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Introducing WikiPathways to link molecular pathways to Adverse Outcome Pathways

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Objective

Our research question is: **How can Adverse Outcome Pathways be supported by molecular pathway knowledge (to allow the use of omics approaches)?**

Background

Adverse Outcome Pathway concept

The Adverse Outcome Pathway (AOP) has become a useful tool to support regulatory decision making for chemical compounds. AOPs provide a mechanistic representation of toxicological effects, from the initial molecular interaction of a chemical towards an adverse outcome on a biological level relevant for risk assessment (Figure 1A). This will lead to more rapid and cost-effective, high-throughput methods to aid regulatory risk assessment and serving as a basis for generating integrated approaches to testing and assessment [1,2]. To guide the increasing development and use of AOPs, the OECD, JRC and US EPA together launched the AOP knowledge base (Figure 1B) [2,3].

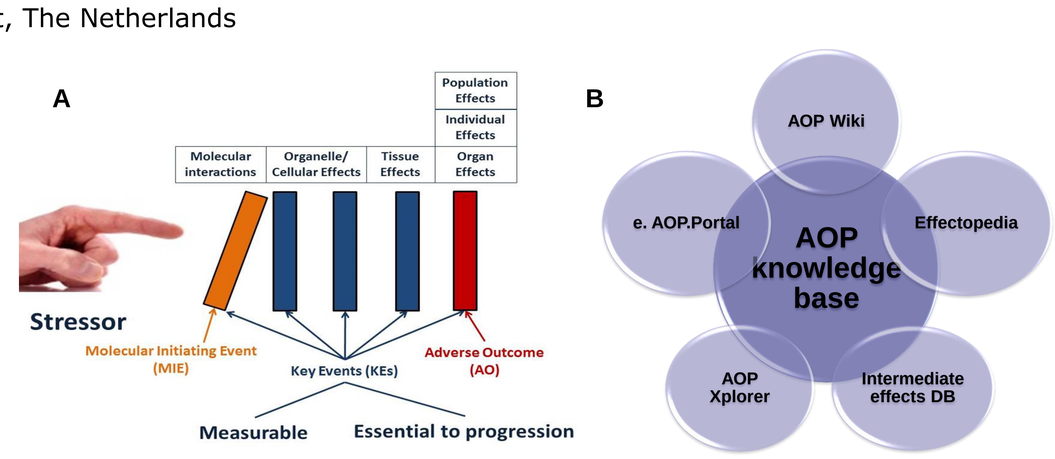

Figure 1: Graphical representation of the Adverse Outcome Pathway concept (A) and the modules of the AOP knowledge base (B).

Omics data

Over the last decade, omics approaches such as transcriptomics, metabolomics and proteomics have been used in experimental toxicology for characterization of adverse effects and mechanistic analysis. However, for omics approaches to become a useful tool for regulatory purposes, there is an ongoing debate about several issues related to the integration of omics approaches in AOPs, such as the source of variation in omics data is mainly due to inconsistencies in bioinformatic analyses [4,5,6].

Results

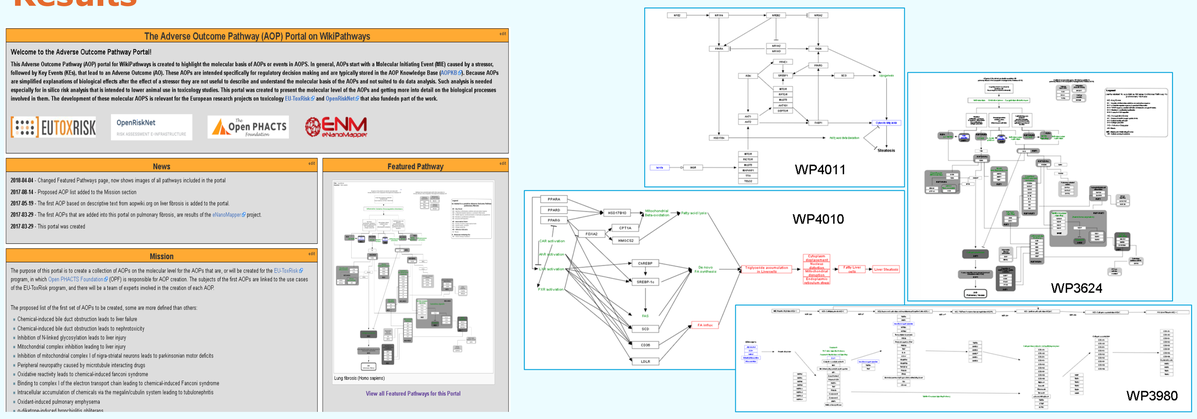

Figure 2: The Adverse Outcome Pathway portal on WikiPathways.org (left). This portal has a growing collection of AOPs, currently in various designs and amount of content (right).

Entity	Amount in WikiPathways
Adverse Outcome Pathways	15
Key Events	110
Genes/proteins/metabolites	340
Linked WikiPathways	42

Table 1: Current statistics of contents in the Adverse Outcome Pathway portal on WikiPathways.org

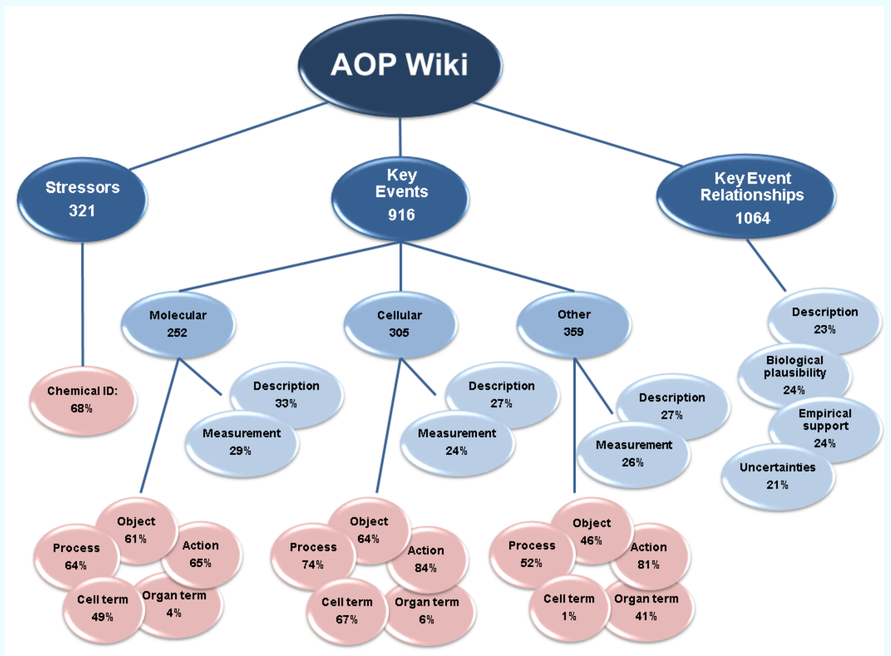

Figure 3: AOP Wiki statistics tree. Pink nodes indicate elements of predefined vocabularies or identifiers.

Currently, **77%** of the Cellular and Molecular Key Events of AOP Wiki are present as molecular pathway on WikiPathways, based on a random selection of 30 AOP Wiki Key Events.

Conclusion

Most of the molecular and cellular Key Events, and the Key Event Relationships that connect these, on AOP Wiki describe molecular pathways by free-text that are already present on WikiPathways.org or as part of it. Clear descriptions of the Key Events with correct use of ontologies are required to allow linking the Key Events and Key Event Relationships to the molecular pathways and for WikiPathways to become a supportive database for AOPs and assisting in the implementation of omics approaches in regulatory risk assessment. Future work will need to focus on linking AOP Wiki Key Events with their corresponding molecular pathways and entities by improving the ontology annotations, linking these to the Pathway Ontology used in WikiPathways and introducing link-outs on the AOP Wiki.

References

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