

# OpenRiskNet

RISK ASSESSMENT E-INFRASTRUCTURE

## Case Study

### Identification and Linking of Data related to AOPs of AOP-Wiki [**AOPLink**]

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## SUMMARY

The Adverse Outcome Pathway (AOP) concept has been introduced to support risk assessment ([Ankley et al., 2010](#)). An AOP is initiated upon exposure to a stressor that causes a Molecular Initiating Event (MIE), followed by a series of Key Events (KEs) on increasing levels of biological organization. Eventually, the chain of KEs ends with the Adverse Outcome (AO), which describes the phenotypic outcome, disease, or the effect on the population.

In general, an AOP captures mechanistic knowledge of a sequence of toxicological responses after exposure to a stressor. While starting with molecular information, for example, the initial interaction of a chemical with a cell, the AOPs contain information of downstream responses of the tissue, organ, individual and population. Currently, AOPs are stored in the [AOP-Wiki](#), a collaborative platform to exchange mechanistic toxicological knowledge as a part of the AOP-KB, an initiative by the OECD.

Normally, AOP development starts with a thorough literature search for existing knowledge, describing the sequence of KEs that form the AOP. However, the use of AOPs for regulatory purposes also requires detailed validation and linking to existing knowledge ([Knapen et al., 2015](#); [Burgdorf et al., 2017](#)). Part of the development of AOPs is the search for data that supports the occurrence and biological plausibility of KEs and their relationships (KERs). This type of data can be found in literature, and increasingly in public databases.

The main goal of this case study is to establish the links between AOPs of the AOP-Wiki and experimental data to support a particular AOP. This will allow finding AOPs related to experimental data, and finding data related to a particular AOP.

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# DESCRIPTION

## Implementation team

Coordination:

- Marvin Martens, Maastricht University, Department of Bioinformatics - BiGCaT
- Egon Willighagen, Maastricht University, Department of Bioinformatics - BiGCaT

Implementers:

- Risk assessors
- Modelers
- AOP developers
- Users of AOPs

## Case Study objective

The objective of this case study is to establish how existing AOPs on AOP-Wiki can be linked to experimental bioassay data. The approach here is to link assay data via assay types to key events (KEs) in the AOP.

For this case study we aim to develop:

- FAIR (Findable, Accessible, Interoperable and Reusable) version of [AOP-Wiki](#);
- Identifier mappings for MIEs, KEs, and biological and chemical entities (genes, proteins, metabolites);
- Establish links between MIEs and KEs to biological assays and experimental data;
- Establish links between assays and biological and chemical entities;
- Establish interoperable databases.

## Risk assessment framework

The AOPLink case study covers a range of steps across different tiers of the SEURAT-1 risk assessment framework ([Berggren et al., 2017](#)). AOPLink allows finding relevant experimental data for given compounds and nanomaterials and KEs (Tier 0, step 3), identify biological processes affected by exposure to those chemicals supporting hypothesis generation (Tier 1, step 6), and using these sources of information to determine if an AOP can be applied to that chemical and if not what information is missing (Tier 3, step 9).

## Link to other case studies

With respect to the other OpenRiskNet case studies, AOPLink has a strong link to DataCure, as the primary goal of AOPLink is the search for experimental datasets related to AOPs of interest. Furthermore, AOPLink can take as input from **SysGroup** on similar chemicals (same group) in case no direct search results are found with the chemical of interest. Also, **TGX** may provide predicted data to complement experimental data, to support searching, and predicting the activation of a range of Molecular Initiating Events (MIEs). Because AOPLink may result in hypothesis and list KERs, these results can be passed to **ModelRX** for further prediction and read-across.

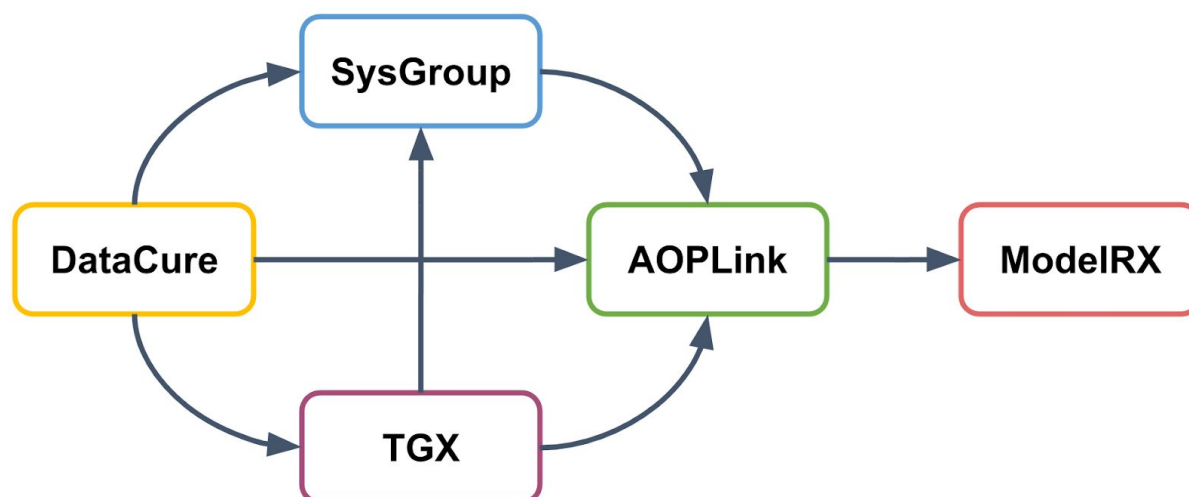


Figure 1: AOPLink and links to other case studies

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# DEVELOPMENT

## Databases and tools

The following sets of repositories and services are used in the AOPLink case study.

- AOP-related repositories:
  - AOP-Wiki
  - AOP-DB
- Biological pathway databases/tools
  - WikiPathways
  - Reactome
- Experimental data repositories
  - diXa data warehouse
  - BioStudies
  - ArrayExpress
  - ToxCast
  - ToxRefDB
  - TG-GATEs
  - eNanoMapper
  - EPA Chemistry Dashboard
  - NORMAN Network
- Identifier mapping services
  - BridgeDb
  - ChemIdConverter
- Pathway analysis
  - PathVisioRPC

## Service integration

### Services integrated for AOPLink

#### AOP-Wiki:

The AOP-Wiki repository is part of the AOP Knowledge Base (AOP-KB), a joint effort of the US-Environmental Protection Agency and European Commission - Joint Research Centre. It is developed to facilitate collaborative AOP development, storage of AOPs, and therefore allow reusing toxicological knowledge for risk assessors. This Case Study has converted the AOP-Wiki XML data into an RDF schema, which has been exposed in a public SPARQL endpoint in the OpenRiskNet e-infrastructure.

#### EPA AOP Database (AOP-DB):

The EPA AOP-DB supports the discovery and development of putative and potential AOPs. Based on public annotations, it integrates AOPs with gene targets, chemicals, diseases, tissues, pathways, species orthology information, ontologies, and gene interactions. The AOP-DB facilitates the translation of AOP biological context, and associates assay, chemical and disease endpoints with AOPs ([Pittman et al., 2018](#); [Mortensen et al., 2018](#)).

The AOP-DB won the first OpenRiskNet implementation challenge of the associated partner program and is therefore integrated into the OpenRiskNet e-infrastructure. After the conversion of the AOP-DB into an RDF schema, its data will be exposed in a Virtuoso SPARQL endpoint.

#### WikiPathways and Reactome:

WikiPathways is a community-driven molecular pathway database, supporting wide-spread topics and supported by many databases and integrative resources. It contains semantic annotations in its pathways for genes, proteins, metabolites, and interactions using a variety of reference databases, and WikiPathways is used to analyze and integrate experimental omics datasets ([Slenter et al., 2017](#)). Furthermore, human pathways from Reactome ([Fabregat et al., 2018](#)), another molecular pathway database, are integrated with WikiPathways and are therefore part of the WikiPathways RDF ([Waagmeester et al., 2016](#)). On the OpenRiskNet e-infrastructure, the WikiPathways RDF, which includes the Reactome pathways, is exposed via a Virtuoso SPARQL endpoint.

#### eNanoMapper:

The eNanoMapper database hosts nanomaterials characterization data and biological and toxicological information. It allows users to upload and explore data and information about nanomaterials through a REST web services API and a web browser interface, which is available in the OpenRiskNet e-infrastructure, using a newly developed Docker image.

#### BridgeDb:

In order to link databases and services that use particular identifiers for genes, proteins, and chemicals, the BridgeDb platform is integrated into the OpenRiskNet e-infrastructure. It allows for identifier mapping between various biological databases for data integration and interoperability ([van Iersel et al., 2010](#)).

#### PathVisioRPC:

To allow the analysis and visualization of transcriptomics or metabolomics data, PathVisioRPC ([Bohler et al., 2015](#)) will be used in AOPLink workflows. It is an XML-RPC interface, available for use in a variety of coding environments. It supports the use of pathways from WikiPathways for pathway statistics, exporting of results and providing data visualization on the pathways.

## Services provided by other case studies

### **DataCure:**

EdelweissData: Curated datasets are made available through the EdelweissData Explorer, the main data provisioning tool in the DataCure case study. It is a web-based data explorer tool that gives users the ability to filter, search and extract data through the use of API calls. The EdelweissData Explorer serves data from ToxCast, ToxRefDB, and TG-GATES.

ChemIdConverter: The ChemIdConverter allows users to submit and translate a variety of chemical descriptors, such as SMILES and InChI, through a REST API.

### **SysGroup:**

Grouping service that classifies a chemical or nanomaterial and provides structurally

and/or biologically similar chemical substances or compounds.

### **TGX:**

API to access predicted data for the activation of a selective set of Molecular Initiating Events.

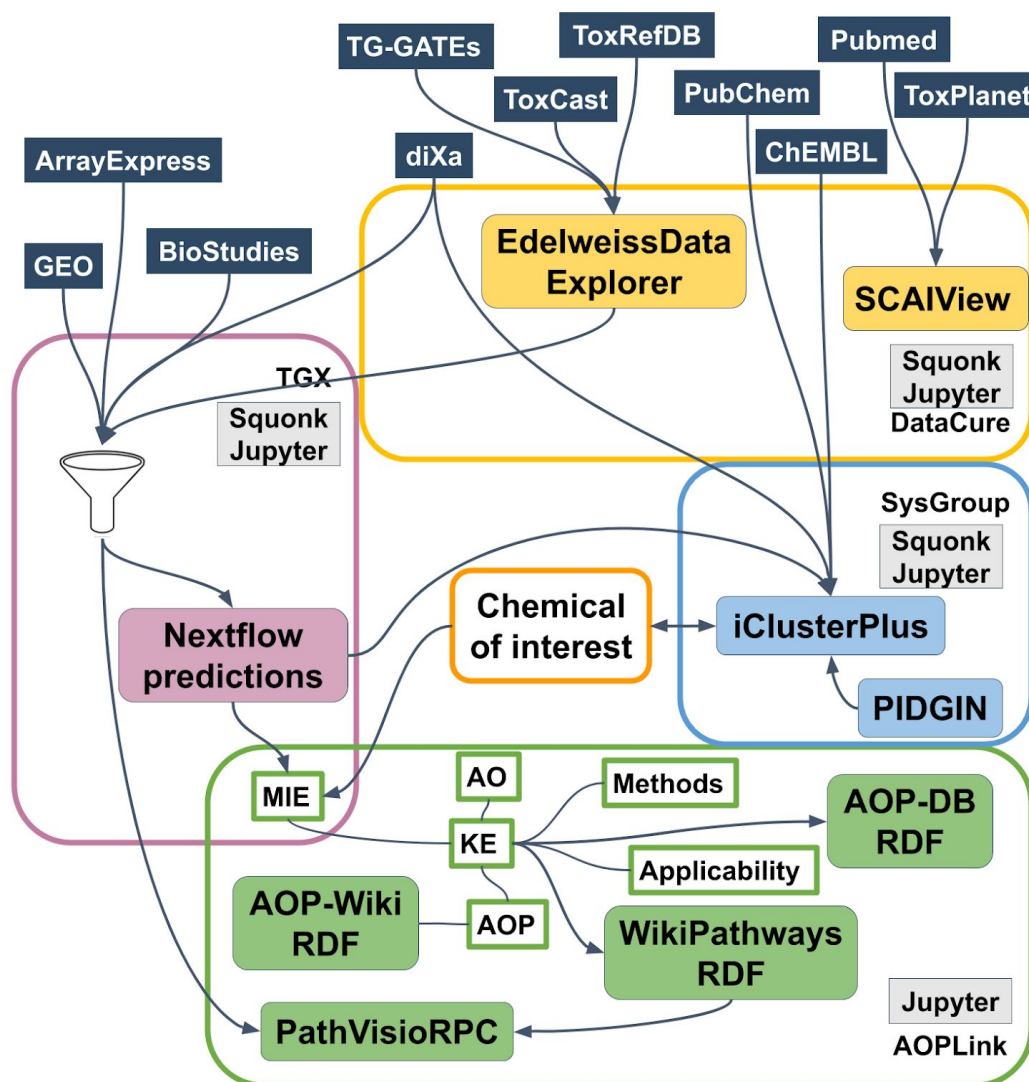


Figure 2: Network of services and databases from the case studies AOPLink, DataCure, SysGroup and TGX.

## Technical implementation

Jupyter Notebooks will be used to integrate the tools into reproducible workflows. Of the services, data from the AOP-Wiki, AOP-DB, and WikiPathways are available through SPARQL endpoints and are easily queried with the SPARQLwrapper python library. The other services, which have OpenAPI 2 or 3 definitions, are called through direct API calls. Combining the various tools and databases into workflows, the research goals are answered with modular, reproducible Jupyter Notebooks. For example, workflows are developed to find public experimental data that supports AOPs and to retrieve AOPs that are related to available data. Furthermore, we aim to develop complete data analysis workflows using WikiPathways and PathVisioRPC and relate the results to the knowledge captured in AOP-Wiki and AOP-DB.



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# OUTCOMES

This case study focused mainly on the use of AOP knowledge, and extend it with additional information, or experimental data. The main repository in those analyses was the AOP-Wiki, which was converted into RDF, deployed in a Virtuoso SPARQL endpoint.

## AOPs linked to WikiPathways

One of the first analyses in the AOPLink case study was the assessment of the possible links between AOPs of AOP-Wiki, and the molecular pathways of WikiPathways. This task involved the identification of ontology usage for describing biological processes, and looking for the overlap of chemical coverage in both repositories. This exercise showed that few of the AOP-linked chemicals are found in WikiPathways, whereas 70% of all mapped genes are present in molecular pathways on WikiPathways. A manual assessment indicated that 67% of all low-level KEs, including molecular, cellular, tissue and organ KEs, can be linked (partially) to molecular pathways. [Martens M et al.]

## Workflow for finding data related to an AOP

One of the main questions to solve in AOPLink is the finding of data that supports an AOP of interest. To answer that, we have developed a Jupyter notebook that does that by using the AOP-Wiki RDF, AOP-DB RDF, BridgeDb, EdelweissData explorer, and WikiPathways services. The workflow, which was also presented during the workflow tutorial at the final workshop of OpenRiskNet, AOP 37 was selected as the AOP of interest.

First, the AOP-Wiki RDF was used to extract information about the AOP by using a variety of SPARQL queries that directly access the data through the SPARQL endpoint with the SPARQLWrapper library. Information of the AOP, such as the title, abstract, KEs and stressors, were extracted and written in a data frame, along with an AOP network that displays the connected AOPs.

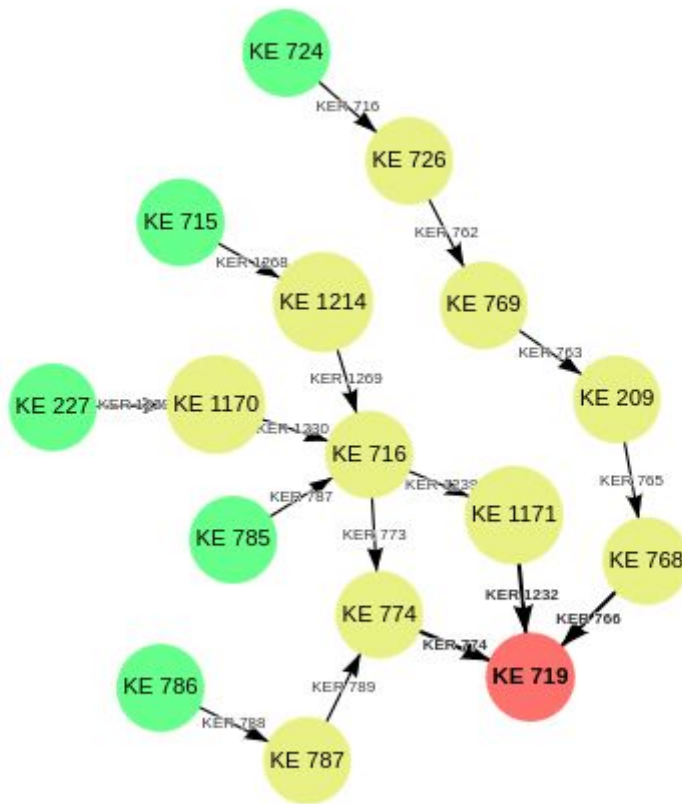


Figure 3: AOP network of AOP 37 with other AOPs extracted from AOP-Wiki RDF

```

sparqlquery = '''
PREFIX ncit: <http://ncicb.nci.nih.gov/xml/owl/EVS/Thesaurus.owl#>
SELECT ?CAS_ID (fn:substring(?CompTox,33) as ?CompTox_ID)
WHERE{
?AOP_URI a aopo:AdverseOutcomePathway; ncit:C54571 ?Stressor.
?Stressor aopo:has_chemical_entity ?Chemical.
?Chemical cheminf:CHEMINF_000446 ?CAS_ID.
OPTIONAL {?Chemical cheminf:CHEMINF_000568 ?CompTox.}
FILTER (?AOP_URI = aop:'''+AOPid +'')
'''

aopwikisparql.setQuery(sparqlquery)
aopwikisparql.setReturnFormat(JSON)
results = aopwikisparql.query().convert()

Chemical_names = {}

for result in results["results"]["bindings"]:
    try: Chemical_names[result["CAS_ID"]["value"]] = result["CompTox_ID"]["value"]
    except: pass

Chemdata = pd.DataFrame(columns=['CAS_ID', 'CompTox_ID'])
for CAS_ID in Chemical_names:
    Chemdata = Chemdata.append({
        'CAS_ID' : CAS_ID,
        'CompTox_ID': Chemical_names[CAS_ID],
    }, ignore_index=True)
display(Chemdata)

```

	CAS_ID	CompTox_ID
0	117-81-7	DTXSID5020607
1	25812-30-0	DTXSID0020652
2	3771-19-5	DTXSID8020911
3	41859-67-0	DTXSID3029869
4	49562-28-9	DTXSID2029874
5	50892-23-4	DTXSID4020290
6	52214-84-3	DTXSID8020331
7	637-07-0	DTXSID3020336

Figure 4: Extracting chemicals from AOP-Wiki using SPARQL in a Jupyter notebook

Next, all chemical IDs were extracted from the found list of stressors, which were then used as an input for the ChemIdConverter to retrieve a variety of chemical descriptors, such as SMILES and InChI through the REST API.

```

compoundstable = pd.DataFrame(columns=['CAS_ID', 'Smiles', 'Image'])

# Fill "compounds" with the "smiles" by the compound name.
for compound in compounds:
    smiles = requests.get(chemidconvert + 'cas/to/smiles', params={'cas': compound}).json()['smiles']
    compoundstable = compoundstable.append({'CAS_ID': compound, 'Smiles': smiles, 'Image': smiles}, ignore_index=True)

def smiles_to_image_html(smiles): # "smiles" shadows "smiles" from outer scope, use this function only in "to_html().
    """Gets for each smile the image, in HTML.
    :param smiles: Takes the "smiles" form "compounds".
    :return: The HTML code for the image of the given smiles.
    """
    return ''

# Return a HTML table of "compounds", after "compounds" is fill by "smiles_to_image_html".
HTML(compoundstable.to_html(escape=False, formatters=dict(Image=smiles_to_image_html)))

```


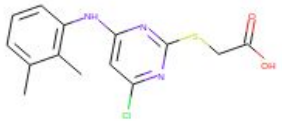
CAS_ID	Smiles	Image
0 25812-30-0	<chem>Cc1ccc(C)c(OCCCC(C)(C)C(O)=O)c1</chem>	
1 50892-23-4	<chem>Cc1cccc(Nc2cc(Cl)nc(SCC(O)=O)n2)c1C</chem>	

Figure 5: Chemical structures extracted through ChemIdConverter in a Jupyter notebook

To highlight that users of the AOP-Wiki are not required to learn SPARQL to access the data, the workflow shows how to access the content by using one of the predefined API calls, which was built using grlc.

```

import io
aopwiki_api = 'http://grlc.io/api/marvinm2/AOPWikiQueries/'
chemforaop = 'get-chemicals-for-aop'
headers={'accept': 'text/csv'}
result = requests.get(aopwiki_api+chemforaop+'?aopfilter='+AOPid, headers = headers)
resultClean = io.StringIO(result.content.decode("utf-8"))
df = pd.read_csv(resultClean, sep = ",")
df = df.drop(['callret-1'], axis=1)
display(df)

```

	CASID
0	117-81-7
1	25812-30-0
2	3771-19-5
3	41859-67-0
4	49562-28-9
5	50892-23-4
6	52214-84-3
7	637-07-0

Figure 6: Using the grlc API loaded with AOP-Wiki SPARQL queries to extract chemicals for AOP of interest in a Jupyter notebook

In order to extract all protein targets for the KEs of the AOP 37, the AOP-DB RDF was used. The data, which was converted to RDF and exposed in a SPARQL endpoint as part of the implementation challenge, was queried for all Entrez IDs linked to the AOP. Those were later used to extract all ToxCast Assay IDs from the AOP-DB RDF which have those genes as their target.

```
Assays = pd.DataFrame(columns=['Assay_ID', 'Assay_title', 'Entrez', 'Tissue', 'Species_name'])

for gene in Genes:
    sparqlquery = '''
    SELECT ?Assay_title ?Assay_ID ?Tissue ?Species_name WHERE{
    SELECT * WHERE{
    ?Assay a mmo:0000441; bao:BAO_0003064 ?Entrez_URI; rdfs:label ?Assay_title; foaf:group ?Assay
    SERVICE <http://aopwiki-rdf.prod.openrisknet.org/sparql/>{
    ?Species_URI dc:title ?Species_name.
    }
    FILTER (?Entrez_URI = ncbigene:'''+gene +''')}
    '''
    aopdbsparql.setQuery(sparqlquery)
    aopdbsparql.setReturnFormat(JSON)
    results = aopdbsparql.query().convert()
    for result in results["results"]["bindings"]:
        Assays = Assays.append({'Assay_ID' : result["Assay_ID"]["value"],
                                'Assay_title' : result["Assay_title"]["value"],
                                'Tissue' : result["Tissue"]["value"],
                                'Species_name' : result["Species_name"]["value"],
                                'Entrez' : gene}, ignore_index=True)

display(Assays)
```

	Assay_ID	Assay_title	Entrez	Tissue	Species_name
0	269	NVS_NR_hPPARa	5465		Homo sapiens
1	6	ATG_TRANS	5465	liver	Homo sapiens
2	6	ATG_TRANS	5465	liver	Homo sapiens

Figure 7: Using the AOP-DB to extract ToxCast assays related to our AOP of interest using SPARQL in a Jupyter notebook

Because Entrez IDs don't provide information about the gene name, or the species it belongs to, BridgeDb was used to map the Entrez IDs to HGNC and Ensembl IDs, showing that one of the four Entrez IDs was the human gene PPARA.

	Entrez	HGNC	Ensembl
0	5465	PPARA	ENSG00000186951
1	403654		ENSCAFG00000000788
2	19013		ENSMUSG00000022383
3	25747		ENSRNOG00000021463

Figure 8: Results after Entrez identifier mapping for HGNC and Ensembl using BridgeDb

The next part focused on extracting transcriptomics data from TG-GATES using the EdelweissData explorer Python library, which accesses the EdelweissData API and queries for all datasets which were generated with the chemicals that were found earlier from the AOP-Wiki RDF. This resulted in a list of 181 datasets for different chemicals, species, dosings, and experimental design, of which we decided to focus on *in vivo* rat data with a high dose of exposure.

Finally, the data were analyzed by identifying the significantly affected molecular pathways. After querying all genes present in molecular pathways on WikiPathways for rats, pathway analysis was performed using the transcriptomics dataset from TG-GATES.

This indicated that 6 pathways from WikiPathways were significantly altered by the chemicals that activate the AOP 37.

	Genes	nGenes	nSigGenes	percentSigGenes	Zscore
WP1286	{108348148, 171341, 64305, 286954, 25279, 154985, 362228, 25428, 499422, 246245, 25429, 24294, 113992, 64352, 108348061, 24422, 116631, 681913, 140568, 364476, 64570, 494499, 246767, 288108, 29633, 316325, 100910462, 24404, 83783, 316435, 690050, 116686, 25086, 29326, 396551, 302302, 29328, 29725, 246248, 307859, 24426, 685402, 24192, 81924, 293779, 292915, 25256, 24421, 499302, 301264, 24297, 154516, 361510, 24902, 24861, 24424, 25315, 290623, 65030, 292155, 24298, 299566, 294449, 361631, 25426, 368066, 29680, 363618, 291770, 116632, 311257, 308445, 499689, 295934, 289197, 24267, 100910526, 65185, 303218, 574523, 58953, 25458, 58981, 103690051, 25147, 684979, 308511, 297029, 310848, 54246, 302489, 307838, 361718, 500257, 314694, 24912, 171072, 25427, 498489, 25355, ...}	143	16	11.188811	5.152989
WP1307	{29367, 117243, 364975, 170670, 25363, 25288, 25330, 24849, 171155, 100911615, 94340, 311849, 113976, 29740, 361676, 113965, 25062, 289481, 298942, 50682, 79223, 114024, 25413, 24158, 117035, 64304, 311569, 25756, 24539, 140547, 25287, 117543, 24538, 25757, 25014}	35	16	45.714286	5.152989
WP372	{29367, 117243, 364975, 170670, 25363, 25288, 25330, 24849, 171155, 100911615, 94340, 311849, 113976, 361676, 113965, 25062, 289481, 298942, 50682, 79223, 114024, 25413, 24158, 117035, 64304, 311569, 25756, 24539, 140547, 25287, 24538, 25757, 25014}	33	14	42.424242	4.422721
WP358	{311743, 25317, 25054, 108348113, 25597, 81649, 170593, 58960, 24629, 24674, 497961, 60587, 303823, 311341, 140726, 66017, 309452, 170630, 365355, 299618, 691905, 171492, 170633, 170920, 314384, 170632, 24518, 306243, 500526, 116663, 296091, 79240, 116596, 170580, 297682, 315994, 24653, 363855, 170851, 286993, 81647, 311245, 314322, 25114, 25272, 24628, 293847, 84488, 257648, 287398, 361715, 29717, 116457, 81504, 25266, 140729, 308267, 29349, 50658, 24329, 58942, 24681, 25443, 24525, 24592, 29332, 501099, 63995, 362332, 304786, 300160, 25676, 100910732, 65179, 24577, 25388, 25625, 140926, 171337, 29568, 309361, 170538, 310533, 81737, 85384, 314436, 25233, 24493, 60661, 170579, 309295, 300980, 25636, 25112, 114856, 363875, 94202, 24559, 309165, 24680, ...}	237	10	4.219409	2.962183
WP2376	{108348148, 29741, 81749, 171341, 81649, 363131, 58819, 24565, 58960, 301555, 24534, 170924, 57298, 54244, 83688, 689130, 365355, 24252, 85243, 81633, 300711, 83619, 64352, 305540, 117254, 108348061, 366960, 25319, 117263, 64191, 25283, 84006, 363855, 84509, 497932, 170851, 314322, 25260, 79130, 116686, 100361457, 314856, 289021, 50658, 29326, 24681, 29702, 24525, 24919, 300084, 85252, 64557, 24189, 24426, 103690044, 29568, 295549, 170538, 291084, 81822, 25256, 113894, 24421, 54349, 108348130, 29224, 681050, 301252, 65052, 29437, 497672, 24424, 24778, 25315, 81827, 29677, 24680, 170911, 24377, 366598, 367858, 25023, 313121, 116643, 289990, 25073, 24516, 499689, 289197, 24605, 24787, 60664, 116667, 293621, 361632, 24451, 84027, 25352, 246760, 25458, ...}	167	8	4.790419	2.231914
WP419	{25541, 114024, 25287, 25413, 170670, 24158, 117035, 64304, 113976, 113956, 171142, 25363, 25288, 29740, 25757, 113965}	16	8	50.000000	2.231914

Figure 9: Pathway analysis results using WikiPathways and TG-GATES data

**WP1286** Metapathway biotransformation  
**WP1307** Fatty Acid Beta Oxidation  
**WP372** Beta Oxidation Meta Pathway  
**WP358** MAPK Signaling Pathway  
**WP2376** Nuclear factor, erythroid-derived 2, like 2 signaling pathway  
**WP419** Mitochondrial LC-Fatty Acid Beta-Oxidation

Figure 10: Pathway titles of significantly affected pathways from WikiPathways

#### Further reading:

Martens, M., Verbruggen, T., Nymark, P., Grafström, R., Burgoon, L. D., Aladjov, H., Torres Andón, F., Evelo, C.T., Willighagen, E. L. (2018). Introducing WikiPathways as a Data-Source to Support Adverse Outcome Pathways for Regulatory Risk Assessment of Chemicals and Nanomaterials. *Frontiers in Genetics*, 9, 661. doi:10.3389/fgene.2018.00661

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