Molecular Initiating Events (MIEs) in Adverse Outcome Pathways (AOPs) – The Chemistry Perspective

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Consumer and environmental safety decisions are based on exposure and hazard data interpreted using risk assessment approaches. The Adverse Outcome Pathway (AOP) conceptual framework [1] has been presented as a logical sequence of events or processes within biological systems which can be used to understand adverse effects and refine the current risk assessment practice. Although originally described as an approach to ecotoxicology risk assessment, this has now been extended into the human safety area. The AOP shifts the risk assessment focus from traditional toxicological apical endpoints to the development of increased mechanistic understanding of a chemical’s interactions and effects at a molecular level.

Within the AOP framework the molecular initiating event (MIE) is defined as the first point of chemical-biological interaction within an organism which starts the adverse outcome pathway. Fundamentally MIEs can be considered as molecular interactions occurring in a dynamic and complex matrix system. The properties of the matrix will strongly influence the kinetics of the reaction and the mechanisms involved through variations in pH, lipophilicity, protein content etc. These interactions will in turn define the qualitative and quantitative aspects of the MIE along with the biokinetic and biodynamic profile of a chemical.

Identification of key MIEs can be approached from either an exposure or chemical driven approach or via a chemical’s biological effect. For the former, predictive chemistry techniques including quantitative structural activity relationships (QSARs) can be developed based on existing data and through mapping networks of chemicals, MIE’s and subsequent pathways. To develop a retrospective response based approach, in-vitro assays can be used to provide a biological signature for a chemical. This data can be used to inform a risk assessment both from a hazard perspective and also to provide additional evidence for read-across to toxicologically similar chemicals of established pathways.

To obtain this level of detail in a pathway, chemistry in all its disciplines has a key role to play. Measurement techniques will be important in understanding chemical characterisation, free concentration and exposure at the site of interest. Such measurements will be vital in developing structure based toxicological alerts and informing predictive models. A thorough understanding of the physical chemistry will inform the mechanisms involved and help identify those key experimental or predicted values required to build a model.