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EDITORIAL

Adverse outcome pathways

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Recently, Leist et al. (2017) have contributed a comprehensive article about adverse outcome pathways (AOP) to our journal. In recent years, the AOP concept has attracted some attention in the field of toxicology (Vinken et al. 2017; Ankley et al. 2010). An AOP is defined as a sequence of events that begins with a molecular initiating event, progressed through a series of key events to finally lead to an adverse outcome (Leist et al. 2017). Given this definition one may be surprised why some regulators consider the AOP concept a new toxicological construct, because toxicologists have known since decades that it is important to identify initial molecular events and mechanisms that finally cause an adverse effect. The current terminology used by scientists in the field of AOPs may be new but not the concept. Nevertheless, it is out of question that a careful consideration of all mechanisms from first molecular interactions to adverse outcomes is of high importance. A strength of the current article of Leist and colleagues is that it critically discusses also the limitations and open questions of the current AOP concept. From my point of view, the following aspects are particularly relevant:

- Leist and colleagues questioned, whether it is useful to exclude metabolism and compound distribution from pharmacodynamics. This criticism is certainly justified, since metabolism is not only relevant before a molecular initiating event occurs.
- Moreover, it is questioned whether the current unidirectionality and linearity assumptions are justified. Currently, AOPs have to be presented as a unidirectional chain of events (Leist et al. 2017). However, a mechanism of toxicity may include positive feedback loops. The authors present the example of vinyl acetate that forms two metabolites, one that may cause cytotoxicity and a second metabolite that induces DNA–protein adducts. Both events synergize. It is difficult to present such complex mechanisms in a linear AOP.
- Often effect duration is critical, for example in case of lifer fibrosis. The current concept has to be optimized to include this aspect.

The article highlights that the AOP concept will support the further development of in vitro systems. Currently, large research projects focus on establishing alternative methods for skin toxicity (Natsch and Emter 2015; Golka 2015; Jaworska et al. 2015; Sonnenburg et al. 2015), nephrotoxicity (Jennings et al. 2015; Aschauer et al. 2015a, b; Vedula et al. 2017; Choi et al. 2016; Leclerc et al. 2016; Carneiro et al. 2015), hepatotoxicity (Hammad et al. 2016; Godoy and Aranda 2015, 2016; Deharde et al. 2016; Gómez-Lechón and Tolosa 2016; Grinberg et al. 2014) and toxicity of further organs and cell types. A strength of systematically established AOPs is that they can clearly indicate which specific key event or even molecular initiating event is detected by a certain readout of an in vitro system.

It will be exciting to see how the present review will influence the work on the AOP platform and whether it will help to overcome the discussed shortcomings.

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