

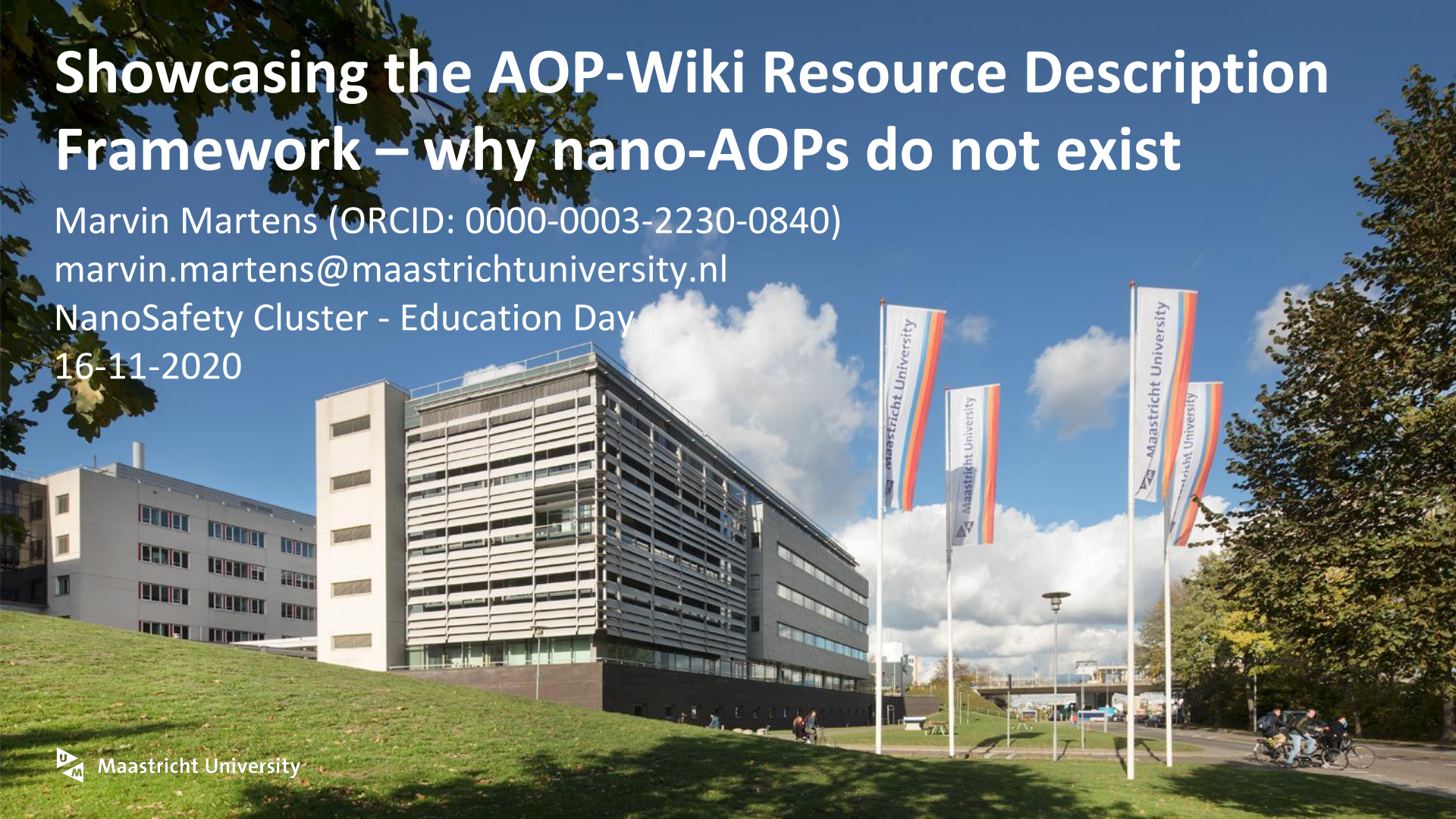
Showcasing the AOP-Wiki Resource Description Framework – why nano-AOPs do not exist

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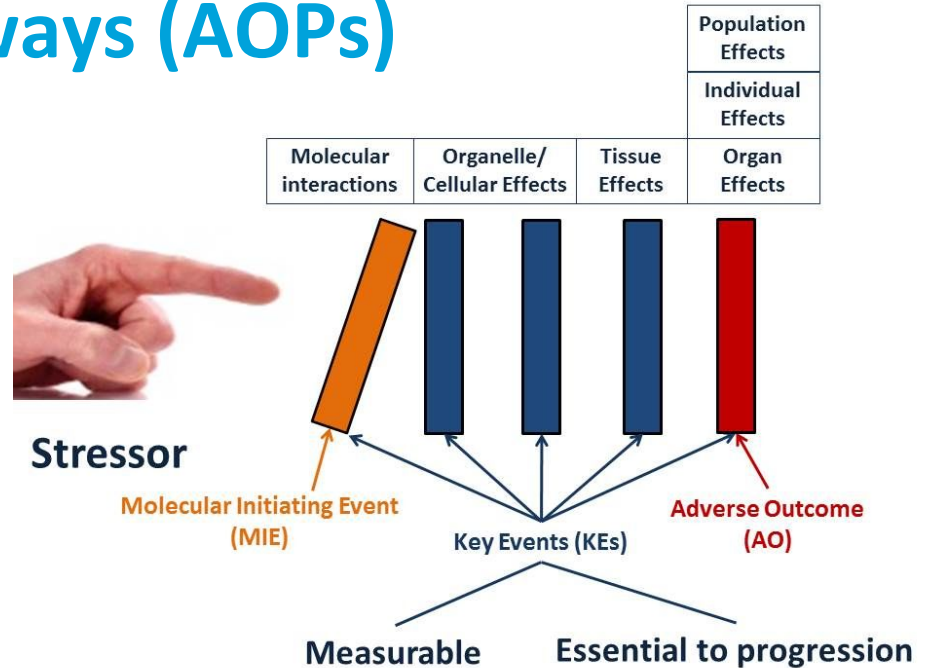
NanoSafety Cluster - Education Day

16-11-2020



Adverse Outcome Pathways (AOPs)

Framework that captures mechanistic knowledge of toxicological processes to support decision making in risk assessments



Toxicology data



Knowledge-based
regulatory risk
assessment

AOP-Wiki to capture, store and explore AOPs

Main repository for qualitative AOPs
OECD initiative, Joint effort between
EC-JRC and US EPA

Exploration:

- Free-text search
- XML download

AOP Knowledge Base (AOP-KB)



Element	Number
Adverse Outcome Pathways	306
Key Events	1118
Key Event Relationships	1338
Stressors	499

Poll: Have you ever searched for nanomaterial-content in the AOP-Wiki?

--> <https://app.wooclap.com/NANOSAFE> <--

**Question: What search-terms
would you enter for
nanomaterial-content?**

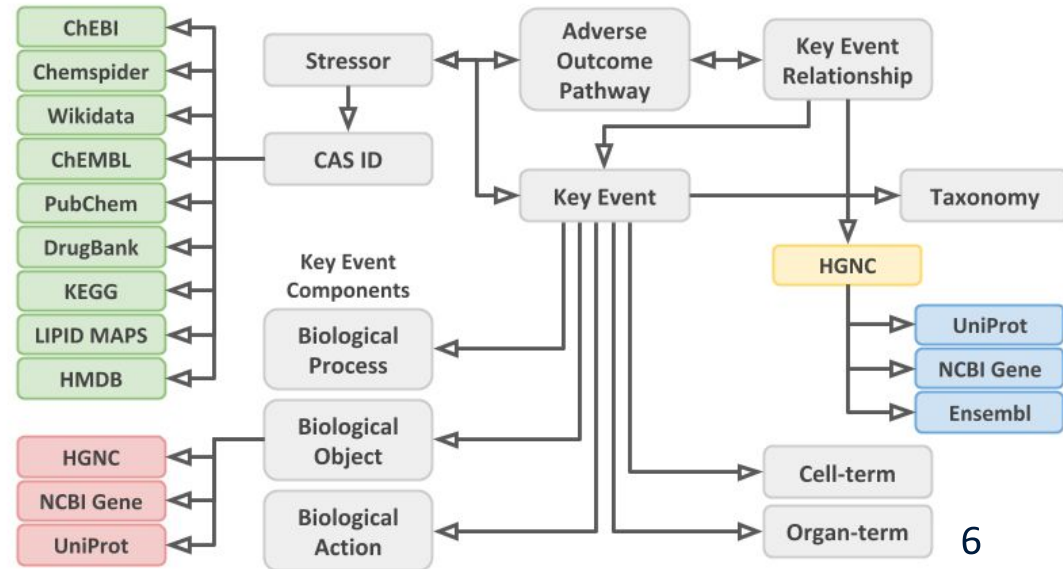
--> <https://app.wooclap.com/NANOSAFE> <--

The AOP-Wiki Resource Description Framework (RDF) is developed for new ways of exploring and using AOP content

Implements linked data standards

- (metadata) ontologies
- persistent identifiers

Improved interoperability
Improved accessibility



Ways of using the AOP-Wiki RDF

SPARQL Endpoint:

<http://aopwiki-rdf.prod.openrisknet.org/sparql/>

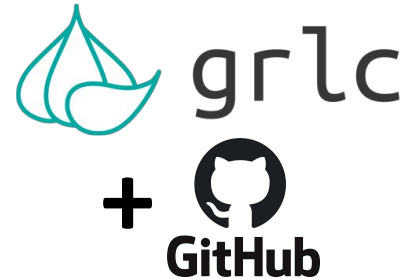
grlc Application Programming Interface (API):

<http://grlc.io/api-git/marvinm2/AOPWikiQueries>

Coding environments (Jupyter notebook)



SNORQL (SPARQL explorer)



SPARQL Query for AO “fibrosis”

SPARQL query:

```
SELECT ?KE ?AOP ?AOPshortname WHERE {  
  ?KE a aopo:KeyEvent ;  
      dc:identifier ?AOLookup ;  
      dc:title ?KEname .  
  ?AOP a aopo:AdverseOutcomePathway ;  
      dcterms:alternative ?AOPname ;  
      aopo:has_adverse_outcome ?AOLookup .  
  FILTER regex (?KEname, "fibrosis", "i")}  
ORDER BY DESC (?KEname)
```

KENAME	AOP	AOPshortname
"Pulmonary fibrosis"	http://identifiers.org/aop/173	"Substance interaction with the lung cell membrane leading to lung fibrosis"
"Pulmonary fibrosis"	http://identifiers.org/aop/241	"Latent TGFbeta1 activation leads to pulmonary fibrosis"
"Pulmonary fibrosis"	http://identifiers.org/aop/347	"TLR4 activation, PPAR gamma activation and Pulmonary fibrosis"
"N/A, Liver fibrosis"	http://identifiers.org/aop/144	"lysosomal uptake induced liver fibrosis"
"N/A, Liver fibrosis"	http://identifiers.org/aop/38	"Protein Alkylation to Liver Fibrosis"
"Lung fibrosis"	http://identifiers.org/aop/206	"PPARγ inactivation leading to lung fibrosis"
"Lung fibrosis"	http://identifiers.org/aop/319	"ACE2 inhibition, lung fibrosis"
"Formation, Liver fibrosis"	http://identifiers.org/aop/130	"Phospholipase A inhibitors"

grlc makes a more user-friendly API

Linked to GitHub repository
Pre-written SPARQL queries

- Variables
- Filters

Export as csv tables or json
Request URL (Curl)

The screenshot shows a web interface for a gRPC endpoint. At the top, it displays the HTTP method 'GET' and the endpoint path '/get-stressors-for-ao (literal)'. A description reads: 'Get Stressor Chemicals described to initiate AOPs that lead to selected Adverse Outcome (literal)'. Below this is a dark text area containing a SPARQL query with variables and filters. The query includes prefixes for DC, AOP, AOP Ontology, KE, and NCI, and a SELECT statement filtering by a KE filter. Below the query is a 'Parameters' section with a 'Cancel' button. A table lists parameters, with 'KEfilter' marked as required and having a description: 'A value of type string@en that will substitute ?_KEfilter_en in the original query'. The value 'fibrosis' is entered in the input field. At the bottom, there are 'Execute' and 'Clear' buttons. The 'Responses' section at the very bottom shows the 'Response content type' set to 'text/csv'.

```
#+ endpoint_in_url: False

prefix dc: <http://purl.org/dc/elements/1.1/>
prefix aop: <http://identifiers.org/aop/>
prefix aopo: <http://aopkb.org/aop_ontology#>
prefix ke: <http://identifiers.org/aop.events/>
PREFIX nci: <http://ncicb.nci.nih.gov/xml/owl/EVS/Thesaurus.owl#>

SELECT ?AO ?AOname ?StressorName ?ChemicalName WHERE {
  ?AO a aopo:KeyEvent ;
  dc:identifier ?AOLookup ;
  dc:title ?AOname .
  ?AOP a aopo:AdverseOutcomePathway ;
  aopo:has_adverse_outcome ?AOLookup ;
  nci:C54571 ?Stressor .
  ?Stressor dc:title ?StressorName .
  OPTIONAL {?Stressor aopo:has_chemical_entity ?Chemical .
    ?Chemical dc:title ?ChemicalName .}
  FILTER regex (?AOname, ?_KEfilter_en, "i")
  ORDER BY DESC (?AO)
```

Name	Description
KEfilter <small>required</small>	A value of type string@en that will substitute ?_KEfilter_en in the original query
string (query)	

fibrosis

Execute Clear

Responses Response content type text/csv

Jupyter notebook example

```
from SPARQLWrapper import SPARQLWrapper, JSON
aopwikisparql = SPARQLWrapper("http://aopwiki-rdf.prod.openrisknet.org/sparql/")
```

```
#function to return Adverse Outcome KE ID by free-text input
```

```
def findao(filterword):
    output = []
    sparqlquery = '''
SELECT DISTINCT ?KE WHERE {
    ?KE a aopo:KeyEvent ;
        dc:identifier ?AOLookup ;
        dc:title ?KEname .
    ?AOP aopo:has_adverse_outcome ?AOLookup.
FILTER regex (?KEname, "'' + filterword + ''", "i")
'''
    aopwikisparql.setQuery(sparqlquery)
    aopwikisparql.setReturnFormat(JSON)
    results = aopwikisparql.query().convert()
    for result in results["results"]["bindings"]:
        output.append(result['KE']['value'])
    return output
```

```
display(findao('fibrosis'))
```

```
['http://identifiers.org/aop.events/1458',
'http://identifiers.org/aop.events/1276',
'http://identifiers.org/aop.events/344',
'http://identifiers.org/aop.events/840']
```

```
import requests
import pandas as pd
pd.set_option('display.max_colwidth', -1)
from io import StringIO
```

```
grlc = 'http://grlc.io/api-git/marvinm2/AOPWikiQueries/'
```

```
#function to find AOP based on KE ID input
```

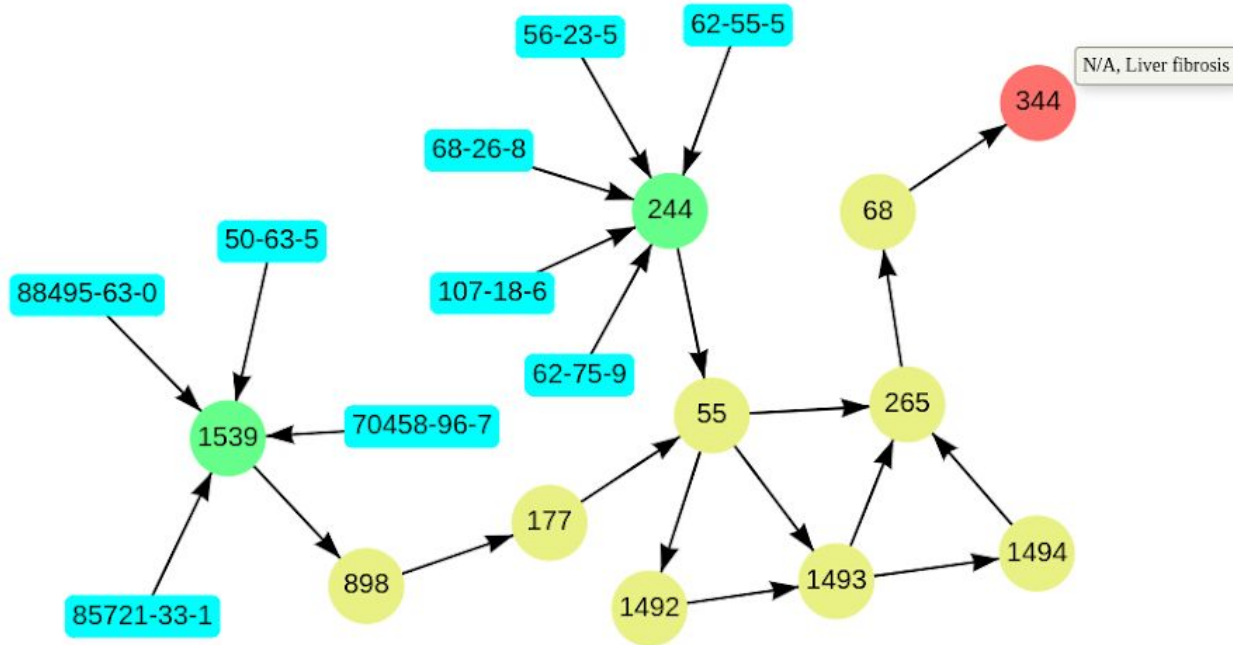
```
def findaop(KEID):
    output = []
    url = grlc+'get-aop-for-ao-uri?aofilter='+KEID
    headers = {'accept': 'text/csv'}
    result = requests.get(url, headers=headers)
    return result
```

```
for ao in aos:
    print(ao)
    result = findaop(ao)
    data_grlc = pd.read_csv(StringIO(result.text))
    display(data_grlc)
```

```
http://identifiers.org/aop.events/344
```

	AOP	AOPTitle
0	http://identifiers.org/aop/144	Endocytic lysosomal uptake leading to liver fibrosis
1	http://identifiers.org/aop/38	Protein Alkylation leading to Liver Fibrosis

Jupyter notebook example



SNORQL as semantic web browser

Pre-loaded SPARQL queries from GitHub repository
Easy to use, flexible



Ammar Ammar

SPARQL Query:

```
1 SELECT ?AO ?AOname ?AOP (CONCAT(' ', GROUP_CONCAT(?ChemicalName;SEPARATOR=', '), '') AS ?Ch
2 ?AO a aopo:KeyEvent ;
3 dc:identifier ?AOLookup ;
4 dc:title ?AOname .
5 ?AOP a aopo:AdverseOutcomePathway ;
6 aopo:has_adverse_outcome ?AOLookup ;
7 nci:C54571 ?Stressor .
8 ?Stressor dc:title ?StressorName.
9 OPTIONAL {?Stressor aopo:has_chemical_entity ?Chemical.
10 ?Chemical dc:title ?ChemicalName.}
11 FILTER regex (?AOname, "fibrosis", "i")
12 ORDER BY DESC (?AO)
13
```

Query Reset Export CSV Export JSON Export XML

SPARQL Examples:

https://github.com/marvinm2/AOPWikiSNC

Type part of the query file name to search for...

Search Clear

- A. Metadata
- B. Datadump
- C. Search
- ChemicalforAO.rq**
- D. Simpleconversions

Question: What makes an AOP nano-specific?

--> <https://app.wooclap.com/NANOSAFE> <--

Nanomaterials are challenging: endless number of possible effects

AOP definition:

- From Molecular Initiating Event to Adverse Outcome
- **Chemical-agnostic**

Physicochemical properties vary a lot

- Leading to different effects (MIE activation)
- Assay interference
- No consistent characterization
- Media of exposure and conditions at contact site

There are nanomaterials as Stressors in AOP-Wiki

Fibrosis mostly linked to chemicals

Nanomaterials are present

Total: 8 “nano”-stressors

AOname	StressorName	CAS
"Pulmonary fibrosis"	"Bleomycin"	"11056-06-7"
"Pulmonary fibrosis"	"Carbon nanotubes"	
"Pulmonary fibrosis"	"Carbon nanotubes, Multi-walled carbon nanotubes, single-walled carbon nanotubes, carbon nanofibres"	
"N/A, Liver fibrosis"	"Carbon tetrachloride"	"56-23-5"
"N/A, Liver fibrosis"	"Dimethyl nitrosamine"	"62-75-9"
"N/A, Liver fibrosis"	"artesunate"	"88495-63-0"
"N/A, Liver fibrosis"	"Chloroquine bis(phosphate)"	"50-63-5"
"N/A, Liver fibrosis"	"Norfloxacin"	"70458-96-7"
"N/A, Liver fibrosis"	"Ciprofloxacin"	"85721-33-1"
"N/A, Liver fibrosis"	"Retinol"	"68-26-8"
"N/A, Liver fibrosis"	"Thioacetamide"	"62-55-5"
"N/A, Liver fibrosis"	"Allyl Alcohol"	"107-18-6"
"N/A, Liver fibrosis"	"nanoparticles"	
"N/A, Liver fibrosis"	"ROS"	
"N/A, Liver fibrosis"	"o-methyl-serine dodecylamide hydrochloride (MSDH)"	



AOPs that describe nanomaterials

AOP ID	Adverse Outcome Pathway title	Adverse Outcome
AOP 106	Tubulin binding and aneuploidy	Increase, Aneuploid offspring
AOP 144	lysosomal uptake induced liver fibrosis	N/A, Liver fibrosis
AOP 152	Transthyretin interference	Cognitive Function, Decreased
AOP 173	Substance interaction with the lung cell membrane leading to lung fibrosis	Pulmonary fibrosis
AOP 207	NADPH oxidase activation leading to reproductive failure	Reproductive failure
AOP 208	JAK/STAT and TGF-beta pathways activation leading to reproductive failure	Reproductive failure
AOP 209	Cholesterol and glutathione leading to hepatotoxicity: Multi-OMICS approach	Hepatotoxicity
AOP 210	JNK, FOXO and WNT alteration leading to reproductive failure: Multi-OMICS approach	Reproductive failure
AOP 237	Secretion of inflammatory cytokines leading to plaque progression	Plaque progression in arteries
AOP 241	Latent TGFbeta1 activation leads to pulmonary fibrosis	Pulmonary fibrosis
AOP 293	Increased DNA damage leading to breast cancer	Increased, Ductal Hyperplasia; Increase, Mutations; N/A, Breast Cancer
AOP 294	RONS leading to breast cancer	Increase, Mutations; N/A, Breast Cancer; Increase, DNA damage; Increased, Ductal Hyperplasia
AOP 296	Oxidative DNA damage, chromosomal aberrations and mutations	Increase, Chromosomal aberrations; Increase, Mutations
AOP 303	Frustrated phagocytosis-induced lung cancer	Lung cancer

Poll: Can we use AOPs for nanomaterials?

--> <https://app.wooclap.com/NANOSAFE> <--

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