The WHO Framework for Combined Exposures and MOA/AOP Analysis; Implications for Euromix

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Euromix Kick Off Meeting

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Contents of the WHO IPCS Framework on Combined Exposures

- When to conduct a combined assessment
  - i.e., considering several chemicals at once
- Generic description of the framework approach
  - "Fit for purpose"
  - Pragmatic tiered structure with increasingly detailed consideration of both exposure and hazard
  - ***Exposure*** influential in setting priorities
- Three case studies (examples, only)
  - Priority setting for drinking water contaminants, based on the threshold for toxicological concern
  - Screening assessment on PBDEs
  - Full assessment on carbamates

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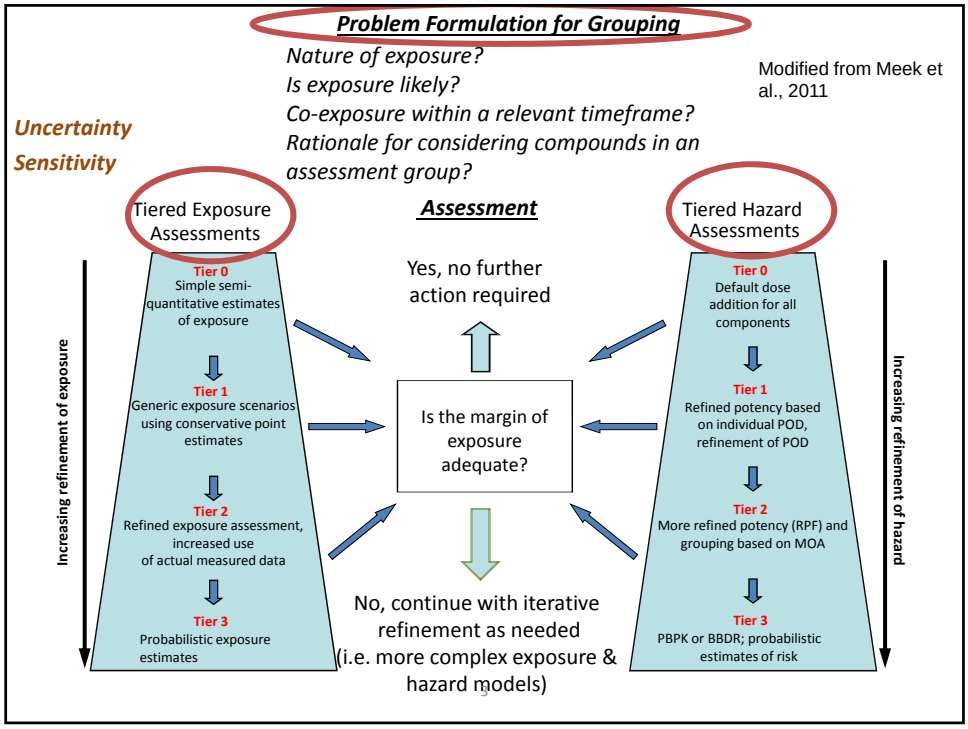

Learnings

- Limited numbers of regulatory examples
  - Legislative drivers critical
- Exposure more discriminating than hazard
- Limited use of predictive/screening methods
  - Combined assessments sometimes more complex than necessary; focussed on hazard
  - Limited use of exposure profiling to "group"
- Importance of problem formulation
  - "Fit for purpose" assessment; Communication
- Importance of "framing" output of tiers
  - Degree of conservatism, understanding the most influential parameters

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Limited use of predictive/screening methods The Challenge to the Exposure Community

- Broadly drawing upon the assessment experience on data rich chemicals, to develop first order estimates of exposure:
  - ***Identification of a limited number of key parameters as exposure determinants (n = ?),***
  - And their relevant information sources,
    - Which could include data generation
- But recognizing: that readily accessible information not necessarily the most informative

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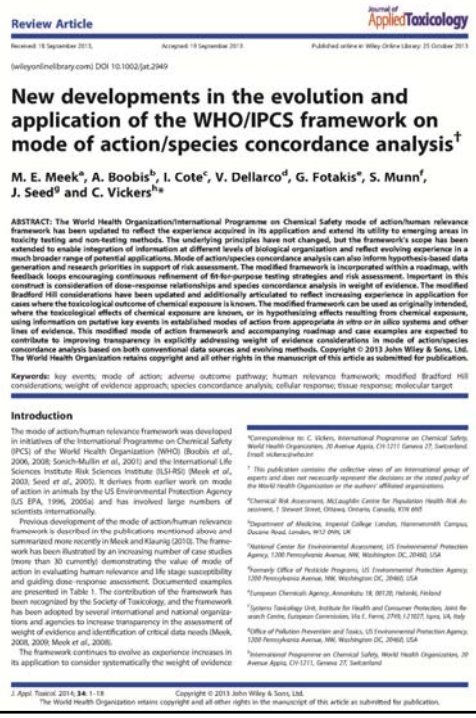

Review Article

Journal of Applied Toxicology

(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†

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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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† This publication contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization or the authors' affiliated organizations.

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Screening of Hazard

- need for simpler, more predictive measures of potency
- Some progress

Applied Toxicol.34: 1-18 (2014 a).

- Roadmap for fit-for-purpose testing strategies and risk assessment
- MOA analysis in more predictive context
- Case examples

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Case example 6: Mode of Action in Grouping and Potency Estimates for Combined Exposures

Anchoring the results of (new) in vitro approaches to relevant outcomes based on existing knowledge and concepts:

- Class of pesticides, same well established mode of action and insecticidal effects
  - reversible neurotoxicity through interaction with neuronal sodium channels
- Members of the class expected to share key events
  - Interaction with sodium channels
- Consider grouping and rank for potency for broader group of compounds in suitable *in vitro* system for this key event

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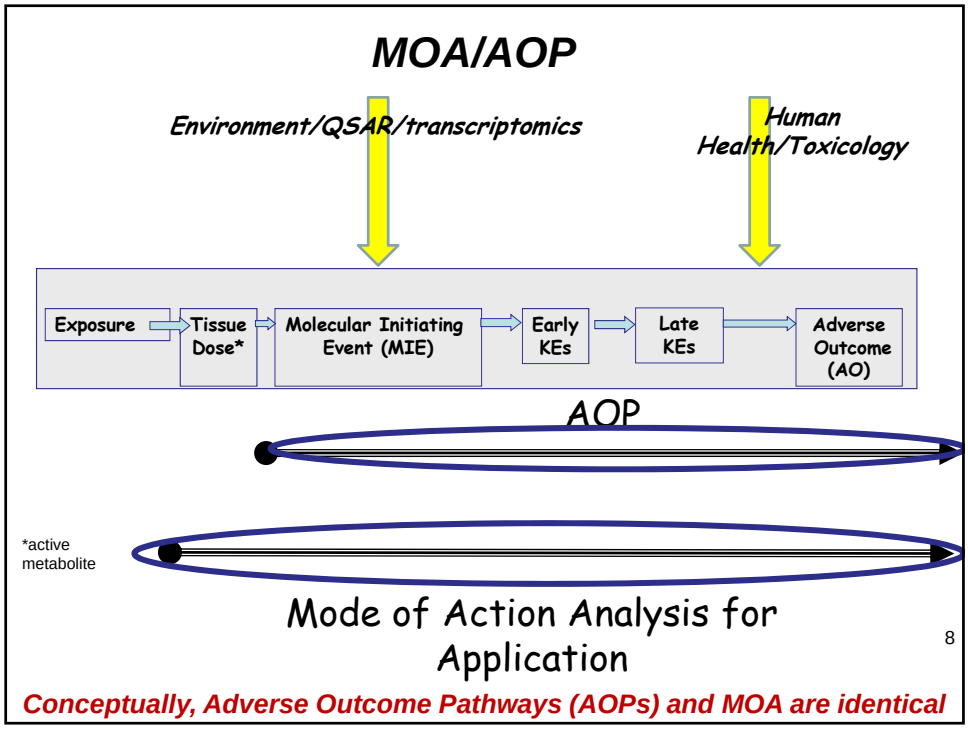

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Conceptually, Adverse Outcome Pathways (AOPs) and MOA are identical

MOA/AOP "Conceptually Identical"

But: Different Objectives & Contributing Communities (Human Health & Environment)

- 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

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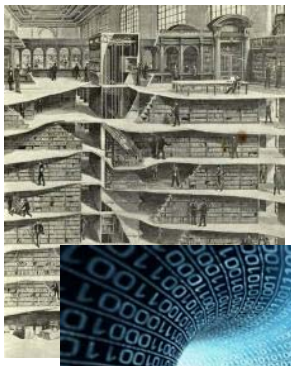
21st Century Regulatory Decision-Making



The data are there….

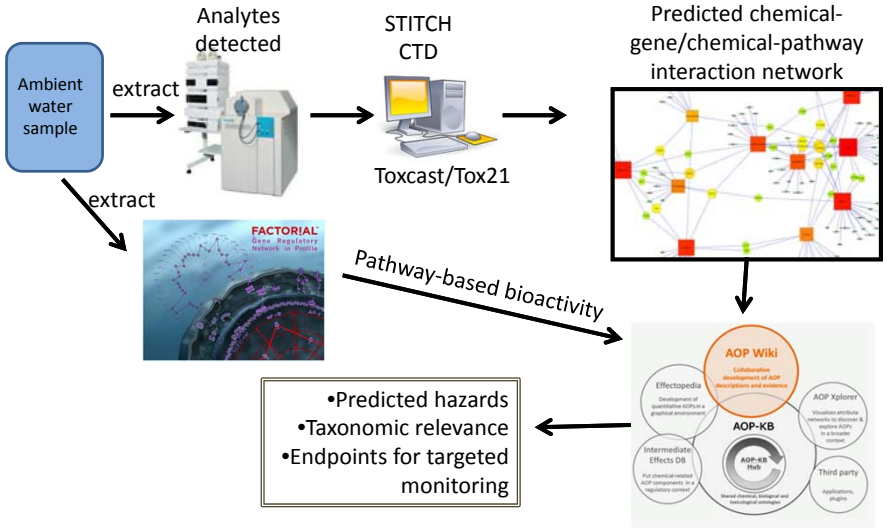
We have entire libraries of scientific publications available at our fingertips…..

Scientific challenge of the 21st C….

How do we make effective use of those data and our wealth of existing scientific knowledge to support regulatory decision-making?

AOPs are part of the solution.

The Vision



AOP Knowledge-base (aopkb.org)

Increasing Confidence in Hypothesized MOAs/AOPs

Review Article

Journal of Applied Toxicology

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

Introduction

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

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OECD AOP Template

Background
AOP Identifier
Authors
Date of Updating
Abstract/Background (Optional)
Summary of AOP and Key Event Descriptions
KER Descriptions • Qualitative Weight of Evidence for KERs Biological Plausibility Empirical Support • Quantitative Understanding
Assessment of the AOP • Domain of Applicability • Relative Level of Confidence • 1. Biological Plausibility – KERs • 2. Essentiality – KEs • 3. Empirical Support for the KERs
Quantitative Understanding of Each of the KERs
Potential Application (Optional)

(OECD, 2014) Users' Handbook Supplement To The Guidance Document For Developing And Assessing AOP

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(OECD, 2014) Users' Handbook Supplement To The Guidance Document For Developing And Assessing AOP

Annex 1 – Assessing Confidence
Definition, Basis for Calls, Examples

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

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

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More Recent International Developments

- ***OECD Task Force on Hazard Assessment (June, 2014)***
  - Developing more guidance based on the WHO framework/2011 workshop (Canada co-lead with OECD)
    - Substances with limited hazard data; Estimated daily intake from biomonitoring; risk based criteria for moving to higher tiers
- ***WHO Drinking Water Guidelines***
  - Toolbox of methodologies framed in the context of tiers of the WHO framework
  - Several case studies in development
    - Pharmaceuticals (Statins, Non-Steroidal Anti-Inflammatories), Pesticides, Microcystins and Estrogens

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Importance of "Framing" of the Tiers Considering Uncertainty, Variability and Sensitivity in Hazard Values

- Tiered assessment requires explicit consideration of uncertainty/variability
  - exposure ***and*** effect (***not*** "uncertainty" factors)
- Need to specify which aspects are most important for refinement of assessment and data generation
  - Sensitivity analysis
- Consideration of MOEs has identified important sources of uncertainty and variability and their weighting for hazard
  - Beyond "uncertainty factors" for reference doses

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Implications for Combined Exposure Assessment

- Consider exposure at outset in problem formulation
  - Do use profiles indicate likely co-exposure?
- The value of hierarchically addressing combined exposures
  - efficiency in assessment and management
- Maximizing understanding and availability of context specific tools for both exposure and hazard

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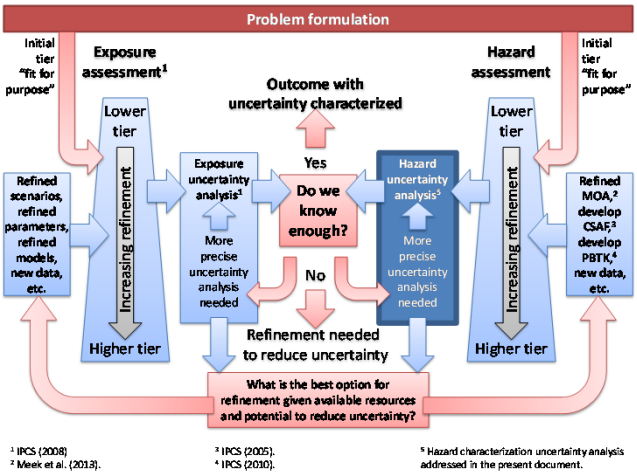
"Mapping" of Tiering of Recent WHO Guidance



[1] IPCS (2008)
[2] Meek et al. (2013).
[3] IPCS (2005).
[4] IPCS (2010).
[5] Hazard characterization uncertainty analysis addressed in the present document.

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More Information

Meek, M.E. (2012) Toxicology: http://dx.doi.org/10.1016/j.tox.2012.09.015

IPCS Harmonization Website

http://www.who.int/ipcs/methods/harmonization/areas/aggregate/en/index.html :

Report of the 2007 Workshop

Case study on carbamates

Publication

Meek, Boobis, Crofton, Heinemeyer, Van Raaij & Vickers (2011) Reg. Tox. & Pharmacol. 60, Issue 2, Supplement 1, Pages S1-S14 , Including:Framework & Case Studies (TTC – Boobis et al., 2011; PBDEs – Meek)

http://www.sciencedirect.com/science/article/pii/S0273230011000638

Report of the WHO/OECD/ILSI - HESI Workshop

http://www.oecd.org/document/24/0,3746,en_2649_34377_47858904_1_1_1_1,00.html

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