Ontology-based Semantic Mapping of Adverse Outcome Pathways

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Abstract

Most of the nearly 85,000 chemicals currently listed in the US TSCA (Toxic Substances Control Act) inventory are not characterized toxicologically. A paradigm shift has been well underway to move away from animal toxicity tests, and towards more resource-efficient in vitro, in silico, and short-term in vivo screenings. As such, there is a great need to link toxicity phenotypes at molecular levels to those with greater regulatory relevance at higher levels of biological organization. The framework of adverse outcome pathway (AOP) was proposed to address this need (1), and has been increasingly adopted in recent years to organize toxicity information along such a biological hierarchy. Many AOPs, each consisting of a molecular initiating event, several key events, and an adverse outcome, have been developed (https://aopwiki.org/).

With abundant phenotypic data from ongoing public phenomics efforts and years of toxicity studies, ontology-based semantic mapping (OS-Mapping) offers a promising approach to bridge the gaps between molecular phenotypes and traditional endpoints provided by animal tests. To study the applications of OS-Mapping in evaluating existing AOPs and aiding their future development, over 1100 key events belonging to more than 200 AOPs were annotated by using entity-quality (EQ) statements. Also included in the study were toxicity responses previously annotated from more than 700 exposure studies of ten chemicals in six vertebrate species (2). Together, they were assembled into over 200 phenotypic profiles as queries, and compared semantically to more than 37 thousand phenotypic profiles organized by genes, diseases, and biological pathways (KEGG, Kyoto Encyclopedia of Genes and Genomes, https://www.genome.jp/kegg/; Reactome, https://reactome.org/) of human, mouse, and zebrafish. The Java application for semantic analysis was developed in-house based on OWLAPI (version 4.2.5)(3), several publicly available reasoners, and the Semantic Measure Library (SML, version 0.9.4d)(4). The analyses proved to be insightful. For example, many AOPs appeared to be quite robust, as suggested by their respective key events having mutual similarities significantly above background. However, most of the key event pairs curated to be adjacent to each other (i.e., KE X upstream biologically leads to KE Y downstream) had similarities, ranging between zero and one, less than 0.2. Some of the key events from different AOPs were found to be highly similar to one another, leading to their hosting AOPs to become substantially related too. Many AOPs were also mapped to various genes, KEGG/Reactome pathways, and diseases. The findings like these will help to delineate the biology underlying these AOPs and provide some independent evidence for their robustness. Furthermore, semantic characterization of key events and AOPs will also provide an approach to construct AOP networks complementary to the current reliance on the manually defined key event relationships, and aid the future development of additional AOPs.

Keywords:

adverse outcome pathway, chemical toxicity, semantic analysis

References

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