Emergent Adverse Outcome Pathways and Their Potential to Contribute Novel Toxicological Knowledge

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Objective

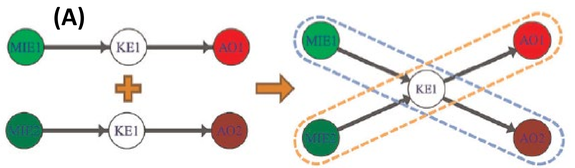
The AOP Knowledge base contains vast amounts of potentially valuable and novel toxicology information. In 2019, Pollesch et al., identified that the 219 AOPs in the AOP-Wiki led to 9876 *unique linear AOPs*. Of those, only ≈ 4% (471) were *user-specified*, and the rest were *emergent* (9405)

Semantic analysis can be used to assess the quality of AOPs. The goal of this research was to apply the semantic analysis methods of Wang (2020), to the Emergent AOPs present in the AOP-Wiki to determine quality and prioritize them for human inspection to determine if they are computational artifacts or novel toxicological information.

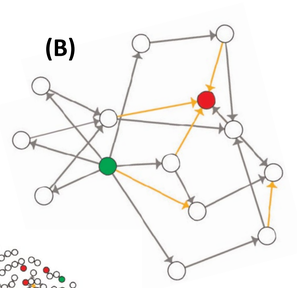
Method

- Emergent AOPs were identified using the graph theoretic and network analysis techniques presented in Pollesch et al., (2019)
- Emergent AOPs were Analyzed using the semantic analysis techniques presented in Wang (2020).

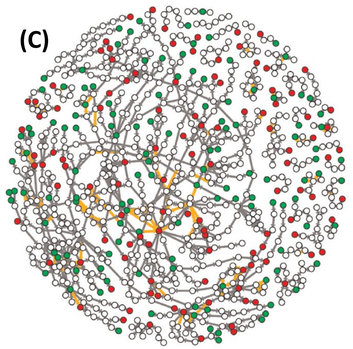
(A) How Key Event Sharing leads to Emergent AOPs : A Linear AOP (LAOP) is a direct path from MIE to AO. Two linear AOPs ($MIE1 \rightarrow KE1 \rightarrow AO1$) and ($MIE2 \rightarrow KE1 \rightarrow AO2$) share $KE1$ and create two Emergent LAOPs, ($MIE1 \rightarrow KE1 \rightarrow AO2$) and ($MIE2 \rightarrow KE1 \rightarrow AO1$) (From Pollesch et al., 2019)

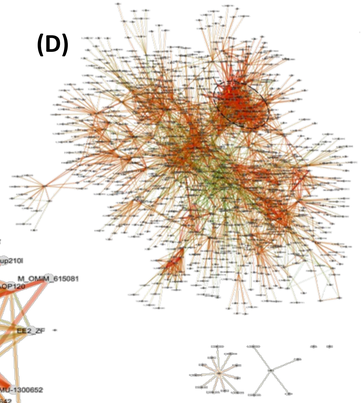


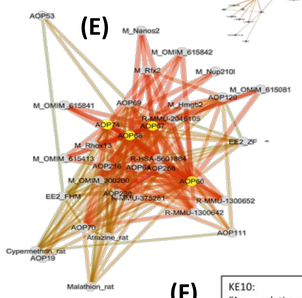
(B) A single AOP can contain multiple Linear AOPs: A Component of AOP ID 58 is shown. Although considered a single AOP (58). This MIE:AO pair contains 18 unique Linear AOPS (LAOPs), owing to multiple unique paths from the MIE to the AO. Since these 18 LAOPs are all user-specified, since they all share the same AOP ID (58) (Adapted from Pollesch et al., 2019)



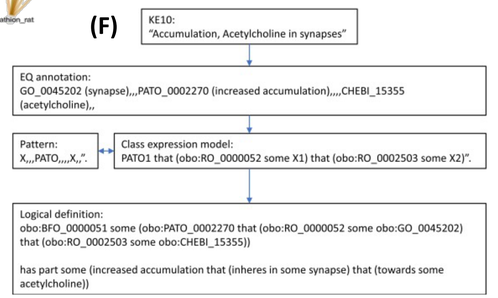
(C) A Snapshot of the AOP-Wiki Network: A snapshot of the AOP-Wiki showing all Key Events and Key Event Relationships. Molecular Initiating Events are in green, Adverse Outcomes are in red. Key event sharing between AOPs has created a highly connected network and Emergent AOPs (From Pollesch et al., 2019)







(F) AOP Key Event Semantic Analysis Encoding: An example of the how KE10 is encoded. Starting with the AOP definition and ending with the logical definition (Adapted from Wang, 2020)



(D & E) Semantic Networks: Semantic similarity networks of AOPs, CSPPs (chemical-species phenotype profiles), genes, pathways, and diseases. The networks were constructed based on the top five mappings of genes, pathways, diseases, chemicals, and other AOPs by each of the 220 AOP queries at P0.01 with a total number of 1041 unique nodes. The anchors (chemicals, genes, pathways, diseases, AOPs, etc.) of these profiles served as nodes and connected by non-directional edges weighed by their corresponding similarity scores, with a wider edge in darker red color denoting a higher similarity. **(D)** all 1041 nodes and 3072 edges, and **(E)** AOP68 and its first neighbors (34) and all their edges (175). Four highlighted AOPs also form a subnetwork due to their shared events. AOP68, Modulation of Adult Leydig Cell Function Subsequent to Alterations in the Fetal Testis Proteome (Adapted from Wang, 2020)

Disclaimer: *This poster presents preliminary results. The research and these results neither constitute nor necessarily reflect USEPA policy*

Results

Emergent AOPs have, on average, comparable if not higher levels of biological coherence as user-defined AOPs, as measured by semantic similarities of pairwise events within AOPs and those between the phenotypic profiles of AOPs and existing genes/pathways/diseases. These results indicate that emergent AOPs represent a large amount of valuable, untapped, AOP knowledge. They reiterate the value of further enhancing user-contributed public knowledgebases, such as the AOP-Wiki, and broader AOP knowledgebases. Further, this research demonstrates that both network analysis and semantic analysis techniques are valuable tools to make the most of these resources and utilize AOP knowledge

Coherence measure and total targets mapped	User-specified AOPs P0.05 (102)	Emergent AOPs P0.001 (100)
Mean pairwise event similarity	**0.252**	**0.339**
Genes (human, mouse, zebrafish)	6017 (492, 4982, 543)	5892 (452, 4940, 500)
Pathways (Reactome, KEGG)	234 (222, 12)	239 (226, 13)
Diseases (OMIM, ORPHA)	1414 (1247, 167)	1326 (1155, 171)
AOPs	212	202
CSPPs	7	8

Linear AOP semantic coherence and biological mappings: The 102 User-specified AOPs significant at P0.05 and the top 100 Emergent AOPs significant at P0.001 were compared to over 37,000 profiles. AOP mappings to target profiles were based on P0.01 with 1000 bootstraps *(Pollesch et al., in prep)*

References

Pollesch et al., (2019) Extracting and benchmarking emerging adverse outcome pathway knowledge. *ToxSci 168*(2), 349-364.

Wang, R. L. (2020). Semantic characterization of adverse outcome pathways. *Aquatic Toxicology*, *222*, 105478.