

Low Dose Effects: Is the Lowest the Most Relevant?

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Thesis:

The ideal risk assessment
(in search of the relevant endpoint)
is based on an understanding of the
Mode of action (MOA)
of the compound

To achieve this goal, the following steps are suggested:

Step 1: Literature identification and selection process

- Identify studies which may be relevant for the understanding of the MOA. Establish a bibliography of key references and make them available to all panel members via a shared website.
- Key papers generally focused on human studies, animal (rodent etc.) *in vivo* studies, or *in vitro* studies using relevant cell types. Moreover, studies using (wide) dose-ranges including no-effect levels are given greater weight. Data on mechanistic or early molecular responses are examined as being reflective of potential key events in the MOA identified by individual expert panel members.
- Discussions generate suggestions for additional areas for follow-up evaluation. To reflect these suggestions, a supplemental literature search is conducted. All selected papers are then analyzed for relevance to the mode of action.

Step 2: Hill's* modified considerations for causality

1. **Strength of correlation** (is the effects related to the exposure?)
 2. **Consistency** (Has the correlation been repeatedly observed by different researchers, in different places, circumstances and times?)
 3. **Specificity** (is the effect only/mainly observed in the exposed/treated?)
 4. **Temporality** (is there a plausible temporal association between exposure and effects?)
 5. **Biological gradient** (is the strength of the effect related to the exposure level?)
 6. **Coherence** (is the association in agreement with the principles of science?)
 7. **Plausibility** (depends on the state of scientific understanding)
 8. **Intervention and experiment** (does experimental or interventional modification of exposure lead to the expected results?)
 9. **Analogy** (is the association also observed under similar circumstances?)
- Test for statistical significance

*Hill AB (1965) The environment and disease: association or causation? Proc R Soc Med 58:295-300

Step 3: Classification of events

The following definitions for use in evaluating the related biological steps in a proposed MOA follow the IPCS (2007) framework* classifying events into:

- **Key Event:** An empirically observable causal precursor step to the adverse outcome that is itself a necessary element of the mode of action. Key events are required events for the MOA, but often are not sufficient to induce the adverse outcome in the absence of other key events.
- **Associative Event:** Biological processes that are themselves not causal necessary key events for the MOA, but are reliable indicators or markers for key events. Associative events can often be used as surrogate markers for a key event in a MOA evaluation or as indicators of exposure to a xenobiotic that has stimulated the molecular initiating event or a key event.
- **Modulating Factor:** There are many factors or biological responses that are not necessary to induce the adverse outcome, but could modulate the dose-response behavior or probability of inducing one or more key events or the adverse outcome. Such biological factors are considered modulating factors

*Boobis AR, Doe JE, Heinrich-Hirsch B, Meek ME, Munn S, Ruchirawat M, Schlatter J, Seed J, Vickers C (2008) IPCS framework for analyzing the relevance of a noncancer mode of action for humans. *Crit Rev Toxicol* 38, 87-96.

Step 4: Identification of mode of action (MOE)

- The evaluation of the literature is organized around a series of relevance parameters (questions). The discussion questions are designed to elicit a robust evaluation of the key aspects of current MOA evaluation frameworks (e.g. Boobis *et al.*, 2006; Boobis *et al.*, 2009; Cohen *et al.*, 2004; Cohen *et al.*, 2003; EPA, 2005; Holsapple *et al.*, 2006; Julien *et al.*, 2009; Meek, 2008; Meek *et al.*, 2003; Seed *et al.*, 2005; Sonich-Mullin *et al.*, 2001).
- Alternative MOA hypotheses are developed and tested based on the Hill considerations, including identifying key events (KE), associative events (AE), and modulating factors (ModF)
- Uncertainties, inconsistencies and data gaps are identified
- Human relevance of the proposed MOA (on qualitative and quantitative terms) is tested; the dose-response implications of the proposed MOA are evaluated.

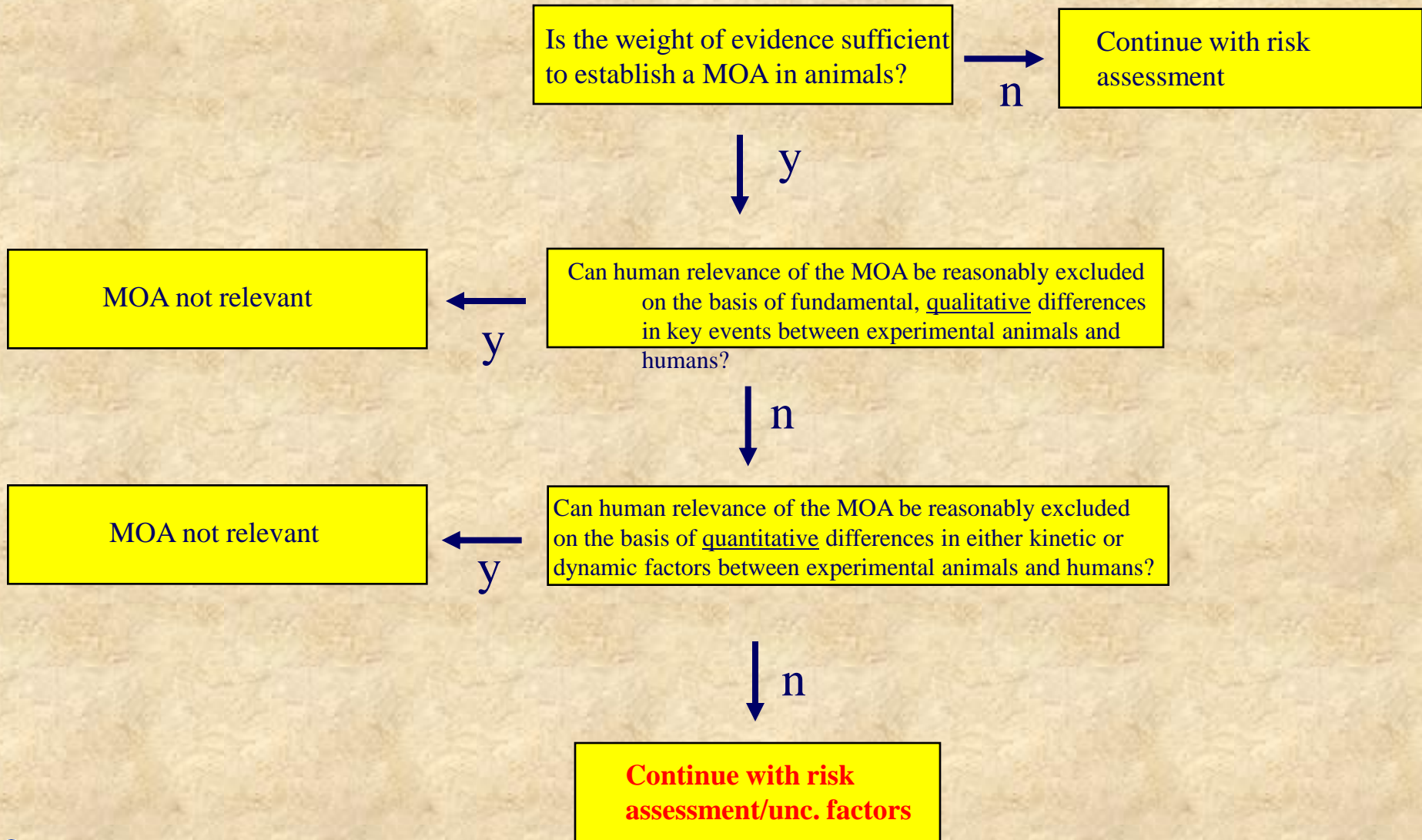
Step 5: Human relevance

Questions*:

1. Is the weight of evidence sufficient to establish a MOA in animals?
2. Can human relevance of the MOA be reasonably excluded on the basis of fundamental, qualitative differences in key events between experimental animals and humans?
3. Can human relevance of the MOA be reasonably excluded on the basis of quantitative differences in either kinetic or dynamic factors between experimental animals and humans?
4. Are there any quantitative differences in key events such that default values for uncertainty factors for species or individual differences could be modified?

*Boobis AR, Doe JE, Heinrich-Hirsch B, Meek ME, Munn S, Ruchirawat M, Schlatter J, Seed J, Vickers C (2008) IPCS framework for analyzing the relevance of a noncancer mode of action for humans. Crit Rev Toxicol 38, 87-96.

Step 5: Human relevance

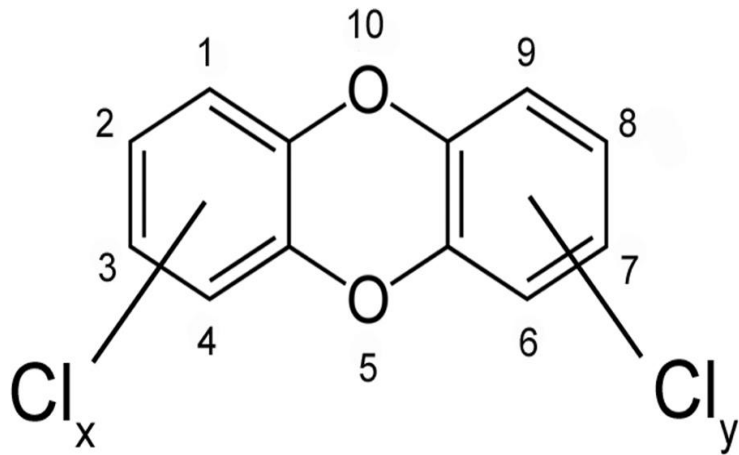


Step 5: Human relevance

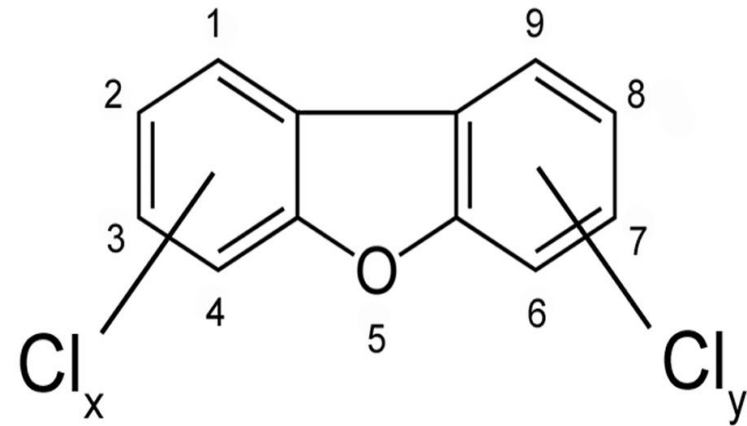
Continue with risk assessment/unc. factors:

Are there any quantitative differences in key events such that default values for uncertainty factors for species or individual differences could be modified?

Case study: Dioxins and cancer

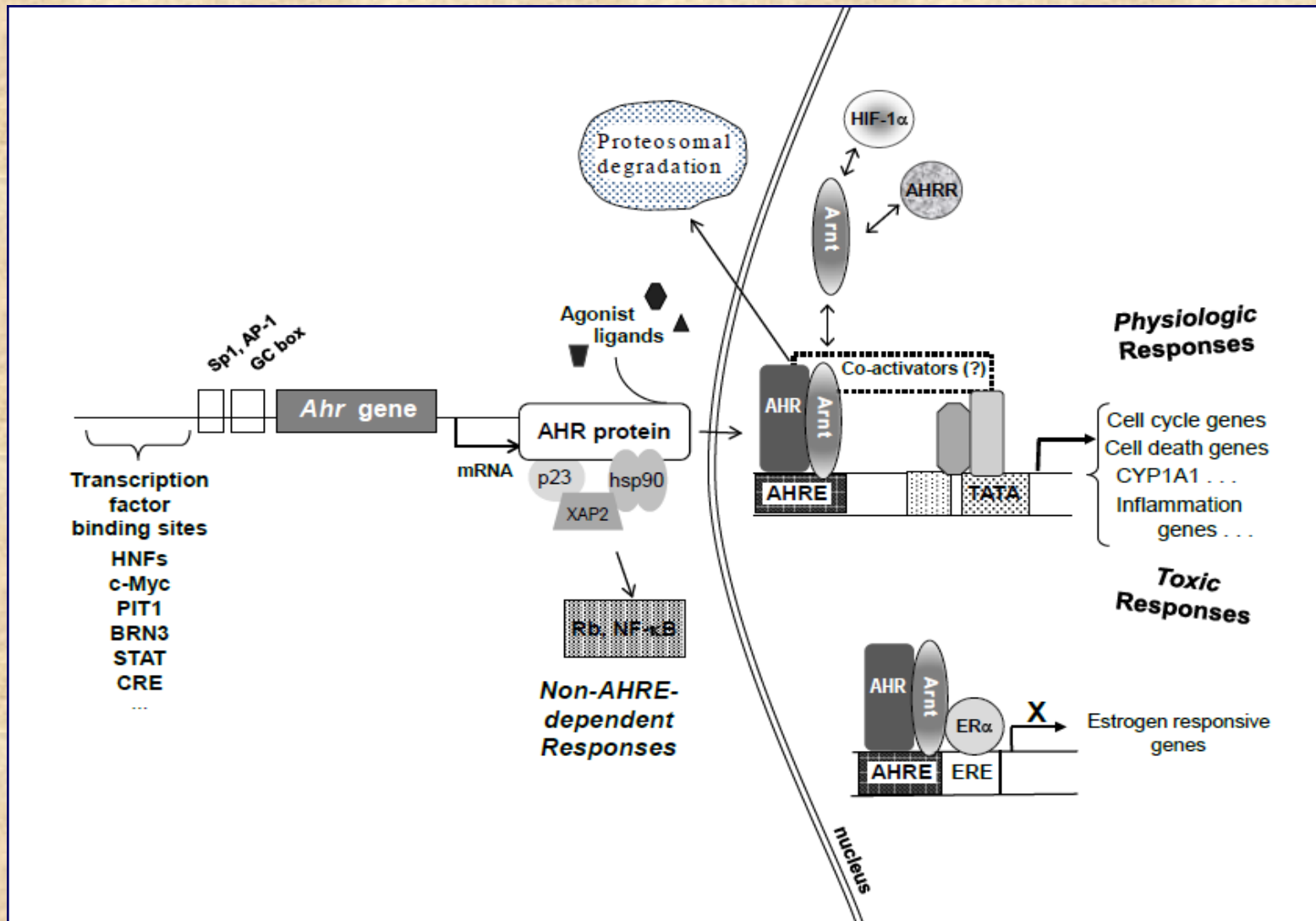


PCDD



PCDF

Case study: Dioxins and cancer



Step 5: Human relevance

Questions*:

1. Is the weight of evidence sufficient to establish a MOA in animals? **Yes**
2. Can human relevance of the MOA be reasonably excluded on the basis of fundamental, qualitative differences in key events between experimental animals and humans? **No**
3. Can human relevance of the MOA be reasonably excluded on the basis of quantitative differences in either kinetic or dynamic factors between experimental animals and humans? **No**
4. Are there any quantitative differences in key events such that default values for uncertainty factors for species or individual differences could be modified? **Yes**

*Boobis AR, Doe JE, Heinrich-Hirsch B, Meek ME, Munn S, Ruchirawat M, Schlatter J, Seed J, Vickers C (2008) IPCS framework for analyzing the relevance of a noncancer mode of action for humans. *Crit Rev Toxicol* 38, 87-96.

Case study: Dioxins and cancer

AHR case study panel members and affiliations.

	Participant Names	Affiliations
Co-Chairs	Robert Budinsky, PhD Dieter Schrenk, PhD, MD	Dow Chemical Company University of Kaiserslautern
Rapporteurs	Martin van den Berg, PhD Ted Simon, PhD, DABT Andrew Maier, PhD, CIH, DABT	Utrecht University Ted Simon LLC Toxicology Excellence for Risk Assessment (TERA)
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Summary and conclusions

- 1. In any risk assessment the type and quality of the literature eventually considered should be defined, if possible, before the risk assessment starts.**
- 2. After selection of studies based on the aforementioned quality criteria, the most sensitive endpoints are selected and scrutinized according to the Hill criteria.**
- 3. A mode-of-action-analysis is aimed at identifying key events, associated events, and modulating factors.**
- 4. A target (human) relevance decision is made.**
- 5. Dose-response considerations (comparison model vs. target) for the critical MOA are made.**

Thank you for your attention!

