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Quantitative weight of evidence to assess confidence in potential modes of action

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ABSTRACT

The evolved World Health Organization/International Programme on Chemical Safety mode of action (MOA) framework provides a structure for evaluating evidence in pathways of causally linked key events (KE) leading to adverse health effects. Although employed globally, variability in use of the MOA framework has led to different interpretations of the sufficiency of evidence in support of hypothesized MOAs. A proof of concept extension of the MOA framework is proposed for scoring confidence in the supporting data to improve scientific justification for MOA use in characterizing hazards and selecting dose-response extrapolation methods for specific chemicals. This involves selecting hypothesized MOAs, and then, for each MOA, scoring the weight of evidence (WOE) in support of causality for each KE using evolved Bradford Hill causal considerations (biological plausibility, essentiality, dose-response concordance, consistency, and analogy). This early proof of concept method is demonstrated by comparing two potential MOAs (mutagenicity and peroxisome proliferator activated receptor-alpha) for clofibrate, a rodent liver carcinogen. Quantitative confidence scoring of hypothesized MOAs is shown to be useful in characterizing the likely operative MOA. To guide method refinement and future confidence scoring for a spectrum of MOAs, areas warranting further focus and lessons learned, including the need to incorporate a narrative discussion of the weights used in the evaluation and an overall evaluation of the plausibility of the outcome, are presented.

1. Introduction

Since its introduction in 2001, the mode of action (MOA) and human relevance framework (hereafter referred to as the MOA framework) has proved to be a useful tool for organizing and evaluating data to inform human health risk assessments of chemical exposures (Sonich-Mullin et al., 2001; USEPA, 2001; USEPA, 2005a,b; Boobis et al., 2006; Boobis et al., 2008; Carmichael et al., 2011; Meek et al., 2014a; Elcombe et al., 2014; Budinsky et al., 2014; Corton et al., 2014). The MOA framework is an analytical approach to evaluate the weight of evidence (WOE) in support of a postulated MOA. Table 1 presents a number of the

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Table 1
MOA analysis: common terms and definitions.

Adverse Outcome or Adverse Effect: A change in morphology, physiology, growth, development, reproduction, or life span of a cell or organism, system, or (sub) population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences (Ankley et al., 2010; Keller et al., 2012).

Adverse Outcome Pathway (AOP): The AOP describes a specific biological pathway (that any number of chemicals may act through), which, when perturbed sufficiently, leads to a specific adverse outcome. The AOP construct includes chemical agnostic key events in a sequence that starts with the molecular initiating event and proceeds through a series of higher order biological events leading to the adverse outcome of interest to risk assessment (see for example Becker et al., 2015; OECD, 2016). Understanding of an AOP emanates from the amassed knowledge of one or more stressors inducing disease processes.

Key Event (KE): An empirically observable, reproducible step (which may be measured directly or indirectly, or reasonably inferred based on knowledge of the pathogenesis of the adverse effect) which is a necessary element of the MOA and critical to the outcome (i.e., necessary, but not necessarily sufficient in its own right) (see for example Meek et al., 2014a,b).

Key Event Relationship (KER): A scientifically-based relationship that connects one KE to another, defines a direct relationship between the two (i.e., identifies one as upstream and the other as downstream), and facilitates inference or extrapolation of the state of the downstream KE from the known, measured, or predicted state of the upstream KE (OECD, 2016).

Mode of Action (MOA): A biologically plausible series of chemical-specific KEs starting with exposure and proceeding through the interaction of an agent within a cell, subsequent physiological and tissue or organ changes, resulting in an adverse effect or outcome (Sonich-Mullin et al., 2001; Dellarco and Fenner-Crisp, 2012). An MOA analysis involves evaluation of the extent to which available evidence indicates that the specific chemical acts via a biological pathway to cause an adverse outcome. Note: in contrast, "mechanism of action" would describe the detailed biochemical and molecular interactions and responses of every step. Therefore, the KE in MOA analysis must be sufficient "to draw a reasonable working conclusion of the agent's influence on key processes without having to establish the sequence of molecular processes in detail" (Dellarco and Fenner-Crisp, 2012). In the early quantitative confidence scoring method proof of concept presented herein, the likely operative MOA is defined as the MOA for which supporting evidence is greatest.

Molecular Initiating Event (MIE): A specialized type of KE that represents the initial point of chemical interaction on the molecular level within the organism that results in a perturbation that starts the chemical-specific MOA (adapted from OECD, 2016). Whether it leads to an adverse effect depends on sufficient perturbation and on other ensuing biological processes.

Weight of Evidence (WOE): An approach for integrating relevant and reliable information and data from mechanistic research, animal toxicity studies and human epidemiological investigations to arrive at a conclusion pertinent to causation (NRC, 2014; Linkov et al., 2009). Rhomberg et al. (2013), in a survey of best practices, note that the four phases of WOE analysis encompass "(1) defining the causal question and developing criteria for study selection, (2) developing and applying criteria for review of individual studies, (3) evaluating and integrating evidence, and (4) drawing conclusions based on inferences." Similarly ANSES (2015) has issued guidance on distinguishing stages of primary study review and evaluation, weighting and integration of different types of data.

fundamental terms and definitions of the critical elements of the MOA framework. The MOA framework has been widely adopted in regulatory guidance and hazard characterizations/risk assessments around the world, including those of the European Food Safety Authority (EFSA), the Joint Food and Agriculture Organization (FAO)/WHO Meeting on Pesticide Residues (JMPR), the European Chemicals Agency (ECHA), and the United States Environmental Protection Agency (USEPA). This framework has evolved and advanced largely due to improved understanding of biological pathways/disease processes and experience in applying causality criteria to evaluate different lines of scientific evidence. The MOA framework has been extended to enable the holistic integration of evidence at multiple levels of biological organization, and the evaluation for species concordance of effects in the context of environmental levels of exposure (Meek et al., 2014a,b).

While the MOA framework continues to evolve as a basis to increase transparency and defensibility of decisions, explicit and systematic analysis of the WOE supporting postulated MOAs is at times lacking. There is also noticeable variation in the application of the MOA framework within and across users, often leading to different interpretations of the sufficiency of scientific evidence to support a given MOA and conclusions regarding relative support for alternative MOAs (Dourson et al., 2013). The scientific justification for assessing human relevance and selecting dose-response extrapolation methods for quantifying risks at environmentally relevant levels of exposure is highly dependent upon the determination of the likely operative MOA. For example, USEPA's Cancer Guidelines (USEPA, 2005b) invoke a linear extrapolation approach when there is indication of a mutagenic MOA and as a default option "in the absence of sufficiently, scientifically justifiable mode of action information." Thus, to enhance documentation and demonstration of "sufficiently, scientifically justifiable mode of action information" there is a pressing need to improve the approaches for conducting comparative quantitative WOE evaluations to aid in identifying the likely operative MOA, particularly for carcinogens where quantitation of cancer risks is a key factor underpinning many risk management actions. Hence, as an initial proof of concept, we have extended the MOA framework by proposing an approach for evaluating the supporting data for potential MOAs that enables quantitative scoring of the confidence in each. The method is illustrated by analyzing the dataset of clofibrate, a rodent liver carcinogen, and comparing confidence scores for two postulated MOAs: mutagenic and peroxisome proliferator activated receptor-alpha (PPARα) agonism.

2. Quantitative comparative confidence scoring methodology

A MOA framework analysis presupposes that the WOE for an adverse effect in experimental animals has been evaluated and deemed sufficient as a basis for delineation of the critical effect (Boobis et al., 2006). After such a determination, potential MOAs are postulated to describe how the chemical exposure and adverse effect may be biologically linked, and the relative WOE and scientific confidence in the supporting mechanistic data for these hypothesized MOAs is compared (Meek et al., 2014a,b; Borgert et al., 2015). This qualitative analysis in support of a MOA involves two stages: (1) scoping of potential MOAs; and (2) consideration of qualitative comparative WOE of the supporting data. Our method, which is the focus of this paper, adds quantitative WOE confidence scoring as a third stage. This third stage has been organized into eight discrete steps which are presented in Table 2 and discussed in greater detail in the following sections. This quantitative approach builds on the qualitative assessment step by scoring the evolved Bradford Hill causal considerations relied upon in the qualitative evidence integration and evaluation (Meek et al., 2014a,b; OECD, 2016; Becker et al., 2015). This quantitative scoring facilitates identification of the more likely operative (i.e., best supported) MOA therein informing the appropriate methodology for dose-response analysis to estimate potential human risks at environmental levels of exposure and/or assessing human relevance. In addition, the approach provides for a transparent and explicit delineation of science judgment versus science policy approaches based on the selection of higher or lower confidence options. An established MOA or AOP, while desirable, is not necessarily a requirement; the methodology proposed here can also be applied early in the AOP/MOA development process as a basis to identify