From Mode of Action to Adverse Outcome Pathways – Moving Towards Regulatory Applicability

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Adverse Outcome Pathways: From Research to Regulation
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Outline

- Challenges and Priorities in Risk Assessment
  - Focus on mechanistic data
  - MOA/AOP
- Experience in Addressing these Priorities – AOPs are not new!
  - Engagement of the Research/Regulatory Communities
- Principles for Engagement – Getting to Regulatory Acceptance
- Continuing Challenges
- Conclusions/Recommendations

Evolving International Mandates for Existing Chemicals

- Canada
  - "Categorization" for 23, 000 chemicals - Sept., 2006 & multi tiered assessment program
- Europe
  - ***R***egistration, ***E***valuation and ***A***uthorization of ***C***hemicals (REACH) (2007)
- Japan Stepwise Assessment under the ***C***hemical ***S***ubstances ***C***ontrol ***L***aw (CSCL)" (2009)
- Australia ***I***nventory ***M***ulti ***T***iered ***A***ssessment and ***P***rioritization (IMAP) (2012)
- New Zealand Group Standards for Industrial Chemicals (HSNO)
- U.S.
  - Research Initiatives /Legislative Renewal?

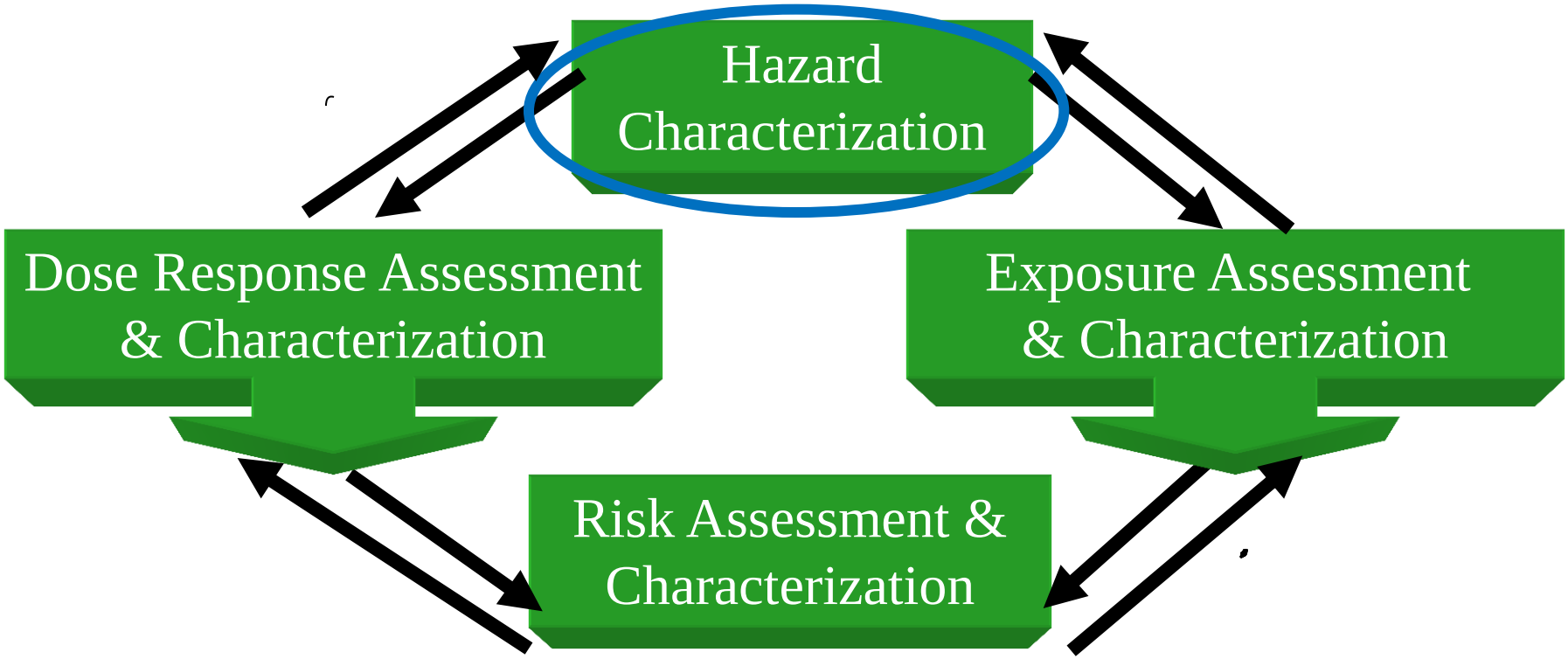
The Need to Evolve Tox Testing for Risk Assessment

- Better predictability
  - Broader application to larger numbers of chemicals
- Higher relevance
  - Moving from default to more biologically based to more accurately estimate risk
    - Relevant pathways
    - Relevant doses
    - Relevant species
- Requires early assimilation in a mode of action context (taking into account kinetic and dynamic data)
- Regulatory risk assessment needs to provide the impetus and market for more progressive testing strategies

Revised NAS 4-Step Paradigm

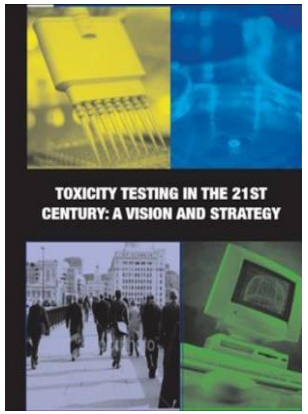
Problem Formulation

Communication



Hazard Characterization (early focus not only on effect but how the effect is induced - mode of action)

U.S. NRC Toxicity Testing in the 21st Century



Dose Response Assessment

Chemical Characterization

Mode of Action

Compounds

Metabolite(s)

Assess Biological Perturbation

Affected Pathway

Measures of dose in vitro

Dose Response Analysis for Perturbations of Toxicity Pathways

Population Based Studies

Calibrating in vitro and human Dosimetry

Exposure Guideline

Human Exposure Data

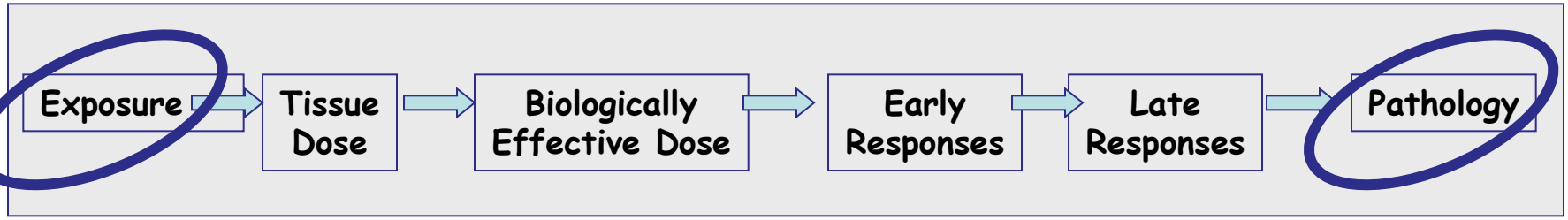
Hazard Characterization

Exposure Assessment

Risk Characterization

Exposure-Response Continuum

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



Physiologically Based Pharmacokinetic Models

Tissue Dose Metric

Toxicokinetics (tk)

Toxicodynamics (td)

Mode of Action

Mode of Action Analysis

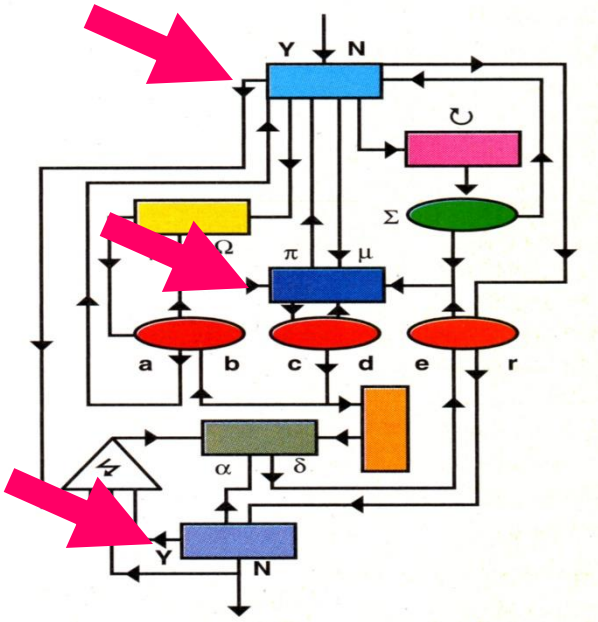
Mode vs. Mechanism

Plausible Hypothesis

Key event (e.g. biochem; histopath):

- Critical
- Can measure
- Repeatable

Detailed Molecular Description

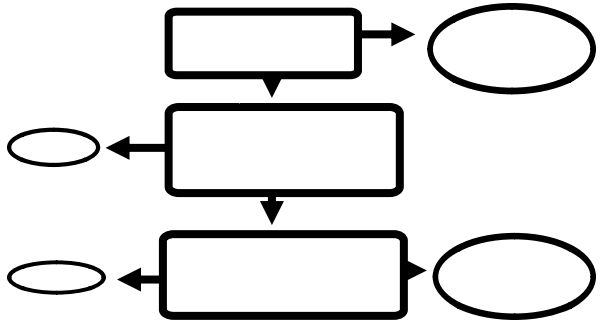


Evolution of "Key Event"

- 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, but interdependent networks of events
- Originally considered in context of late stage cellular, biochemical and tissue events, e.g.,
- Evolving to incorporate data from lower levels of biological organization and non-test methods

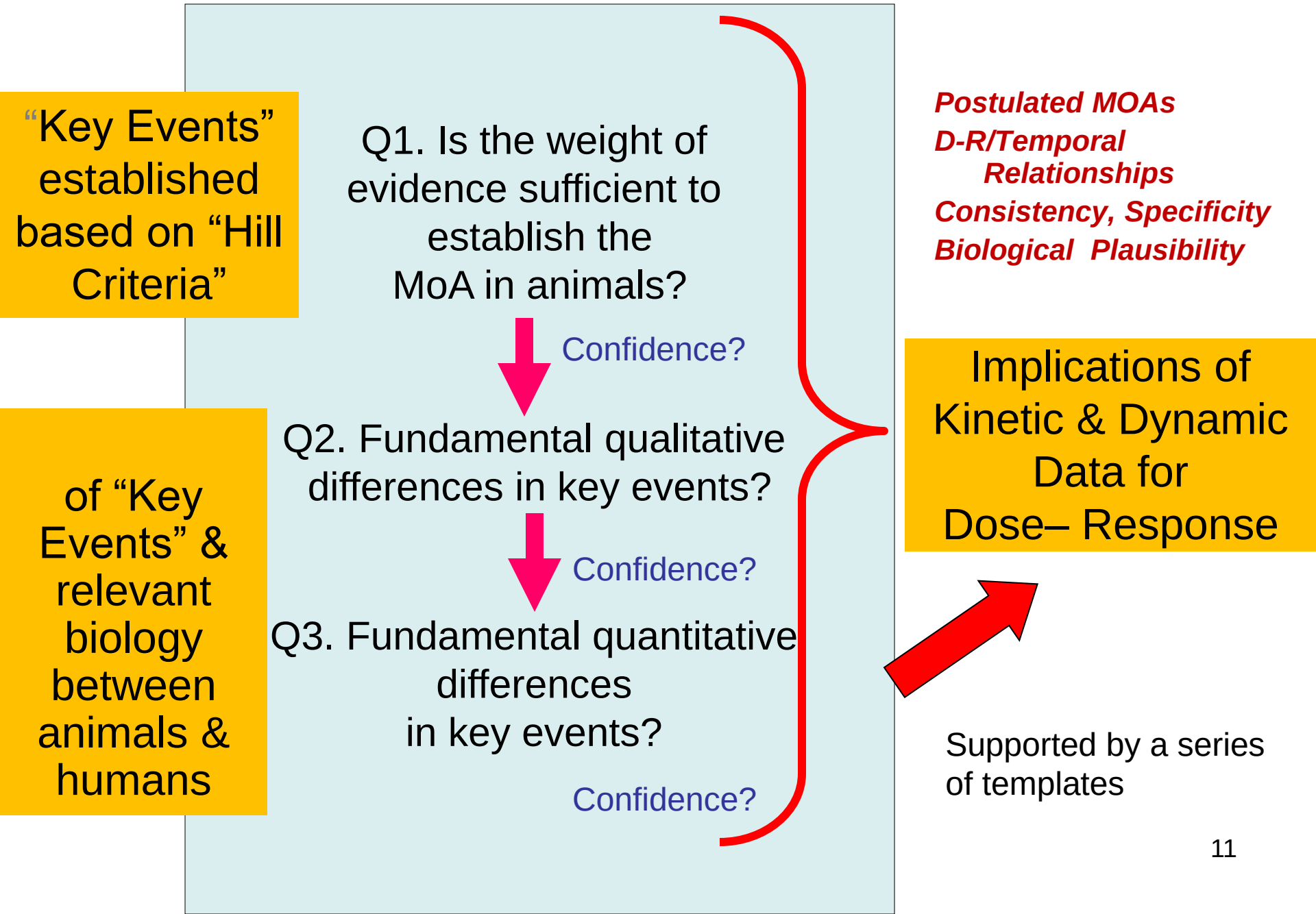
Mode of Action/ Human Relevance Analysis

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



- Derived from early US EPA/ILSI work
- since 1999, 100s of experts internationally involved in its development
- widely incorporated in program guidance internationally (US EPA, EFSA, EU TGD, JMPR,OECD)/adopted in risk assessments, training
- Recent update that extends and builds on international regulatory experience (Meek et al., 2014)

IPCS/ILSI MOA/HR (WOE) Framework



WHO IPCS Mode of Action/Human Relevance Framework (Boobis et al., 2006; 2008)

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IPCS Framework for Analyzing the Relevance of a Cancer Mode of Action for Humans

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The use of structured frameworks can be invaluable in promoting harmonization in the assessment of chemical risk. IPCS has therefore updated and extended its mode of action (MOA) framework for cancer to address the issue of human relevance of a carcinogenic response observed in an experimental study. The first stage is to determine whether it is possible to establish an MOA. This comprises a series of key events along the causal pathway to cancer, identified using a weight-of-evidence approach based on the Bradford Hill criteria. The key events are then compared first qualitatively and then quantitatively between the experimental animals and humans. Finally, a clear statement of confidence, analysis, and implications is produced. The IPCS human relevance framework for cancer provides an analytical tool to enable the transparent evaluation of the data, identification of key data gaps, and structured presentation of information that would be of value in the further risk assessment of the compound, even if relevancy cannot be excluded. This might include data on the shape of the dose-response curve, identification of any thresholds and recognition of potentially susceptible subgroups, for example, the basis of genetic or life-stage differences.

Keywords Animal–Human Concordance, DNA-Reactive, Carcinogens, Human Relevance Framework for Cancer, Key Events, Mode of Action, Risk Assessment

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Fundamental to the evolution of cancer risk assessment over the last three decades has been our increasing understanding of the biology of cancer and the identification of key events in carcinogenesis. Through the mid-1980s, national and international assessments of human cancer hazard and risk depended primarily on lifetime assays in rodents of potentially carcinogenic agents. For few agents was there sufficient human evidence on which to base retrospective cancer assessments, and

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IPCS Framework for Analyzing the Relevance of a Noncancer Mode of Action for Humans

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Focus on MOA/HR Analysis
Increasing predictive capacity and utility of risk assessment

- Drawing maximally and early on the most relevant information
  - 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

Issues in MOA/HR WOE Analysis in Practice

- Perception that it is "labour intensive" add on
  - Focus on hazard identification rather than characterization
- Lack of early consultation to robustly define hypothesized MOAs
  - Research/regulatory risk assessment
- Inconsistent use and interpretation of weight of evidence considerations
  - Application being interpreted by the evaluation program
  - Lack of transparency in separating science policy/judgment
- ***Need for simplicity for broad applicability, including evolving technology***

Review Article

Journal of Applied Toxicology

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

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ABSTRACT: The World Health Organization/International Programme on Chemical Safety mode of action/human relevance framework has been updated to reflect the experience acquired in its application and extend its utility to emerging areas in toxicity testing and non-testing methods. The underlying principles have not changed, but the framework's scope has been extended to enable integration of information at different levels of biological organization and reflect evolving experience in a much broader range of potential applications. Mode of action/species concordance analysis can also inform hypothesis-based data generation and research priorities in support of risk assessment. The modified framework is incorporated within a roadmap, with feedback loops encouraging continuous refinement of fit-for-purpose testing strategies and risk assessment. Important in this construct is consideration of dose–response relationships and species concordance analysis in weight of evidence. The modified Bradford Hill considerations have been updated and additionally articulated to reflect increasing experience in application for cases where the toxicological outcome of chemical exposure is known. The modified framework can be used as originally intended, where the toxicological effects of chemical exposure are known, or in hypothesizing effects resulting from chemical exposure, using information on putative key events in established modes of action from appropriate *in vitro* or *in silico* systems and other lines of evidence. This modified mode of action framework and accompanying roadmap and case examples are expected to contribute to improving transparency in explicitly addressing weight of evidence considerations in mode of action/species concordance analysis based on both conventional data sources and evolving methods. **Copyright © 2013 John Wiley & Sons, Ltd. The World Health Organization retains copyright and all other rights in the manuscript of this article as submitted for publication.**

Keywords: key events; mode of action; adverse outcome pathway; human relevance framework; modified Bradford Hill considerations; weight of evidence approach; species concordance analysis; cellular response; tissue response; molecular target

Introduction

The mode of action/human relevance framework was developed in initiatives of the International Programme on Chemical Safety (IPCS) of the World Health Organization (WHO) (Boobis *et al.*, 2006, 2008; Sonich-Mullin *et al.*, 2001) and the International Life Sciences Institute Risk Sciences Institute (ILSI-RSI) (Meek *et al.*, 2003; Seed *et al.*, 2005). It derives from earlier work on mode of action in animals by the US Environmental Protection Agency (US EPA, 1996, 2005a) and has involved large numbers of scientists internationally.

Previous development of the mode of action/human relevance framework is described in the publications mentioned above and summarized more recently in Meek and Klaunig (2010). The framework has been illustrated by an increasing number of case studies (more than 30 currently) demonstrating the value of mode of action in evaluating human relevance and life stage susceptibility and guiding dose–response assessment. Documented examples are presented in Table 1. The contribution of the framework has been recognized by the Society of Toxicology, and the framework has been adopted by several international and national organizations and agencies to increase transparency in the assessment of weight of evidence and identification of critical data needs (Meek, 2008, 2009; Meek *et al.*, 2008).

The framework continues to evolve as experience increases in its application to consider systematically the weight of evidence

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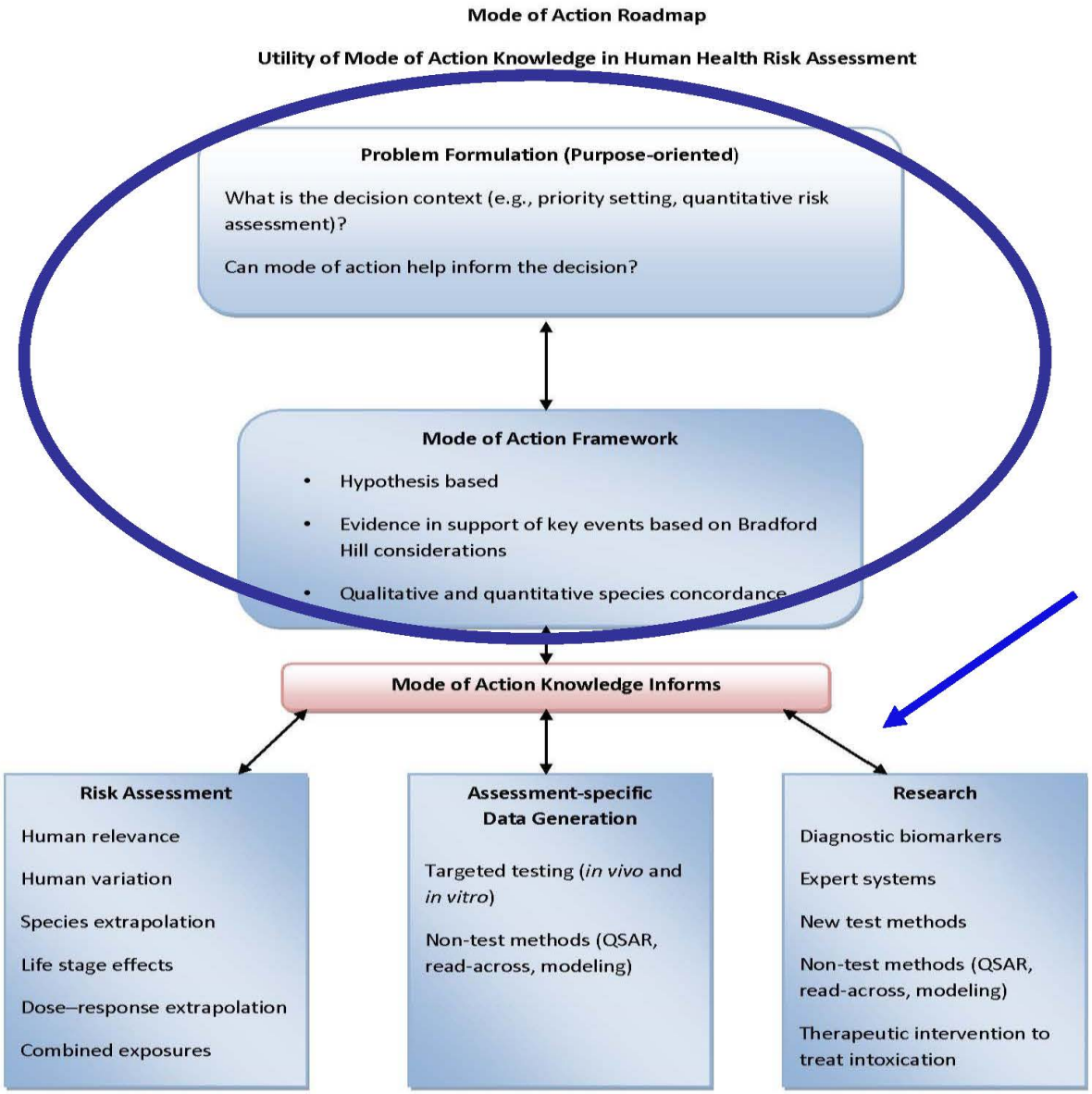
Objectives of the WHO Guidance Update

- To clarify terminology **(MOA conceptually = AOP)**
  - Value of rebranding?
- To tailor analysis to issue at hand
  - Problem formulation
- To extend utility to new areas in toxicity and non-toxicity testing, providing practical examples
- ***Need for simplicity for broad applicability, including evolving technology***
  - Simplifying /"codifying" experience in application
    - E.g., modified Bradford Hill considerations for weight of evidence for MOA wiki
    - Incorporating dose-response analysis (quantitation)



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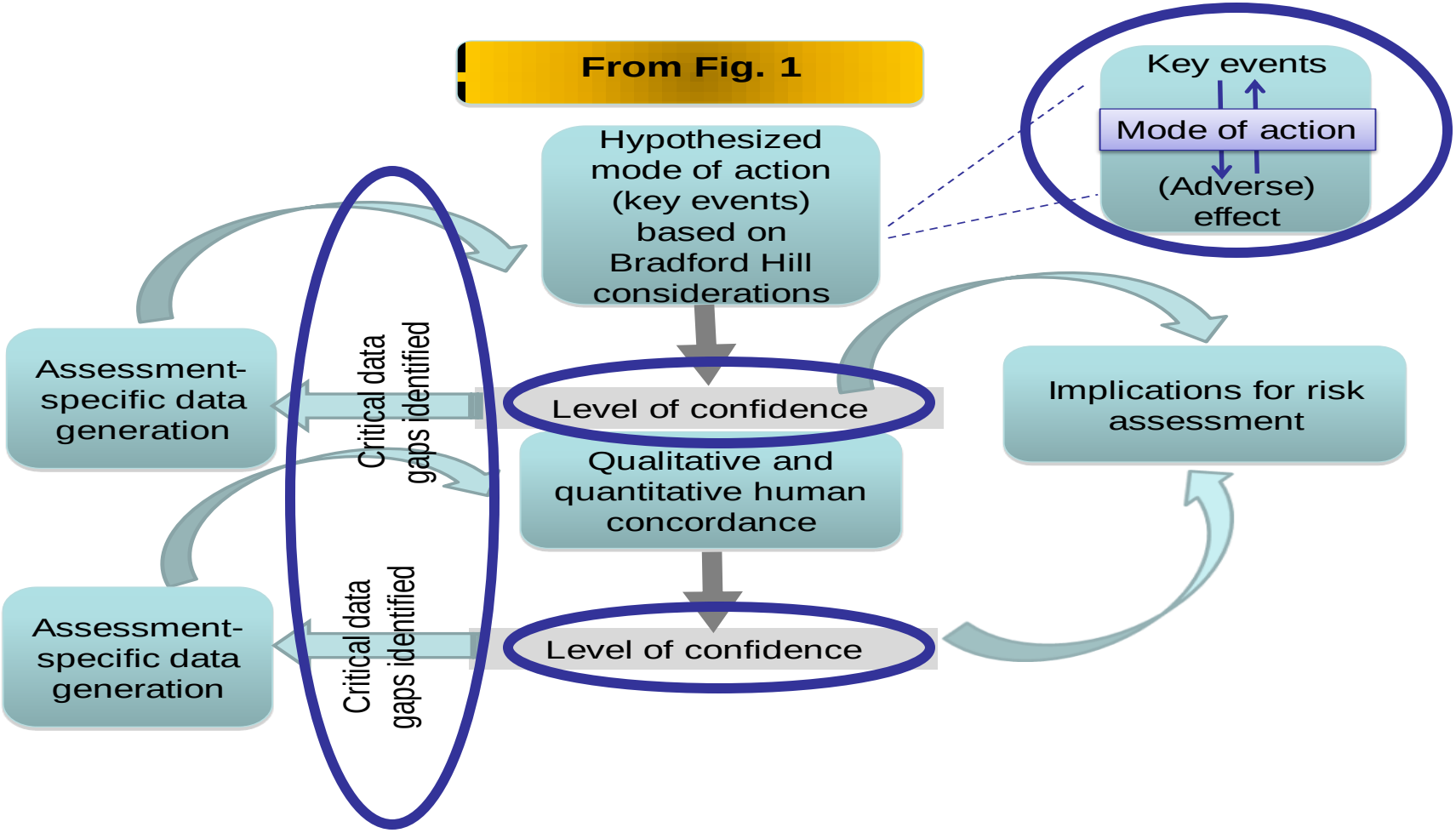
Modified MOA Framework



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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

Review Article

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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

ABSTRACT: The mode of action human relevance (MOA/HR) framework increases transparency in systematically considering data on MOA for end (adverse) effects and their relevance to humans. This framework continues to evolve as experience increases in its application. Though the MOA/HR framework is not designed to address the question of "how much information is enough" to support a hypothesized MOA in animals or its relevance to humans, its organizing construct has potential value in considering relative weight of evidence (WOE) among different cases and hypothesized MOA(s). This context is explored based on MOA analyses in published assessments to illustrate the relative extent of supporting data and their implications for dose–response analysis and involved comparisons for chemical assessments on trichloropropane, and carbon tetrachloride with several hypothesized MOA(s) for cancer. The WOE for each hypothesized MOA was summarized in narrative tables based on comparison and contrast of the extent and nature of the supporting database versus potentially inconsistent or missing information. The comparison was based on evolved Bradford Hill considerations rank ordered to reflect their relative contribution to WOE determinations of MOA taking into account increasing experience in their application internationally. This clarification of considerations for WOE determinations as a basis for comparative analysis is anticipated to contribute to increasing consistency in the application of MOA/HR analysis and potentially, transparency in separating science judgment from public policy considerations in regulatory risk assessment. Copyright © 2014. The Authors Journal of Applied Toxicology Published by John Wiley & Sons Ltd.

Keywords: human relevance framework; mode of action; weight of evidence; key events; evolved Bradford Hill considerations

Introduction

The mode of action/human relevance (MOA/HR) framework is an analytical framework designed to increase transparency in the systematic consideration of the weight of evidence (WOE) of hypothesized MOA(s) for critical effects and their relevance to humans. It was developed in initiatives of the International Life Sciences Institute Risk Sciences Institute (ILSI RSI) and the International Programme on Chemical Safety (IPCS) and derives from earlier work on MOA by the US Environmental Protection Agency (USEPA) and IPCS (Sonich-Mullin *et al.*, 2001).

The development and evolution of the IPCS ILSI RSI MOA/HR framework, which has involved large numbers of scientists internationally, is described in several publications (Boobis *et al.*, 2006, 2008; Meek, 2008; Meek *et al.*, 2003; Seed *et al.*, 2005). Potential application in a broader range of relevant contexts has been considered more recently (Carmichael *et al.*, 2011; Meek and Klaunig, 2010). The framework has been illustrated by an increasing number of case studies ($n = 30$, currently), and is widely adopted in international and national guidance and assessments (Meek *et al.*, 2008), including those of the USEPA (Dellarco and Baetcke, 2005; Manibusan *et al.*, 2007; SAB, 1999, 2007; SAP, 2000; USEPA, 2005a). Building on this collective experience, the framework has been updated recently, to address uncertainty additionally and to extend its utility to emerging areas in toxicity testing and non-testing methods. The update includes incorporation within a roadmap, encouraging continuous refinement of fit-for-purpose testing strategies and risk assessment (Meek *et al.*, 2014).

In addition to increasing transparency through structured articulation of the evidence and uncertainties upon which conclusions are based, MOA/HR analysis also contributes to the transparent assimilation of all available data in both a risk assessment and research context. This is important because it facilitates identification of critical data needs and contributes to transparency in the separation of science judgment (i.e., weighting of options based on systematic consideration of available scientific support) from public health protection policy, the latter

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Objectives/Approach Meek et al. DOI 10.1002/jat.2984 (2014b).

- Application of B/H Considerations for WOE in MOA Analysis
- Evolved (simplified & rank ordered) B/H considerations based on acquired experience to increase:
  - -Transparency
  - -Consistency
- Illustration through application to existing regulatory risk assessments in comparative WOE analysis

Weight of Evidence for Stressor Specific Hypothesized MOAs/AOPs

Evolved BH Considerations	Defining Questions
Biological Concordance	Does the hypothesized AOP conflict with broader biological knowledge? How well established is the AOP?
Essentiality of Key events	Is the sequence of events reversible if dosing is stopped or a key event prevented?
Concordance of Empirical Observations	**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? **Incidence** – Is the frequency of occurrence of the adverse effect less than that for the key events?
Consistency	Is the pattern of effects across species/strains/organs/test systems what would be expected based on the hypothesized AOP?
Analogy	Would the mode of action be anticipated based on broader chemical specific knowledge?

Meek et al., 2014b

Evolving Guidance for WOE – Stressor Specific MOA/AOP

Evolved BH Considerations	Stronger	Weaker
Biological Concordance	MOA is well established in scientific knowledge	Contrary to well established biological understanding MOA requires biological processes that are novel or poorly established
Essentiality of Key events	Direct experimental evidence for essentiality of key events (*i.e.,* absence/reduction of later events when a key event is blocked or diminished)	Data on reversibility only. Indirect measures only of key events and/or lack of data to assess
Concordance of Empirical Observations	**Dose Response & Temporality** – expected pattern of temporal and dose-response relationships based on robust database (multiple studies with examination of key events at interim time periods at multiple doses) **Incidence** – incidence of early key events > than (adverse) effect	All key events occur at all dose levels and all time points and/or limited data available to assess (e.g., inadequate dose spacing, missing key time periods for effect development, or failure to assess incidence at early time points).
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

Adverse Outcome Pathways: A Conceptual Framework To Support Ecotoxicology Research And Risk Assessment (Ankley et al., 2010)

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Hazard/Risk Assessment

ADVERSE OUTCOME PATHWAYS: A CONCEPTUAL FRAMEWORK TO SUPPORT ECOTOXICOLOGY RESEARCH AND RISK ASSESSMENT

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Abstract—Ecological risk assessors face increasing demands to assess more chemicals, with greater speed and accuracy, and to do so using fewer resources and experimental animals. New approaches in biological and computational sciences may be able to generate mechanistic information that could help in meeting these challenges. However, to use mechanistic data to support chemical assessments, there is a need for effective translation of this information into endpoints meaningful to ecological risk—effects on survival, development, and reproduction in individual organisms and, by extension, impacts on populations. Here we discuss a framework designed for this purpose, the adverse outcome pathway (AOP). An AOP is a conceptual construct that portrays existing knowledge concerning the linkage between a direct molecular initiating event and an adverse outcome at a biological level of organization relevant to risk assessment. The practical utility of AOPs for ecological risk assessment of chemicals is illustrated using five case examples. The examples demonstrate how the AOP concept can focus toxicity testing in terms of species and endpoint selection, enhance across-chemical extrapolation, and support prediction of mixture effects. The examples also show how AOPs facilitate use of molecular or biochemical endpoints (sometimes referred to as biomarkers) for forecasting chemical impacts on individuals and populations. In the concluding sections of the paper, we discuss how AOPs can help to guide research that supports chemical risk assessments and advocate for the incorporation of this approach into a broader systems biology framework. Environ. Toxicol. Chem. 2010;29:730–741. © 2009 SETAC

Keywords—Toxic chemicals Ecological effects Adverse outcomes Risk assessment

INTRODUCTION

Ecological risk assessors face increasing demands to assess more chemicals, with greater speed and accuracy, and to do so using fewer resources and experimental animals. Legislation such as the Food Quality Protection Act (FQPA) and Safe Drinking Water Act (SDWA) in the United States and the Registration, Evaluation and Authorisation of Chemicals (REACH) program in the European Union (EU) creates mandates to assess potential risks from an expanding number of chemicals or to consider a broader suite of effects than has commonly been considered in previous assessment efforts. Regulatory programs are also faced with the need to assess emerging contaminants of concern, such as pharmaceuticals and nanomaterials, for which existing assessment procedures may be inadequate [1].

At the same time, the fields of biology and toxicology have seen a number of important developments. Advances in computational capabilities and bioinformatics, measurement technologies (e.g., genomics), and fundamental toxicological understanding at the molecular level have increased the amount and types of information available and potentially useful to risk assessors. However, for most regulatory assessments, broad suites of in vivo toxicity tests continue to provide the basic information underlying the decision-making process. The time and resources necessary to support this approach run counter to the demands being faced. As argued by Bradbury et al. [2], circumstances require that we move away from an overdependence on in vivo testing and make greater use of computational, molecular, and in vitro tools.

Similar challenges are faced by scientists involved in human health risk assessment. In 2007, the National Academies of Science released an expert panel report, *Toxicity Testing in the 21st Century* [3], which described a vision for the future of toxicity testing to support human health risk assessments. That report acknowledged many of the issues identified above for ecological risk assessment and emphasized the need to develop a focused assessment approach that maximizes use of existing knowledge and the efficient and targeted search for critical new knowledge, while minimizing reliance on resource-intensive testing approaches. Strategies proposed by Bradbury et al. [2] and the National Research Council (NRC) [3] have as a common recommendation the need to collect basic information about biological systems and how chemicals perturb them, in order to improve the ability to predict which chemicals are likely to cause adverse effects or, for retrospective assessments, deduce which chemicals are most likely to be causing observed effects.

Bringing the full range of emerging tools and understanding to bear on ecological risk assessment requires the development of a framework within which data and knowledge collected at many levels of biological organization can be synthesized in a

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MOA/AOP – "Conceptually Identical"

- ***But: Different Objectives & Contributing Communities (Human Health & Environment)***
- Variation in focus/experience of different communities , designed for different purposes
  - **Focus** for AOPs often on the "molecular initiating event," (QSAR)
    - the first point of interaction of a stressor with a chemically defined biological component
  - **Focus** for MOA is often on quantitative dose-response for later key events
- AOPs include adverse outcome of regulatory interest, MOA doesn't imply adversity

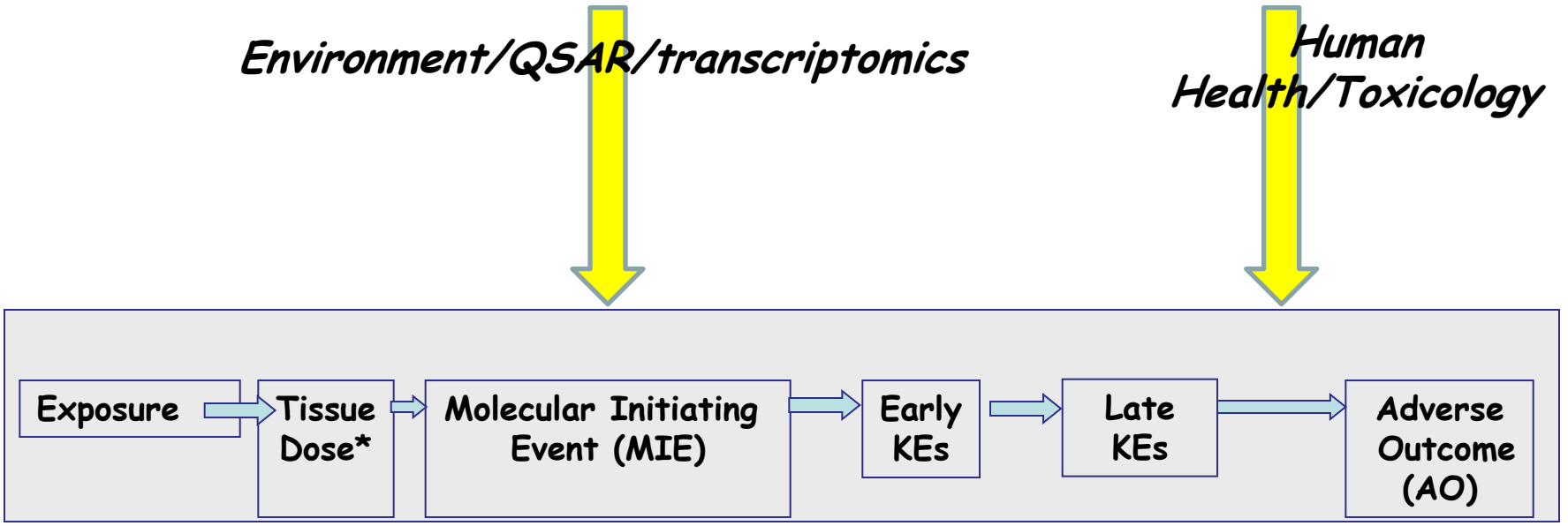
MOA/AOP – "Conceptually Identical"

- ***But: Different Objectives & Contributing Communities (Human Health & Environment)***
- AOPs are limited to the post metabolism component of MOAs
  - biological pathways – which could be tripped by any stressor; no kinetics or metabolism
    - facilitates building networks of interrelated pathways
- **MOA** takes into account metabolism to the toxic entity
    - As an early key event
- **MOA/species concordance analysis** also addresses tk and td aspects relevant to species scaling

In a Nutshell – MOA/AOP

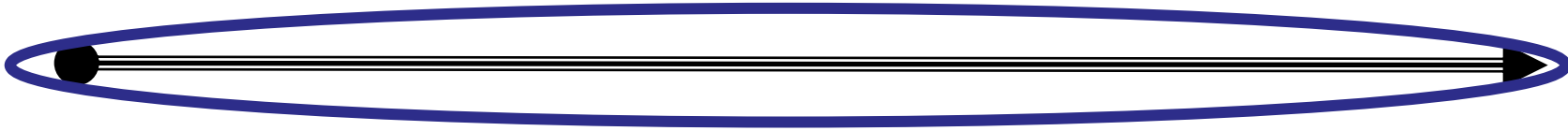
- Essentially conceptually identical constructs which organize mechanistic knowledge at a range of levels of biological organization to facilitate its evaluation for specified application
- Traditionally, MOAs have been established for individual chemicals within a finite universe of AOPs additionally taking into account metabolism; ***MOA*** species concordance ***analysis*** takes into account tk
- Different communities have experience in different parts of the continuum
  - All are essential to continued progress

MOA/AOP



AOP

*active metabolite



Mode of Action Analysis

Conceptually, Adverse Outcome Pathways (AOPs) and MOA are identical

Principles – Facilitating Regulatory Uptake

- 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

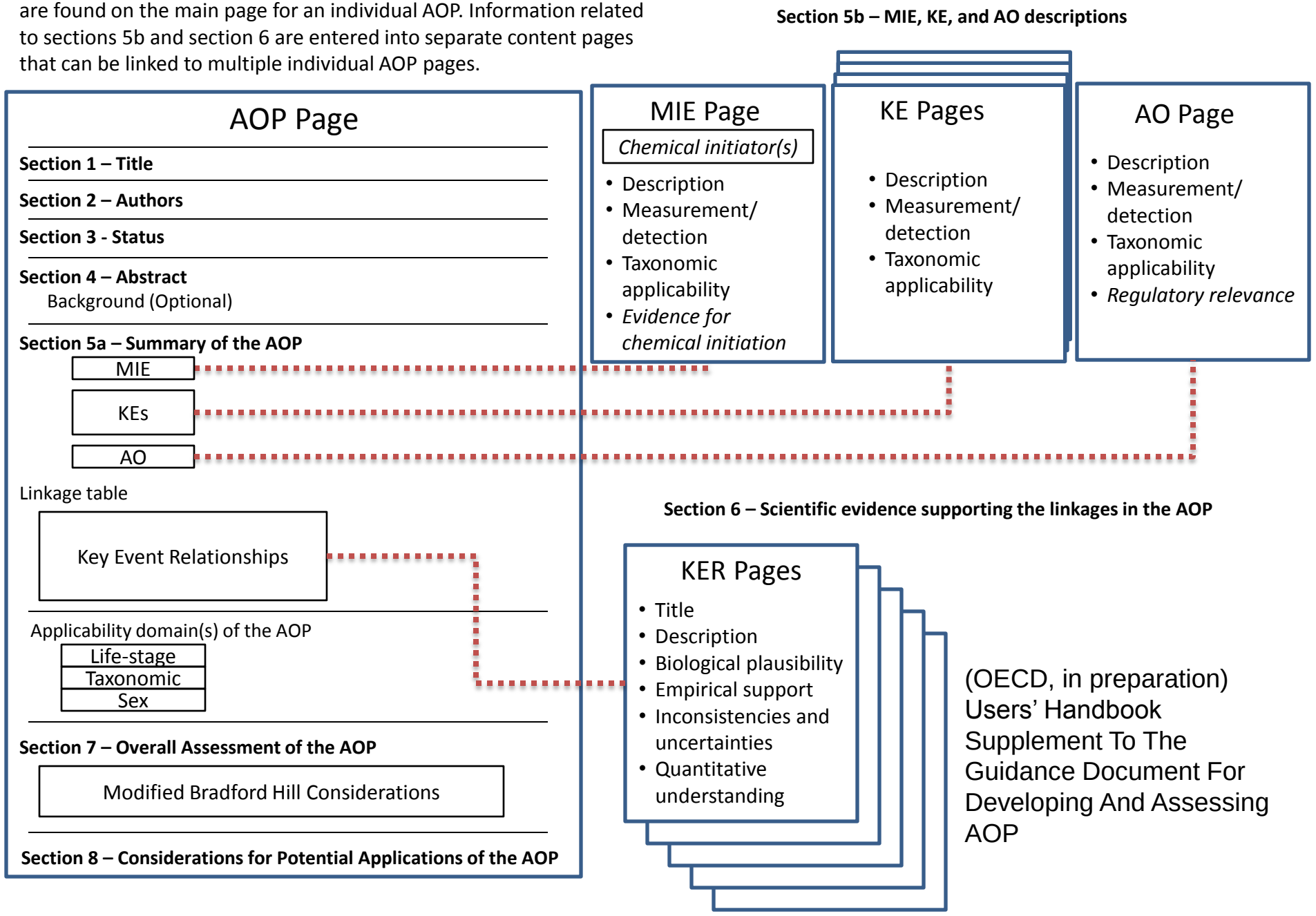
Meek, & Lipscomb, Toxicol. (submitted)

Refined AOP Template

Section 1 - AOP identifier/Title
Section 2: Author(s) of AOP
Section 3a - Status
Section 3b - Date of updating the AOP
Section 4a - Abstract
Section 4b – Background (optional)
Section 5– Summary of the AOP & KE Descriptions **a) Summary of the AOP in Figure or Table Format** **b) KE Descriptions** **○ Description** **○ Measurement/detection** **○ Taxonomic applicability/relevance**
Section 6 – KER Descriptions • **Title of KER** • **Description of KER** • **Weight of Evidence for the KER** **○ Biological Plausibility** **○ Empirical support** • **Inconsistencies / Uncertainties** • **Quantitative understanding**
Section 7 - Overall Assessment of the AOP • **Domain of Applicability** • **Relative Level of Confidence** **○ Biological Plausibility of KERs** **○ Essentiality of KEs** **○ Empirical support for KERs** **○ Completing Table 2** **○ Quantitative Understanding** **○ Overall AOP**
Section 8 – Considerations for Potential applications of the AOP (optional)

(OECD, in preparation) Users' Handbook Supplement To The Guidance Document For Developing And Assessing AOP

Figure 2. Overview of the organization of content pages in the AOP-wiki relative to sections of the AOP template. Sections 1, 4, 5a, and 7 are found on the main page for an individual AOP. Information related to sections 5b and section 6 are entered into separate content pages that can be linked to multiple individual AOP pages.



Incorporating New Technologies Into Toxicity Testing and Risk Assessment: Moving From 21st Century Vision to a Data-Driven Framework (Thomas et al., 2013)

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Incorporating New Technologies Into Toxicity Testing and Risk Assessment: Moving From 21st Century Vision to a Data-Driven Framework

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Based on existing data and previous work, a series of studies is proposed as a basis toward a pragmatic early step in transforming toxicity testing. These studies were assembled into a data-driven framework that invokes successive tiers of testing with margin of exposure (MOE) as the primary metric. The first tier of the framework integrates data from high-throughput *in vitro* assays, *in vitro-to-in vivo* extrapolation (IVIVE) pharmacokinetic modeling, and exposure modeling. The *in vitro* assays are used to separate chemicals based on their relative selectivity in interacting with biological targets and identify the concentration at which these interactions occur. The IVIVE modeling converts *in vitro* concentrations into external dose for calculation of the point of departure (POD) and comparisons to human exposure estimates to yield a MOE. The second tier involves short-term *in vivo* studies, expanded pharmacokinetic evaluations, and refined human exposure estimates. The results from the second tier studies provide more accurate estimates of the POD and the MOE. The third tier contains the traditional animal studies currently used to assess chemical safety. In each tier, the POD for selective chemicals is based primarily on endpoints associated with a proposed mode of action, whereas the POD for nonselective chemicals is based on potential biological perturbation. Based on the MOE, a significant percentage of chemicals evaluated in the first 2 tiers could be eliminated from further testing. The framework provides a risk-based and animal-sparing approach to evaluate chemical safety, drawing broadly from previous experience but incorporating technological advances to increase efficiency.

***Key Words:* *in vitro* and alternatives; biotransformation and toxicokinetics; predictive toxicology; risk assessment; safety evaluation; exposure.**

Shortly after the turn of the century, there was increasing recognition and acceptance within government agencies that new approaches were needed to evaluate the safety of the relatively large number of chemicals in commerce and the environment (EPA, 2003; Kavlock *et al.*, 2005; Meek and Armstrong, 2007; NTP, 2004). Following this recognition, the release of the National Research Council's Report "Toxicity Testing in the 21st Century: A Vision and a Strategy" (NRC, 2007) initiated a broad-based movement in the toxicology community to reassess how toxicity testing and risk assessment are performed. Since the release of the report, multiple efforts in the United States and abroad have added to the momentum with the shared goal of transitioning toxicity testing and risk assessment from an outdated, inefficient, costly, and animal-centric process to one that is more efficient, economical, less animal intensive, and more relevant to human health by utilizing new technologies that provide a better understanding of the underlying biological system. However, the majority of these efforts have focused more on a vision of how things should be done rather than the development of a pragmatic path forward that can be iteratively refined as greater understanding is achieved.

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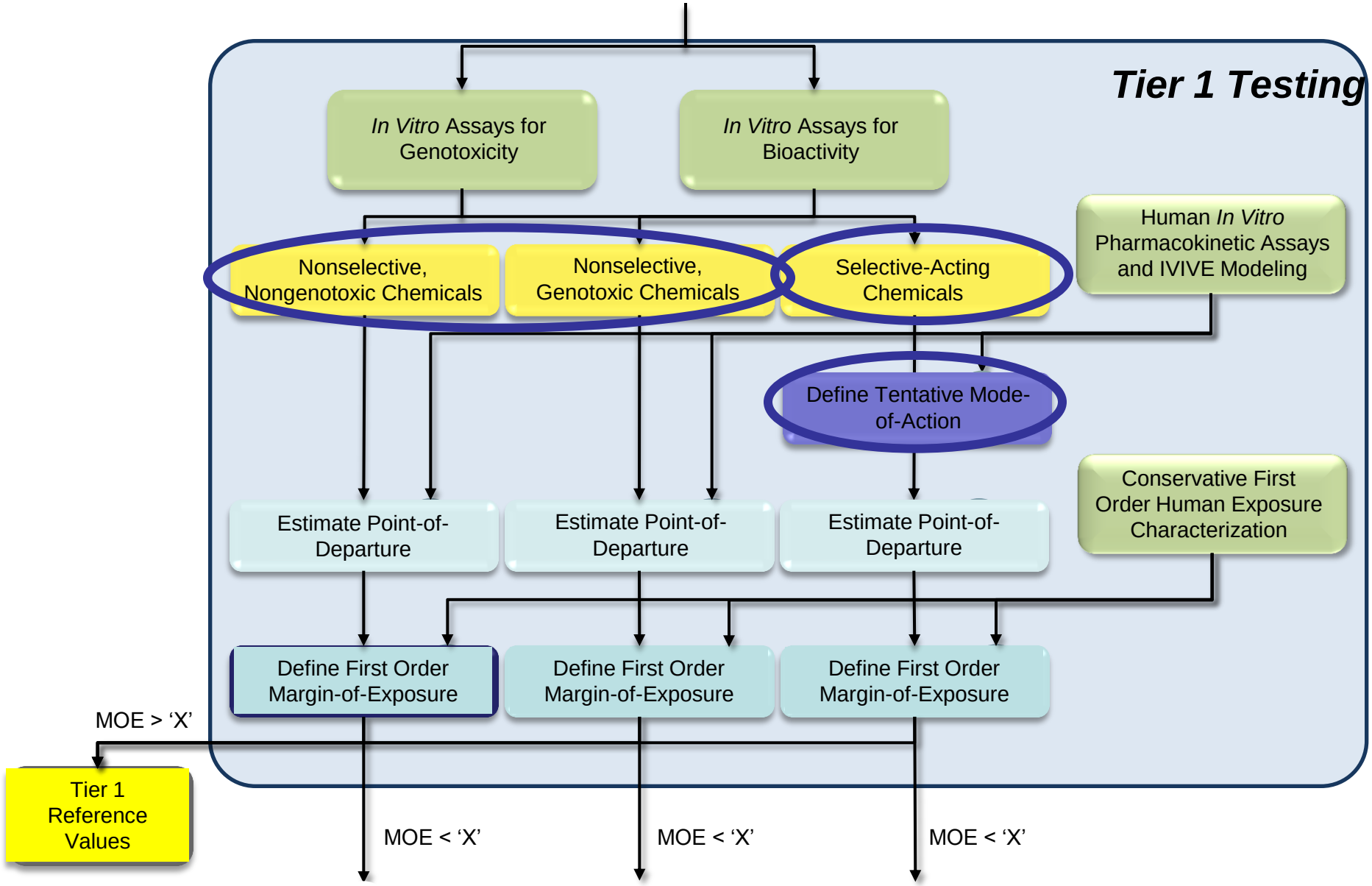
New and Legacy Chemicals with Minimal Toxicity Data



Thomas et al., 2013

Challenges in Regulatory Engagement

- Continuing advancement of the science
- Constraints/Opportunities - Regulatory Mandates
  - Lack of harmonization
  - Lack of flexibility
    - E.g., timelines/process for revision of program guidance

    - But on the other hand, it's progressive regulatory mandates that have driven the research agenda, here
- Constraints in Resources
  - E.g., Regulatory timelines
    - Short vs. longer term objectives

Additional Opportunity?

- Balance of early engagement/training vs. methodology development
- Tailoring of the products from outset to meet training objectives
  - Early communication/training strategy
  - Need for broadly applicable communication and training materials
    - Not only scientific/technical staff but their management
  - Development of IT tools
- Getting the model for engagement right
  - Tried and true "models"

Recommendations/Conclusions

- MOA/AOPs builds on long standing regulatory experience & provides a construct for coordinating input of the research community
- Early engagement/training of all of the relevant communities is advised
  - Research (QSAR/transcriptomics/toxicology, etc.)
  - Regulatory (risk assessment/policy makers)
- "Rebranding"/terminology often creates artificial barriers between communities
- User friendly repository and tools building on past experience ("codified") are critical
  - Knowledge base/wiki