Developing and applying the adverse outcome pathway concept for understanding and predicting neurotoxicity

Abstract:
To support a paradigm shift in regulatory toxicology testing and risk assessment, the Adverse Outcome Pathway (AOP) concept has recently been proposed. This concept is similar to that for Mode of Action (MOA), describing a sequence of measurable key events triggered by a molecular initiating event in which a stressor interacts with a biological target. The resulting cascade of key events includes molecular, cellular, structural and functional changes in biological systems, resulting in a measurable adverse outcome. Thereby, an AOP ideally provides information relevant to chemical structure-activity relationships as a basis to predict effects for structurally similar compounds. AOPs could potentially also form the basis for qualitative and quantitative predictive modeling of the human adverse outcome resulting from molecular initiating or other key events for which higher-throughput testing methods are available or can be developed. A variety of cellular and molecular processes are known to be critical to normal function of the central (CNS) and peripheral nervous systems (PNS). Because of the biological and functional complexity of the CNS and PNS, it has been challenging to establish causative links and quantitative relationships between key events that comprise the pathways leading from chemical exposure to an adverse outcome in the nervous system. Following introduction of principles of the description and assessment of MOA and AOPs, examples of adverse outcome pathways specific for developmental or adult neurotoxicity are summarized and assessed. Their possible application in developing mechanistically informed Integrated Approaches to Testing and Assessment (IATA) is also discussed.

URI:
http://dx.doi.org/10.1016/j.neuro.2016.05.010 [1]

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Publication Year: