2020 Lhasa Limited Virtual Symposium: The Application of Adverse Outcome Pathways (AOPs) for Risk Assessment

Q&A Session

October 2020

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Lhasa AOP Symposium
Q&A Session

Session 1 - 5th October 2020 - The application of adverse outcome pathways (AOPs) to improve risk assessments for development and reproductive toxicity (DART)

How does the knowledge that you have captured for DART pathways compare to what is available in the AOPwiki?
The knowledge described in Lhasa AOPs has been curated from review of relevant literature and therefore is similar to the type of knowledge found in the AOPwiki. Differences can exist in terms of the depth of knowledge captured, which can be attributed to how extensive an AOP has been developed. AOPs are living documents that can be continually updated. A review of AOPs relating to DART highlighted that there is a high degree of concordance in the knowledge between the two sources. However, one difference worth noting is how the data is represented. Control of the features in the AOP network allow the network to connect to additional resources such as *in silico* models and databases to enable reasoning and predictions based on AOPs.

How can these frameworks be used for compounds which interact with novel targets which have limited information regarding their involvement in developmental toxicity?
AOPs express consolidated knowledge of toxicity pathways and therefore this information may be lacking for new compound classes targeting novel targets. However, the AOP framework can be used to start to organise any evidence relating to a potential toxicity pathway, which can then be shared more easily through applications like Kaptis or the AOPwiki. The addition of holistic assays which attempt to model the adverse outcome to the AOP framework could also help support the assessment of novel chemicals. Having these types of assays annotated to the network, would allow for chemical similarity queries for new chemicals to be focused on data relevant to the adverse outcome of interest.

Session 2 - 12th October 2020 - Application of adverse outcome pathways (AOPs) to support integrated approaches to testing and assessment (IATA)

What public sources do you use? Are these in AOP wiki?
Answer 1: So, we start with a literature review and as part of that we will look at AOP Wiki and PubMed mechanistic relationships. We also look in data repositories like ChEMBL, ToxCast and PubChem for relevant mechanistic data.
Answer 2: Information to support the development of AOPs can come from a variety of sources. Generally, any information that is used to support the development of any AOP in the OECD knowledgebase is cited in their respective "reference" sections. So, yes, all referenced information is captured in the AOP-knowledgebase (which can be accessed using the AOPwiki). Much of this information comes from the scientific literature, but can also come from various databases, and also publications from the regulatory domain. Regardless of the source, it is always cited.

Is the Carcinogenicity AOP network for humans or rodents?
Answer 1: We include all the pathways that are relevant for both human and rodents and the network is supported with evidence mostly from rodent, but it also contains other mammals. The components (AOPs, KEs and KERs) have a "context" field and this is where we'd specify any relevant species information like human or rat. That should allow us to come to a conclusion based on human risk.
Answer 2: AOPs in the OECD knowledgebase attempt to identify which AOPs are relevant to humans or not (this is also important and challenging! for ecologically relevant species as well). However, I must admit that this is not currently done very effectively. One of the major challenges is that most of the evidence used to support the development of AOPs in the knowledgebase comes from non-human models. How to best identify and indicate which AOPs are relevant/not relevant to humans (and other species) is an area of active investigation at the OECD (I am on a subcommittee that trying to address this challenging issue).

Session 3 - 19th October 2020 - The potential utility of AOPs in the future of regulatory decision-making

Can the AOP approach you have described for assessment be used in other situations?
Yes! The AOP network can be used to assess carcinogenicity for any regulation/guideline that requires it, regardless of the industry. In fact, it is possible that this could be used throughout the development cycle of a compound. In the discovery phase, the AOP approach could be used to decide what risk is related to a target of interest, thus helping to make a decision on prioritisation or dropping of potential leads. In early development, the framework could help determine the appropriate assays to run next to provide confidence in a prediction of risk.

Is there any plan at Lhasa to develop the approach for ED? Would it be possible?
Endocrine disruption in the context of AOPs hasn't been investigated thus far but could potentially be an area we look into in the future. We do currently have pathways relating to androgen receptor activation, oestrogen receptor activation and thyroid dysregulation within the carcinogenicity AOP network which may be linked to endocrine disruption endpoint in the future.

Have the AOPs in Kaptis been compared to those in the AOP wiki?
The AOPs in Kaptis are developed in-house at Lhasa through literature review. This includes harvesting knowledge that may also have been captured and published in AOP-wiki and in some cases expanding on these or manipulating them in order to fit our knowledge structure within Kaptis. This allows us to create a unified network of AOPs on which our evidence can be associated in the most appropriate places and used in order to reach decisions.

Session 4 - 26th October 2020 - Harnessing the potential of adverse outcome pathways in the assessment of genotoxicity

How will biomarker and omics data coming from emerging assays be incorporated into the existing AOPs? Will more key events or delineation of biological pathways be required?
The beauty of AOPs is that they are 'living documents' and can be revised/update as new tests and data are available. Thus, as omic or other biomarkers are produced, existing KE can be updated as required. In addition, as we have a more complex set of mechanistic biomarkers, we may need to split KE as new tests are available. Just a note that KE and KER in AOPs typically represent a fairly broad swath of biology, thus an individual KE can be measured as perturbation of an entire gene expression pathway or network.

How can we link related concepts between our AOPs? A key event that may not be the same but may be linked to an existing key event either at a higher or lower level?
It is useful to know when key events are related to one another in terms of the concepts that they're describing, even when they are not directly linked via a key event relationship. Knowing when there are associations between different key events in terms of their description of more or less specific concepts may be useful when searching or filtering knowledge in the context of an AOP. A good example of this in this context would be the idea of 'genotoxicity'. This is a more general umbrella term which may encompass terms like 'mutations', 'chromosome aberrations' and 'aneuploidy'. It would be useful to be able to filter or search AOP knowledge based on this general concept and bring back AOPs or KEs relating to these more specific terms. This is where ontologies can be employed to make these associations. It is possible to link these related terms using an appropriate ontology and if we structure the description of our KEs using the concepts of process, object, action and context as proposed by Ives et al (https://pubmed.ncbi.nlm.nih.gov/30057931/) we can link each of these to the appropriate ontology and search or filter using each of these terms within the structure of the ontologies.

How do you determine the applicability domain and performance characteristics of an AOP, compared to a single *in vitro* assay?

Answer 1: An *in vitro* assay may, of course, have its own applicability domain and general performance in terms of how well it relates a broad coverage of chemical space with a specific adverse outcome. However, positioning the assay in the context of an AOP and other events with which hypotheses are associated may define a more specific area of chemical space where the performance of the *in vitro* assay for predicting the adverse outcome may change from the more general predictivity. The relevance of the *in vitro* assay result within the context of an AOP may also change depending on the other evidence on the AOP which support or contradict any findings. Synthesising evidence in this way as a weight of evidence on an AOP framework means that a meaningful conclusion can be reached from multiple sources of evidence at an AOP level. Once this conclusion is reached each AOP can be compared to a (preferably human relevant) test set of adverse outcomes to calculate the performance characteristics of an AOP. The applicability domain of an AOP may, as Carole discussed, relate to multiple levels of context from which evidence for or against an AOP have been generated. Some knowledge of the applicability of an AOP may also be gained based on the types of stressor compounds associated with building and providing evidence for the AOP.

Answer 2: Relating to the biology of the AOP: Applicability domains in AOPs are defined for each KE and KER during development and are found in the AOP wiki. This helps to provide context to the inferential strength of the assays that are measuring a specific KE(R). Domains of applicability that are described include taxonomic, life stage and species sensitivity. I would consider the technology and the inferential strength of the assay based on these descriptions.

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