Concept Article
Why Adverse Outcome Pathways Need to be FAIR

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Abstract

Adverse outcome pathways (AOPs) provide evidence for demonstrating and assessing causality between measurable toxicological mechanisms and human or environmental adverse effects. AOPs have gained increasing attention over the past decade and are believed to provide the necessary steppingstone for more effective risk assessment of chemicals and materials and moving beyond the need for animal testing. However, as with all types of data and knowledge today, AOPs need to be reusable by machines, i.e., machine-actionable, in order to reach their full impact potential. Machine-actionability is supported by the FAIR principles, which guide findability, accessibility, interoperability, and reusability of data and knowledge. Here, we describe why AOPs need to be FAIR and touch on aspects such as the improved visibility and the increased trust that FAIRification of AOPs provides.

Plain language summary

New approach methodologies (NAMs) can detect biological phenomena that occur before they add up to serious problems like cancer, infertility, death, and others. NAMs detect key events (KE) along well-proven and agreed adverse outcome pathways (AOP). If a substance tests positive in a NAM for an upstream KE, this signals an early warning that actual adversity might follow. However, what if the knowledge about these AOPs is a well-kept secret? And what if decision-makers find AOPs too exotic to apply in risk assessment? This is where FAIR comes in! FAIR stands for making information findable, accessible, interoperable and re-useable. It aims to increase availability, usefulness, and trustworthiness of data. Here, we show that by interpreting the FAIR principles beyond a purely technical level, AOPs can ring in a new era of 3Rs applicability – by increasing their visibility and making their creation process more transparent and reproducible.

1 A need for FAIR AOPs

Science and consequently decision-making on both political and regulatory levels are moving towards an increasingly data- and knowledge-intensive future; a future strongly dependent on decision support provided by machines, from computational modelling to artificial intelligence (AI). However, machine-driven analytics requires structured data management in line with the FAIR principles, which guide implementation of social and technical solutions to make data findable, accessible, interoperable and re-usable by machines and their human users (Wilkinson et al., 2016; Schultes et al., 2022). In addition, the provenance of information provided by these decision-support tools is essential for use of that information in a regulatory setting.

Machine-driven solutions supporting policy and regulatory decision-making are best informed by real-time automation of information flow into databases connecting partner authorities with the most up-to-date scientific information. This applies also to regulatory toxicology, which encompasses the collection, processing, and evaluation of epidemiological as well as experimental toxicology data to permit toxicologically based decisions directed towards the protection of health against harmful effects of chemical substances. Adverse outcome pathways (AOP) are conceptual constructs that portray existing knowledge concerning the linkage between a molecular initiating event (MIE) and an adverse outcome (AO), via key events (KEs) at all biological levels of organization relevant to health risk assessment (Ankley et al., 2010).

AOPs are intended to provide the necessary evidence needed for assessing causality between experimental toxicological test measurements and human/environmental health effect-related processes that can easily be tested in laboratory settings, based on inference from mechanism-based, non-animal toxicity testing.

Tab. 1: The FAIR guiding principles (Wilkinson et al., 2016)
The principles show the relation of each principle to either content-related, domain-relevant standards and practices or to technical implementation as defined by Schultes et al. (2023). In this paper the focus lies on the content-related, domain-relevant principles.

Principle	Content-related, domain-relevant	Technical
Findable		
F1	Persistence of (meta)data identifiers	Globally unique identifiers
F2	Richness of metadata (see R1)	
F3		Metadata clearly and explicitly include data identifier
F4		(Meta)data registered or indexed in searchable resource
Accessible		
A1		Standardized communications protocol
A1.1		Open, free and universally implementable protocol
A1.2	Determine need for authentication to access data	Protocols to allow for authentication and authorization
A2	Metadata permanently accessible	
Interoperable		
I1		(Meta)data is represented by a formal, accessible, shared, and broadly applicable language for knowledge representation
I2	(Meta)data use vocabularies that follow FAIR principles	
I3	(Meta)data include qualified references	
Reusable		
R1	Rich description of accurate and relevant attributes	
R1.1	Clear and accessible data usage license	
R1.2	Detailed provenance associated with (meta)data	
R1.3	Follow domain-relevant community standards	

The AOP framework provides a systematic approach for organizing knowledge that could support such inference, and in the best case, support machine-driven prediction approaches (Edwards et al., 2015; Wittwehr et al., 2017).

While the term "adverse outcome pathway" is not trademarked, and in theory different flavors and variants of AOPs could exist, there is a clear mainstream AOP concept derived from Ankley et al. (2010). Any AOP following the principles laid out in the "*Users' Handbook*" (OECD, 2018) and adhering to the AOP-XML standard is covered by this paper. AOPs defined in this manner are championed by the Organisation for Economic Co-operation and Development (OECD) in support of the 3R principles (replacement, reduction and refinement of animal testing). As stated in the OECD (2021) "*Draft Guidance Document for the scientific review of Adverse Outcome Pathways*", the AOP concept is expected to guide decision-makers such as risk asses-

sors in their work to use existing and emerging information on the effects of chemicals on various test systems (e.g., *in silico*, *in vitro*, *in vivo*), and to target the generation of additional information needed for regulatory decision-making. Thus, a regulatory community more receptive to AOP knowledge is a prerequisite for the increased regulatory uptake of new approach methodologies (NAMs), which encompass non-animal-based alternative methods for hazard and risk assessment of chemicals. The AOP-Wiki[1] is the central information and communication technology (ICT) system in which AOP knowledge is collected, reviewed, stored, and disseminated. Keeping AOPs updated with the latest research is currently a manual approach that requires significant time and skills from AOP developers, both in terms of understanding the principles of AOP development (OECD, 2018) and the technical aspects of the AOP-Wiki itself. As a result, the strategies used to assemble AOP information and capture its prov-

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[1] https://aopwiki.org/

enance vary widely. This is a challenge for regulators when using the information to support decisions.

The community has identified a number of challenges for reaching the full impact potential of the AOP framework (Carusi et al., 2018). These include:

(i) a lack of incentives for AOP developers to deposit their data and knowledge with sufficient detail in the AOP-Wiki,
(ii) risks associated with the credibility of the AOPs,
(iii) uncertainty about the quality of AOPs,
(iv) a lack of understanding and/or conflicting perception about the applicability of AOPs,
(v) ethical, legal and social issues, including provenance and intellectual property rights, and finally
(vi) governance and in particular sustainability issues.

Related to the challenges described above is the need to depict a sufficiently high level of complexity, while maintaining an equally high level of utility of AOPs, i.e., the paradox of complex simplicity (Knapen, 2021). AOPs are intended to provide a simple and trustable interface to the decision-maker, without the need to fully understand the underlying complexities of biology and toxicity. However, if the interface is too simple and does not provide enough contextual information (biology/toxicology, susceptible populations, etc.) coupled with the possibility to dig deeper into the complexities, when necessary, then there is a possibility of misinterpretation of the underlying information and the overall interface is not considered trustworthy.

Increased adherence to FAIR principles can be expected to overcome these challenges. The aim of this paper is to provide a first overview and discussion around the need for FAIR AOPs. A full assessment of the FAIRness of the AOP-Wiki is beyond the scope of this paper as it is a matter of extensive technical discussion and review. However, this paper lays the basis for such assessment by initiating the necessary domain-specific discussions in order to establish the social contracts for improved FAIRification of AOPs and the AOP-Wiki. Thus, the current paper addresses the content-related domain-relevant FAIR principles (also known as the blue principles) that define implementation standards and practices relevant to the specific field that is to be FAIRified (Tab. 1). These represent the choices and agreements that must be made by practicing domain experts, e.g., relating to minimum information requirements, standards and (meta)data format templates (Schultes et al., 2023). Another aspect of the FAIR principles is encompassed by the technical principles (also known as the red principles), which define implementation of (more) generic ICT technicalities and infrastructures supporting machine-actionability and consequently susceptibility to interoperability across the Internet (Schultes et al., 2023). These two aspects of the principles guide the two phases of FAIR implementation, which involve domain experts on the one hand and data system engineers on the other.

Overall, this paper is aimed at a broad number of AOP enthusiasts, but mainly at the end users of AOPs, including but not limited to risk assessors, regulators, and policymakers, and thus targets the challenges associated with application of AOPs by those groups and the needs for improving (re)use among them, including in particular the needs for:

− Improved *visibility* of the AOP knowledge among relevant stakeholders, which is key to an improved understanding and uptake of the AOP concept in regulatory domains.
− Increased *trust*, among stakeholders, in the knowledge disseminated in the AOP-Wiki, since even if knowledge is visible, it will never be applied in policy if it is not credible.

2 Purposes of AOP-Wiki FAIRification

FAIRification of a resource is never an end in itself, and the question whether AOPs are "FAIR enough" cannot be answered as such; instead, the question must be "Are AOPs FAIR enough to fulfil the intended purpose?"

This purpose must be derived from the original motivation for which the AOP framework was introduced, and from the reason for which individual AOPs are assembled and disseminated. The "birth certificate" of the AOP framework (Ankley et al., 2010) describes AOPs as "*a conceptual construct that portrays existing knowledge concerning the linkage between a direct molecular initiating event and an adverse outcome at a biological level of organization relevant to risk assessment*". This last part ("relevant to risk assessment") is key: AOPs as such might have a certain academic value, but in order for the framework to demonstrate its full potential, it must have a tangible impact on regulatory decisions in the area of toxicology.

Here, the FAIRification of the AOP-Wiki comes into play. Stakeholders in the regulatory community (i.e., both the regulators and the regulated, plus the parties that support them) must (i) be aware of the framework, (ii) be able to trust the content, and (iii) ideally have the possibility to (semi-)automate the interaction of their ICT systems and the AOP-Wiki.

Being aware of the framework is on the one hand supported by the OECD governance, but on the other hand also by the visibility of the framework. Visibility in turn is supported by use and reuse of AOPs in various and broad aspects. Visibility also supports trust together with transparency regarding the content and origin of the information used to develop AOPs. Finally, (semi-)automated interaction with the AOP-Wiki is strongly supported by the implementation of technical solutions to improve interoperability between AOPs and other systems. In the following, we discuss some ongoing efforts and future needs for improving visibility and trust, and how the FAIR principles (in particular the domain-relevant principles) support those needs.

2.1 Increased visibility and (re)useability

The best ICT resource is of little value if the intended target audience does not know about it or is not able to use it. Following the principle "Build it, and they will come!" is a flawed approach, and limited awareness may be a major factor contributing to the failure of many well-intended public ICT systems. Strengthening the "findability" aspect of FAIRification is therefore crucial for the AOP-Wiki's impact in regulatory affairs.

Improvements in visibility can be achieved by providing relevant metadata information about the available content. Once metadata are indexed, a potentially larger number of stakehold-

ers can find the resource, learn about it, and eventually reuse its content. Rich and relevant metadata may support findability of information across interdisciplinary communities with diverse social and scientific perspectives on the knowledge required for the task at hand. However, it is not a trivial task to identify which knowledge and in what format it is required by all potential end users. For example, before scientific information is incorporated into a chemical assessment supporting toxicity values by the Integrated Risk Information System (IRIS)[2], that information must be found, aggregated, evaluated, synthesized, and integrated for dissemination (U.S. EPA, 2022). The disseminated information provides the scientific foundation supporting decisions and is key for gaining trust and acceptance. Transparency is essential in the process, introducing the requirement that any information sourced from the AOP-Wiki include data provenance (discussed further below). The typical life cycle of an AOP foresees that it runs through a series of validation and review steps – organized by the OECD – with the goal for each AOP to be peer reviewed and assigned the "(WPHA/WNT) Endorsed" status. Before that happens, only the original data source can be incorporated into a risk or hazard assessment. This also excludes AOPs published in journal articles with no original data. AOP FAIRification solves these provenance issues.

Previous efforts to improve visibility and (re)usability of AOPs in a machine-driven fashion have included various approaches to support increased metadata inclusion and links to external data sources. Some examples worth mentioning include semantic annotation, application of linked open data solutions, integrated association networks, and diverse third-party tools (Ives et al., 2017; Martens et al., 2018, 2022; Pittman et al., 2018; Mortensen et al., 2021, 2022), allowing for novel ways of exploring AOPs through automated workflows for various purposes (Nymark et al., 2018; Pollesch et al., 2019; Wiklund et al., 2023). Nevertheless, these efforts all depend on a certain level of FAIRness in the original information source, i.e., the AOP-Wiki, which needs to be populated with constantly evolving AOPs, which are consistently organized, curated, accessible, shareable, and fit for purpose in regulatory and other decision-making contexts (Carusi et al., 2018; Whaley et al., 2020).

One level of consistency comes from standardization of AOP concepts and use of ontological annotations, and it has become increasingly evident that these are extremely important in the AOP-Wiki. Although important steps towards semantic annotation of AOPs have taken place in the AOP-Wiki (Ives et al., 2017), there are further needs to harmonize in order to enable researchers to communicate in the same language by improving consistency and reducing fragmentation (i.e., not naming the same things differently). Fragmentation confounds AOP network development and

leads to the need for tedious curation efforts highly prone to errors (Wiklund et al., 2023). A notable example of network fragmentation in the AOP-Wiki are KE-1276 and KE-1458, two KEs named lung fibrosis[3] and pulmonary fibrosis[4], respectively. These KEs, although they refer to the same biological event, are semantically different and are, inevitably, handled computationally as components of different AOPs, leading to the network fragmentation effect. Semantic annotation also facilitates interoperability (the "I" in FAIR) and harmonization with other biomedical resources such as those containing molecular and biological processes (e.g., WikiPathways (Martens et al., 2021)), or clinical and pharmacoepidemiological data (e.g., FAERS (Kumar, 2019), VigiBase (Lindquist, 2008), EudraVigilance (Postigo et al., 2018)), ultimately expanding the scope and utility of the AOP-Wiki to regulators.

Computational reasoning and biological network visualization are important downstream applications of exploring and communicating facts and knowledge in a machine-readable format (Ives et al., 2017). In the collaborative AOP-Wiki environment, the need for tools that not only enable the AOP community to find (F), access (A) and reuse (R) existing information, but also to discover unanticipated links between AOPs and biological concepts, is emerging. Visualization tools based on standardized AOP concepts can be used by AOP developers to retrieve relevant information but also by the general public who want to explore and better understand existing AOPs, their networks, and emerging patterns. Owing to the current discovery-intensive setting, the connection of AOP-Wiki based visualization tools with external resources (e.g., MEDLINE) is particularly useful. Moreover, as high-throughput genomic data are becoming an important component of toxicology testing assays, annotation of KEs will promote the visualization and analysis of genomics data in the AOP context (Wittwehr et al., 2017; Nymark et al., 2018; Martens et al., 2018).

Visualization is also a means to identify and highlight inconsistencies in the current AOP-Wiki setting. Given that the AOP-Wiki is already FAIR to some extent, it opens the road to a number of visualization applications already available from its third-party tools page[5]. In addition, the AOP-Wiki content is made available as a new XML file[6] that is updated every day with AOP concepts and their relationships entered into the Wiki. Any third-party application that utilizes this XML file can produce AOP-related views of the available data. However, while the information exported in the XML file covers all relevant bits of information currently captured in the AOP-Wiki, it is still affected by the aforementioned standardization issues. These issues, although they can pose impediments in visualization and link-out attempts, represent mostly growing pains that can be addressed through systematic approaches, continuous integration (automatic tests), and more thorough coaching of AOP developers, goals that are currently the aim of

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[2] The IRIS Program is located within EPA's Center for Public Health and Environmental Assessment (CPHEA) in the Office of Research and Development (ORD). The placement of the IRIS Program in ORD ensures that IRIS can develop impartial toxicity information independent of its use by EPA's program and regional offices to set national standards and clean up hazardous sites.

[3] https://aopwiki.org/events/1276

[4] https://aopwiki.org/events/1458

[5] https://aopwiki.org/info_pages/8

[6] https://aopwiki.org/downloads/aop-wiki-xml.gz

respective AOP focus groups (e.g., the Society for Advancement of Adverse Outcome Pathways, the SAAOP).

In many research disciplines, visualizations are crucial to the scientific workflow, used for both question formulation and confirmation of hypotheses, and act as an anchor for the communication of ideas and discussion (Rittenbruch et al., 2022). In our case, visualization can be further enhanced by implementing FAIR principles within the AOP-Wiki, by extending the already established schemas in a well-standardized and unified manner. As a result, the visual representations will streamline complex information, thereby enabling efficient data exploration, communication, and comprehension. Ultimately, this will facilitate the utilization and extraction of value from diverse data sources in various domains.

2.2 Increased trustworthiness and use in policy-making circles

The FAIR principles do not directly address trust, but it is obvious that by providing more metadata, including provenance information (original record/information) which provides transparency, the trustworthiness of the AOP-Wiki knowledge increases. Provenance information ideally contains details on the different parts of the AOP life cycle, including the selection of source data, their analysis, the reasoning behind the conclusions, the involved stakeholders (e.g., authors), and used data and/or tools (e.g., algorithms/workflows). Recent developments in the AOP-Wiki include "AOP Development Strategy"-fields, allowing for detailed descriptions of the underlying approach (i.e., scope, databases searched and search strategies, how the analysis was performed, etc.) taken to develop the AOP.

Another effort to improve provenance information is the initiative Methods2AOP (Wittwehr et al., 2023), which explores ways to highlight and strengthen links between modelling and test methods (*in silico* and *in vitro*) and KEs in AOPs. The aim is to develop a standardized way of reporting test method descriptions in the AOP-Wiki and link those to the related outcomes, including documentation that clearly communicates what exactly the test method is measuring. In other words, providing rich metadata (a component of almost all FAIR principles, see Tab. 1) for the test methods that were used to underpin AOPs. Such rich description and curated linkage build a basis for improved trust through better and more transparent means to validate methods and integrated testing strategies supporting information generation for AOP-driven decision-making (Halappanavar et al., 2020, 2021; Nymark et al., 2021; Carusi et al., 2022).

In addition, the improved AOP-Wiki visualizations support mutual understanding of relations between information presented in the AOP integrative framework. For example, biologically based transcriptomics is of interest as a non-animal testing strategy potentially useful for chemical prioritization and potentially even toxicity value derivation where no other information exists. However, for application of transcriptomics data in a chemical assessment, the assessment developer must know how that information relates to an endpoint and if that endpoint is a possible hazard. Visualization of the transcriptomics data made possible by AOP FAIRification supports visual interrogation by the assessment developer of those transcriptomics data, making available not only

the data source but also related endpoints and other domain-specific characteristics (including species, exposure route, life stage) that are important to understanding if there is any potential human or environmental concern (Halappanavar et al., 2021; Nymark et al., 2018). Currently, a simple box (KE), arrow (KER)-based diagram is used to visually depict AOPs. This might not be intuitive enough for everyone to immediately grasp the meaning of an AOP. For example, the current modest focus on the arrows in the depiction underestimates the importance of the vast amount of information underlying KERs. Thus, visualizations geared more towards the expectations and habits of the target community might be more appropriate.

A further aspect of trust couples to the need to be able to "dig deeper", i.e., allowing the use of a simple interface to explore the underlying information that was used to build the AOP. This is where the FAIR principles play a central role regarding the support for increased interoperability between the AOP-Wiki and neighboring data resources and systems. Interoperability depends on the one hand on technical infrastructures, but on the other hand, is highly reliant on the social agreements and standardization of metadata inclusion and semantic annotation within the domain. Many of the efforts described above, related to improving the visibility and (re)usability of AOPs, support interoperability both with external data sources and third-party tools (as in some cases the AOPs themselves are tools created by third parties). However, the challenges for genuine interoperability between the AOP-Wiki and other resources remain and require further refinement of the AOP-Wiki data model while incorporating the FAIR principles.

3 Outlook and next steps

It is obvious from the many aspects described above that a FAIRer AOP-Wiki would be desirable to first and foremost improve visibility, (re)usability and trustworthiness of the knowledge resource. However, implementation of the FAIR principles is challenged by the complexity of the information contained in it, and by the multidisciplinarity of the actors involved in its development and use, both within and between those two far ends. Developers may be biologists, toxicologists, epidemiologists, data scientists, and data system engineers, while the end users may include risk assessors, regulators, and policy-makers, with highly variable knowledge of biology and toxicity.

Nevertheless, the FAIR principles should support and guide the refinement of the AOP-Wiki, especially when considering the domain-specific needs as separate entities for discussion in line with the FAIR principles, which provide freedom to operate without considering the necessary technicalities of FAIR orchestration (Schultes et al., 2023). Such efforts have been initiated within the domain, including the upcoming revision of the AOP-Wiki 2.6 to the 3.0 data model, currently being discussed at the OECD level, as well as the initiation and ongoing activities on development of a FAIR implementation profile (FIP; Schultes et al., 2020) for AOPs within the European project Partnership for the Assessment of Risks of Chemicals (PARC; Marx-Stoelting et al., 2023). A FIP is a set of technology decisions made by a specific community to
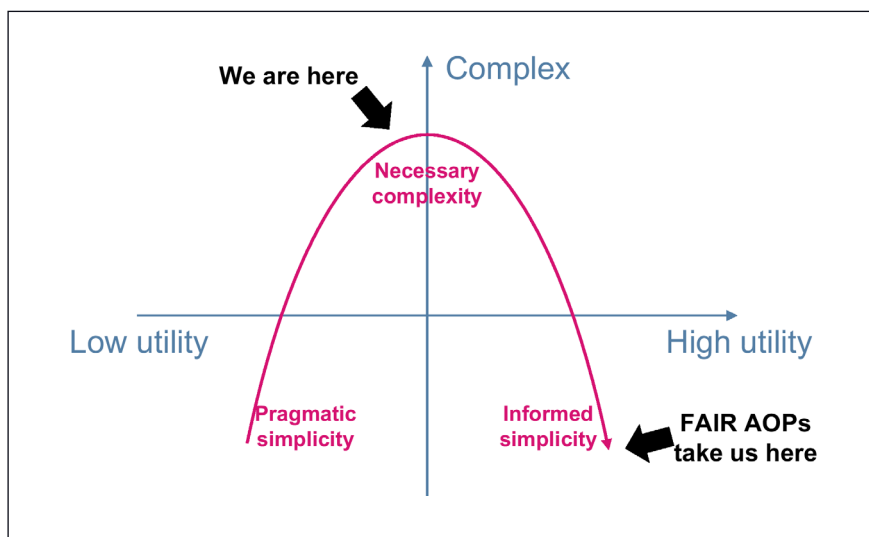
Fig. 1: The evolution of adverse outcome pathways (AOPs)
AOPs evolve from pragmatic to informed simplicity, where only by implementation of the FAIR (findable, accessible, interoperable, reusable) principles can we reach the full impact of AOPs that are informed enough to be trusted but simple enough to be useful in decision-making. Figure adapted from Knapen et al. (2021) under copyright permission from both the author and the original journal.

comply with the FAIR principles that are documented, e.g., using tools such as the FIP Wizard (Schultes et al., 2022). FIPs are published as open, machine-readable data that can be reused by other communities, promoting consistency in FAIR practices.

Overall, the optimistic outlook is that a FAIRer AOP-Wiki would allow us to reach the state of informed simplicity that is necessary to provide a high level of utility (Fig. 1). The next steps include coordinated action by the global community to advance these and other initiatives and to support the continued endeavor to simplify the current complexity of the AOP-Wiki to the level of pragmatic utility for decision-making, while retaining the possibility to dive into the underlying information.

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Conflict of interest

The authors declare no conflicts of interest.

Data availability

No data sets were generated or analyzed during the study.

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