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AOPs in hazard characterization for human health

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Abstract

Mode of Action (MOA) and Adverse Outcome Pathways (AOP) are conceptually similar constructs which organize mechanistic knowledge at a range of levels of biological organization. These constructs have been proposed as a basis to facilitate the integration and evaluation of mechanistic data for regulatory application. AOPs address chemically agnostic biological pathways from the molecular initiating event to adverse outcome. MOA analysis for specific chemicals includes consideration additionally of chemical space, metabolism and toxicokinetics.

The AOP provides a convenient organizational construct as one element of broader strategies to advance more efficient and predictive integrated testing and assessment approaches. It is anticipated to increase focus on earlier key events (often measured in vitro or in non-test methods) at lower levels of biological organization by relating them to traditionally measured endpoints. Development of AOPs in an OECD program with formalized descriptions being assimilated in a publically accessible electronic knowledge base is anticipated to contribute to this advancement. These descriptions which include structured consideration of supporting qualitative weight of evidence and associated quantitation are anticipated to increase transparency in the extent of supporting data as a basis to consider potential regulatory application. A range of applications is envisaged, such as mode of action analysis and integrated assessment and testing strategies. Experience currently in application in hazard assessment for human health relates principally to priority setting for testing, due in part, to gaps in biological knowledge, lack of quantitation for dose response modelling and the need for additional development and acceptance of quantitative in vitro to in vivo extrapolation models.

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Keywords

Mode of action, Adverse outcome pathways, Key event, Key event relationship, Weight of evidence, Quantitation.

Abbreviations

AO, adverse outcome; AOP, adverse outcome pathway; AOP-KB, adverse outcome pathway knowledge base; B/H, Bradford-Hill; EAGMST, OECD Extended Advisory Group on Molecular Screening and Toxicogenomics; HTT, high-throughput toxicity testing; IATA, integrated approaches to testing and assessment; KE, key event; KER, key event relationship; KE up, upstream key event; MIE, molecular initiating event; MOA, mode of action; OECD, Organisation for Economic Co-operation and Development; PBPK, physiologically based pharmacokinetic models; QSAR, quantitative structure activity relationship; WHO/IPCS, World Health Organization International Programme on Chemical Safety; WOE, weight of evidence.

1. Introduction

The potential of mechanistic data to contribute to reducing uncertainty and increasing predictive capacity of toxicity testing in hazard characterization has long been recognized. In spite of this long standing knowledge, gains in the extent of its impact on regulatory decisions have been relatively modest, despite continuing advancement also in its systematic consideration. Limited progress to date relates in part, to the continued reliance on guideline studies designed principally to identify hazard in experimental animals at high doses.

Recent developments provide stimulus, however, to expedite the assimilation, development and application of mechanistic toxicological data as a basis to tailor more efficient and predictive testing strategies in the short term. In the longer term, the potential transition of toxicity testing from a largely empirical science based on direct observation of apical outcomes in animals to a more predictive one in which outcomes and risk are inferred from accumulated mechanistic understanding is envisaged [1]. This is necessitated in part, by the introduction and evolution of regulatory mandates internationally, within Europe, North America and the Asian Pacific Region. These mandates require the systematic consideration of priorities for assessment and management from amongst thousands of unassessed existing chemicals (see, for example [2–5]). Concomitant advances in technology to measure effects at lower levels of biological organization in high throughput technologies provide additional incentive and means to transition toxicological testing. Prerequisites for such transition include not only the development of data and novel methodologies in hazard assessment but early and continuing coordination among a range of relevant communities (in particular, the regulatory and research communities).

Adverse Outcome Pathways (AOP) are anticipated to contribute to this evolution by organizing mechanistic knowledge at a range of levels of biological organization

to facilitate its compilation, integration and evaluation for research and regulatory application. International initiatives on AOPs draw upon evolved experience on the conceptually similar construct of Mode of Action (MOA) but refocus emphasis on molecular initiating and earlier key events in chemically agnostic biological pathways leading to adverse outcomes of current regulatory significance.

2. Mode of action and adverse outcome pathways

Both mode of action and adverse outcome pathways are based on the premise that any (adverse) health effect caused by exposure to an exogenous substance can be described by a series of causally linked key events at various levels of biological organization (i.e., steps leading to an often adverse effect) [6,7]. And while simply conceptualized and illustrated as a linear series of key events, in reality both represent interdependent networks of events with feedback loops in which disease outcomes are initiated or modified [8,9].

Reference to "key" events in MOA/AOP relates to the envisaged importance of measured changes to impact in a regulatory context. Essentially, the objective is to identify the most important steps in a plausibly hypothesized pathway leading to adverse outcome, at a sufficient level of biological organization, relevant to regulatory application. By definition, key events need to be measurable and reproducible. Mechanism, in contrast, involves a much more detailed molecular description of causality. This distinction serves as an important basis to promote tailoring of mechanistic research to meaningfully inform hazard characterization in a regulatory context.

Frameworks for the systematic consideration of the weight of supporting evidence for mode of action in animals and subsequently, relevance to humans have been developed. These frameworks, which take into account both qualitative and quantitative differences between experimental animals and humans have been adopted in international and national guidance and assessments [10–15]. A recent update of the WHO/IPCS MOA human relevance or species concordance framework addresses the implications of developments in toxicity testing and non-testing methods. It includes a roadmap for the refinement of fit-for-purpose mechanistically based testing strategies and risk assessment, including integration of key events at lower levels of biological organization with the measured late-stage cellular, biochemical and tissue changes determined in traditional toxicity guideline studies [8].

Concomitantly with progression of concepts in the assessment and application of MOA for specific chemicals in human health assessment, the Adverse Outcome Pathway (AOP) emerged from the field of ecotoxicology for predicting effects of chemical exposure in wildlife populations [7]. Consistent with the focus of QSAR modelling in ecotoxicology, molecular initiating events were an important focus. AOPs are conceptualized, then, as a subset of measurable KEs originating from a molecular initiating event (MIE) (e.g., binding to a receptor) in a target tissue resulting in cellular, structural and functional changes and ultimately, adverse outcomes (AOs) in organisms and populations [9].

Key event relationships (KERs) (i.e., defining the structural and functional relationship between a pair of KEs) are also a critical focus of AOPs, representing their largely predictive element. KERs facilitate inference or extrapolation based on the premise that if the upstream KE is altered to a sufficient degree, predictable changes (qualitative or quantitative) can be expected in the downstream event in the hypothesized AOP [16].

Consistent with the origin of the term, AOPs reference taxonomic relevance (to encompass the range of species considered in eco toxicological assessment). The corollary for mode of action is human relevance or species concordance analysis. The former is commonly assessed based on the level of conservation of the various key events and their underlying molecular components and functionality across the levels of biologic organization and overall phylogenetic diversity. The latter (human relevance) is most often considered on the basis of known disease process in humans.

AOPs have also evolved to be considered chemically agnostic, being confined to the biological cascade of events following interaction with a molecular target. They are often developed and documented based on supporting information that includes challenge by reference chemicals. However, AOPs draw collectively upon such data solely as a basis to define biological pathways rather than the assessment of individual (e.g., chemical) stressors [17].

AOP contrasts, then with MOA, the latter traditionally being established for individual chemicals (or groups), taking into account chemical (or group) specific metabolism as a key event and toxicokinetics in considering human relevance and or species concordance (Fig. 1). MOAs can be considered, then, as being established for individual chemicals (or groups) within a finite universe of chemically agnostic toxicodynamic pathways (i.e., AOPs). The latter is confined to characterizing the key events in a biological progression of disease from the MIE to adverse outcome.

The terms MOA and AOP are, then, conceptually similar, representing essentially the subdivision of the pathway between exposure and effect in either individuals or populations into a series of hypothesized