Optimization of an adverse outcome pathway network on chemical-induced cholestasis using an artificial intelligence-assisted data collection

Commonly used acronym: *AOP*

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Organisation

Name of the organisation Vrije Universiteit Brussel (VUB)

Department In Vitro Toxicology and Dermato-Cosmetology

Specific Research Group or Service In Vitro Toxicology and Dermato-Cosmetology

Country Belgium

SCOPE OF THE METHOD

The Method relates to	Human health
The Method is situated in	Translational - Applied Research
Type of method	Other: Adverse Outcome Pathways (AOPs)

DESCRIPTION

Method keywords

AOP network

Adverse outcome pathway

Shiny application

artificial intelligence

weight-of-evidence assessment

key events

Data Collection

Scientific area keywords

cholestasis
Mechanistic toxicology
risk assessment
chemical
Drug-induced liver injury (DILI)
Hepatotoxicity

Method description

Adverse outcome pathway (AOP) networks are versatile tools in toxicology and risk assessment that capture and visualize mechanisms driving toxicity originating from various data sources. They share a common structure consisting of a set of molecular initiating events and key events, connected by key event relationships, leading to the actual adverse outcome. AOP networks are to be considered living documents that should be frequently updated by feeding in new data. Such iterative optimization exercises are typically done manually, which not only is a time-consuming effort, but also bears the risk of overlooking critical data. The present study introduces a novel approach for AOP network optimization of a previously published AOP network on chemical-induced cholestasis using artificial intelligence to facilitate automated data collection followed by subsequent quantitative confidence assessment of molecular initiating events, key events, and key event relationships. Artificial intelligence-assisted data collection was performed by means of the free web platform Sysrev. The optimized AOP network was visualized using Cytoscape with the node size representing the incidence of the key event and the edge size indicating the total confidence in the key event relationship. This resulted in the identification of 38 and 135 unique key events and key event relationships, respectively. Transporter changes was the key event with the highest incidence, and formed the most confident key event relationship with the adverse outcome, cholestasis. This process led to the creation of an extensively informative AOP network focused on chemical-induced cholestasis. This optimized AOP network may serve as a mechanistic compass for the development of a battery of *in vitro* assays to reliably predict chemical-induced cholestatic injury.

Lab equipment

- Access to the free web platform Sysrev,
- Cytoscap.

Method status

Published in peer reviewed journal

PROS, CONS & FUTURE POTENTIAL

Advantages

The optimized and fully assessed AOP network resulting from the present study provides an important contribution to this goal, and will thus assist in delivering safer chemicals, including pharmaceutical drugs, while using fewer animals.

Challenges

The AOP network optimized in the present study is in the first instance being used as the conceptual mechanistic basis for setting up a battery of *in vitro* assays to predict cholestatic liver injury induced by chemical compounds from various applicability domains. In fact, this is embedded in a 2-tiered testing approach, whereby first tier testing relies on measuring transcriptional changes indicative of cholestatic liver injury. Unlike other types of hepatotoxicity, such transcriptional signature for chemical-induced cholestatic liver insult does not have sufficient predictive value on its own, and hence cannot be used as a stand-alone method.

Modifications

Predictive power can be considerably increased when following up with second tier testing by applying a battery of *in vitro* assays mechanistically anchored in the AOP network, in which each assay monitors a selected MIE and KE individually at the translational level, but preferably at the activity level.

REFERENCES, ASSOCIATED DOCUMENTS AND OTHER INFORMATION

Links

Optimization of an adverse outcome pathway network on chemical-induced cholesta...

Other remarks

This work was performed in the context of the ONTOX project (https://ontox-project.eu/) supported by the European Commission under the Horizon2020 Research and Innovation Framework program (grant number 963845 “ONTOX”).