Adverse outcome pathways coming to life

Impact

This chapter outlines the impact this thesis has on society. It outlines how this research is being picked up outside academia, and explains how which societal problems this work addresses.

Molecular plausibility of Adverse Outcome Pathways

The main problem that this thesis focused on was the currently limited implementation of transcriptomic data in risk assessments of chemicals and other toxicants, while it has proven potential in studying and understanding toxicological mechanisms. This is mainly due to the complexity of the data, its analysis and interpretation, and the lack of consensus and validation of producing and handling such data. Whereas the production and handling of the data have been addressed by the Organisation for Economic Co-operation and Development (OECD) in the past years resulting in an OECD reporting framework [1], the analysis and interpretation of such data remain unspecified and unformulated. This is why we introduced the molecular Adverse Outcome Pathways (AOPs) to provide a clear, simple method to perform transcriptomic data analysis that is directly aligned with AOPs, which have become an accepted framework of toxicological knowledge to support Integrated Approaches to Testing and Assessment (IATA) development. Additionally, the molecular AOPs can bridge the AOPs and molecular biological and toxicological studies, forming a graphical representation of complex biological systems. By integrating transcriptomic data into AOPs, researchers can better understand the potential adverse effects of exposure and identify early biomarkers of toxicity. This knowledge can inform regulatory decisions and ultimately lead to the development and use of safer chemicals and nanomaterials. Additionally, the integration of transcriptomic data into AOPs can facilitate collaborations among researchers from diverse fields, leading to more comprehensive and innovative approaches to toxicity assessment. Overall, extending AOPs with molecular entities through pathways and transcriptomic data can accelerate scientific progress and promote the protection of public health and the environment.

With the introduction of molecular AOPs in the WikiPathways database and showing their value in analysing transcriptomic datasets, the results of this thesis provide new and informative ways to analyse and interpret transcriptomic data. Case studies were performed on various AOPs involving mitochondrial dysfunction, liver steatosis, Pleural Mesothelioma (PM), liver cancer, and pulmonary fibrosis by multi-walled carbon nanotubes and by SARS-CoV-2 exposure, thyroid-related neurodevelopmental toxicity, and pharmacovigilance in kidneys. All of these case studies resulted in molecular AOP models, or drafts thereof, that are stored in the AOP Portal on WikiPathways (`aop.wikipathways.org`). This has shown us that not all toxicological pathways are fully understood yet and that in some cases, the approach to linking pathways to Key Events (KEs) requires additional refinement regarding directionality and differentiating between causal and consequential gene expression changes. While the approach of molecular AOP development is clarified in Chapter 7, we should aim to develop general guidelines for other researchers to engage in molecular AOP development, using them for data analysis of omics data, and compare with other methods of measuring KE activation. This would give us better insights into the validity and generalizability of using transcriptomic data to assess KE activation and generate hypotheses or inform IATA strategies.

While this thesis presents a method of connecting molecular pathways to AOPs to perform analyses of omics data, the process of generating these has its limitations and assumptions, as discussed in Chapter 7. To further explore methods of linking molecular entities to AOPs and their KEs, we have submitted a project proposal to the European Food Safety Authority (EFSA) to test various methods of (semi-)automatically annotating KEs with genes, proteins and molecular pathways. This proposal, which has been accepted, also involves comparing the approach of molecular AOPs with the more data-driven approach of the TXG-MAPr tool [2].

Reusable AOPs

The thesis also aimed to enhance the usability of AOP content through a Findable, Accessible, Interoperable, and Reusable (FAIR) approach in the AOP-Wiki. This was achieved by implementing the Resource Description Framework (RDF), improving accessibility and interoperability of the AOP-Wiki for seamless integration with other datasets and tools. We maintain a publicly accessible and regularly updated SPARQL endpoint to reflect the latest AOP-Wiki data release. Additionally, in collaboration with the United States Environmental Protection Agency (US EPA), we developed RDF for the AOP-DB as part of the OpenRiskNet implementation challenge. This expanded the available AOP-related content for exploration and integration. The AOP-Wiki RDF and SPARQL Protocol and RDF Query Language (SPARQL) endpoint are utilized in ongoing projects such as VHP4Safety and NanoSolveIT, where virtual infrastructures host the SPARQL endpoints for data integration and AOP-Wiki exploration. These resources are also utilized in the Partnership for the Assessment of Risks from Chemicals (PARC) (`eu-parc.eu`), a significant European partnership focused on chemical risk assessment for human and environmental protection.

While Chapters 3, 4, 5, and 6 describe, apply and utilize methods to make the contents of the AOP-Wiki more accessible and interoperable, there are other aspects of the AOP-Wiki that can be improved for increased FAIRness. With the release of the AOP-Wiki version 2.5 on July 16, 2022, the resource was made more structured and introduced direct links to third-party tools. This is also the case for the AOP-Wiki SNORQL User Interface (UI) and AOP-DB SPARQL endpoint described in Chapter 4 and 5, respectively. The majority of current efforts in the AOP-Wiki are aimed at complying with the FAIR principles and increasing data usability, and extensive analysis on the FAIRness of the AOP-Wiki is currently ongoing to explore how the underlying data model can be improved to comply with the FAIR principles. Additionally, the AOP-Wiki has started linking to Wiki Kaptis (`wikikaptis.lhasacloud.org`), a tool by the UK-based company Lhasa, from KE pages, which is also planned for the molecular pathways of WikiPathways based on the KE-pathway mapping performed for molecular AOPs.

An initiative that preceded this thesis project and focused on the future integration of tools, data and information on AOPs was the development of the AOP Ontology (AOPO) [3]. As its original implementation, the AOPXplorer utilizes the AOPO to visualize AOP networks, and it has been used for studying various AOPs including neurotoxicity [4] and hepatotoxicity [5], with a focus on gene expression data just like the molecular AOPs. However, the AOPO has not yet been implemented to annotate AOP-related content in the AOP-Wiki itself. Therefore, developing the AOP-Wiki RDF model (Chapter 4) also aimed to include the AOPO to annotate relationships within the data model. The chapter also highlighted the potential additions to the AOPO in order to cover the full domain of AOPs and related information, and work is ongoing to expand the AOPO for complete coverage of the AOP-Wiki data model. The alignment of resources with the AOP-Wiki and the direction of its development was also a result of our involvement with the AOP Knowledge Base (AOP-KB) development group, which manages the AOP-Wiki and future developments are discussed. This involvement also offered the opportunity to attend the AOP-KB face-to-face meeting in 2019 at the US EPA in Research Triangle Park, North Carolina, USA, to discuss approaches and share ideas for improving the AOP-Wiki contents and structure.

As is clear from this thesis and the previous paragraphs, the AOP-Wiki plays a central role in this thesis, which is a resource where researchers can collaborate and develop AOPs. Although there are centralized AOP development efforts pushed by the OECD AOP Development Programme work plan, most of the AOPs in the resource are developed by researchers across the globe, based on individual projects, or large consortia focusing on particular toxicities. We were involved in coordinating and pushing AOP development in EU-ToxRisk (`eu-toxrisk.eu`), leading to a public deliverable (`eu-toxrisk.eu/media/articles/files/EU-ToxRisk_D5.1_FINAL_R1.0.pdf`) and a total of twelve AOPs, of which the majority was entered into the AOP-Wiki, including AOPs on adverse effects on the brain, liver, kidneys, lungs and tissue development. These are currently available for AOP users to explore or refine further. These AOPs have the potential to establish AOP-informed IATAs for the risk assessment of a variety of chemicals. Besides our role in EU-ToxRisk, we were involved in the development of COVID-19 AOPs in the community-driven project called Modelling the Pathogenesis of COVID-19 Using the Adverse Outcome Pathway Framework (CIAO), which is described in a later section.

Overall, this thesis had a clear focus on making AOP-related content accessible, interoperable and therefore reusable, in line with the FAIR principles. By making AOP contents more FAIR, researchers, policymakers, and the public can better access and understand the potential risks associated with exposure to certain chemicals, substances, or nanomaterials. This increased accessibility and understanding can lead to more informed decision-making regarding the regulation and use of these substances, ultimately improving public health and safety. Additionally, making AOP content more FAIR can help promote transparency and accountability in the scientific community, leading to more trustworthy and reliable scientific research.

WikiPathways: community collaboration

As described in the section on molecular AOPs, the WikiPathways database served as the second main resource of this thesis, which is widely used in various biological research fields, as an information resource, an integration resource, and to perform analyses of omics datasets. As presented in Chapter 2, the focus of WikiPathways' current and future developments is on the involvement of user communities. This community-driven aspect of WikiPathways can have a significant societal impact by promoting open and collaborative knowledge-sharing in the field of biological pathways. By allowing researchers, educators, and the public to contribute to and access high-quality pathway information, WikiPathways helps to disseminate scientific knowledge and promote openness and responsibility in scientific research and knowledge sharing. This can lead to faster and more accurate scientific discoveries, improved education efforts, and ultimately, better health outcomes for individuals and communities. Additionally, the community-driven aspect of WikiPathways can help foster a sense of belonging and shared purpose among individuals interested in advancing the field of biology, leading to more robust and impactful collaborations. WikiPathways has also been utilized in the development of a literature-based molecular pathway of PM, a rare type of lung cancer (`wikipathways.org/instance/WP5087`) [6]. The development of this molecular pathway of PM allows researchers to analyse and interpret their data, and the pathway figure can serve as an educational resource for understanding the molecular aspects of the disease, and this will be extended with the development of a molecular AOP of asbestos leading to PM. This ultimately aids in the increased awareness of the biological complexity and causes of the disease and therefore, supports the research toward better diagnosis, prognosis and treatment.

One project that had a specific interest in making the AOP-Wiki more interoperable with other databases such as WikiPathways is the CIAO project (`ciao-covid.net`), consisting of a network of partners from industry, policymakers, clinicians, and academic institutes. This project focused on the development of AOP networks for COVID-19, and evaluating the AOP-Wiki data model through workshops and case studies regarding the data structure, annotation of its components, and overall FAIRness. During this project, a molecular AOP model was developed for ACE2 inhibition leading to pulmonary fibrosis, which was used to analyse transcriptomic data. This work was presented during the final workshop in February 2023.

In summary, WikiPathways played a key role in this thesis and related parallel projects, acting as a central hub that fosters collaboration between academia, research institutes, and industry, and facilitates the modeling of intricate molecular pathways. The pathways developed through WikiPathways offer valuable resources for analysing diverse datasets and interpreting the complexities of biology. Moreover, the utility of WikiPathways extends to the development of molecular AOPs, introducing an innovative approach to analyse transcriptomic data and evaluate KE activation through gene expression data. The integration of these molecular AOPs into risk assessments has the potential to enhance the practicality of transcriptomic data and, consequently, contribute to the promotion of human and environmental safety.

References

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