purpose testing strategies and risk assessment, to:
  - Integrate information from different levels of biological organization and to extend utility to emerging areas
- Updated framework
  - Delineating comparative uncertainty
  - Emphasizing the feedback to research/testing
- Supporting templates
  - Simplification/articulation of the B/H considerations
  - Comparative weight of evidence

Contents of the WHO Guidance Update (Cont'd)

Case Examples illustrating application of MOA analysis in:

1: Lack of human concordance

2: Use of kinetic and dynamic data in concordance analysis and implications for dose–response analysis

- Contribution of well-designed genomic studies

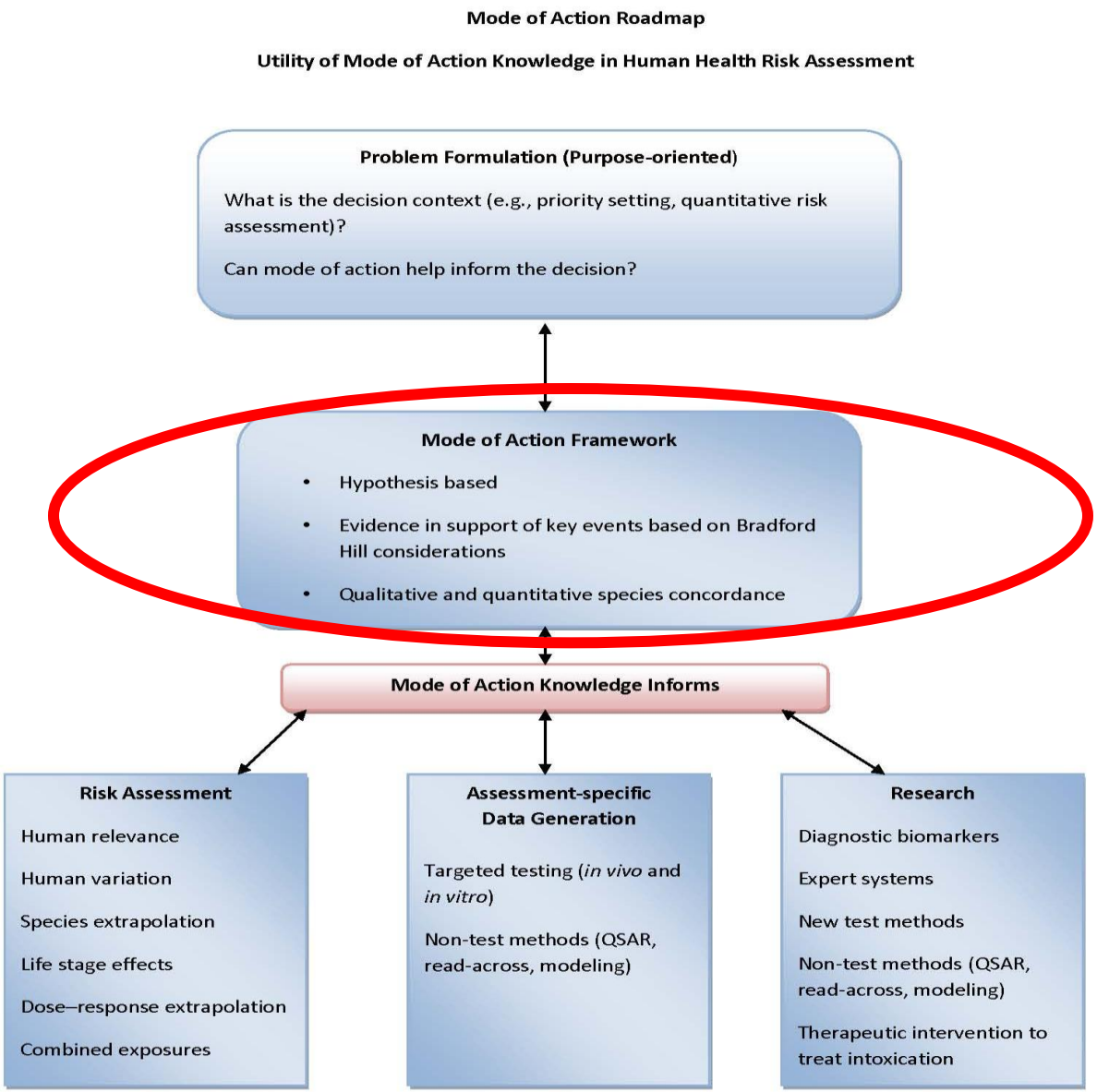
3: The evaluation of epidemiological data

4: Development of more efficient testing strategies

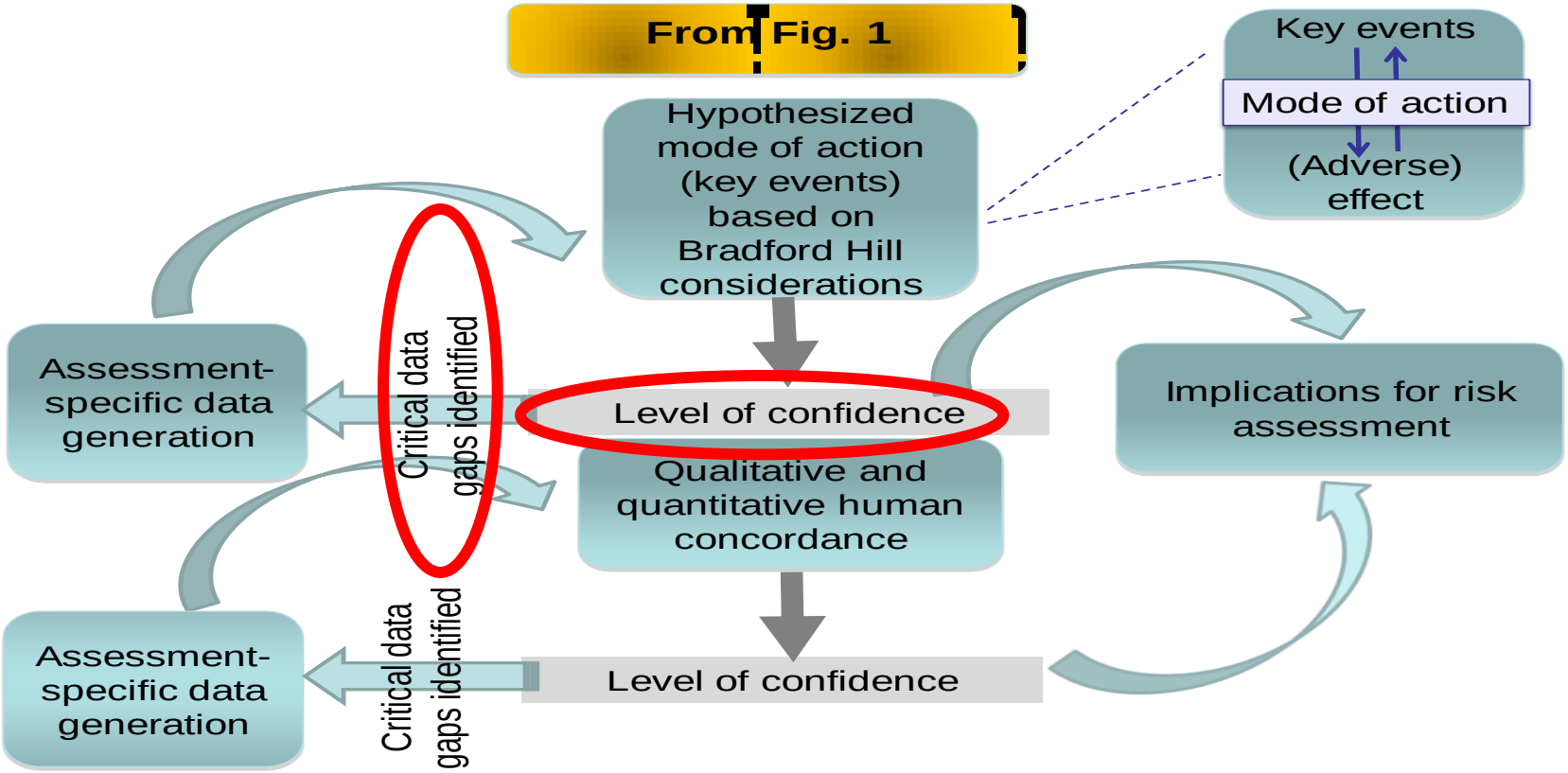
5: Prioritizing substances for further testing

6: Creation of chemical categories

7: Identifying critical data gaps and testing strategies in read-across



Modified MOA Framework



Modified BH Considerations

Dose Response & Temporal Concordance	**Dose response** – Are the key events observed at doses below or similar to those associated with the apical effect? **Temporality** – Are the key events observed in hypothesized order?
Consistency, specificity	Is the incidence of the toxic effect consistent less than that for the key events? Is the sequence of events reversible if dosing is stopped or a key event prevented?
Biological plausibility	Is the pattern of effects across species/strains consistent with the hypothesized MOA? Does the hypothesized MOA make sense based on broader knowledge (e.g., biology, established ?)

Comparative Weight of Evidence

Cytotoxic Mode of Action

Bradford Hill criterion/factor	Supporting Weight of Evidence	Potentially Inconsistent Evidence
Dose Response Temporal Concordance	Metabolism, cytotoxicity, proliferation precede tumours; tumors observed only at cytotoxic (BMD Analysis) *(qualify based on nature & number of studies)*	
Strength, consistency, specificity	Consistency in repeated studies & different labs & across species, sexes routes & levels of biological organization *(#s)* correlating with extent of metabolism . No adverse effects without relevant enzyme in null mice. Incidence for tumors less than that for key events & tissue recovery in reversibility studies	
Biological Plausibility	Consistency with state of knowledge on cancer	

Mutagenic Mode of Action

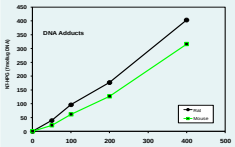
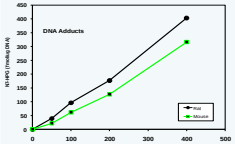
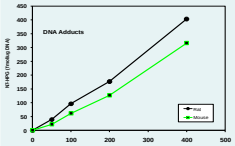
Bradford Hill criterion/factor	Supporting Weight of Evidence	Potentially Inconsistent Evidence
Dose Response Temporal Concordance		Parent compound negative for mutation in a range of in vitro and in vivo bioassays *(qualify based on nature and number of studies)*
Strength, consistency, specificity		The pattern of genotoxicity results consistent with what would be expected for the hypothesized mode of action (e.g., not mutagenic in a range of assays; metabolite induces mutation at cytotoxic doses)
Biological Plausibility		Pattern of results for genotoxicity inconsistent with that observed for chemicals known to act via a mutagenic mode of action

Weight Of Evidence Evaluation

1. Causal Question Definition and Data Selection
   - define question or hypothesis, plan literature search, develop criteria for study selection
2. Individual Study Review
   - systematic review of pertinent studies using pre-defined criteria and applying them uniformly
3. Data Synthesis and Evaluation **MOA/HR**
   - integration of data across studies and broader knowledge
4. Application to Decision-Making **Comparative WOE**
   - draw conclusions based on inference, sufficiency of evidence to support a decision

presented at ACC ARASP Workshop: A Review of Weight-of-Evidence (WoE) Frameworks. Dec 3-4, 2012

Concordance Table with Dose-Response

Key Event	**Animal**	**Human**	**Strength**	**Quantitative Concordance**	**Quant. Dose-Resp.**
Metabolism by CYP2E1	Correlation with binding of metabolites	Relevant enzyme in kidney and liver	Considerable In animals; limited but relevant to humans	PBPK model incorporating metabolic rates, enzyme affinities and distribution based on *in vitro* human data supported by *in vivo* data	
Sustained cell damage and repair (cytotoxicity; proliferation)	In all cases at doses that induce tumours	Liver and kidney target organs in humans	Considerable in animals, possible in humans but limited data	No data	
Liver & kidney tumours	Mice & rats	Possible	Considerable in animals,; highly plausible in humans	No data	

Case example 6: Mode of action in the creation of chemical categories

- Class of pesticides, same well established mode of action and insecticidal effects
- Members of the class expected to share key events
  - Interaction with sodium channels
- Rank for potency in suitable *in vitro* system for this key event
- Consider toxicokinetic aspects
- Choose reference point from amongst those class members tested
- Anchoring the results of new *in vitro* approaches to relevant outcomes by using existing knowledge and concepts

WHO International Steering Group on Mode of Action

- October, 2010 – WHO/IPCS convened a Steering Group to develop a global umbrella plan for work on MOA (AOP)
  - Representatives of Imperial College, US EPA, University of Ottawa, EFSA, ECHA, JRC, IARC, OECD, and 2 NGOs in official relations with WHO (ECETOC and ILSI/HESI)
  - Extending MOA and MOA/HR framework concepts as the coordinating construct between the ecological/health risk communities; QSAR modelling/risk assessment communities
  - Updating the framework was one of the work areas; knowledge base another
- October, 2010 to Present- WHO Expert Drafting Group to Update MOA Framework
- Updated Framework submitted for approval/publication
- Follow-up ECETOC-WHO/IPCS workshop – February, 2013

MOA Umbrella Plan: 5 work areas and lead organizations

A. Update of WHO MOA framework (completed; ECETOC/WHO workshop in February, 2013)

B. Development of new case studies (WHO expert group: addressed in part in A)

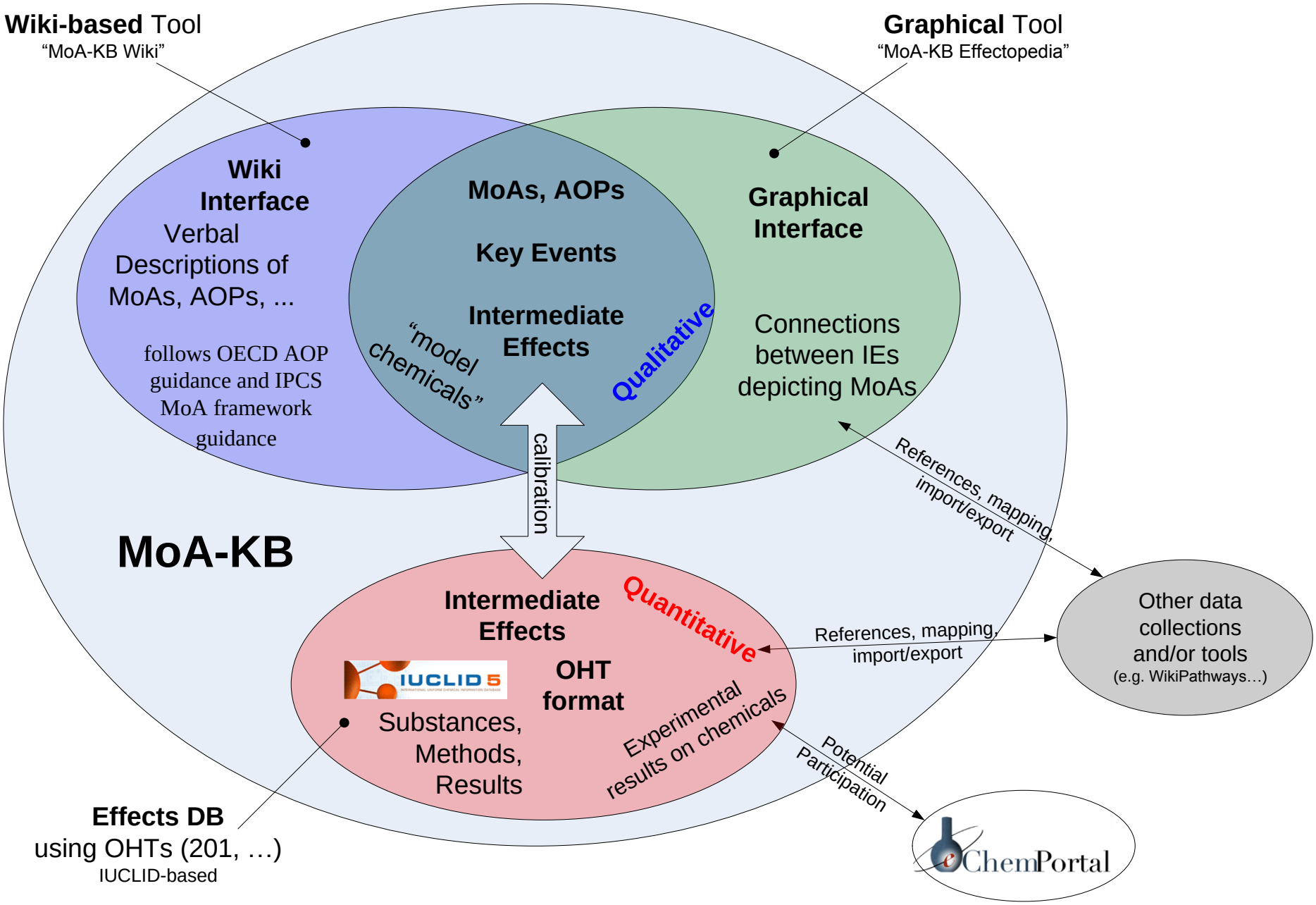
C. Implementation of MOA in category approaches (OECD)

D. Education (for discussion; integration of advances from MOA update in guidance/templates/case studies and experience in application of WOE criteria for knowledge base; training of those inputting)

E. MOA/AOP knowledge base (EPA,JRC and US Army Corps of Engineers)

MOA/AOP Knowledge Base

- Joint OECD project proposal
    - US EPA/US Army Corps of Engineers/EC JRC
- Currently being reviewed at
    - OECD (to adopt), WHO (to discuss collaboration)
- Includes wiki-based tool for widely accessible, collaborative data collection for established AOP/MoAs and building new AOP/MoAs:
  - Implements:
    - the **OECD AOP guidance** and the
    - **IPCS MoA framework guidance**
- Includes a graphical tool with a more sophisticated, intuitive depiction of relationships between key events in an AOP/MoA.


Wiki-based Tool
"MoA-KB Wiki"
Graphical Tool
"MoA-KB Effectopedia"
Wiki Interface
Verbal Descriptions of MoAs, AOPs, ...
follows OECD AOP guidance and IPCS MoA framework guidance
MoAs, AOPs
Key Events
Intermediate Effects
"model chemicals"
Qualitative
Graphical Interface
Connections between IEs depicting MoAs
calibration
References, mapping, import/export
MoA-KB
Intermediate Effects
Quantitative
IUCLID 5
OHT format
Substances, Methods, Results
Experimental results on chemicals
References, mapping, import/export
Other data collections and/or tools
(e.g. WikiPathways…)
Potential Participation
eChemPortal
Effects DB
using OHTs (201, …)
IUCLID-based

Envisaged Workflow - OECD Development of AOPs

- Proposal to develop AOP by stakeholder to Advisory Group on Molecular Screening and Toxicogenomics
- Incorporation into Knowledge Base
- Review by expert groups
- Approval by subgroups of the Joint Meeting, declassification, publication
- Proposed integrated test strategies relevant to Test Guidelines program

Next Steps

- Integrating advances from WHO update in OECD guidance/templates for AOP development
  - Integration of research/regulatory
  - "Fit for purpose" (problem formulation) for envisaged application
  - Simplification/codification of B/H considerations
- Developing "training" materials
  - Sample case studies, user guide and training of those inputting to the KB

More Information?

The ILSI/IPCS Frameworks – Mode of Action

- Including >23 case studies for 10 MOA
  - Meek et al. (2003) Crit Rev Toxicol 33:591
  - Seed et al. (2005) Crit Rev Toxicol 35: 663
  - Boobis et al. (2006) Crit Rev Toxicol 36:781
  - Boobis et al. (2008) Crit Rev Toxicol 38:87
  - Meek (2008) Env Mol Mutagenesis 49:(2) 110
  - Meek et al. (in publication) Toxicol. Appl. Pharmacol.

Evolution of the ILSI/IPCS Frameworks – Mode of Action

- Meek & Klaunig (2010) Chemico-Biological Interactions 184:279–285

The Key Events/Dose Response Framework

- Boobis et al. (2009) Crit Rev Food Science Nutrition 49(8): 690 – 707