OpenRiskNet

RISK ASSESSMENT E-INFRASTRUCTURE

AOP-Wiki Resource Description Framework

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OpenRiskNet: Open e-Infrastructure to Support Data Sharing, Knowledge Integration and *in silico* Analysis and Modelling in Risk Assessment
Project Number 731075

OpenRiskNet case study: AOPLink

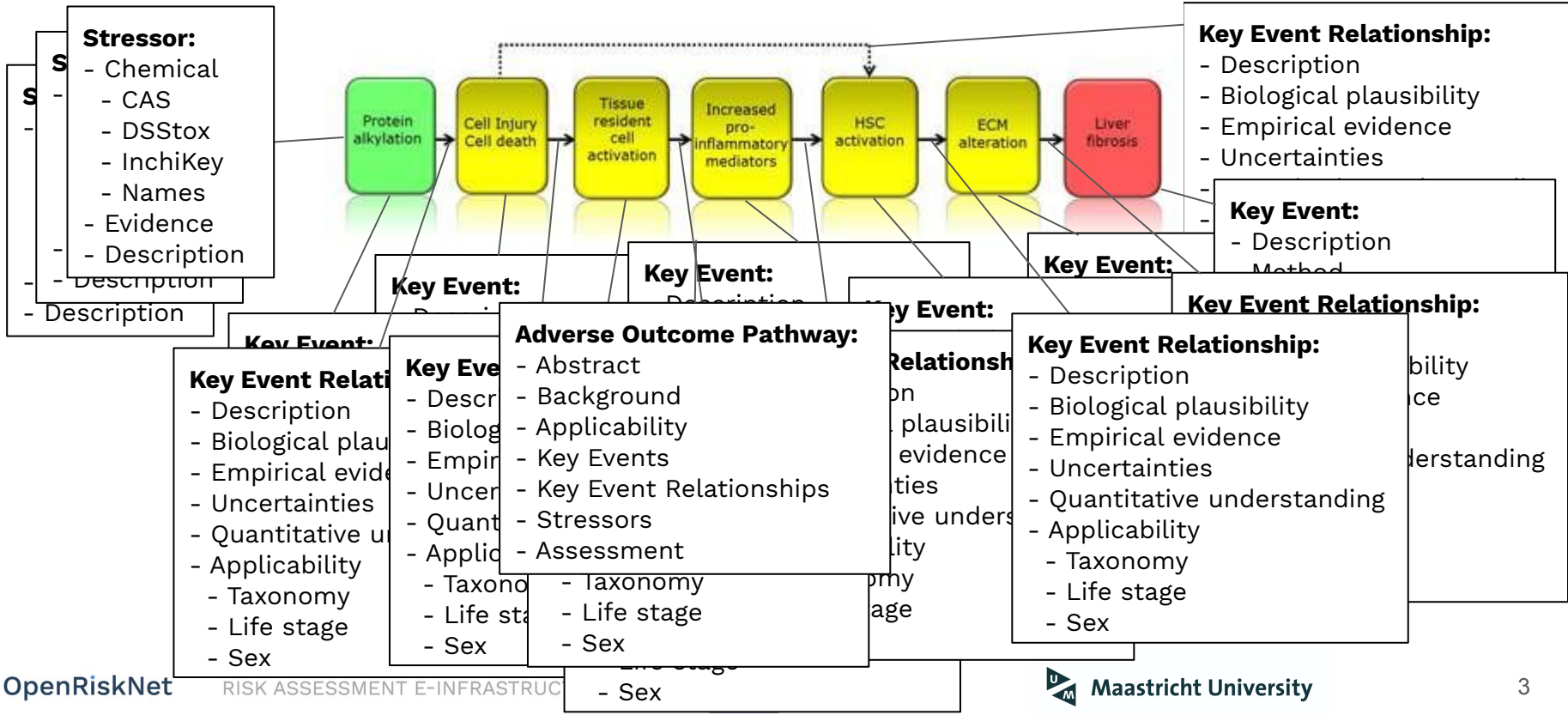
Experimental data ⟷ **Adverse Outcome Pathways**

Problem:

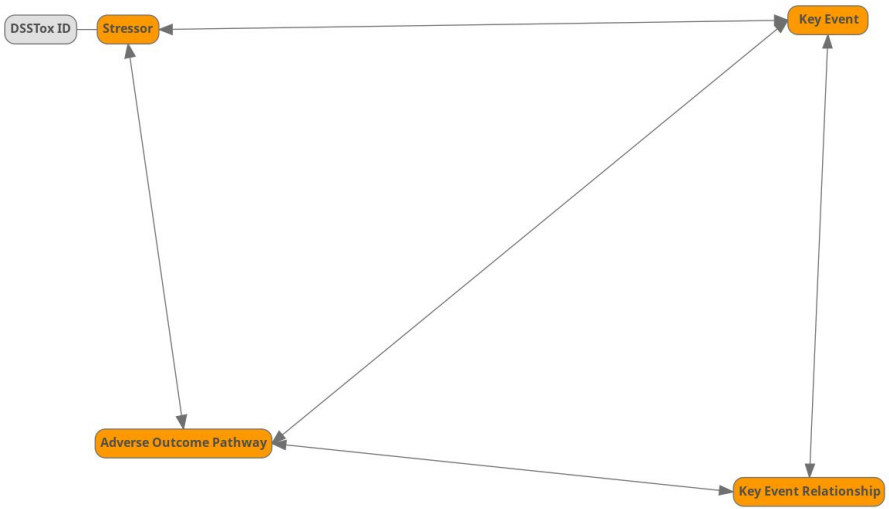
- AOP-Wiki are **blobs of plain text**
- Difficult to extract information **(accessibility)**
- Impossible to harmonize with other databases **(interoperability)**

Solution: **semantic modeling** of the content of the database, including ontological annotations and persistent identifiers

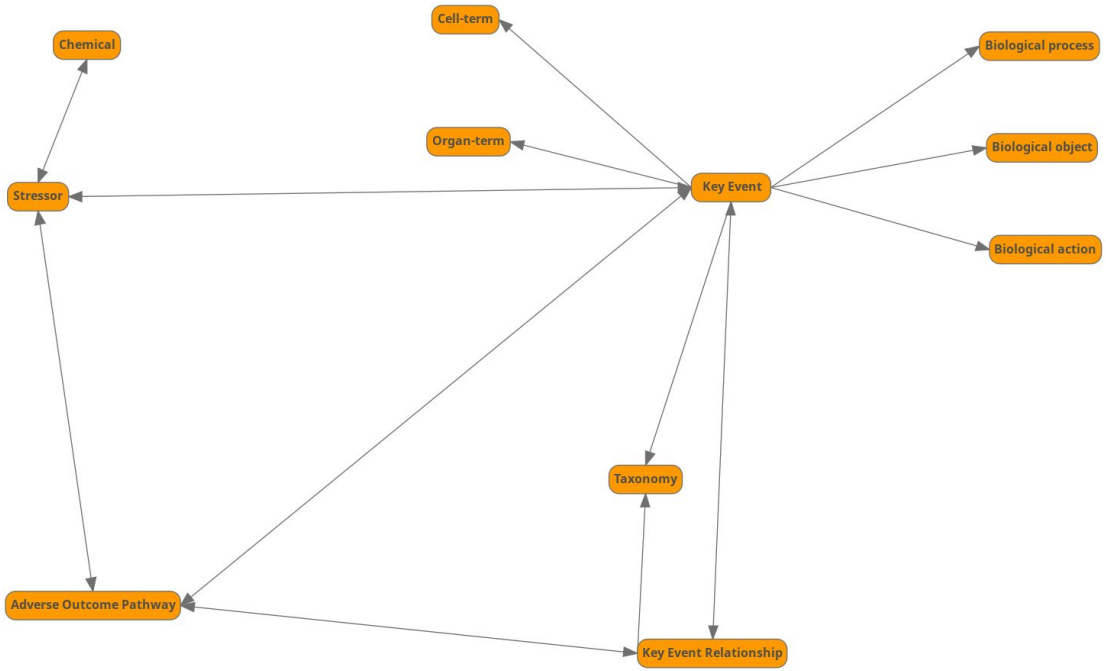
AOPs in AOP-Wiki contain a lot of information



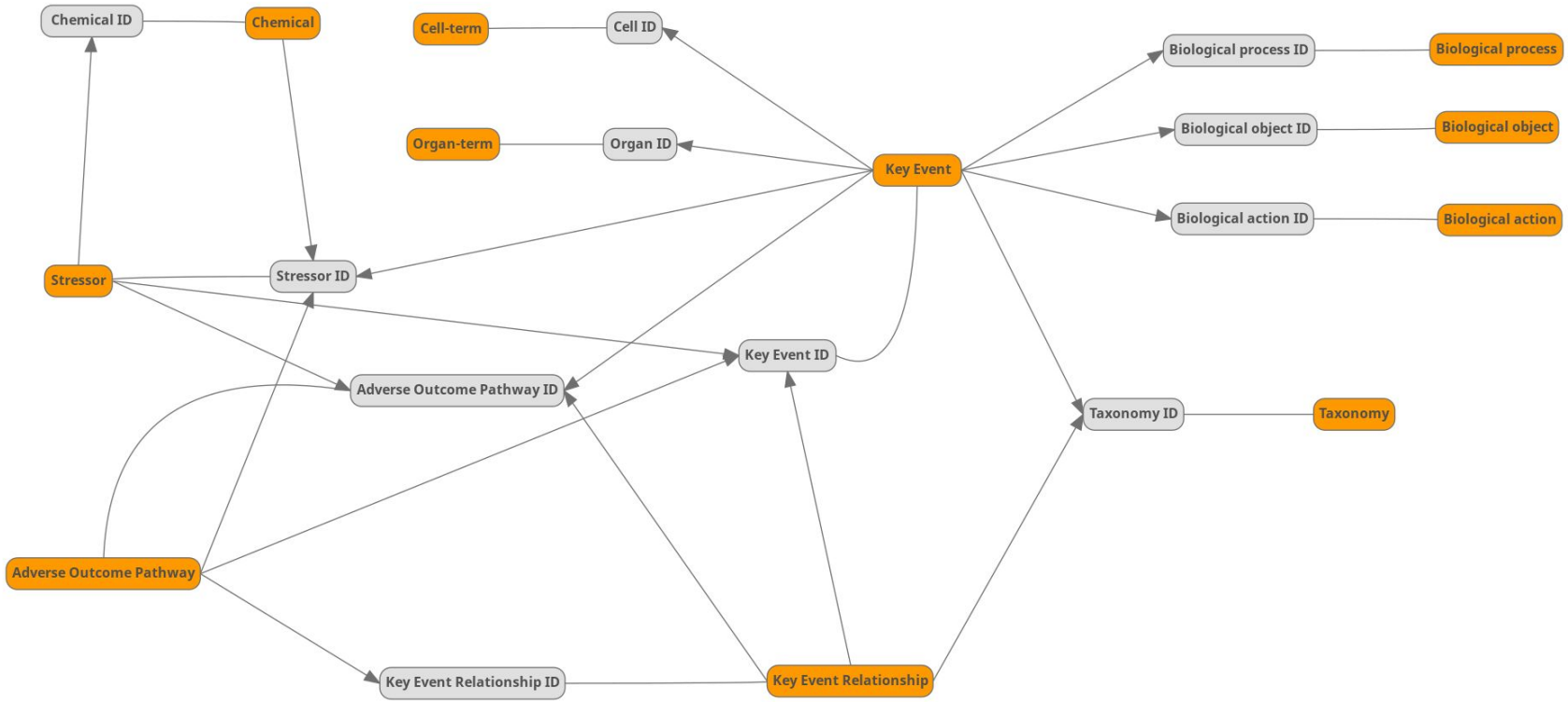
Existing links in the AOP-Wiki



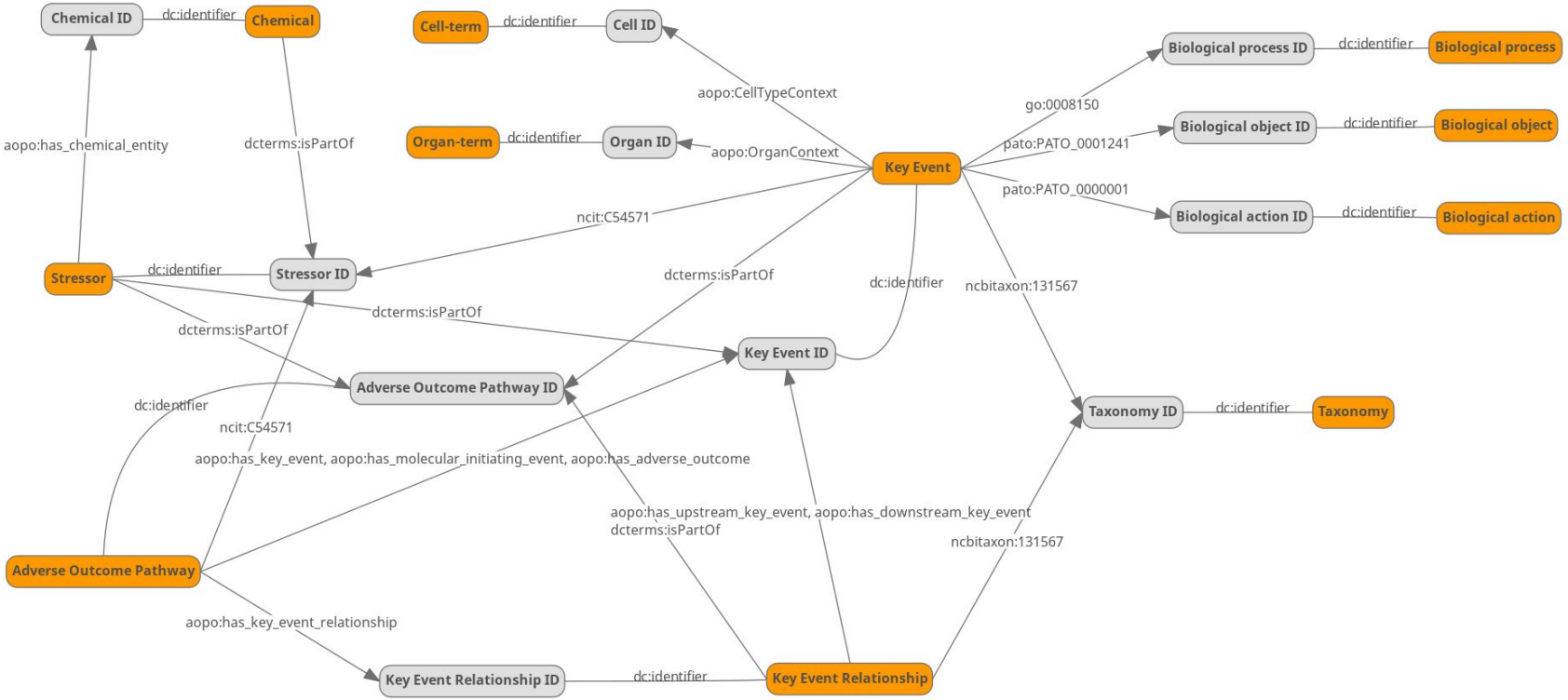
Eleven central components in the data dumps

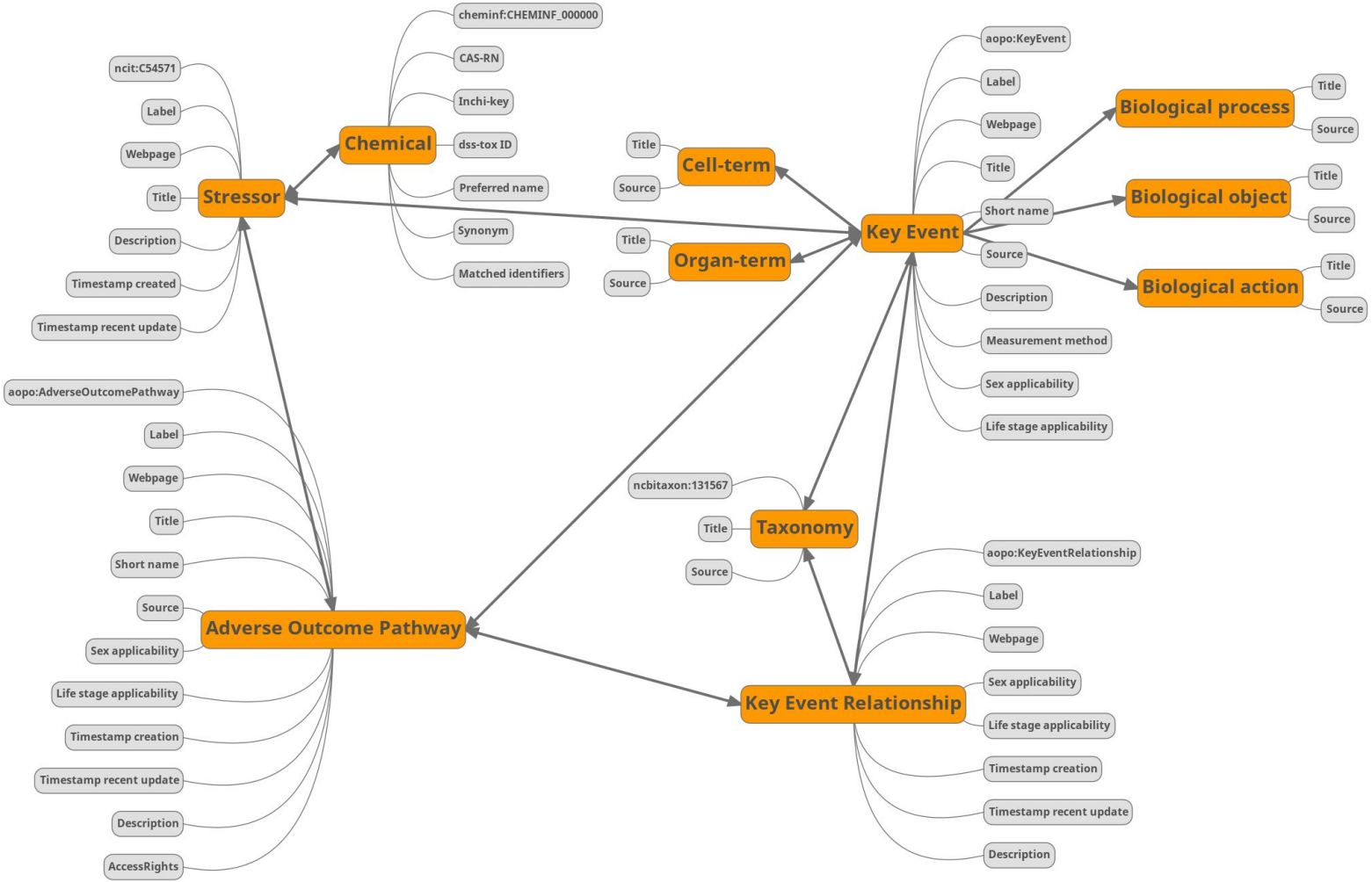


All components are connected through identifiers



Adding meaningful context to links using ontologies




Stressor
ncit:C54571
Label
Webpage
Title
Description
Timestamp created
Timestamp recent update
Chemical
cheminf:CHEMINF_000000
CAS-RN
Inchi-key
dss-tox ID
Preferred name
Synonym
Matched identifiers
Cell-term
Title
Source
Organ-term
Title
Source
Key Event
aopo:KeyEvent
Label
Webpage
Title
Short name
Source
Description
Measurement method
Sex applicability
Life stage applicability
Biological process
Title
Source
Biological object
Title
Source
Biological action
Title
Source
aopo:AdverseOutcomePathway
Label
Webpage
Title
Short name
Source
Sex applicability
Life stage applicability
Timestamp creation
Timestamp recent update
Description
AccessRights
Adverse Outcome Pathway
ncbitaxon:131567
Title
Source
Taxonomy
Key Event Relationship
aopo:KeyEventRelationship
Label
Webpage
Sex applicability
Life stage applicability
Timestamp creation
Timestamp recent update
Description

Increased **accessibility** and **interoperability**

Accessibility

- Allows custom queries
- Query for distant relationships

Interoperability

- Uses of ontologies and persistent identifiers
  - Links to external databases / knowledge sources
  - Standard vocabulary within AOP domain (e.g. the AOP Ontology)
- **Integration in systematic, reproducible workflows**
- **Easy links to external databases**

Thank you for your attention!

Webinar “Connecting AOPs, knowledge and data with AOPLink workflows” on July 15th, 4PM CEST, organized by OpenRiskNet (https://openrisknet.org/events/70/)

Previous webinar “Identification and linking of data related to AOPWiki” (https://openrisknet.org/events/59/)

Improved accessibility: examples

From an AOP, give me all measurement methods.

For **AOP 12**, print me all KE IDs, KE names, and measurement methods text

KeyEventID	KeyEventName	
"KE 188"	"N/A, Neuroinflammation"	"Neuroinflammation, i.e. the activation of glial cells can be measured by quantification of cellular markers (most commonly), or of released mediators (less common). As multiple activation Microglial activation can be detected based on the increased numbers of labeled microglia per volume element of brain tissue (due to increase of binding sites, proliferation, and im The most frequently used astrocyte marker is GFAP (99% of all studies) (Eng et al., 2000). This protein is highly specific for astrocytes in the brain, and antibodies are available All immunocytochemical methods can also be applied to cell culture models. In patients, microglial accumulation can be monitored by PET imaging, using [11C]-PK 11195 as a microglial marker (Banati et al., 2002). Activation of glial cells can be assessed in tissue or cell culture models also by quantification of sets of activation markers. This can for instance be done by PCR quantification Pro- and anti-inflammatory cytokine expression (IL-1β; TNF-α, Il-6, IL-4); or expression of immunostimmulatory proteins (e.g. MHC-II) Itgam, CD86 expression as markers of M1 microglial phenotype Arg1, MRC1, as markers of M2 microglial phenotype (for descriptions of techniques, see also Falsig 2004; Lund 2006 ; Kuegler 2010; Monnet-Tschudi et al., 2011; Sandström et al., 2014; von Tobel et al., 2014) Regulatory example using the KE:Measurement of glial fibrillary acidic protein (GFAP) in brain tissue, whose increase is a marker of astrocyte reactivity, is required by the US EPA in roden "
"KE 195"	"Inhibition, NMDARs"	" Methods that have been previously reviewed and approved by a recognized authority should be included in the Overview section above. All other methods, including those well established in the published literature, should be described here. Consider the following criteria when describing each method: 1. Is the assay fit for purpose? 2. Is the assay directly or indirectly (i.e. a surrogate) related to a key event relevant to the final adverse effect in question? 3. Is the assay repeatable? 4. Is the assay reproducible? No OECD methods are available to measure the activation state of NMDA receptors. The measurement of the activation or the inhibition of NMDA receptors is done indirectly by recording the individual ion channels that are selective to Na+, K+ and Ca+2 by the patch clamp t The whole-cell patch clamp recording techniques have also been used to study synaptically-evoked NMDA receptor-mediated excitatory or inhibitory postsynaptic currents (EPSCs and IPSCs, resp Microelectrode array (MEA) recordings are used to measure electrical activity in cultured neurons in response to NMDA receptor activation or inactivation (Keefer et al., 2001, Gramowski et "
"KE 201"	"Binding of antagonist, NMDA receptors"	"Methods that have been previously reviewed and approved by a recognized authority should be included in the Overview section above. All other methods, including those well established in t 1. Ex vivo: The most common assay used is the NMDA receptor (MK801 site) radioligand competition binding assays (Reynolds, 2001; Gao et al., 2013; http://pdsp.med.unc.edu/UNC-CH%20Protocol% 2. In silico: The prediction of NMDA receptor targeting is achievable by combining database mining, molecular docking, structure-based pharmacophore searching, and chemical similarity searc "
		"In laboratory animals: in rodents, a variety of tests of learning and memory have been used to probe the integrity of hippocampal function. These include tests of spatial learning like the 1) RAM, Barnes, MWM are examples of spatial tasks, animals are required to learn the location of a food reward (RAM); an escape hole to enter a preferred dark tunnel from a brightly lit ope 2) Novel Object recognition. This is a simpler task that can be used to probe recognition memory. Two objects are presented to animal in an open field on trial 1, and these are explored. Or

Find AOPs and their MIEs from searching by CAS-RN.

By single CAS-RN: 107-18-6:

CAS	ChemicalName	AOPwebpage	AdverseOutcomePathwayName	MIEwebpage	MolecularInitiatingEventName
"107-18-6"	"Allyl alcohol"	http://identifiers.org/aop/258	"Renal protein alkylation leading to kidney toxicity"	http://identifiers.org/aop.events/244	"Alkylation, Protein"
"107-18-6"	"Allyl alcohol"	http://identifiers.org/aop/38	"Protein Alkylation leading to Liver Fibrosis"	http://identifiers.org/aop.events/244	"Alkylation, Protein"

By list of CAS-RN: 107-18-6, 103-90-2, 83-79-4 (no limit)

CAS	ChemicalName	AOPwebpage	AdverseOutcomePathwayName	MIEwebpage	MolecularInitiatingEventName
"107-18-6"	"Allyl alcohol"	http://identifiers.org/aop/258	"Renal protein alkylation leading to kidney toxicity"	http://identifiers.org/aop.events/244	"Alkylation, Protein"
"103-90-2"	"Acetaminophen"	http://identifiers.org/aop/260	"CYP2E1 activation and formation of protein adducts leading to neurodegeneration"	http://identifiers.org/aop.events/1508	"CYP2E1 Activation"
"103-90-2"	"Acetaminophen"	http://identifiers.org/aop/260	"CYP2E1 activation and formation of protein adducts leading to neurodegeneration"	http://identifiers.org/aop.events/1509	"Protein Adduct Formation"
"83-79-4"	"Rotenone"	http://identifiers.org/aop/3	"Inhibition of the mitochondrial complex I of nigro-striatal neurons leads to parkinsonian motor deficits"	http://identifiers.org/aop.events/888	"Binding of inhibitor, NADH-ubiquinone oxidoreductase (
"107-18-6"	"Allyl alcohol"	http://identifiers.org/aop/38	"Protein Alkylation leading to Liver Fibrosis"	http://identifiers.org/aop.events/244	"Alkylation, Protein"

Get chemical identifiers for a certain chemical

For CAS-RN 107-18-6, external identifiers for ChEBI, HMDB, ChemSpider, etc.

CAS	ChemicalName	MatchingIDs
"107-18-6"	"Allyl alcohol"	https://identifiers.org/chebi/16605
"107-18-6"	"Allyl alcohol"	https://identifiers.org/chebi/CHEBI:16605
"107-18-6"	"Allyl alcohol"	https://identifiers.org/chebi/CHEBI:2604
"107-18-6"	"Allyl alcohol"	https://identifiers.org/chembl.compound/CHEMBL234926
"107-18-6"	"Allyl alcohol"	https://identifiers.org/chemspider/13872989
"107-18-6"	"Allyl alcohol"	https://identifiers.org/hmdb/HMDB0031652
"107-18-6"	"Allyl alcohol"	https://identifiers.org/hmdb/HMDB31652
"107-18-6"	"Allyl alcohol"	https://identifiers.org/wikidata/Q414553

For CAS-RN 107-18-6, find identifiers for ChEBI

CAS	ChemicalName	ChEBI	MatchingIDs
"107-18-6"	"Allyl alcohol"	"16605"	https://identifiers.org/chebi/16605
"107-18-6"	"Allyl alcohol"	"CHEBI:16605"	https://identifiers.org/chebi/CHEBI:16605
"107-18-6"	"Allyl alcohol"	"CHEBI:2604"	https://identifiers.org/chebi/CHEBI:2604

Search AOPs by ChEBI Identifier

With one of the ChEBI IDs found earlier: CHEBI:16605

ChEBI	ChemicalName	AOPwebpage	AdverseOutcomePathwayName
CHEBI:16605	"Allyl alcohol"	http://identifiers.org/aop/258	"Renal protein alkylation leading to kidney toxicity"
CHEBI:16605	"Allyl alcohol"	http://identifiers.org/aop/38	"Protein Alkylation leading to Liver Fibrosis"

Linking all AOs and MIEs

Give me all Molecular Initiating Events that lead to a particular Adverse Outcome: Learning and memory impairment (KE ID 341)

AOwebpage	AdverseOutcomeName	MIEwebpage	MolecularInitiatingEventName
http://identifiers.org/aop.events/341	"Impairment, Learning and memory"	http://identifiers.org/aop.events/1487	"Binding, Thiol/seleno-proteins involved in protection against oxidative stress"
http://identifiers.org/aop.events/341	"Impairment, Learning and memory"	http://identifiers.org/aop.events/201	"Binding of antagonist, NMDA receptors"
http://identifiers.org/aop.events/341	"Impairment, Learning and memory"	http://identifiers.org/aop.events/201	"Binding of antagonist, NMDA receptors"
http://identifiers.org/aop.events/341	"Impairment, Learning and memory"	http://identifiers.org/aop.events/424	"Inhibition, Na+/I- symporter (NIS)"
http://identifiers.org/aop.events/341	"Impairment, Learning and memory"	http://identifiers.org/aop.events/875	"Binding of agonist, Ionotropic glutamate receptors"

Give me all Adverse Outcomes that can be the result of a particular Molecular Initiating Event: AhR activation (KE ID 18)

MIEwebpage	MolecularInitiatingEventName	AOwebpage	AdverseOutcomeName
http://identifiers.org/aop.events/18	"Activation, AhR"	http://identifiers.org/aop.events/369	"Uroporphyria"
http://identifiers.org/aop.events/18	"Activation, AhR"	http://identifiers.org/aop.events/455	"Accumulation, Liver lipid"
http://identifiers.org/aop.events/18	"Activation, AhR"	http://identifiers.org/aop.events/947	"Increase, Early Life Stage Mortality"

Get chemicals that could lead to a particular Key Event.

In this case, for the Adverse Outcome: Learning and memory impairment

Also possible for any MIE or intermediate KE

KEwebpage	KeyEventName	Stressor	ChemicalName
http://identifiers.org/aop.events/341	"Impairment, Learning and memory"	http://identifiers.org/aop.stressor/59	"Lead"
http://identifiers.org/aop.events/341	"Impairment, Learning and memory"	http://identifiers.org/aop.stressor/59	"Lead"
http://identifiers.org/aop.events/341	"Impairment, Learning and memory"	http://identifiers.org/aop.stressor/336	"Acrylamide"
http://identifiers.org/aop.events/341	"Impairment, Learning and memory"	http://identifiers.org/aop.stressor/40	"Methylmercuric(II) chloride"
http://identifiers.org/aop.events/341	"Impairment, Learning and memory"	http://identifiers.org/aop.stressor/381	"Mercury chloride"
http://identifiers.org/aop.events/341	"Impairment, Learning and memory"	http://identifiers.org/aop.stressor/21	"L-Domoic acid"
http://identifiers.org/aop.events/341	"Impairment, Learning and memory"	http://identifiers.org/aop.stressor/68	"Thiocyanate"
http://identifiers.org/aop.events/341	"Impairment, Learning and memory"	http://identifiers.org/aop.stressor/66	"Perchlorate"
http://identifiers.org/aop.events/341	"Impairment, Learning and memory"	http://identifiers.org/aop.stressor/219	"Econazole"
http://identifiers.org/aop.events/341	"Impairment, Learning and memory"	http://identifiers.org/aop.stressor/67	"Nitrate"