

Case Study Summary

Title:

Scientific Rigor in the Era of New Assessment Methods (NAMs): Key Characteristics Approach and Evidence-Based Weight of Evidence Frameworks

Version: 1

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Panel Advisor:

1. Provide a few sentences summarizing the method illustrated by the case study.

This Case Study evaluates two diametrically opposed methodological philosophies of toxicant characterization. The newer philosophy – the Key Characteristics Approach – posits that a relatively few, typically 8 – 13, “key” types of effects are “characteristic” of various categories of toxicity, such as carcinogens, endocrine disruptors, reproductive toxicants, etc., and can be used to identify chemicals that belong to each category. The more traditional philosophy of systematic evaluation – Evidence-Based Weight of Evidence (WoE) / Mode of Action Approaches (Borgert et al., 2015; Borgert et al., 2011; Borgert et al. 2014; Becker et al., 2025) – rely on a comprehensive evaluation of all data related to the production of toxicity, from kinetics to mechanisms to overt physiological outcomes.

This case study critically compares those two philosophies based on formal rules of logic, internal consistency, external consistency, transparency, replicability, and falsifiability.

2. Describe the problem formulation(s) the case study is designed to address. How is the method described in the case useful for addressing the problem formulation?

IS RTP, TERA, and EPF co-sponsored a series of webinars to evaluate the Key Characteristics Approaches, which have been applied to nearly every category of toxicant. The first two webinars critiqued the KC approach for carcinogens (KCCs) and endocrine disruptors (KC-EDCs) and compared results of the KC approach to evaluation of complete toxicology datasets for various chemicals using systematic evidence-based evaluation methods. The critique and comparisons revealed the KC approach is bereft of scientific integrity and should be abandoned. A manuscript summarizing the critique is in preparation and will include the results of this Case Study.

This Case Study briefly summarizes the critique of the KC approach, but focuses on improvements to the traditional methodologies that might obviate remaining criticisms that they are too resource-intensive to be a mainstay of regulatory assessments.

- 3. Comment on whether the method is general enough to be used directly, or if it can be extrapolated, for application to other chemicals and/or problem formulations. Please explain why or why not.**

The systematic methods advocated in this case study are broadly applicable as evidenced by peer-reviewed publications employing them to evaluate many different types of chemicals and categories of toxicity.

- 4. Discuss the overall strengths and weaknesses of the method.**

The strengths of the systematic methods are in their internal consistency, external consistency, transparency, replicability, and falsifiability. Their weakness is that they are resource-intensive; they require not only subject-matter expertise but dozens, or even hundreds, of man-hours to identify and extract a comprehensive set of relevant data, evaluate the data, and complete the interpretation.

The strength of the KC approach is that it is rapid, fungible to meet different objectives, and requires nothing more than a literature search. Its weaknesses have been stated above: it fails formal rules of logic and lacks internal consistency, external consistency, transparency, replicability, and falsifiability.

- 5. Outline the minimum data requirements and describe the types of data sets that are needed.**

Systematic evaluation methods for hazard identification do not have codified “minimum data requirements,” as these are hypothesis-dependent. For example, minimum data requirements would differ for the hypothesis that a chemical is an estrogen agonist versus the hypothesis that it affects steroidogenesis due to relative reliability of the assays used to test those hypotheses. Data availability, data quality, and the strength and consistency of the extant data affect the level of uncertainty that attends any interpretation.

Does your case study:

A. Describe the dose-response relationship in the dose range relevant to human exposure?

Both evidence-based MoA and WoE frameworks evaluate data according to their dose-response relevance. Both incorporate a consideration of whether effects are dose-relevant due to potentially causal mechanisms versus those unlikely to be causal due to the high-dose-dependency of the mechanism(s).

B. Address human variability and sensitive populations?

The methods belong to the category of hazard-evaluation / hazard characterization and do not explicitly evaluate human variability and sensitive subpopulations. These methods provide a means of evaluating whether a chemical could produce a particular type of toxicity and if so, under what conditions. Those conditions can then be compared with known ranges of human susceptibility.

C. Address background exposures or responses?

Not applicable.

D. Address incorporation of existing biological understanding of the likely mode of action?

Yes; both methods are primarily focused on mechanisms.

E. Address other extrapolations, if relevant – insufficient data, including duration extrapolations, interspecies extrapolation?

Not applicable.

F. Address uncertainty?

Both methods address uncertainties in the form of confidence scores or data gaps.

G. Allow the calculation of risk (probability of response for the endpoint of interest) in the exposed human population?

Risk per se is not addressed, but both methods attempt up/down inferences regarding human relevance of the effects.

H. Work practically? If the method still requires development, how close is it to practical implementation?

The Hypothesis-Driven WoE approach (Borgert et al., 2011; 2014) has been applied in several peer-reviewed publications (Borgert, 2025; Borgert & Burgoon, 2025; Borgert, 2023; de Peyster & Mihaich, 2014; Mihaich & Borgert, 2018; Mihaich et al., 2017). The Evidence-Based Mode of Action Framework (Becker et al., 2025) is based on previously published work that has been applied in numerous publications (Becker et al. 2017; Budinsky et al. 2014; Cohen et al. 2006; 2009; Dellarco et al. 2006; Elcombe et al. 2014; Ellis-Hutchings et al. 2014; Klaunig et al. 2012; McGregor et al. 2006; Meek et al. 2003; 2014; Seed et al. 2005; Thompson et al. 2011; Yamada et al. 2009; Yoshida et al. 2021)

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