AOPWiki

TUTORIAL

This talk does not necessarily reflect the views of the participating organizations. Mention of trade names or commercial products does not constitute endorsement by any organization.

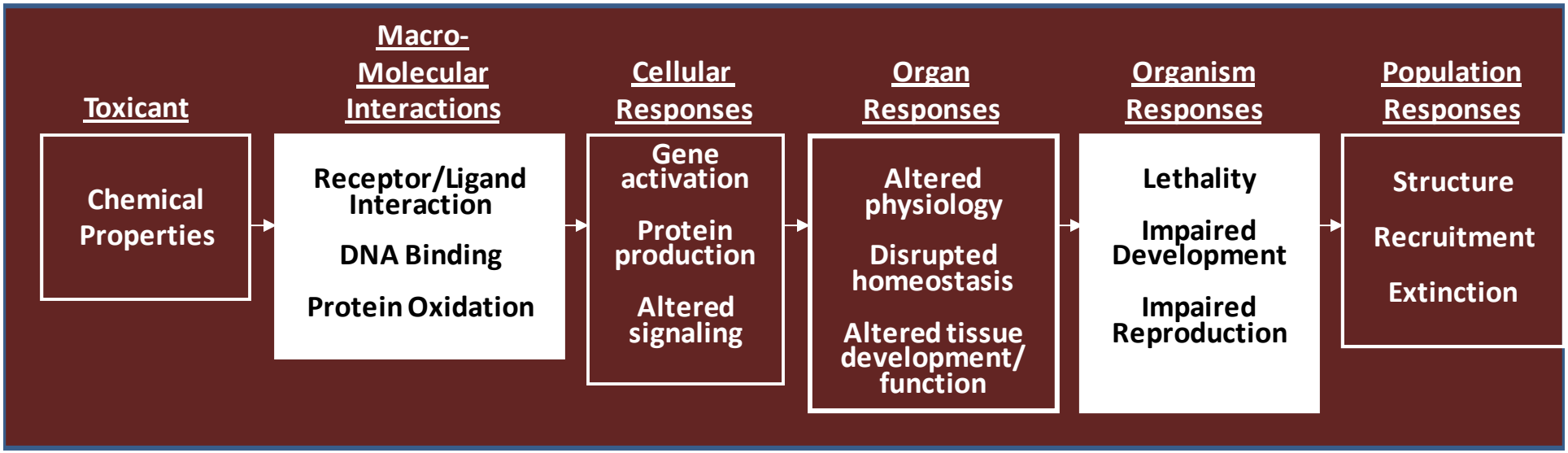
Agenda

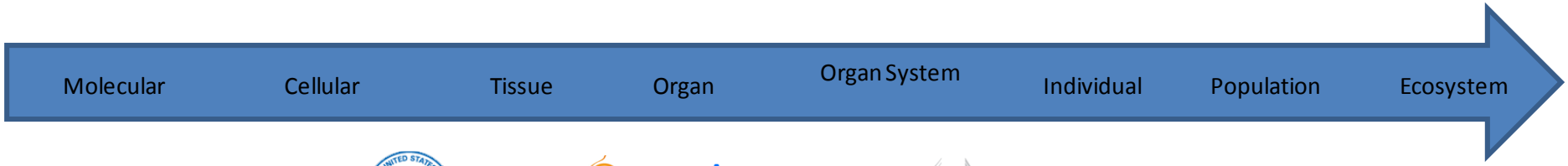
- AOP Framework
- OECD AOP Guidance
- AOP KB and AOPWiki
- AOPWiki Walkthrough
- AOP KB – Other Components & Future Plans

Adverse Outcome Pathway Framework

An Adverse Outcome Pathway (AOP) is a conceptual framework that portrays existing knowledge concerning the linkage between a direct molecular initiating event and an adverse outcome, at a level of biological organization relevant to risk assessment.

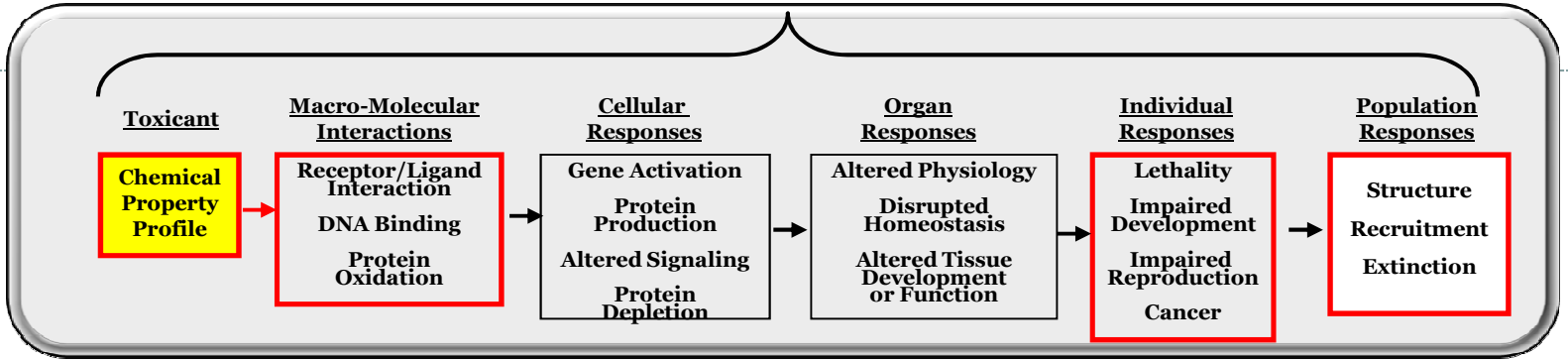
(Ankley et al. 2010, Environ. Toxicol. Chem., 29(3): 730-741.)

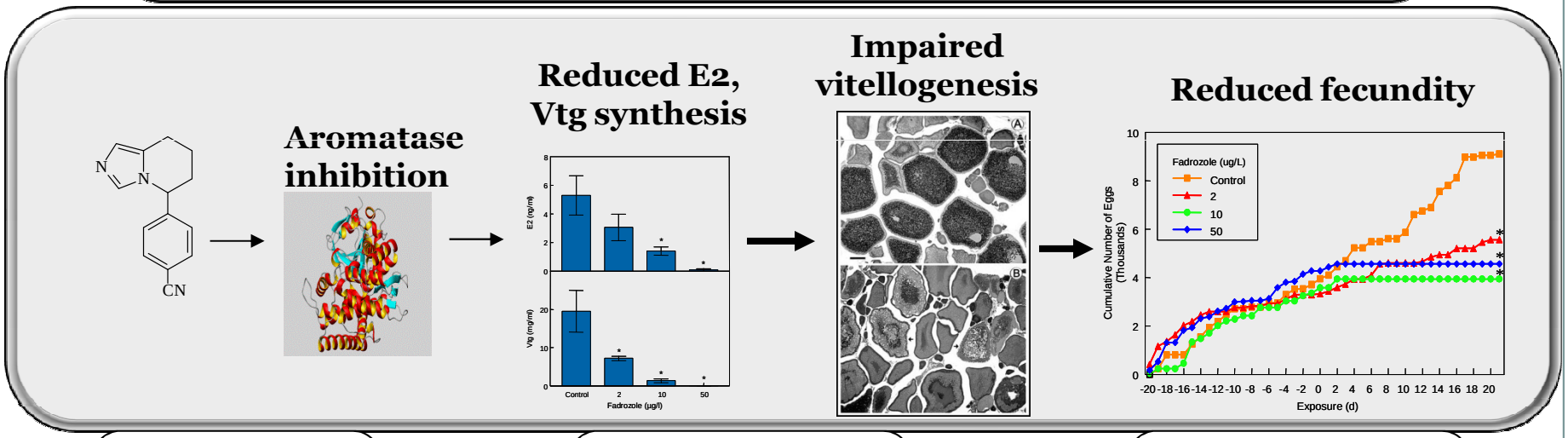




Example

Adverse Outcome Pathway





Molecular initiating event				Key events or predictive relationships spanning levels of biological organization			Adverse outcome relevant to risk assessment

Adverse Outcome Pathway Conventions

Molecular Initiating Event (MIE)

- Key event directly perturbed by interaction with a chemical
- One MIE per AOP
- MIE can link to multiple AOPs

Adverse Outcome (AO)

- Terminal node in an AOP
- One AO per AOP
- AO can link to multiple AOPs

Key Events

- Any number of intermediate key events can link MIE to AO
- Key events can be shared by multiple pathways
- Intermediate key events in one pathway may be MIEs in others

Example of a Key Event Description

6.4. Key Event –17β-estradiol (E2) synthesis by ovarian granulosa cells, reduced

6.4.1. Description: Within the ovary, aromatase expression and estradiol synthesis is primarily localized in the granulosa cells (reviewed in (Norris 2007; Havelock et al. 2004, Yaron 1995) and others). C-19 androgens diffuse from the theca cells into granulosa cells where aromatase can catalyze their conversion to C-18 estrogens.

6.4.2. Measurement/detection: Due to the importance of both theca and granulosa cells in ovarian steroidogenesis, it is generally impractical to measure E2 production by isolated granulosa cells (Havelock et al. 2004). However, this key event can be evaluated by examining E2 production by intact ovarian tissue explants either exposed to chemicals in vitro (e.g., (Villeneuve et al. 2007; McMaster ME 1995) or in vivo (i.e., via ex vivo steroidogenesis assay; e.g., (Ankley et al. 2007)). Aromatase inhibitors should cause a concentration-dependent decrease in E2 production by ovarian explants, at least when exposed in vitro, without reductions in T production. Assuming tissue viability is maintained, reductions in both E2 and T production generally indicate impacts on one or more additional targets in addition to or other than aromatase. For example, inhibitors of upstream steroidogenic enzymes (e.g., CYP11a, CYP17, 3β-HSD) or reductions in gonadotropin signaling (for in vivo systems with intact HPG-axis) can lead to reductions in both T and E2 production. Additionally, reductions in E2 production may not always be observed in the ex vivo assay, following exposure of organisms in vivo, due to compensatory responses that have been demonstrated to occur, presumably as a result of feedback processes within the hypothalamic-pituitary-gonadal axis (e.g., (Ankley et al. 2007; Villeneuve et al. 2009).

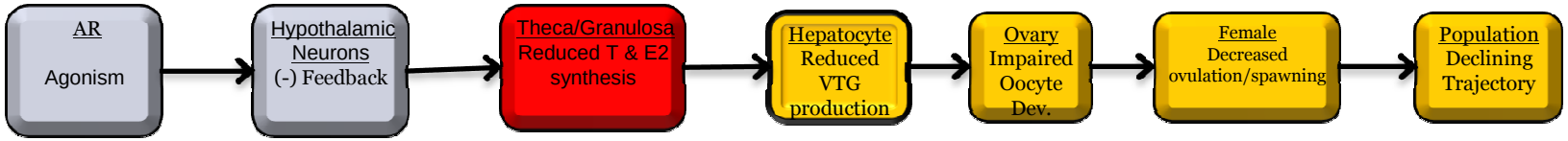
6.4.3. Taxonomic applicability: Key enzymes needed to synthesize 17β-estradiol first appear in the common ancestor of amphioxus and vertebrates (Baker 2011). Consequently, this key event is applicable to most vertebrates.

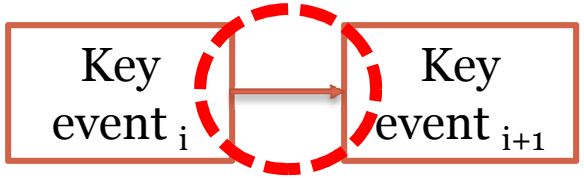
Description of the biology

Methods for measurement/detection

Taxonomic applicability

Adverse Outcome Pathway Conventions





(Edge)

Linkage/Relationship

- Connects a pair of key events (upstream to downstream)
- Defined by k.e.1, nature of relationship, k.e. 2
- Plasma E2, reduced: leads to: VTG transcription, reduced

Weight of evidence lies in the linkages

Example of a Linkage Description

1.Plasma E2 concentrations, reduced: VTG transcription and translation in liver, reduced

1. **Plausibility:** Vitellogenin synthesis in fish is localized in the liver and is well documented to be regulated by estrogens via interaction with estrogen receptors (Tyler et al. 1996; Tyler and Sumpter 1996; Arukwe and Goksøyr 2003). Liver is not regarded as a major site of E2 synthesis (Norris 2007), therefore the majority of E2 in liver comes from the circulation.

2.Empirical support:

- In a number of time-course experiments with aromatase inhibitors, decreases in plasma estradiol concentrations precede decreases in plasma vitellogenin concentrations (Villeneuve et al. 2009; Ankley et al. 2009a; Skolness et al. 2011).
- It was demonstrated in *Danio rerio* that in vivo exposure to the aromatase inhibitor letrozole significantly reduced the expression of mRNA transcripts coding for vtg1, vtg2, and erα, all of which are known to be regulated by estrogens (Sun et al. 2010). However, similar effects were not observed in primary cultured hepatocytes from *Danio rerio*, indicating that letrozole's effects on vtg transcription were not direct. Conversely, many studies have demonstrated that exposure of hepatocytes to estrogens in vitro or in vivo induce vitellogenin mRNA synthesis (e.g., see reviews by (Navas and Segner 2006; Iguchi et al. 2006)).

3.Quantitative understanding: At least two computational models that include functions which link circulating concentrations of E2 to VTG production by the liver have been published (Li et al. 2011a; Murphy et al. 2005; Murphy et al. 2009). However, both models focus on predicting plasma VTG concentrations rather than transcription or translation within the liver. A significant positive correlation (r=0.87) between plasma E2 concentrations corresponding plasma VTG concentrations in female fathead minnows held under laboratory conditions has also been reported (Ankley et al. 2008).

Header refers to a pair of key events (edge)

Biological plausibility

Empirical support

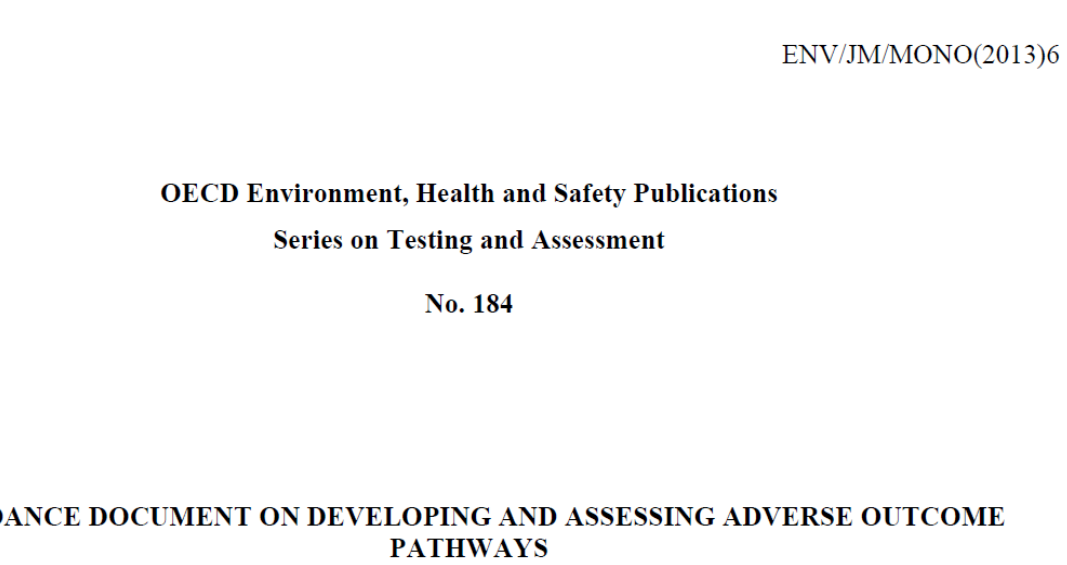
Living documents – particularly relative to KB

Describes quantitative relationships between adjacent key event measurements

- Correlations
- Models
- Thresholds/p.o.d.

Uncertainties or inconsistencies

OECD AOP Guidance



ENV/JM/MONO(2013)6

OECD Environment, Health and Safety Publications

Series on Testing and Assessment

No. 184

GUIDANCE DOCUMENT ON DEVELOPING AND ASSESSING ADVERSE OUTCOME PATHWAYS

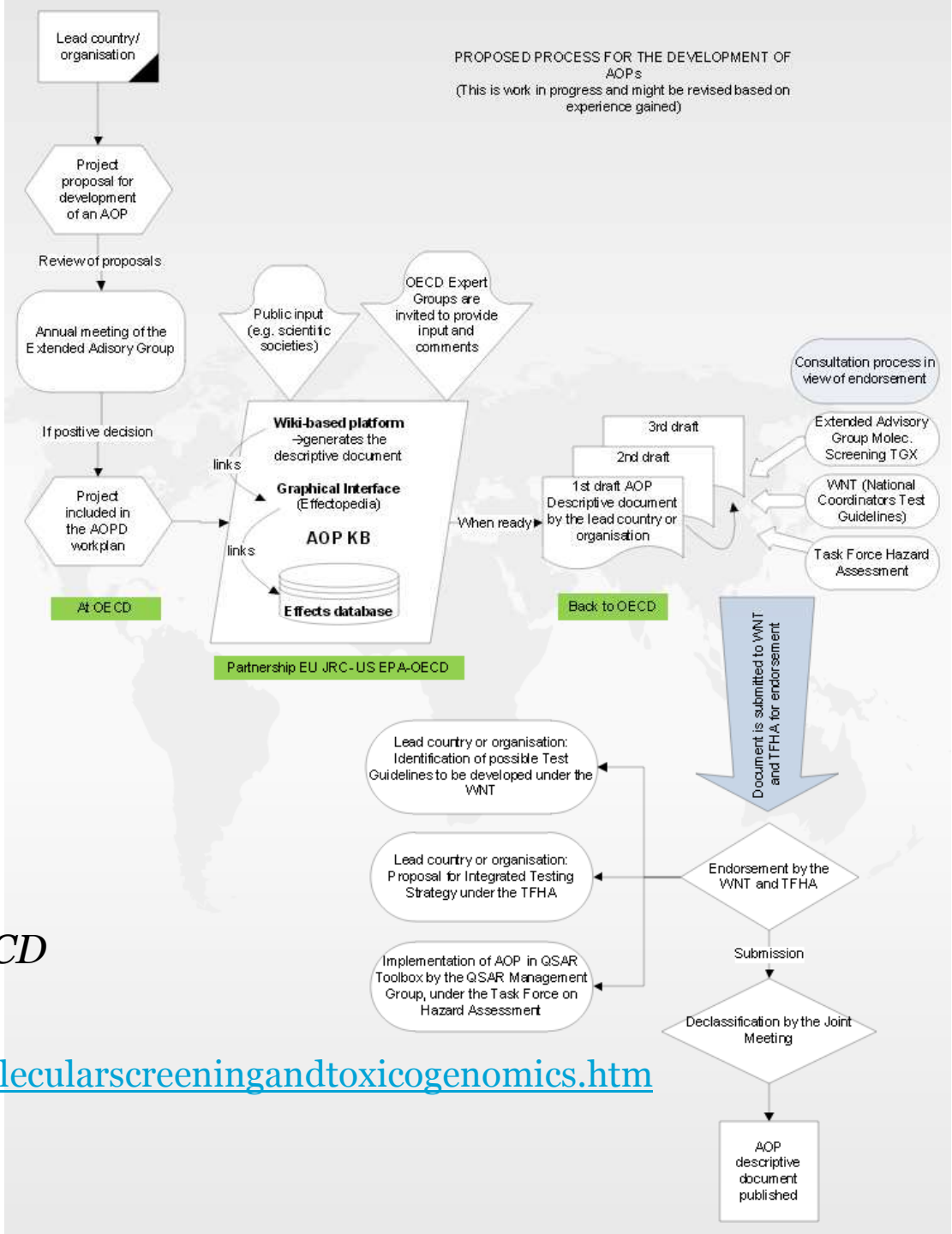
- Downloadable from OECD Web site
  http://search.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono%282013%296&doclanguage=en
- Basis for AOPWiki

OECD AOP Template

- Part II – The AOP Template
- Implemented in AOPWiki

OECD AOP Development Process

1. Proposal by a stakeholder to develop an AOP
2. Development of an AOP on the AOP-KB
3. Review by OECD Expert Groups
4. Approval by sub-bodies of the JM and declassification, publication of the AOP



Courtesy of Anne Gourmelon, OECD

http://www.oecd.org/env/ehs/testing/molecularscreeningandtoxicogenomics.htm

Submitting AOP Development Proposals

1. Template for submission of proposal for AOP development
2. List of Contact Points
3. Listing of AOPs under development/lead organisation

Courtesy of Anne Gourmelon, OECD

OECD ADVERSE OUTCOME PATHWAY

Project Submission Form

(Revised 11 February 2013)

If you require further information please contact the OECD Secretariat
Return completed forms to Lisa Savary (Lisa.SAVARY@oecd.org) and Camilla Francis (Camilla.FRANCIS@oecd.org)

PROJECT TITLE

SUBMITTED BY (Country / European Commission / Secretariat)

DATE OF SUBMISSION TO THE SECRETARIAT

DETAILS OF LEAD COUNTRY/CONSORTIUM

Country/Organisation:	
Agency/ministry/Other:	
Contact person(s):	
Mail Address:	
Phone/fax:	
Email:	

PROJECT CATEGORY

- ☐ Development of an AOP - applicable to a chemical category
- ☐ Development of an AOP Case Study - applicable to a single chemical or a very limited number of chemicals
- ☐ Guidance document related to AOP development including its evaluation
- ☐ Knowledge management tool for supporting AOP development including its evaluation
- ☐ Other, please specify below

If other category, please specify:

http://www.oecd.org/env/ehs/testing/molecularscreeningandtoxicogenomics.htm

Current OECD AOP Development Projects

- Section 1: Development of an adverse outcome pathway
  - 18 projects
- Section 2: Development of an adverse outcome pathway case study
  - 3 projects
- Section 3: Guidance documents related to adverse outcome pathway development including its evaluation
  - 2 projects
- Section 4: Knowledge management tool
  - 2 projects
- Section 5: Others
  - 1 project

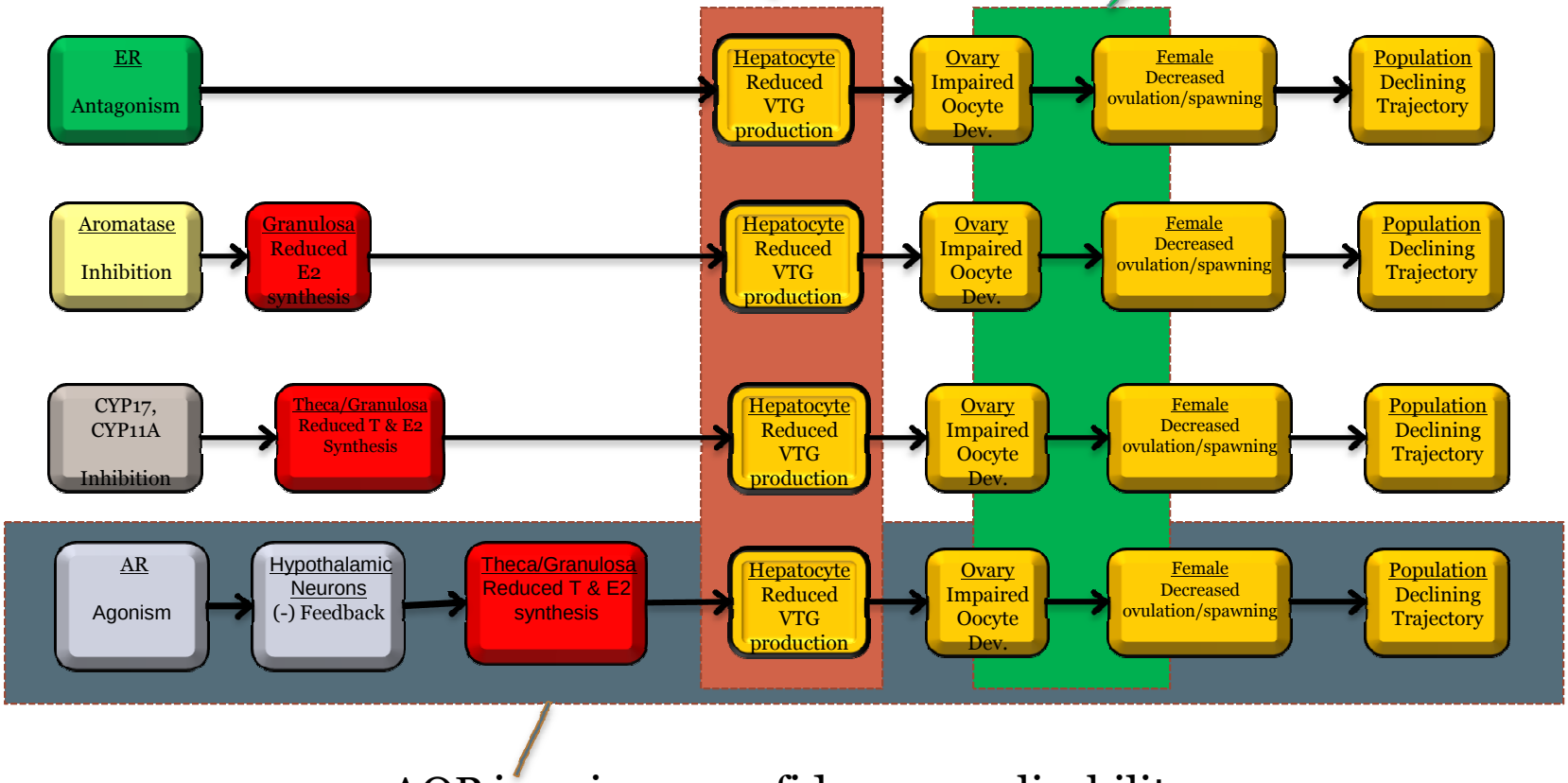
Numbers current as of 9 July 2013
Current list is available at the URL below

http://www.oecd.org/env/ehs/testing/listsofprojectsontheaopdevelopmentprogrammeworkplan.htm

AOP Knowledge-Base: Efficiency

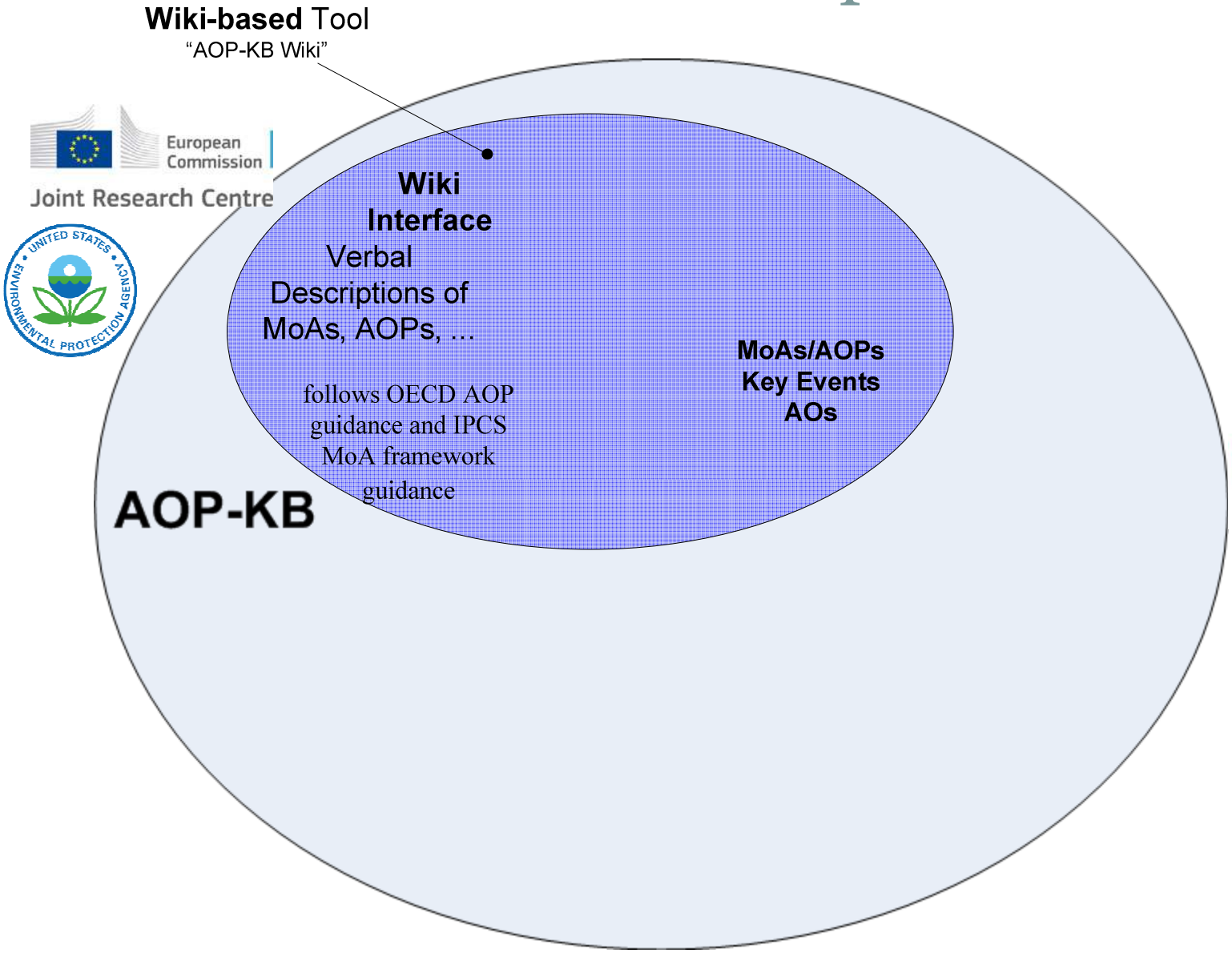
Key events shared by multiple AOPs

Linkages shared by multiple AOPs

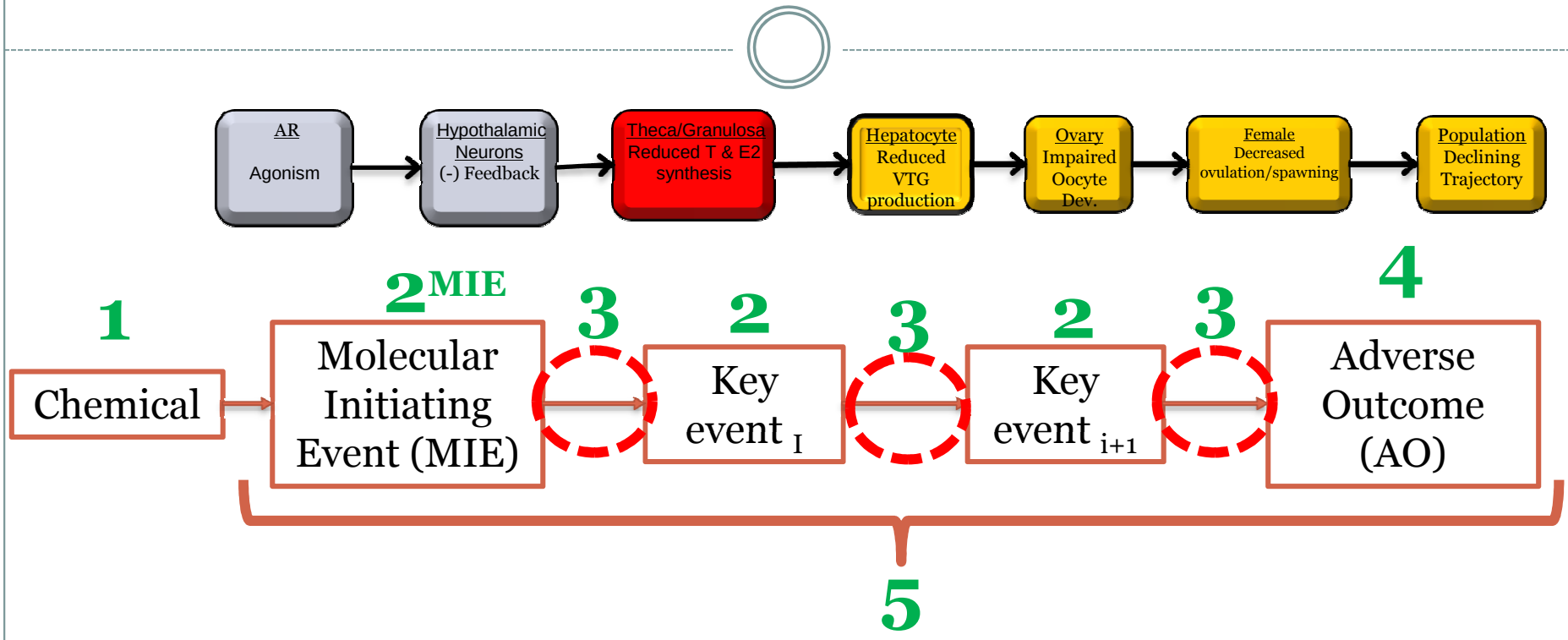


AOP is unique: confidence, applicability

AOP KB Components



Wiki Entities Correspond to AOP Components



5 Categories of Wiki Pages

1. Chemical initiator
2. Key event (including MIE; node)
3. KE Relationship (linkage; edge)
4. Adverse Outcome
5. AOP

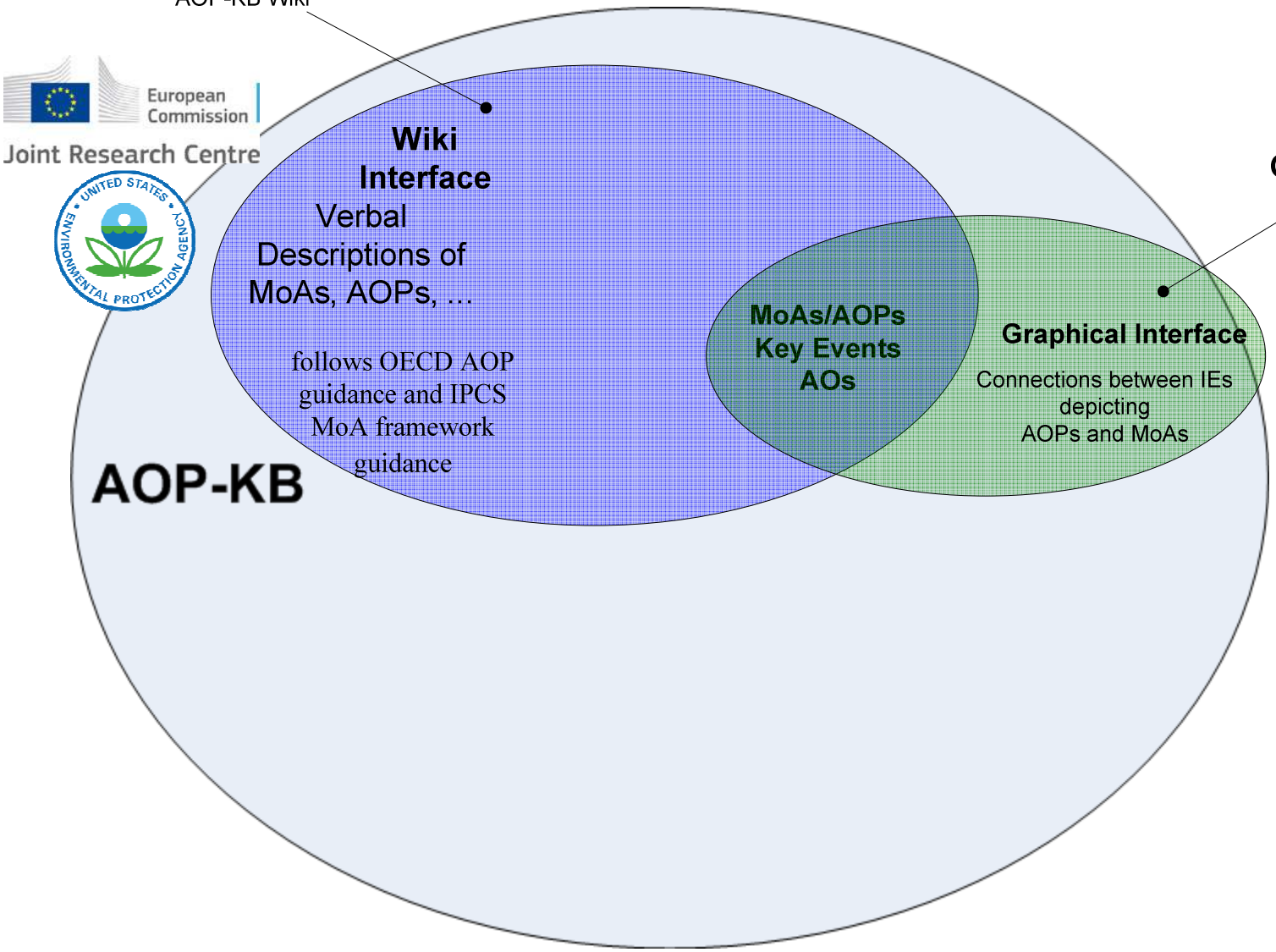
AOP Wiki Demo

- Tour of an Existing AOP
  - Guidance example 1
  - Guidance example 2
- Main Page and Help
- Entering an AOP
  - Introduction to Widgets
  - Creating and Uploading Graphic Representation
  - Introduction to Text Entry

AOP Wiki Development Timeline

- 2013 – Beta version available for OECD AOP development teams
  - Must submit a proposal to the OECD Secretariat
- 2014 – Production release with broader access
  - Defined by OECD External Advisory Group in November
- Integration with other AOP KB components
  - Effectopedia Developed by the International QSAR Foundation
  - AOP Network tool developed by the US Army Corps of Engineers - Engineering Research and Development Center

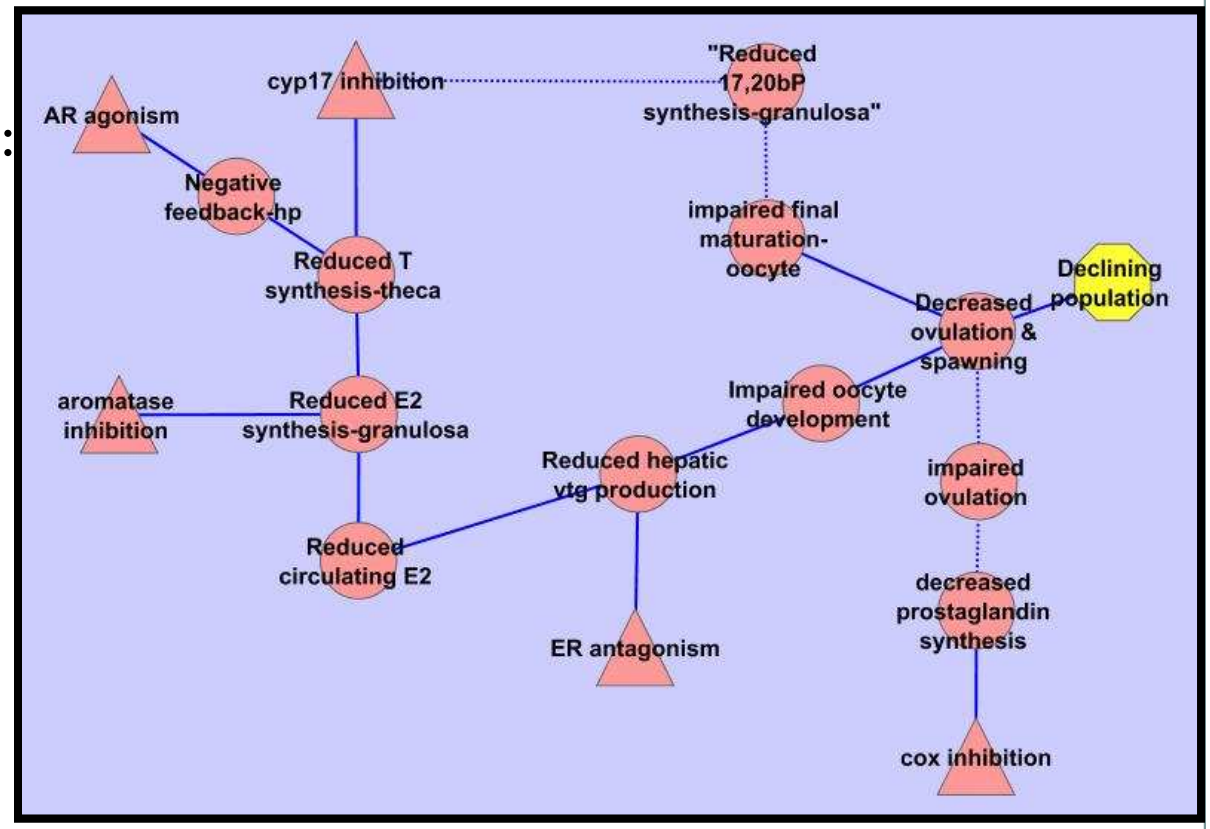
AOP KB Components



AOP Knowledge-Base: Networks

Structured information from AOP-KB
Linked to network visualization software (e.g., Cytoscape)

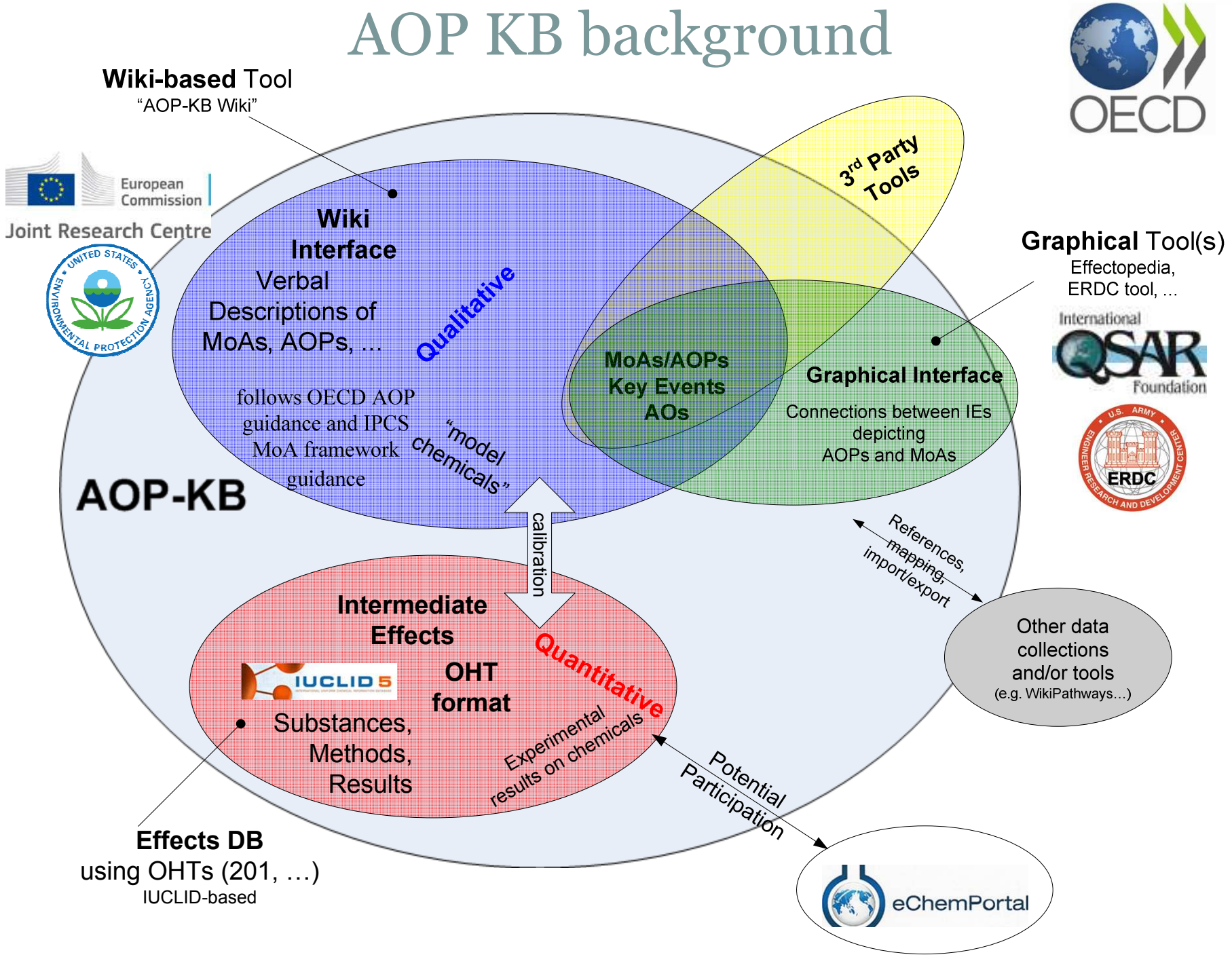
AOP Networks:



AOP Network Thinking

- Mixtures
- Multiple MOA
- Cumulative Risk

AOP KB background



AOP KB Contributors

- EPA/JRC/ERDC Working Group
  - Stephen Edwards
  - Clemens Wittwehr
  - Dan Villeneuve
  - Ed Perkins
  - Kevin Crofton
  - David Lyons
  - Gary Ankley
  - Lyle Burgoon
  - Brigitte Landesmann
  - Marina Goumenou
  - Natalia Garcia Reyero
  - Tanwir Habib
- AOP Wiki Development
  - **Ryan Durden**
  - **David Lyons**
  - **Kyle Painter**
  - Lyle Burgoon
  - Stephen Edwards
  - Wei Jia
- International QSAR Foundation (Effectopedia)
- Collaborative Partners
  - OECD External Advisory Group on AOPs
  - IPCS/WHO Mode of Action Steering Committee
  - EPA AOP Working Group

AOP Wiki and the OECD Template

HTTP://AOPWIKI.ORG

HTTP://SEARCH.OECD.ORG/OFFICIALDOCUMENTS/DISPLAYDOCUMENTPDF/?COTE=ENV/JM/MONO%282013%296&DOCLANGUAGE=EN

Guidance chapters 1-3

1. The Adverse Outcome Pathway Identifier

Name the AOP by defining a clear and concise the final adverse effect together with MIE.

2. Date of Declassification of AOP

Report the date (day/month/year) of AOP declassification.

3. Date of Updating the AOP

Indicate the date (day/month/year) of any update of the AOP. The AOP can be updated for a number of reasons, such as additions of new information and corrections of information.

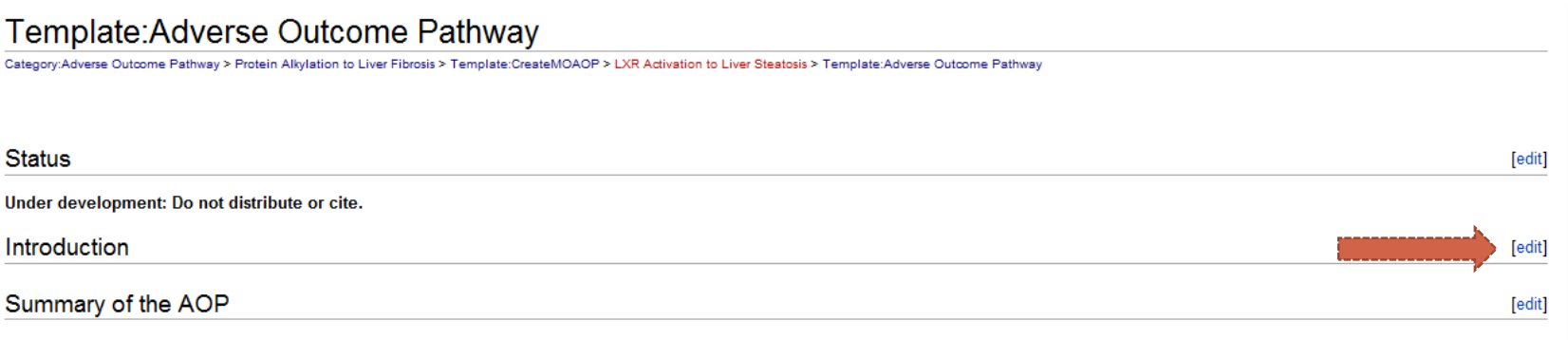
- 1 – Determines the name of the AOP article
- 2 – Goes to the AOPWiki section "Status" (AOP category)
- 3 – Goes to the AOPWiki Section "Status" (AOP category)

Guidance chapter 4

4. The Introduction

Give short background on the current knowledge about the final endpoint of interest.

- 4 – Goes to the AOPWiki section "Introduction" (AOP category)



Guidance chapter 5.1 – 5.2

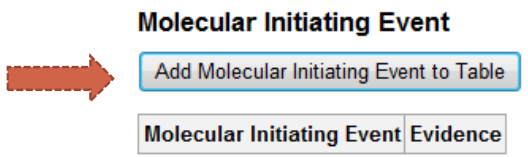
5.1. Characterisation of the exposure

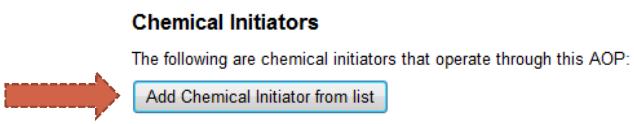
Define the route of exposure.

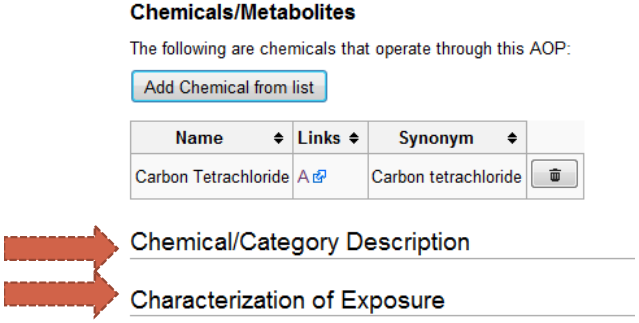
5.2. Characterisation of chemical properties

Identification of properties and/or processes required to initiate the MIE (bioavailability, reactivity, metabolism).

- 5.1 – Goes to the AOPWiki "Characterisation of the exposure" section
  Chemical initiator category, has now to be opened by using widget in the **Molecular Initiating Event** category
- 5.2 – Goes to the AOPWiki "Chemical description" section,
  Chemical initiator category







Guidance chapters 5.3 – 5.4

5.3. Identification of the molecular initiating event

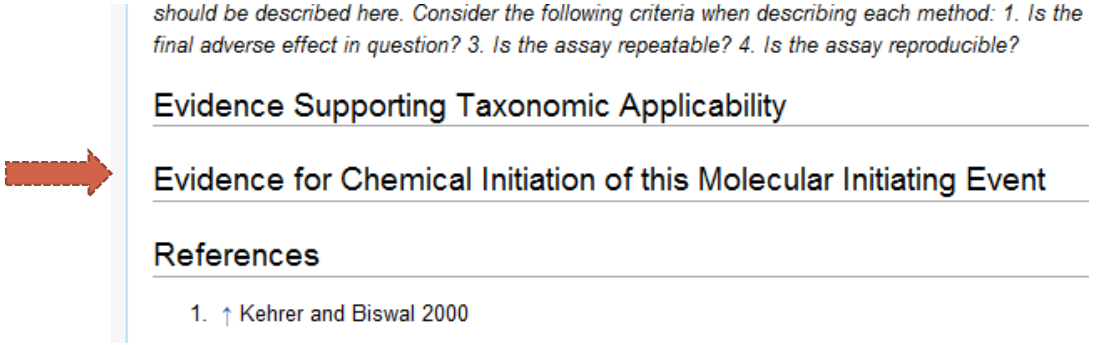
Name and describe the MIE.

5.4. Identification of the site of action

Name the site of the chemical (re)actions which initiates the AOP.

- 5.3 – Determines the name of the MIE article already created/opened in the previous step
- 5.4 – Goes into the "Evidence for Chemical Initiation of this Molecular Initiating Event"

MIE category



Guidance chapters 5.5 – 5.9

5.5. Identification of the responses at the macromolecular level

Describe how the biochemical pathway(s) is affected by the interaction of the chemical(s) with the molecular target.

5.6. Identification of the responses on the cellular/tissue level that may be an adverse outcome or linked to the final adverse outcome

Describe the cellular/tissue outcomes, based on available information.

5.7. Identification of the responses on the organ level that may be the final adverse outcome or linked to the final adverse outcome

Describe the organ level responses, based on available information.

5.8. Identification of the responses on the organism level that may be the final adverse outcome or linked to the final adverse outcome

Describe the key organism response, based on available information.

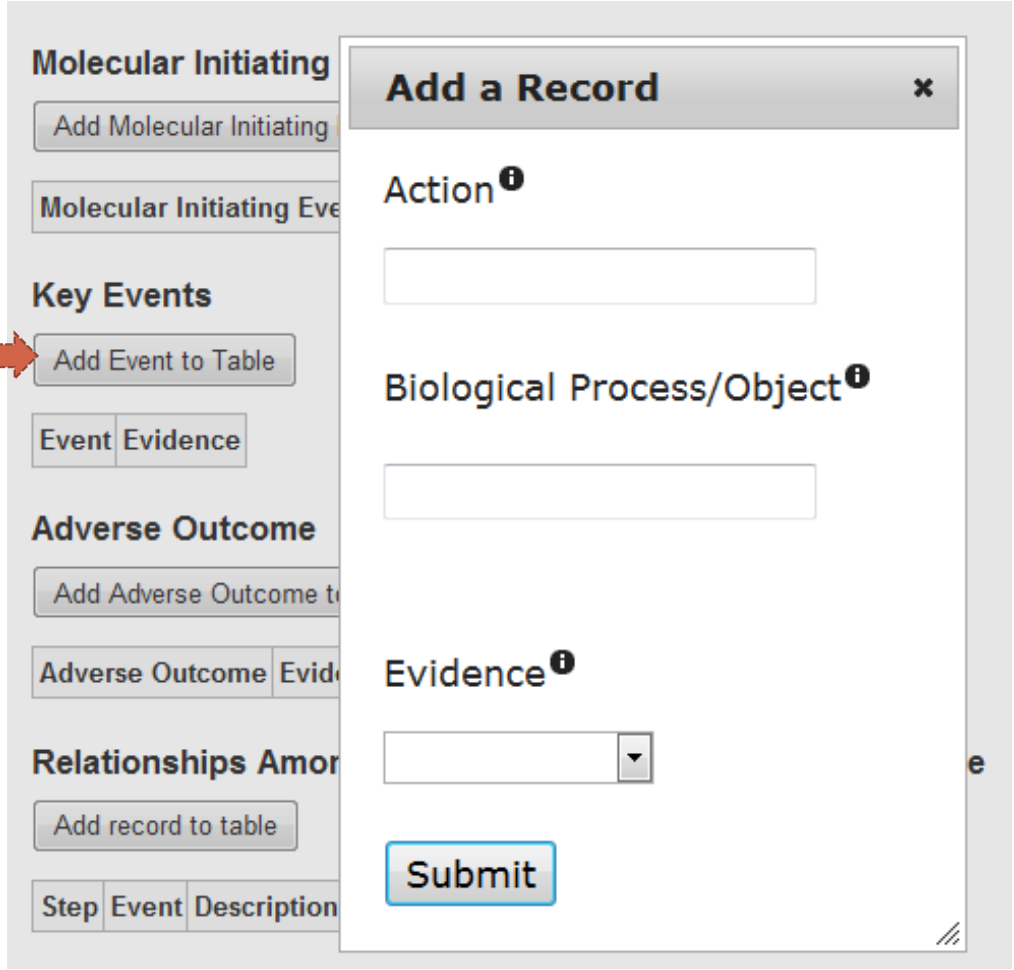
5.9. Identification of the overall effect on the population or ecosystem that may be the final adverse outcome or linked to the final adverse outcome

Describe how the population or ecosystem is affected by the pathway.

- Are treated in the AOPWiki Key Events section
  AOP category

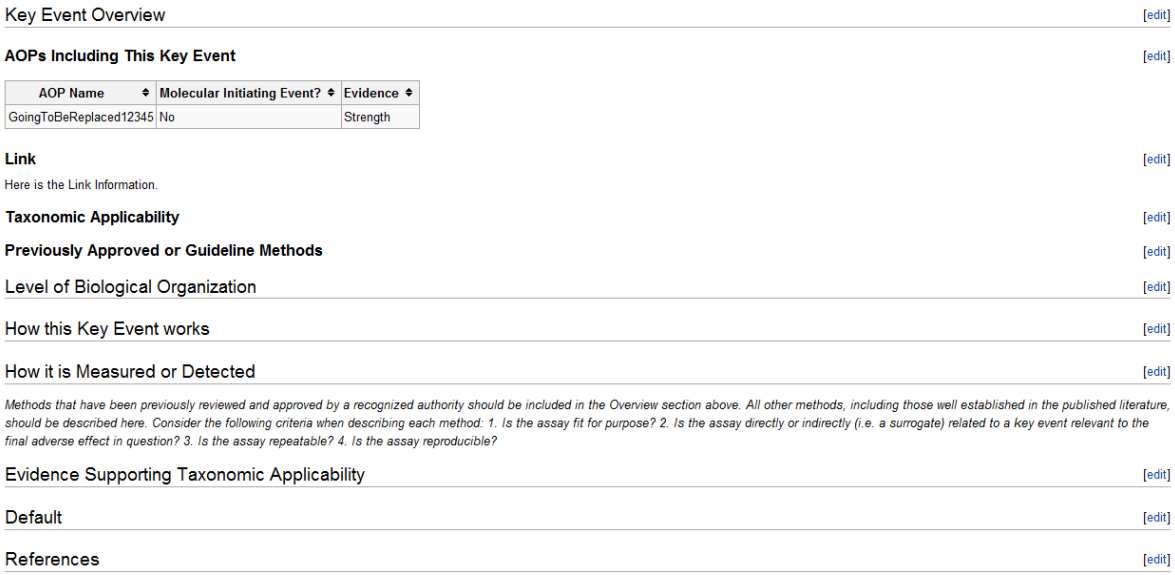
Guidance chapters 5.5 – 5.9

- All levels treated in chapters 5.5 - 5.9 are entered into the table
- New Key Events trigger the creation of new Key Event Articles
- For Evidence, see later



Key Event category

- When entering a **new** Key Event in the Key Event table in the AOP article, an empty Key Event article is created and opened:



Key Event Overview [edit]

AOPs Including This Key Event [edit]

AOP Name	Molecular Initiating Event?	Evidence
GoingToBeReplaced12345	No	Strength

Link [edit]

Here is the Link Information.

Taxonomic Applicability [edit]

Previously Approved or Guideline Methods [edit]

Level of Biological Organization [edit]

How this Key Event works [edit]

How it is Measured or Detected [edit]

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?

Evidence Supporting Taxonomic Applicability [edit]

Default [edit]

References [edit]

- Most information from chapter 7 goes here (per Key Event)

Guidance chapter 6

6. Summary of the Key Events of the AOP

Summarise the qualitative understanding of the AOP by listing them in a table that summarises the key events, documentation of the experimental support for each event, and a subjective evaluation of the strength of the scientific evidence for that event (See Table 1 and Table 2).

Include also a flow diagram of the intermediate events associated with AOP (See Figure 2 as an example).

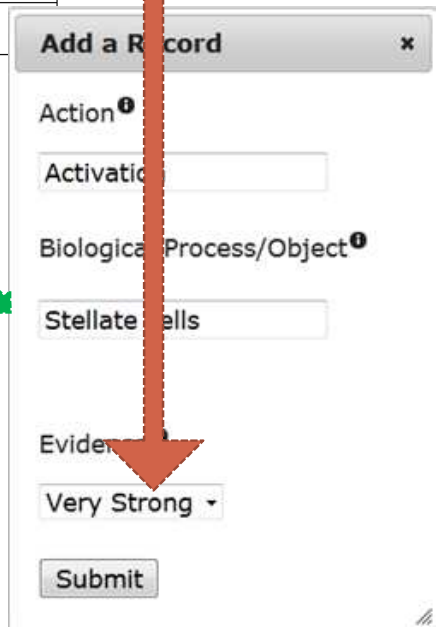
- 6 – Goes into the table "Key Events" in the "Summary of the AOP" section
  (AOP category)

Guidance chapter 6 – "Table 1" A

Table 1: Summary information on the key events of the AOP.

Key Events	Experimental Support (References)	Strength of Evidence
Molecular Initiating Event		
Key Event 1		
Key Event (n-1)		
Key Event n		
Adverse Effect		

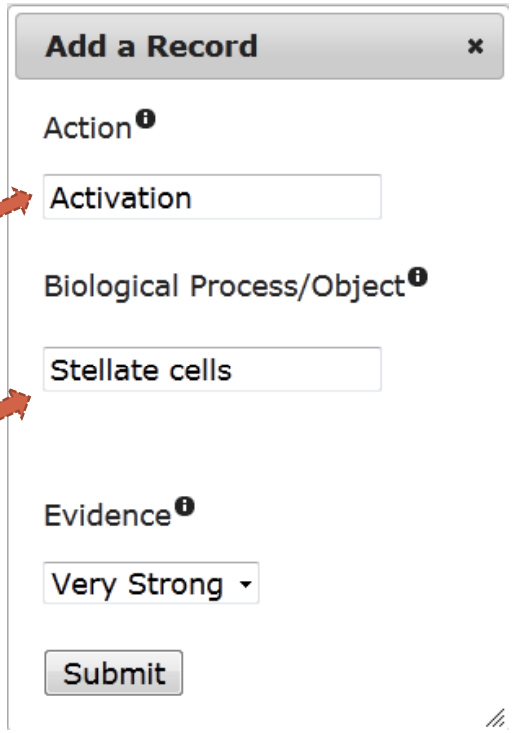
A



- A - Table 1 – column "Strength of Evidence" goes into the table "Key Events" in the "Summary of the AOP" section
  (AOP category)

Key Event naming convention

- Key Events have a two-component name:
  - Action
  - Biological Process/Object
- Action:
  An activity, expressed in an active voice noun
  - Increase, Decrease, Activation, Up-regulation, Down-regulation, …
- Biological Process/Object
  The "target" of the activity
  - Objects like Cells, Genes, …
    But also processes like [cell proliferation, gene transcription]



Guidance chapter 6 – "Table 1" B

Table 1: Summary information on the key events of the AOP.

Key Events	Experimental Support (References)	Strength of Evidence
Molecular Initiating Event		
Key Event 1	B	
Key Event (n-1)		
Key Event n		
Adverse Effect		

- B - Table 1 – column "Experimental Support" goes into the MIE, Key Event or AO article

Level of Biological Organization [edit]

Molecular.

How this Key Event works [edit]

Oxidative stress plays a crucial role in liver fibrogenesis by inducing hepatocyte apoptosis, activation of KCs and HSCs. [1], [2]

Development of oxidative stress is associated with an increase in ROS, including superoxide, hydrogen peroxide, hydroxyl radicals and aldehydic end products, that both initiate and then perpetuate fibrosis.

ROS can derive from hepatocytes, KCs, HSCs, and inflammatory cells and are generated through lipid peroxidation, from hepatocyte cytochrome P450 2E1 and NOX in activated KCs and HSCs. ROS stimulate HSC in a paracrine manner through activation of redox-sensitive intracellular signaling which results in increased collagen production. [3], [4], [5], [6]

Oxidative stress products have shown to be able to induce the synthesis of fibrillar extracellular matrix even in the absence of significant hepatocyte damage and inflammation (increased procollagen I gene expression in activated human HSC). [7]

How it is Measured or Detected [edit]

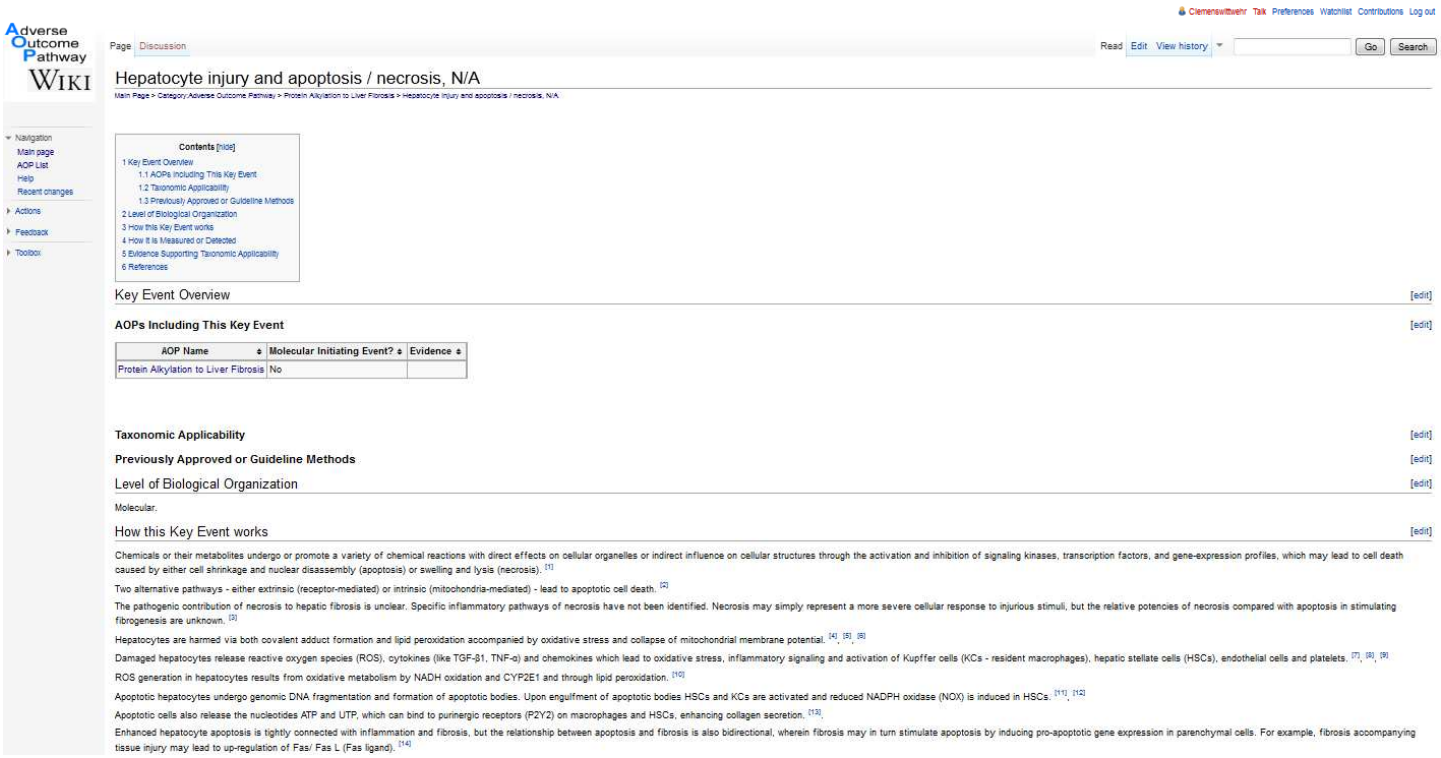
Methods that have been previously reviewed and approved by a recognized authority should be included in the Overview section above. All other methods, including those well established in the published literature, should be described here. Consider the following criteria when describing each method: 1. 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?

Guidance chapter 7

7. Scientific Evidence Underlying the AOP

Include any available information underlying the steps/key events in the AOP. This can include any type of data: in vivo, in vitro, in silico, in chemico, toxicogenomics etc. Each key event should be considered separately in a single sub-section.

- 7 – Goes to the individual Key Event articles



Guidance chapter 8.1.1 – 8.1.6
Bradford Hill criteria

8. Assessment of the AOP

8.1. Assessment of the weight-of-evidence supporting the AOP

Answer the Bradford Hill criteria:

8.1.1. **Concordance of dose-response relationships**

Report any reference/study giving evidence of dose-response relationship.

8.1.2. **Temporal concordance among the key events and adverse effect**

Describe the agreement between the sequences of biochemical and physiological events leading to the final adverse effect together with the evidence in the literature.

8.1.3. **Strength, consistency, and specificity of association of final adverse outcome and MIE**

Give the scientific evidence on the causal linkage between initiating event and final adverse outcome.

8.1.4. **Biological plausibility, coherence, and consistency of the experimental evidence**

Explain the logic, coherence and consistency along with the experimental data supporting the AOP. Describe how the experimental evidence is logical and consistent with the mechanistic plausibility proposed by the theory explaining the initiation of the final adverse effect. If possible, describe the coherence of experimental results for multiple chemicals across different species.

8.1.5. **Alternative mechanism(s) or MIE(s) that logically present themselves and the extent to which they may distract from the postulated AOP. It should be noted that alternative mechanism(s) of action, if supported, require a separate AOP.**

Report other possible mechanisms that can lead to the final adverse effect and state if they can be covered by this AOP.

8.1.6. **Uncertainties, inconsistencies and data gaps**

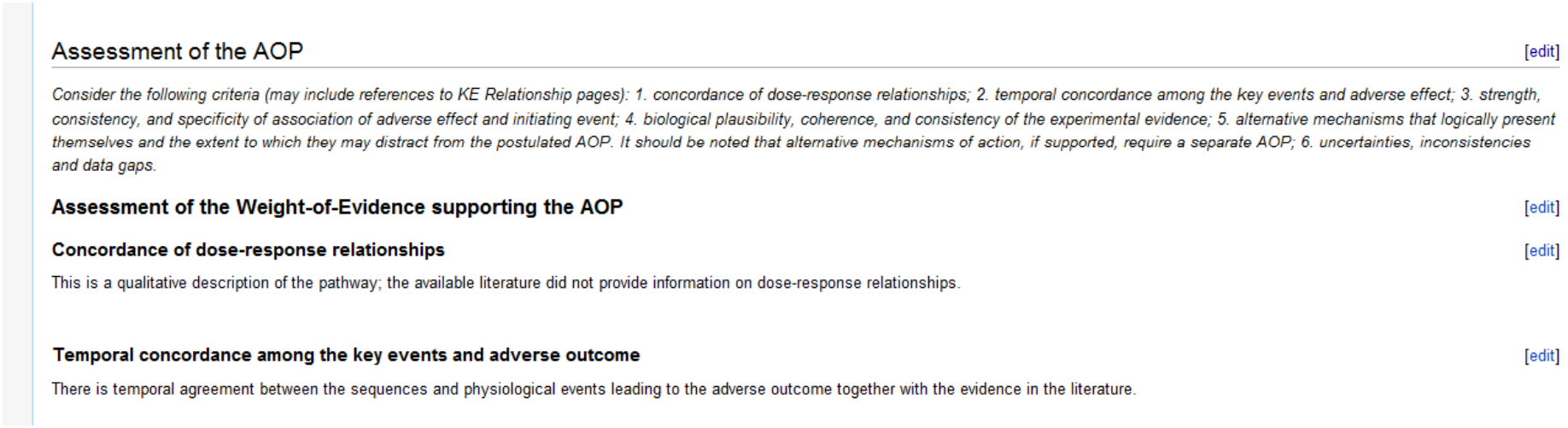
Include any uncertainties about the experimental details, such as uncertainties regarding the differences in sensitivity of different biological targets (e.g. protein binding: cysteine versus lysine, teratogenicity: Type I pyrethroid versus Type II), the measurements of biological activity in different assays. Describe inconsistencies within the reported data, such as differences between in vivo responses for very similar chemicals, and report any data gap that causes the weakness of the AOP.

Guidance chapters 8.1.1 – 8.1.6
Bradford Hill criteria

- An overwiew goes to the "Assessment of the AOP" section
  AOP category
- An overview table is created by filling in the "Relationships Among Key Events and the Adverse Outcome" table
  AOP category
- Details per Key Event pair go into to the "Relationships Among Key Events and the Adverse Outcome" category
  Relationships Among Key Events and the Adverse Outcome category

Guidance chapters 8.1.1 – 8.1.6
Bradford Hill criteria

- An overwiew goes to the "Assessment of the AOP" section
  AOP category



Assessment of the AOP [edit]

Consider the following criteria (may include references to KE Relationship pages): 1. concordance of dose-response relationships; 2. temporal concordance among the key events and adverse effect; 3. strength, consistency, and specificity of association of adverse effect and initiating event; 4. biological plausibility, coherence, and consistency of the experimental evidence; 5. alternative mechanisms that logically present themselves and the extent to which they may distract from the postulated AOP. It should be noted that alternative mechanisms of action, if supported, require a separate AOP; 6. uncertainties, inconsistencies and data gaps.

Assessment of the Weight-of-Evidence supporting the AOP [edit]

Concordance of dose-response relationships [edit]

This is a qualitative description of the pathway; the available literature did not provide information on dose-response relationships.

Temporal concordance among the key events and adverse outcome [edit]

There is temporal agreement between the sequences and physiological events leading to the adverse outcome together with the evidence in the literature.

- Gives general information valid for the whole AOP

Guidance chapters 8.1.1 – 8.1.6
Bradford Hill criteria

- An overview table is created by filling in the "Relationships Among Key Events and the Adverse Outcome" table

  AOP category

Relationships Among Key Events and the Adverse Outcome

Add record to table

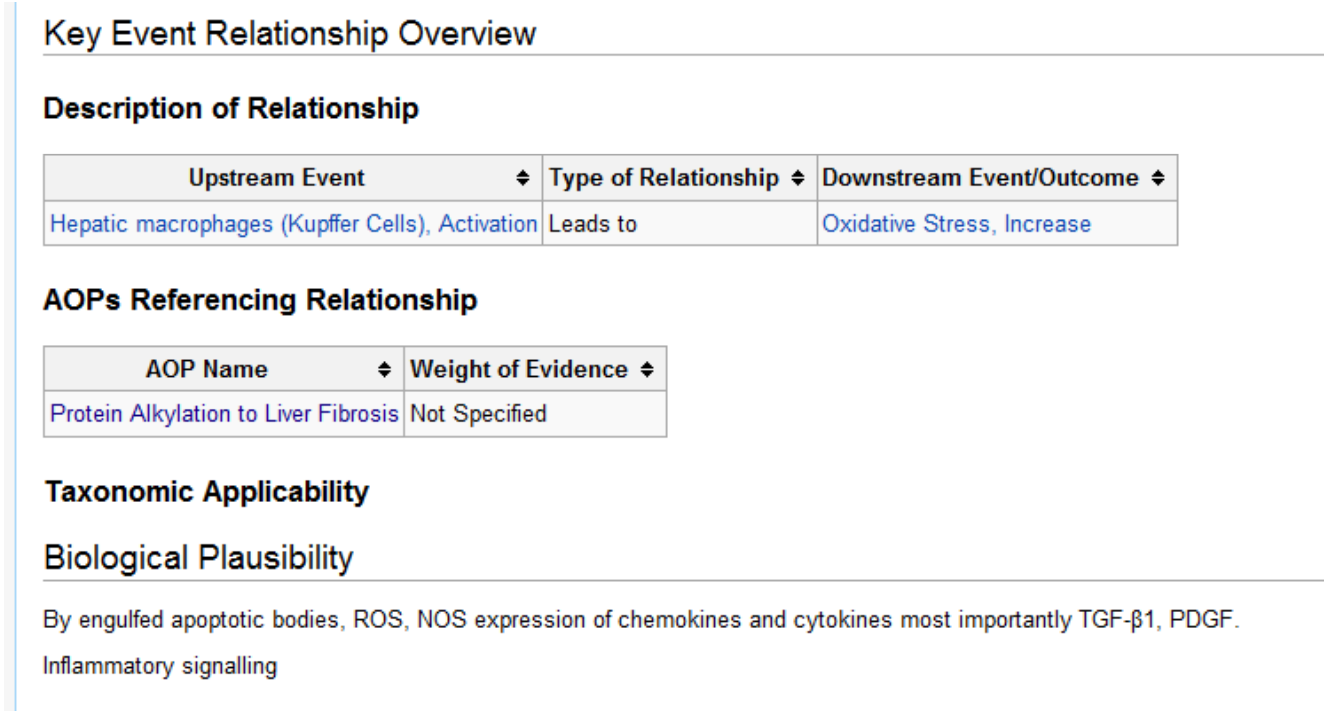
Step	Event	Description	Triggers	Weight of Evidence	
1	Hepatocyte injury and apoptosis / necrosis, N/A	Leads to	Oxidative Stress, Increase	Not Specified	
2	Hepatocyte injury and apoptosis / necrosis, N/A	Leads to	Chronic Inflammation, Increase	Not Specified	
3	Hepatocyte injury and apoptosis / necrosis, N/A	Leads to	Hepatic macrophages (Kupffer Cells), Activation	Not Specified	
4	Hepatic macrophages (Kupffer Cells), Activation	Leads to	Chronic Inflammation, Increase	Not Specified	
5	Hepatic macrophages (Kupffer Cells), Activation	Leads to	Oxidative Stress, Increase	Not Specified	
6	Oxidative Stress, Increase	Leads to	Hepatocyte injury and apoptosis / necrosis, N/A	Not Specified	
7	Oxidative Stress, Increase	Leads to	Hepatic macrophages (Kupffer Cells), Activation	Not Specified	
8	Oxidative Stress, Increase	Leads to	Chronic Inflammation, Increase	Not Specified	
9	Chronic Inflammation, Increase	Leads to	Hepatocyte injury and apoptosis / necrosis, N/A	Not Specified	
10	Chronic Inflammation, Increase	Leads to	Hepatic macrophages (Kupffer Cells), Activation	Not Specified	
10	Chronic Inflammation, Increase	Leads to	Oxidative Stress, Increase	Not Specified	
10	Hepatic macrophages (Kupffer Cells), Activation	Leads to	TGFbeta1 expression, Up Regulation	Not Specified	
10	Protein, Alkylation	Leads to	Hepatocyte injury and apoptosis / necrosis, N/A	Not Specified	
10	Protein, Alkylation	Leads to	Oxidative Stress, Increase	Not Specified	
10	Hepatocyte injury and apoptosis / necrosis, N/A	Leads to	Stellate cells, Activation	Not Specified	

- Evidence link leads to the appropriate "Relationships Among Key Events and the Adverse Outcome" article

Guidance chapters 8.1.1 – 8.1.6
Bradford Hill criteria

- Details per Key Event pair go into the "Relationships Among Key Events and the Adverse Outcome" category

Relationships Among Key Events and the Adverse Outcome category



Key Event Relationship Overview

Description of Relationship

Upstream Event	Type of Relationship	Downstream Event/Outcome
Hepatic macrophages (Kupffer Cells), Activation	Leads to	Oxidative Stress, Increase

AOPs Referencing Relationship

AOP Name	Weight of Evidence
Protein Alkylation to Liver Fibrosis	Not Specified

Taxonomic Applicability

Biological Plausibility

By engulfed apoptotic bodies, ROS, NOS expression of chemokines and cytokines most importantly TGF-β1, PDGF.

Inflammatory signalling

Guidance chapter 8.2

8.2. Assessment of the quantitative understanding of the AOP

Include an evaluation of the experimental data and models to quantify the molecular initiating event and other key events. If possible, describe transparent determination of thresholds and response-to-response relationship to scale in vitro and in chemico effects to in vivo outcomes.

- Like in 8.1
  - Information describing the whole AOP:
    Goes to the **AOP** article
  - Information describing the relationship between two specific Key Events:
    Goes to the **Relationships Among Key Events and the Adverse Outcome** article

Guidance chapter 9

9. Confidence in the AOP

Discuss the summary of the scientific evidence supporting the AOP by answering the following questions:

9.1. How well characterised is the AOP?

Describe how well the final adverse effect is understood qualitatively and quantitatively.

9.1.1. How well characterised is the MIE?

Describe how clearly the molecular initiating event is identified.

9.1.2. How well characterised is the AO?

Describe the relevance of the final adverse effect to the regulatory purpose.

9.1.3. How well are the initiating and other key events causally linked to the outcome?

Give short statement on the relationship between each key event and the final adverse effect.

9.1.4. What are the limitations in the evidence in support of the AOP?

Indicate any lack or disagreement in the scientific evidence supporting the AOP.

9.1.5. Is the AOP specific to certain tissues, life stages / age classes?

Indicate if there are critical life stages, where exposure must occur, to results in the final adverse effect. Or specify if there are key events along the pathway which are dependent on the life stage,

although the AOP is known to be initiated regardless of life stage. Indicate also if the AOP is associated also with age- or sex-dependence.

9.1.6. How much are initiating and key events conserved across species?

State if the key events for this AOP appear to be conserved across any group of animals (e.g. mammals) or if it appears only to be relevant for certain groups of specie.

Guidance chapter 9

- Like in chapter 8
  - Information describing the whole AOP: Goes to the **AOP** article

Confidence in the AOP [edit]

Elaborate on the domains of applicability listed in the summary section above. Specifically, provide the literature supporting, or excluding, certain domains.

How well characterised is the AOP? [edit]

The adverse outcome is well understood qualitatively, but quantitative data are lacking We need dose-response data including threshold values for the MIE and ideally for each of the key events and also to take response-response and temporal relationships into account.

How well are the initiating and other key events causally linked to the outcome? [edit]

As shown in table 1 the relationships between each key event and adverse outcome are well established.

What are the limitations in the evidence in support of the AOP? [edit]

The scientific evidence is quite consistent.

  - 9.1.5 and 9.1.6 have special tables:

Life Stage Applicability

Taxonomic Applicability

Sex Applicability

Guidance chapter 9

- Like in chapter 8
  - Information describing the relationship between two specific Key Events:
    Goes to the **Relationships Among Key Events and the Adverse Outcome** article

AOPs Referencing Relationship [edit]

AOP Name	Weight of Evidence
Protein Alkylation to Liver Fibrosis	Not Specified

Taxonomic Applicability [edit]

Biological Plausibility [edit]

By engulfed apoptotic bodies, ROS, NOS expression of chemokines and cytokines most importantly TGF-β1, PDGF.

Inflammatory signalling

Empirical Support for Linkage [edit]

Include consideration of temporal concordance here

Quantitative Understanding of the Linkage [edit]

Is it known how much change in the first event is needed to impact the second? Are there known modulators of the response-response relationships? Are there models or extrapolation approaches that help describe those relationships?

Uncertainties or Inconsistencies [edit]

Evidence Supporting Taxonomic Applicability [edit]

Guidance chapter 10

10. References

List the bibliographic references to original papers, books or other documents used to support the AOP.

- References are either entered manually…
- … by using the `<ref>…</ref>` tag pairs in the text

Guidance chapter 10

Writing…

…compound CCl4 equally affects lymphoid organs, lungs and kidneys <ref>Kisseleva and Brenner 2008</ref>…

… leads to…

Is the AOP specific to certain tissues, life stages / age classes?

Similarities of fibrogenesis in different organs. The complex mechanism of fibrogene

The described findings in liver fibrosis parallel those in studies of fibrogenesis in lun

compound CCl4 equally affects lymphoid organs, lungs and kidneys [32] Pathogeni

simultaneously. The main pathway from injury leads via inflammatory response to t

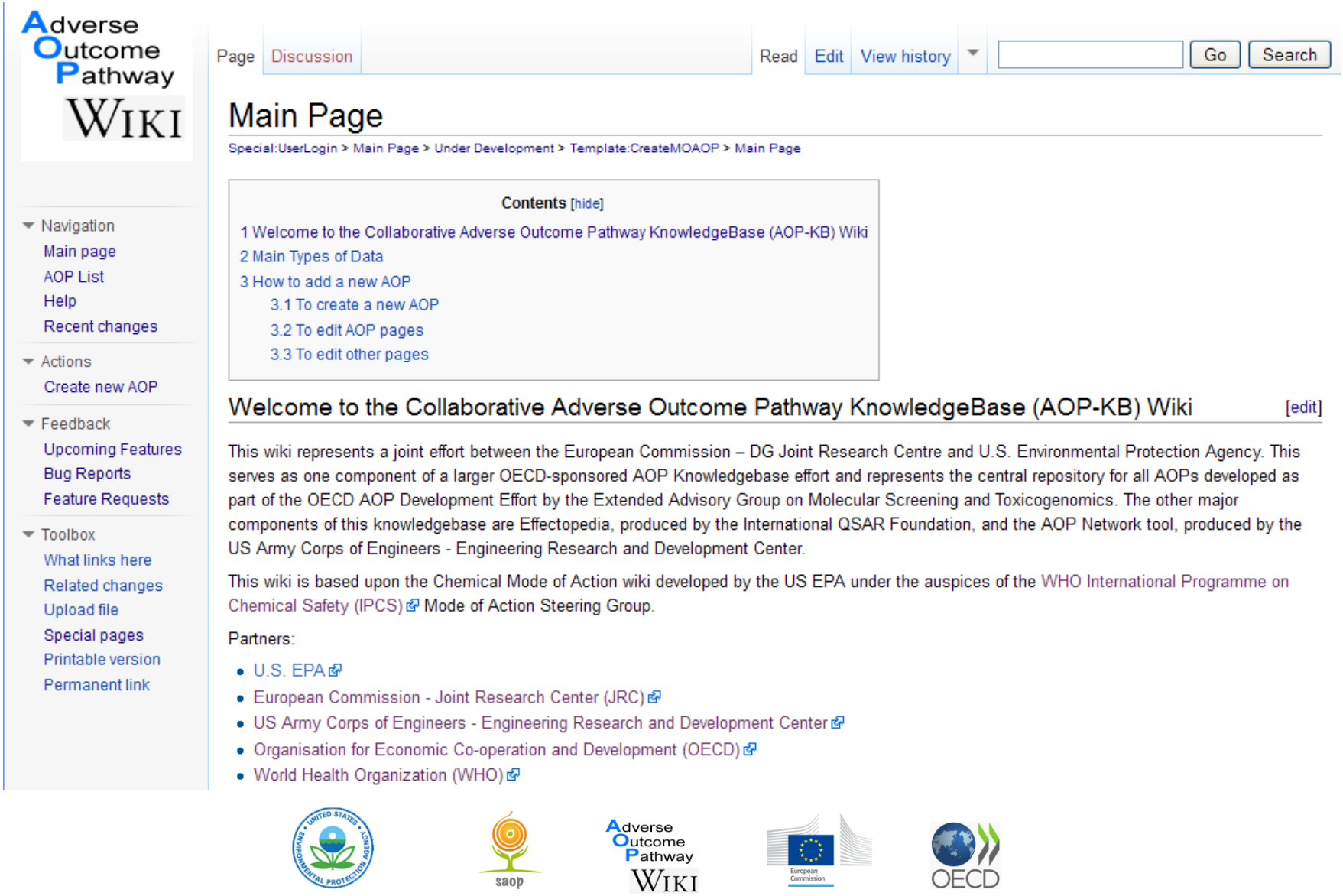
chemokines by inflammatory cells and further to the activation of fibroblastic cells v

28. ↑ Kisseleva and Brenner 2007
29. ↑ Friedman 2010
30. ↑ Lee et al. 2011
31. ↑ Friedman 2002, 2010
32. ↑ Kisseleva and Brenner 2008
33. ↑ Poli 2000

AOP Wiki Demo

HTTP://AOPWIKI.ORG

Main Entry Page (http://aopwiki.org)



Main Page Information

Main Types of Data [edit]

- Adverse Outcome Pathway - or Mode of Action, the way chemicals *act* on an organism, leading to an adverse outcome
  - Molecular Initiating Event - Key Event representing the initial perturbation of the system by a chemical
    - Chemical Initiator - the **actor** (*subject*) in an AOP or MoA that perturbs the pathway represented by the MIE
  - Key Event - the *building block* for MoAs and AOPs
  - Adverse Outcome - or Endpoint, the adverse consequences at the organism or population level that would potentially be of regulatory concern.
  - Key Event Relationship - Describes the relationship between two key events or a key event and an adverse outcome

How to add a new AOP [edit]

For more detailed instructions, please see the main Help page.

To create a new AOP [edit]

1. Click the following link in the Sidebar: Create new AOP
2. Click the View/Create AOP button to create or find an AOP.
3. As you start typing in the text box, existing AOPs that meet your text will be shown.
    1. If one looks like a match, select it and click on the Create/Open AOP button and the corresponding page will be shown. If the page matches the AOP you wished to add, edit the page as needed. If not, you can still create a new one by clicking the sidebar link again.
    2. If none of the existing AOPs match the one you wish to create, keep typing until you have a unique name and click the Create/Open AOP button. If you have an MIE, the current naming convention would include both the MIE and AO in the AOP page name. If the MIE is unknown, use the earliest KE and we'll rename the page once the MIE is defined.

To edit AOP pages [edit]

1. To add text to any section, click the Edit link to the right of the Heading for that section. Type your notes in the resulting text box and click the save page button at the bottom. Don't delete the ==Heading== line at the top. You shouldn't need to manually edit the Summary of the AOP section. Please make those changes via the automated process described below.
2. To add a new item in the Summary section (**If you manually enter text in this section, it may get altered or deleted in subsequent edits using the widgets.**):

Adverse Outcome Pathway WIKI

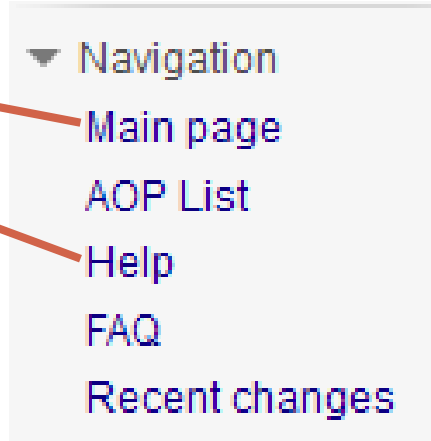
- Navigation
- Main page
- AOP List
- Help
- FAQ
- Recent changes
- Actions
- Create new AOP
- Feedback
- Upcoming Features
- Bug Reports
- Feature Requests
- Toolbox
- What links here
- Related changes
- Upload file
- Special pages
- Printable version
- Permanent link

Sidebar Tools

- Navigation
  - Most commonly accessed pages available anytime
- Actions
  - These links will start a workflow or download
- Feedback
  - Check for known bugs and report bugs
  - Check for new features and request features
- Toolbox
  - Standard wiki tools

Three Layers of Help

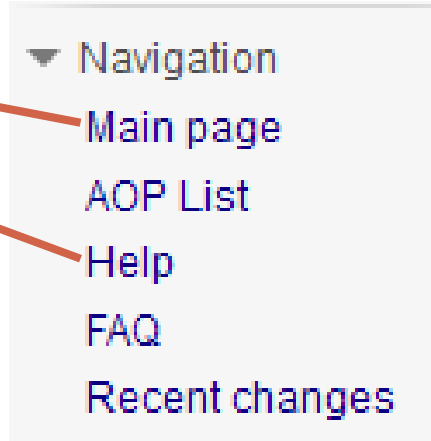
- Main Page – Most concise description of the process
- Help:Contents – More details
  - Very brief page specific information
  - General tips for entering text and using widgets
  - Links to individual help pages



- Individual Help Pages – Detailed descriptions
  - Page by page description of all widgets on each different page type
  - Links to these pages from the Help:Contents page

Three Layers of Help

- Main Page – Most concise description of the process
- Help:Contents – More details
  - Very brief page specific information
  - General tips for entering text and using widgets
  - Links to individual help pages



- Individual Help Pages – Detailed descriptions
  - Page by page description of all widgets on each different page type
  - Links to these pages from the Help:Contents page

Quick Overview of Page Types

Links to detailed help pages

Quick Start [edit]

This section is intended to give a quick overview of the process. Please follow the links for each section to find detailed information. **Warning:** The following symbols have special meaning in MediaWiki and thus, cannot be used in any input fields: [,], {, }, | Use of these symbols in text sections should be restricted to cases where the associated wiki format is desired [1][2][3].

To create a new AOP [edit]

1. Click the following link in the Sidebar: Create new AOP
2. Click the "View/Create AOP" button to create or find an AOP.
3. As you start typing in the text box, existing AOPs that match your text will be shown.
4. Click the "Create/Open AOP" button after selecting an AOP or specifying a new name.

To edit AOP pages [edit]

1. All sections except those contained under the " Summary of the AOP " heading are for entering free text. See below for more details about editing text sections.
2. You should use the widgets provided to make changes to the " Summary of the AOP " section. Detailed instructions for each widget are on the Help:Edit AOP page.

To edit Key Event pages [edit]

1. All sections except those contained under the " Key Event Overview " heading are for entering free text. See below for more details about editing text sections.
2. You should use the widgets provided to make changes to the " Key Event Overview " section. Detailed instructions for each widget are on the Help:Edit Key Event page.

To edit Molecular Initiating Event pages [edit]

As a subcategory of key events, the MIE pages have the same template. See instructions in Key Event section for more details. Unique features of the MIE page are:

1. In the overview section, a subsection for adding chemical initiators will be present. Please use the widget to select chemicals.
2. An additional free text section is included for providing evidence linking the chemicals listed in the overview section to this MIE.

To edit Adverse Outcome pages [edit]

1. All sections except those contained under the " Adverse Outcome Overview " heading are for entering free text. See below for more details about editing text sections.
2. You should use the widgets provided to make changes to the " Adverse Outcome Overview " section. Detailed instructions for each widget are on the Help:Edit Adverse Outcome page.

Tips for Editing Text Sections

Editing tips for text entry sections [edit]

To add text to any section, click the "[Edit]" link to the right hand side of the section header for that section. Type your notes in the resulting text box and click the save page button at the bottom. Don't delete the ==Heading== line at the top as that creates the header line. Type your desired text for that section beneath it.

Some sections include italicized text providing the type of information expected in this section based on the OECD guidance document. This text can be deleted once you begin adding content and should be deleted prior to submitting the AOP for OECD consideration. This text can be easily recognized by the .. tags surrounding it.

Here are a few tips for commonly desired formatting options within the free text sections. Additional options are available here [4].

1. To separate paragraphs, you must include a blank line between them in the edit box.
2. To create subheadings within a section precede the section with ===Heading=== (note 3 equal signs vs. two above) on a line by itself. Additional nesting of subheadings just requires increasing the number of equal signs by one.
3. To create a numbered list, begin each line with the '#' symbol
4. To create a bulleted list, begin each line with the '*' symbol
5. Hovering over the icons at the top of the edit window will provide a brief description of what they do.
    1. The first two provide you the ability to **Bold** and *Italicize* text. Just replace the highlighted text leaving all single quote marks around the text.
    2. The next two create hyperlinks to other wiki pages and external pages respectively. Just replace the highlighted text leaving all "[" & "]" marks around the text.
    3. The second icon from the right will include your wiki signature. Please use this to sign any contributions you make to a "Talk" page (see below).

Tips for Editing Using Widgets

General information on wiki widgets [edit]

Summary (for AOP) and Overview (all other pages) sections are intended for programmatic editing using the widgets in each subsection. **If you manually enter text in this section, it may get altered or deleted in subsequent edits using the widgets.** If you need to make changes and can't determine how to do it through the widgets, contact us at aopwiki@googlegroups.com, and we will help you make the necessary changes.

In cases where a heading does not have a widget yet, check out our Upcoming Features page to see where it stands in the queue. New buttons will be added as soon as the widgets are developed.

1. To add a new item in the Summary/Overview section:
    1. Click the "Add *Item* to Table" button.
    2. Fill out the appropriate boxes in the pop up box. Hovering over the "i" beside each label will provide a brief description of the associated text box. Detailed descriptions of each widget are available on the detailed help page for each page type. Follow the links for the appropriate section above.
    3. The evidence field is never required and can be skipped if you don't have a rating. Once you've filled out the information. Click the Submit button.

Note that the Overview sections on non-AOP pages will have some tables that have no edit widgets associated. These provide links to associated wiki pages and should only be edited via the corresponding AOP page. Otherwise, the relationships among the pages can be lost.

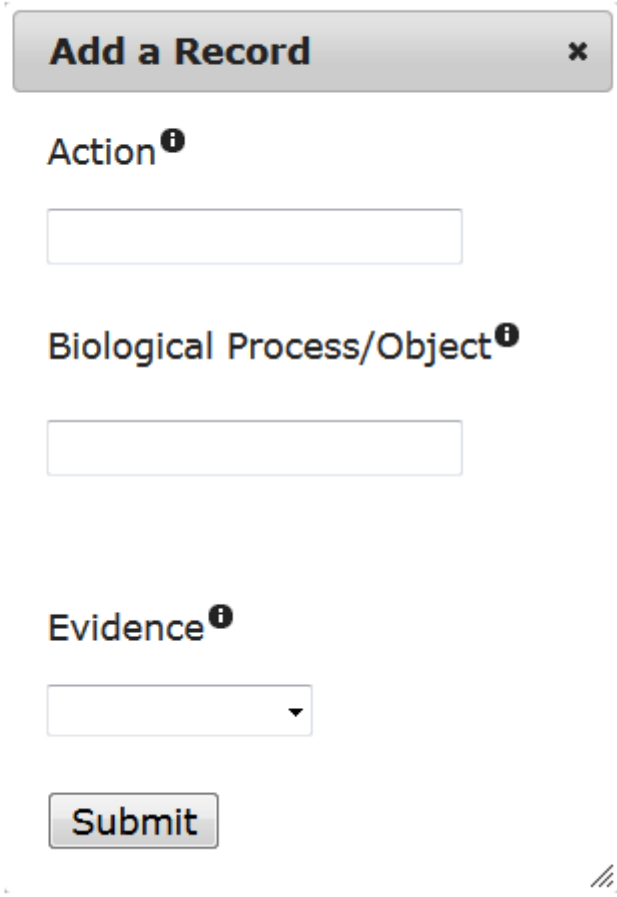
Example of a Detailed Widget Description

Molecular Initiating Event, Key Event, Adverse Outcome Tables [edit]

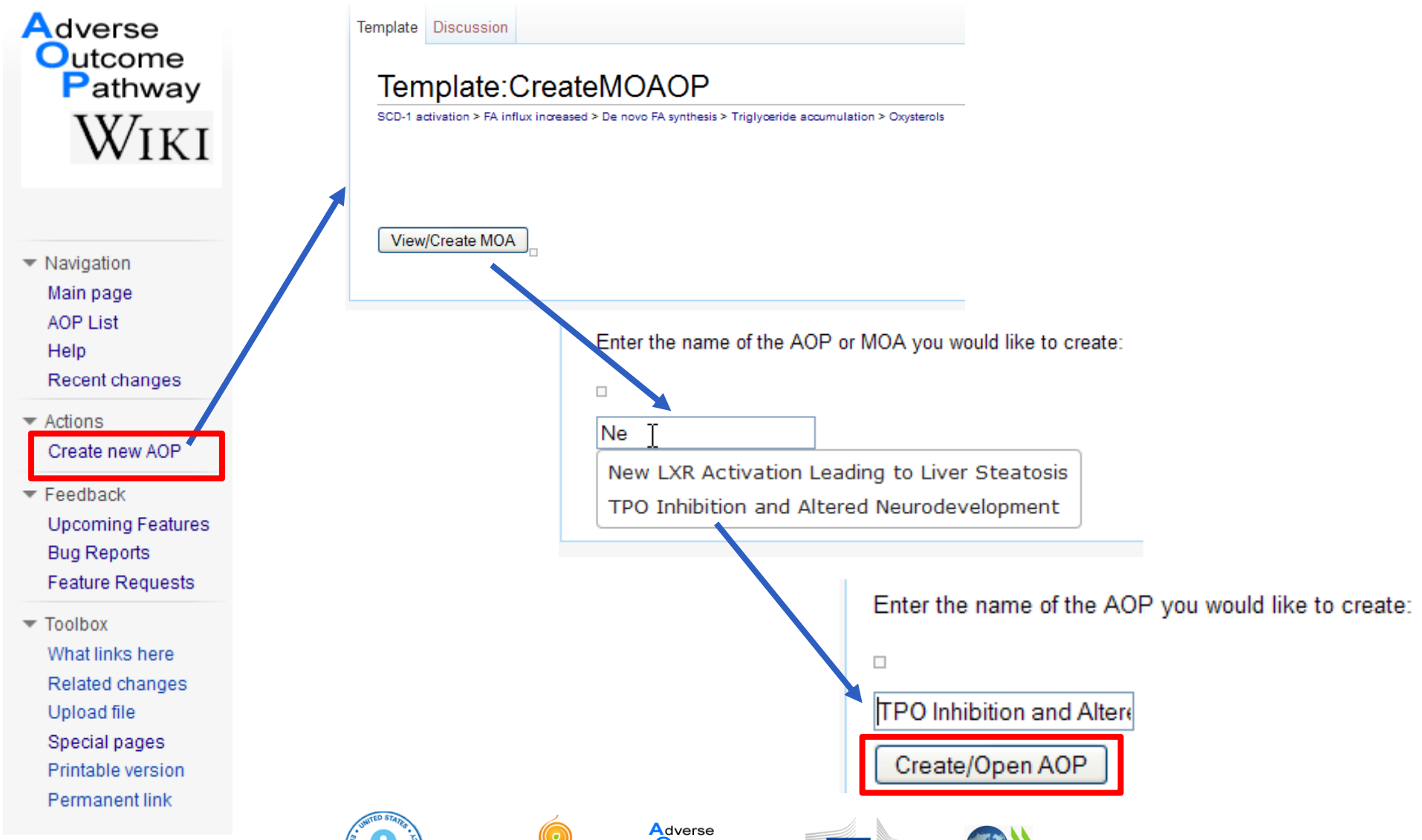
The popup box for these tables contains three fields: The first field captures the action component of the key event. Users are encouraged to use one of the existing options from the autocomplete if it accurately describes the action. Otherwise, the user can enter a new one that will then be available to future users. The second field describes the biological object or pathway that is perturbed. The text box will list existing key events/adverse outcomes (KE/AOs) matching the text entered. If an action has been previously specified in the first box, only KE/AOs matching the specified action will be shown. If an existing item matches the desired KE/AO, select it from the list. If not, type a short description of the biological object/process in the box. If you wish to make an assertion regarding the strength of evidence for the KE/AO, choose an option from the list. Please refer to the OECD guidance for definitions of these rankings.

After clicking submit, a new row will be added to the table. The KE/AO name will have the following format: Biological object/process, Action. This name will be linked to the KE/AO page. The weight of evidence evaluation will be stored in a second column. This value will link to the evidence section of the KE/AO page.

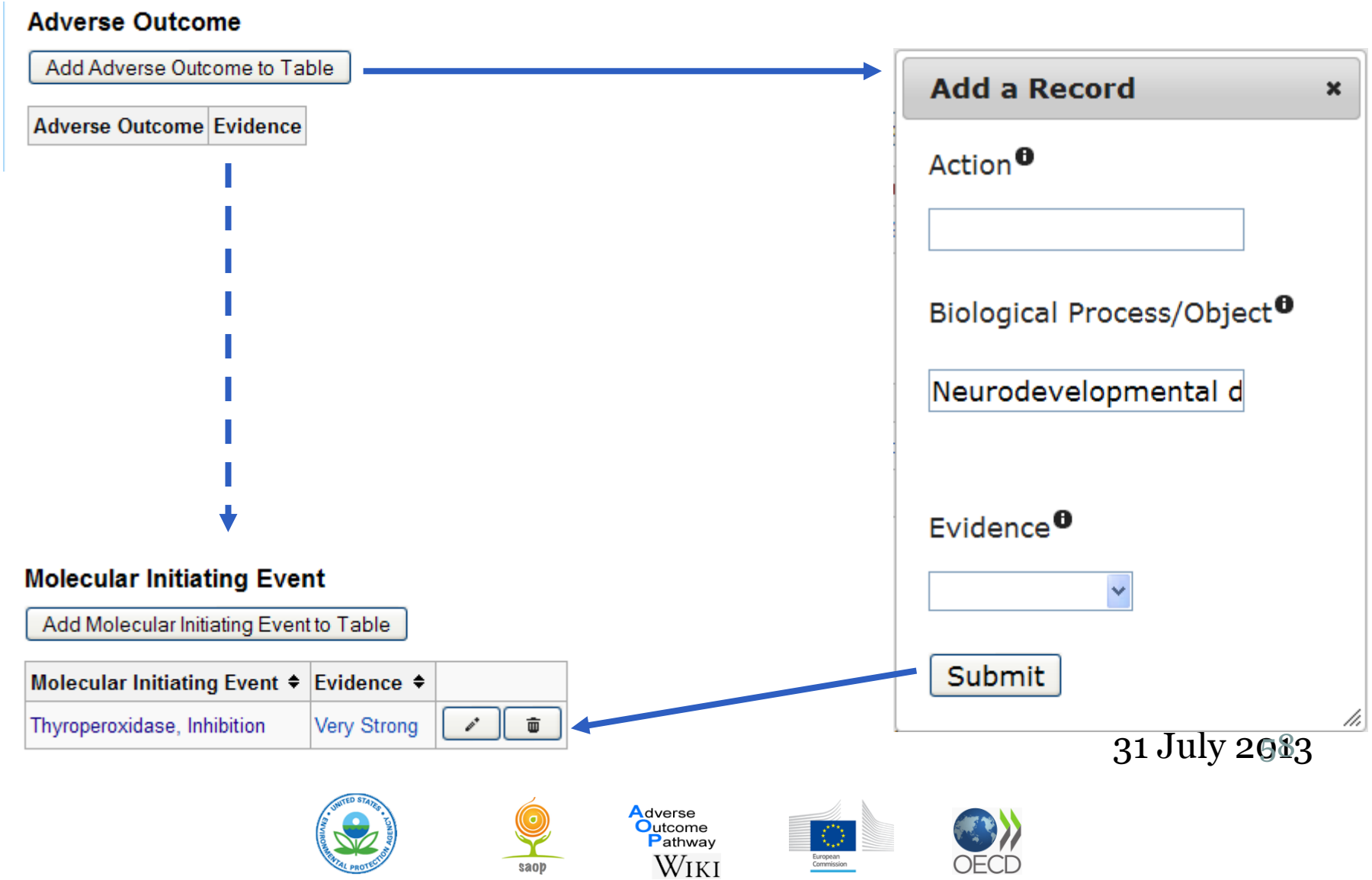
If you create a new KE/AO, a stub page will be created and you will be redirected to that page to fill in any information you have. A new row will be added in AOP table contained in the Overview section of this page. Following the AOP name link will return to the AOP page. If you want to edit information about an existing KE/AO, click the name of the KE/AO in the table, which will take you to the KE/AO page. Make your edits on the KE/AO page, and return to the AOP page via the AOP link in the Overview section.



Create a new AOP



Add Adverse Outcome to AOP



Adverse Outcome Template

Neurodevelopmental deficits, N/A

Category:Adverse Outcome Pathway > TPO Inhibition and Altered Neurodevelopment > Thyroxin (T4) in serum, Decreased > TPO Inhibition and Altered Neurodevelopment > Neurodevelopmental deficits, N/A

Contents [show]

Adverse Outcome Overview [edit]

AOPs Including this Adverse Outcome [edit]

AOP Name	Evidence
TPO Inhibition and Altered Neurodevelopment	

Affected Organs [edit]

Widget Editing

Definition [edit]

How it is Measured or Detected [edit]

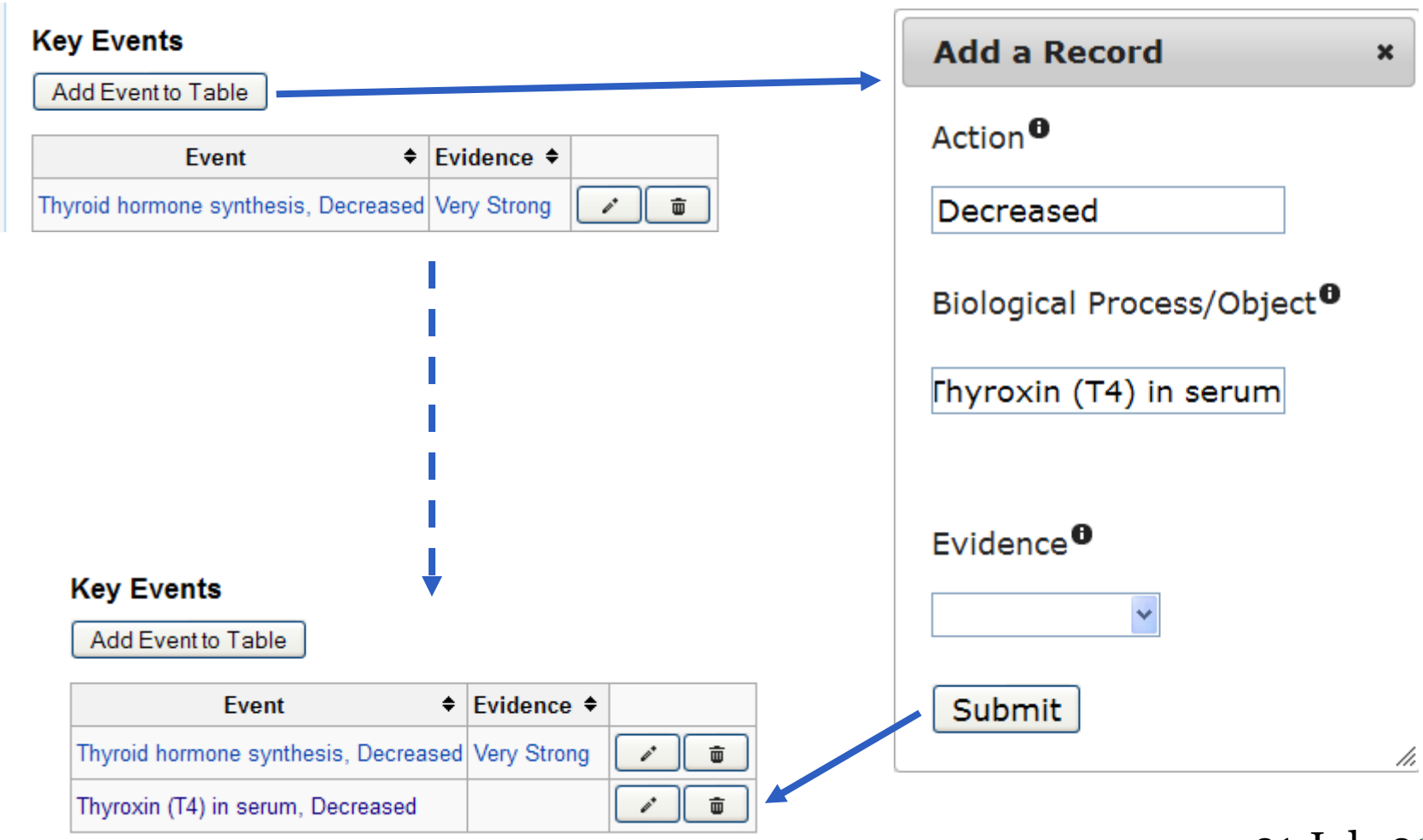
Regulatory Examples Using This Adverse Outcome [edit]

References [edit]

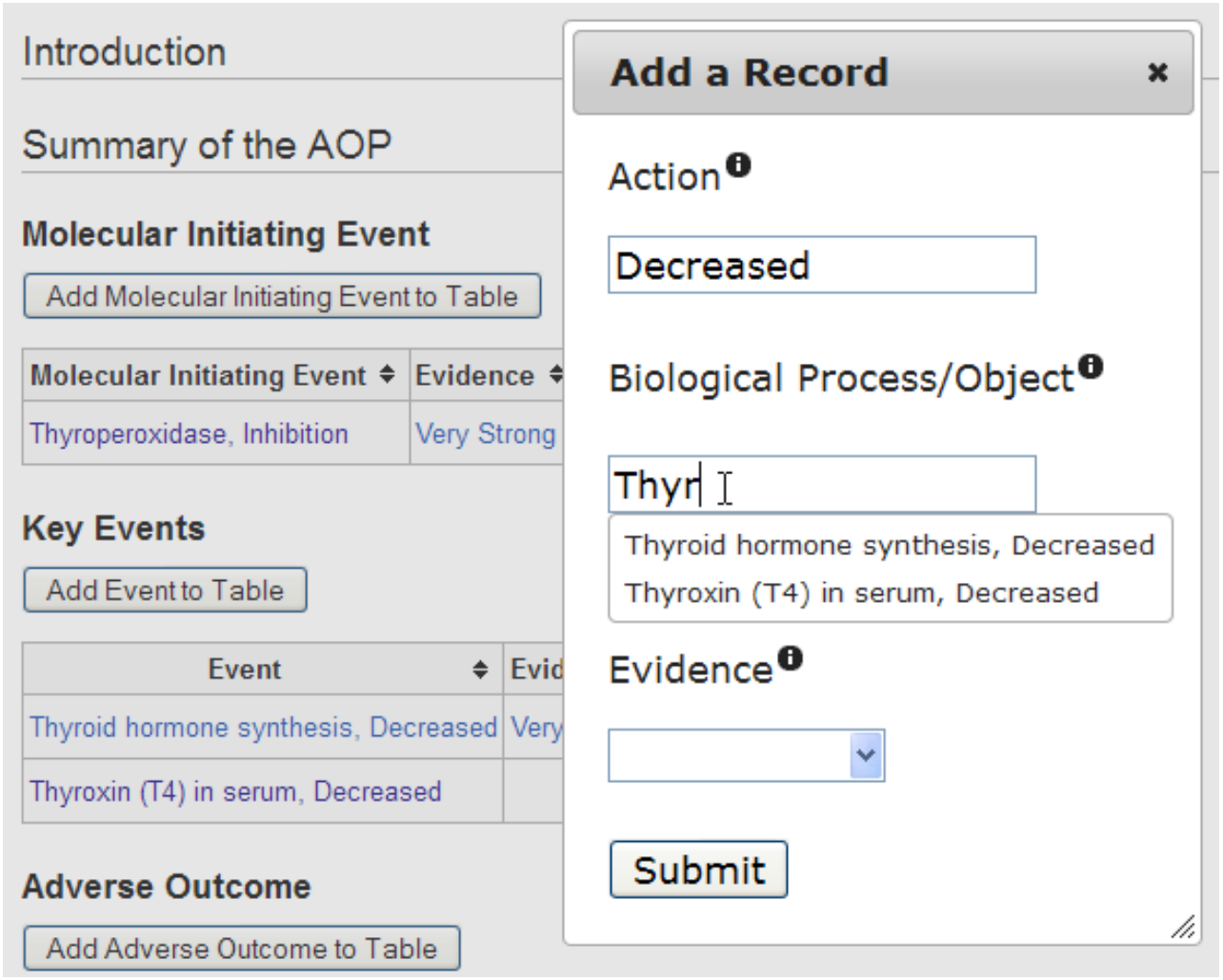
Text Editing

Category: Adverse Outcome

Add Key Event to AOP



Can Select Existing Key Events



Key Event Template

Thyroid hormone-responsive genes in developing brain, Altered regulation

Thyroperoxidase, Inhibition > TPO Inhibition and Altered Neurodevelopment > Thyroxin (T4) in neuronal tissue, Decreased > TPO Inhibition and Altered Neurodevelopment > Thyroid hormone-responsive genes in developing brain, Altered regulation

Contents [show]

Key Event Overview [edit]

AOPs Including This Key Event [edit]

Widget Editing

AOP Name	Molecular Initiating Event?	Evidence
TPO Inhibition and Altered Neurodevelopment	No	

Taxonomic Applicability [edit]

Previously Approved or Guideline Methods [edit]

Level of Biological Organization [edit]

Text Editing

How this Key Event works [edit]

How it is Measured or Detected [edit]

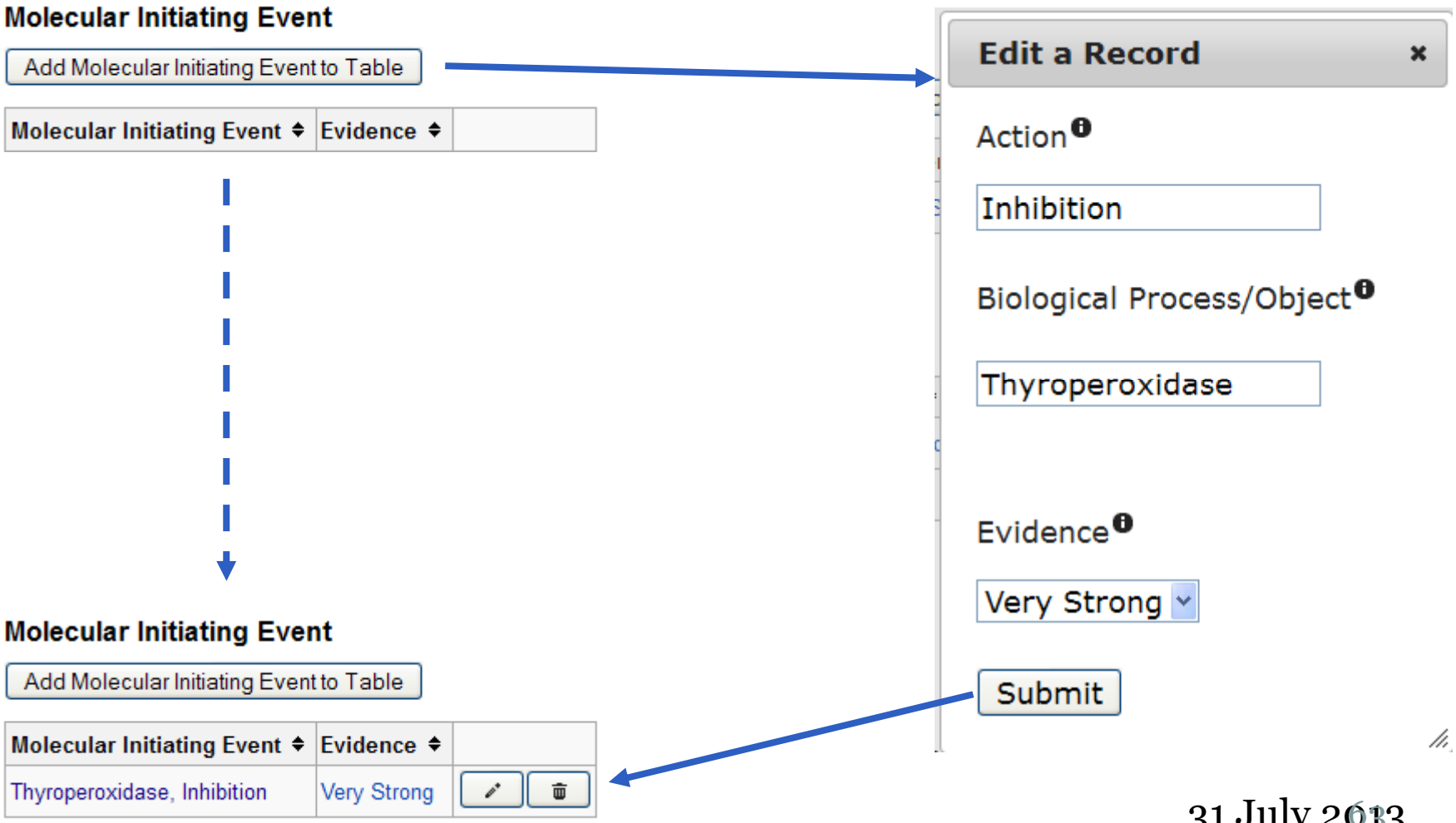
Methods that have been previously reviewed and approved by a recognized authority should be included in the Overview section above. All other methods, including those well established in the published literature, should be described here. Consider the following criteria when describing each method: 1. 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?

Evidence Supporting Taxonomic Applicability [edit]

References [edit]

Category: Key Event

Add Molecular Initiating Event to AOP



Molecular Initiating Event Template

Thyroperoxidase, Inhibition

Revision as of 13:32, 2 July 2013 by Kcrofton (Talk | contribs | block)
(diff) ← Older revision | Latest revision (diff) | Newer revision → (diff)

Thyroxin (T4) in serum, Decreased > TPO Inhibition and Altered Neurodevelopment > Neurodevelopmental deficits, N/A > TPO Inhibition and Altered Neurodevelopment > Thyroperoxidase, Inhibition

Contents [show]

Key Event Overview

AOPs Including This Key Event

AOP Name	Molecular Initiating Event?	Evidence
TPO Inhibition and Altered Neurodevelopment	Yes	Very Strong

Chemical Initiators — **Unique for MIE pages**

The following are chemical initiators that operate through this AOP:

Add Chemical Initiator from list

Taxonomic Applicability

Previously Approved or Guideline Methods

Level of Biological Organization

How this Key Event works

How it is Measured or Detected

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?

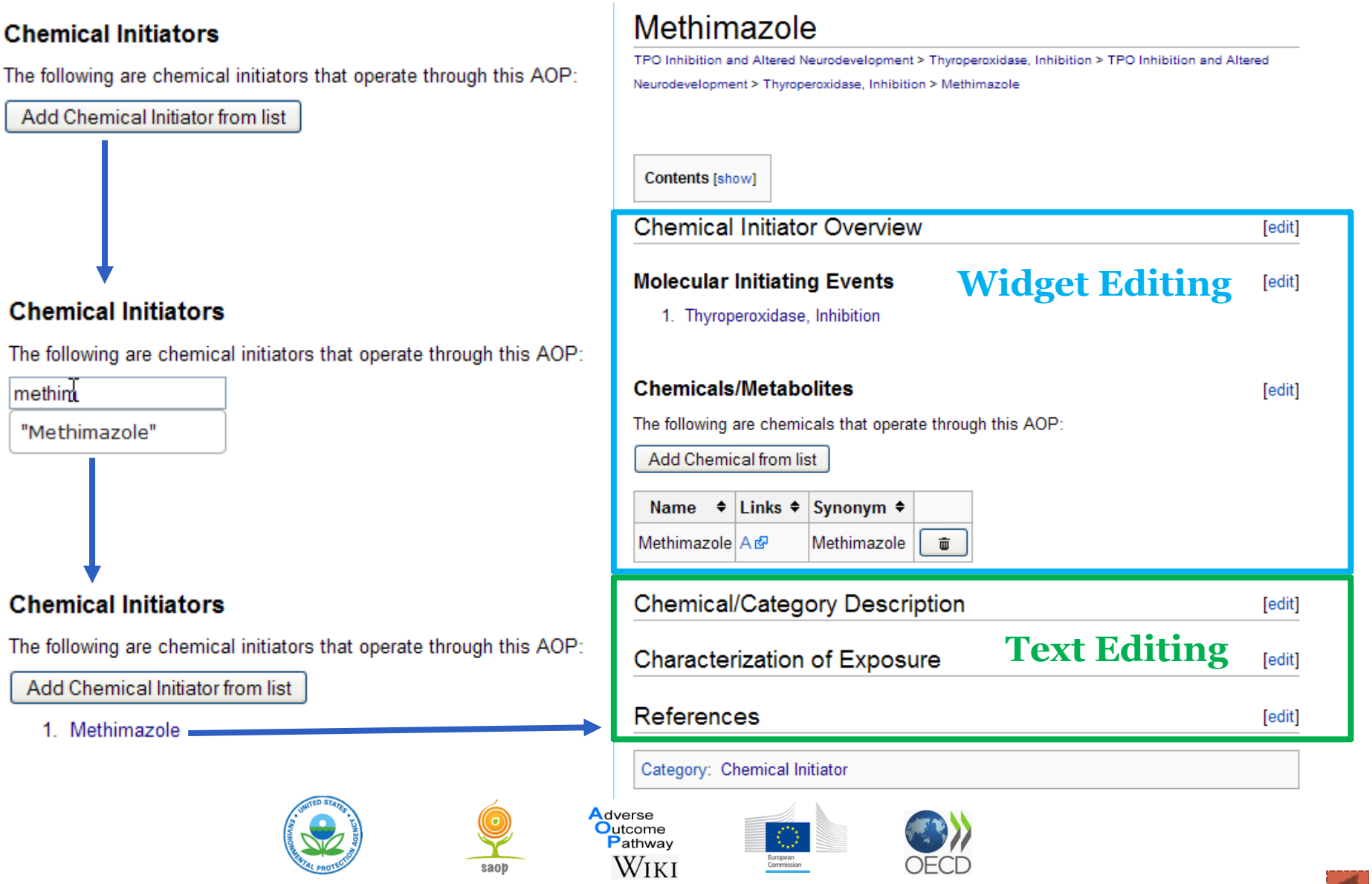
Evidence Supporting Taxonomic Applicability

Evidence for Chemical Initiation of this Molecular Initiating Event — **Unique for MIE pages**

References

Categories: Key Event | Molecular Initiating Event

Add Chemical to Molecular Initiating Event



Chemical Initiators Can Include Groups

Phthalates

Need Template > MIE leading to TPO inhibition > Never seen before, N/A

Contents [hide]

1 Chemical Initiator Overview
- 1.1 Molecular Initiating Events
- 1.2 Chemicals/Metabolites

2 Chemical/Category Description

3 Characterization of Exposure

4 References

Chemical Initiator Overview

Molecular Initiating Events

1. Never seen before, N/A

Chemicals/Metabolites

The following are chemicals that operate through this AOP:

Add Chemical from list

Name	Links	Synonym

Chemical/Category Description

Characterization of Exposure

References

Category: Chemical Initiator

Chemicals/Metabolites

The following are chemicals that operate through this AOP:

phthala

1(2H)-Phthalazinone
1,4-Dichlorophthalazine
Bis(2-butoxyethyl) phthalate
Bis(2-ethylhexyl) terephthalate

Adding chemicals to a chemical initiator via the same process as for MIEs. Repeat until you have all chemicals in your table

Chemicals/Metabolites

The following are chemicals that operate through this AOP:

Add Chemical from list

Name	Links	Synonym
Butyl benzyl phthalate (BBP)	A	Butyl benzyl phthalate
Diallyl phthalate	A	Diallyl phthalate
Dimethyl terephthalate	A	Dimethyl terephthalate
DEHP, Di(2-ethylhexyl)phthalate	A	Di(2-ethylhexyl) phthalate
Diphenyl phthalate	A	Diphenyl phthalate
Diethyl Phthalate	A	Diethyl phthalate
Di-n-butylphtalate	A	Dibutyl phthalate
Di-n-octylphthalate (DNOP)	A	Dioctyl phthalate
Dimethyl phthalate	A	Dimethyl phthalate
Diisononyl Phthalate	A	Diisononyl phthalate
Diisobutyl phthalate	A	Diisobutyl phthalate
Dicyclohexyl phthalate	A	Dicyclohexyl phthalate
Di-n-hexyl phthalate (DnHP)	A	Dihexyl phthalate
Ciclosporin (Cyclosporin A; Cyclosporine)	A	Diisodecyl phthalate
Di(2-methoxyethyl) phthalate	A	Di(2-methoxyethyl) phthalate
Diundecyl phthalate	A	Diundecyl phthalate
Mono(2-ethylhexyl) phthalate	A	Mono(2-ethylhexyl) phthalate
Didecyl phthalate	A	Didecyl phthalate
butyl 2-ethylhexyl phthalate	A	Butyl 2-ethylhexyl phthalate
Dimethyl hexahydroterephthalate	A	Dimethyl hexahydroterephthalate
Dimethyl isophthalate	A	Dimethyl isophthalate
1,4-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester	A	Bis(2-ethylhexyl) terephthalate

aop

Adverse Outcome Pathway Wiki

European Commission

Basic Summary of AOP (building blocks)

Summary of the AOP [edit]

Molecular Initiating Event [edit]

Add Molecular Initiating Event to Table

Molecular Initiating Event	Evidence	
Thyroperoxidase, Inhibition	Very Strong	

Key Events [edit]

Add Event to Table

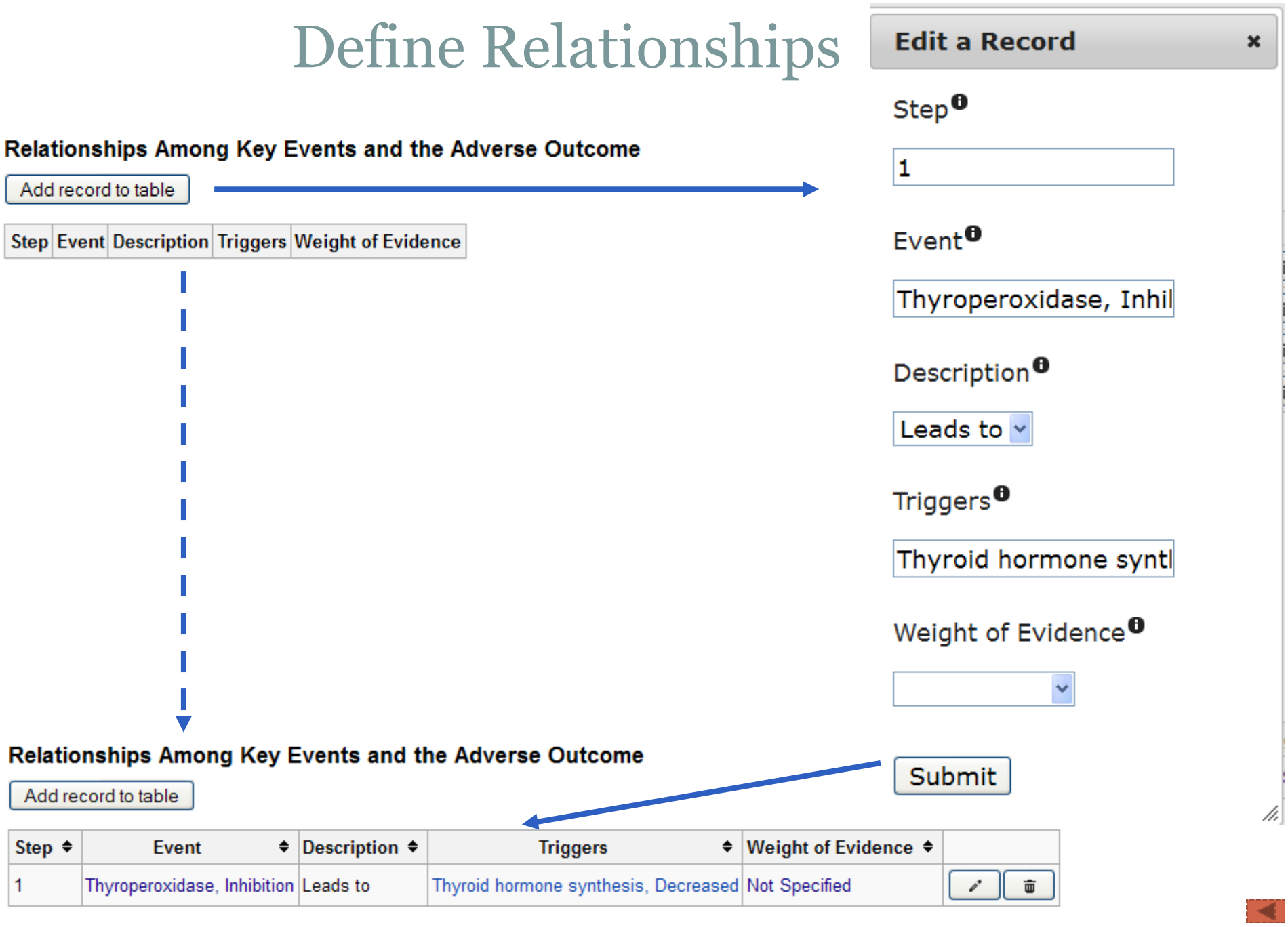
Event	Evidence	
Thyroid hormone synthesis, Decreased	Very Strong	
Thyroxin (T4) in serum, Decreased		
Thyroxin (T4) in neuronal tissue, Decreased		
Thyroid hormone-responsive genes in developing brain, Altered regulation		

Adverse Outcome [edit]

Add Adverse Outcome to Table

Adverse Outcome	Evidence	
Neurodevelopmental deficits, N/A		

Define Relationships



KE Relationship Template

Thyroperoxidase, Inhibition Leads to Thyroid hormone synthesis, Decreased

Thyroxin (T4) in neuronal tissue, Decreased > TPO Inhibition and Altered Neurodevelopment > Thyroid hormone-responsive genes in developing brain, Altered regulation > TPO Inhibition and Altered Neurodevelopment > Thyroperoxidase, Inhibition Leads to Thyroid hormone synthesis, Decreased

Contents [show]

Key Event Relationship Overview [edit]

Description of Relationship [edit]

Upstream Event	Type of Relationship	Downstream Event/Outcome
Thyroperoxidase, Inhibition	Leads to	Thyroid hormone synthesis, Decreased

AOPs Referencing Relationship [edit]

AOP Name	Weight of Evidence
TPO Inhibition and Altered Neurodevelopment	Not Specified

Taxonomic Applicability [edit]

Widget Editing

Biological Plausibility [edit]

Empirical Support for Linkage [edit]

Include consideration of temporal concordance here

Quantitative Understanding of the Linkage [edit]

Text Editing

Is it known how much change in the first event is needed to impact the second? Are there known modulators of the response-response relationships? Are there models or extrapolation approaches that help describe those relationships?

Uncertainties or Inconsistencies [edit]

Evidence Supporting Taxonomic Applicability [edit]

References [edit]

Category: KE Relationship

Basic Summary of AOP (linkages)

Relationships Among Key Events and the Adverse Outcome [edit]

Add record to table

Step	Event	Description	Triggers	Weight of Evidence	
1	Thyroperoxidase, Inhibition	Leads to	Thyroid hormone synthesis, Decreased	Not Specified	
2	Thyroid hormone synthesis, Decreased	Leads to	Thyroxin (T4) in serum, Decreased	Not Specified	
3	Thyroxin (T4) in serum, Decreased	Leads to	Thyroxin (T4) in neuronal tissue, Decreased	Not Specified	
4	Thyroxin (T4) in neuronal tissue, Decreased	Leads to	Thyroid hormone-responsive genes in developing brain, Altered regulation	Not Specified	
5	Thyroid hormone-responsive genes in developing brain, Altered regulation	Leads to	Neurodevelopmental deficits, N/A	Not Specified	

Coming Soon…

AOP Summary Section

Life Stage Applicability

Taxonomic Applicability

Sex Applicability

Key Event Overview Section

Taxonomic Applicability

Previously Approved or Guideline Methods

Planned for Dec. 2013 release

Adverse Outcome Overview Section

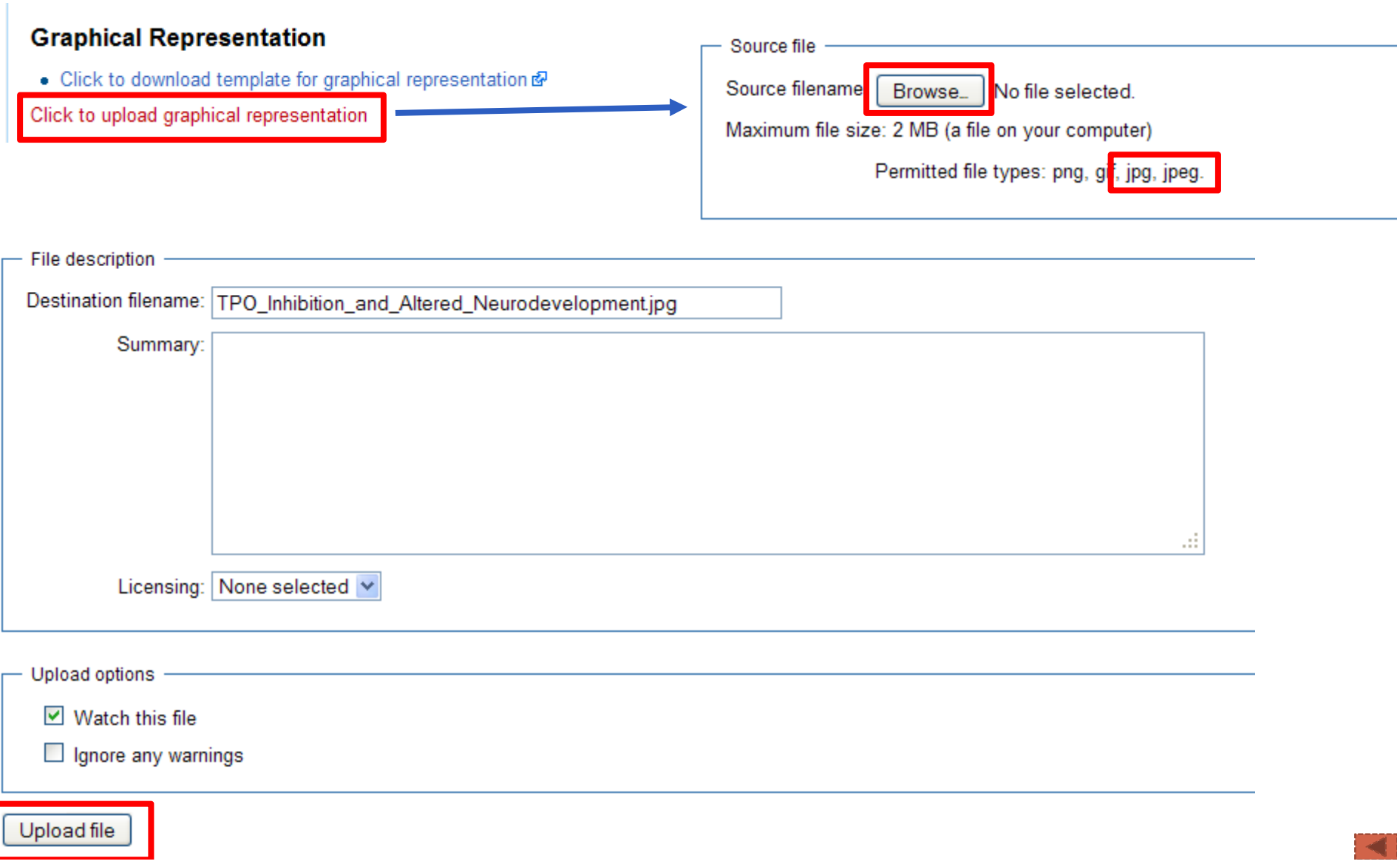
Affected Organs

Key Event Relationship Overview Section

Taxonomic Applicability

Life Stage, Sex, Taxonomic Applicability, & Target Organ released 2013/07/20. Reference slides to demonstrate these widgets coming soon.

Uploading a Graphic



Creating Graphic from Template

Graphical Representation

- Click to download template for graphical representation

Click to upload graphical representation

Instructions

- Select a template slide
- Edit the template as needed to provide the specific details of the AOP you're describing
- While viewing the slide you have edited, click Save As – Other formats (fig1)
- In the save dialog box, select "JPEG File Interchange Format" (fig2)
- In the next box, click "Current Slide Only" (fig3)

Fig 1

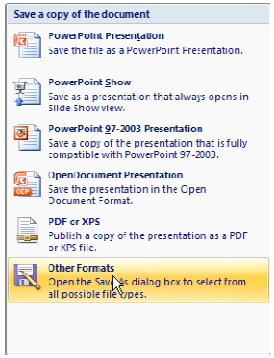


Fig 2

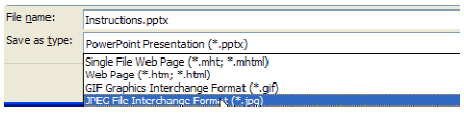
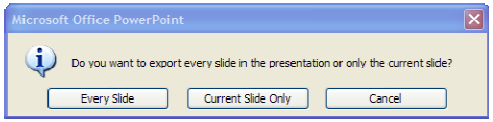
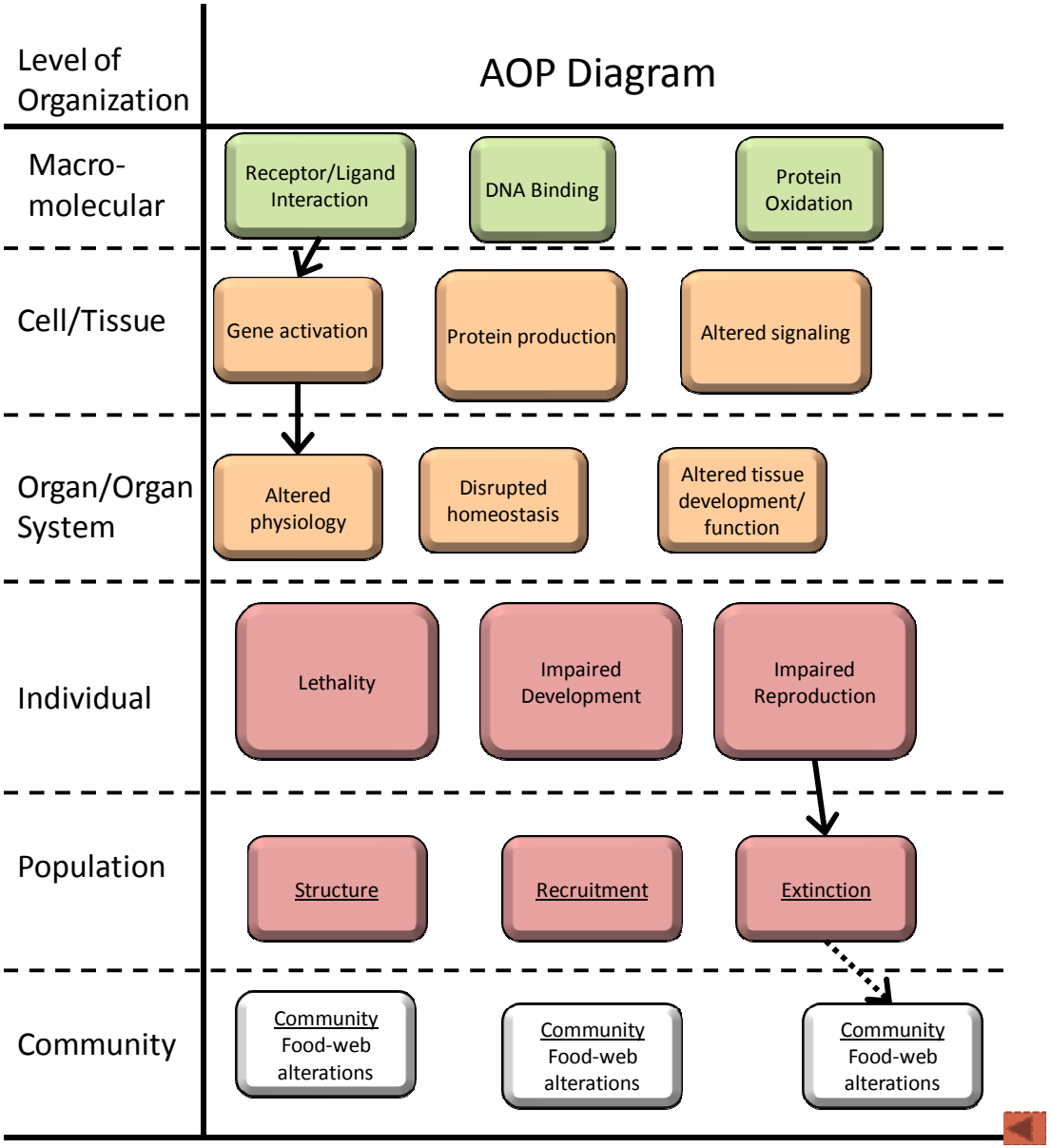
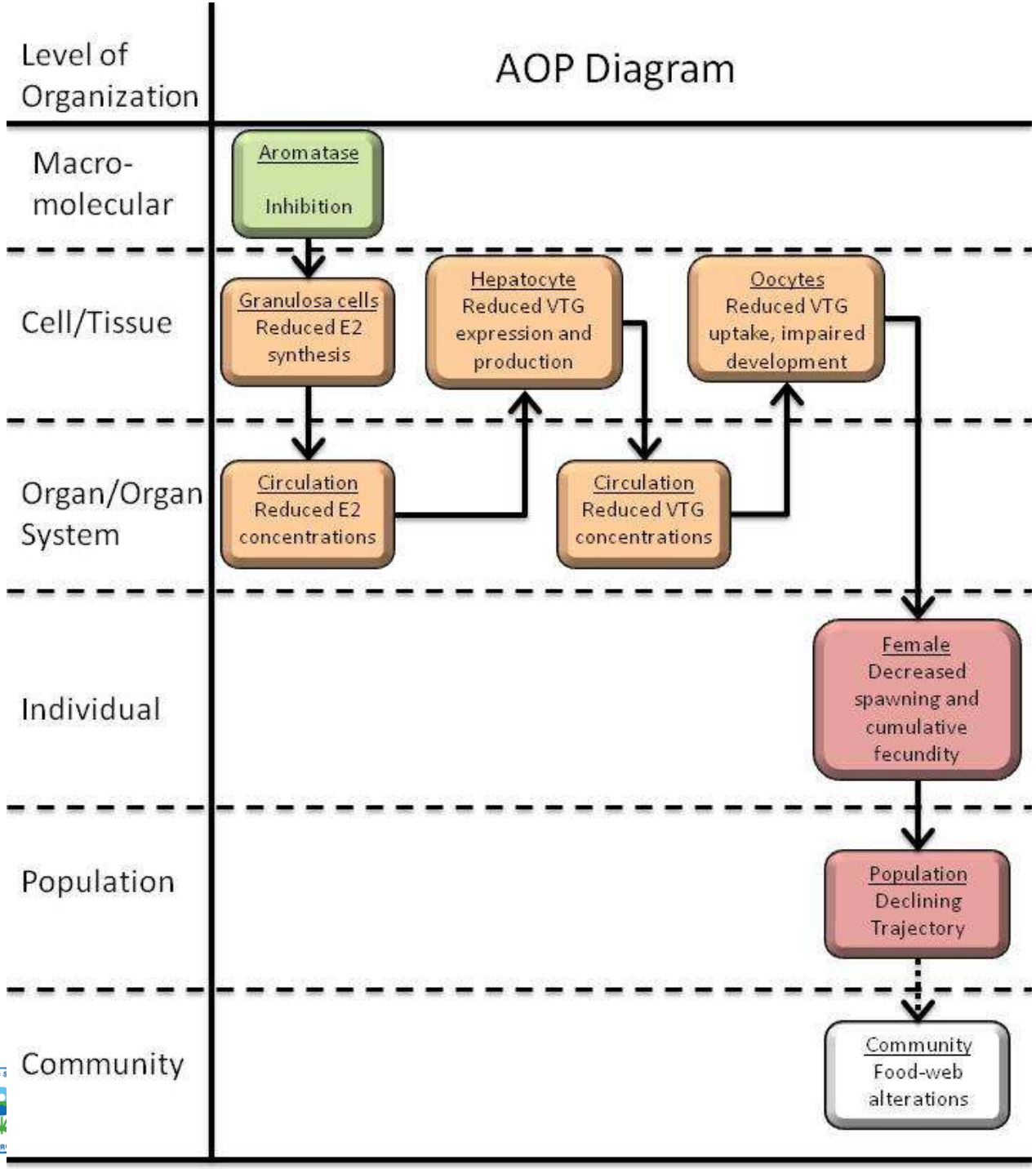


Fig 3





Example showing AOP graphic using the template



Text Entry Sections on AOP Page

Status [edit]

Under development: Do not distribute or cite.

Introduction [edit]

- …

Assessment of the AOP [edit]

Consider the following criteria (may include references to KE Relationship pages): 1. concordance of dose-response relationships; 2. temporal concordance among the key events and adverse effect; 3. strength, consistency, and specificity of association of adverse effect and initiating event; 4. biological plausibility, coherence, and consistency of the experimental evidence; 5. alternative mechanisms that logically present themselves and the extent to which they may distract from the postulated AOP. It should be noted that alternative mechanisms of action, if supported, require a separate AOP; 6. uncertainties, inconsistencies and data gaps.

Confidence in the AOP [edit]

Elaborate on the domains of applicability listed in the summary section above. Specifically, provide the literature supporting, or excluding, certain domains.

References [edit]

Editing Text Sections on Any Page

Most common formatting options available here

```
==   Introduction      ==
```

Don’t modify or delete this line!

Please note that all contributions to aopwiki may be edited, altered, or removed by other contributors. If you do not want your writing to be edited mercilessly, then do not submit it here.
You are also promising us that you wrote this yourself, or copied it from a public domain or similar free resource (see Aopwiki:Copyrights for details). **Do not submit copyrighted work without permission!**

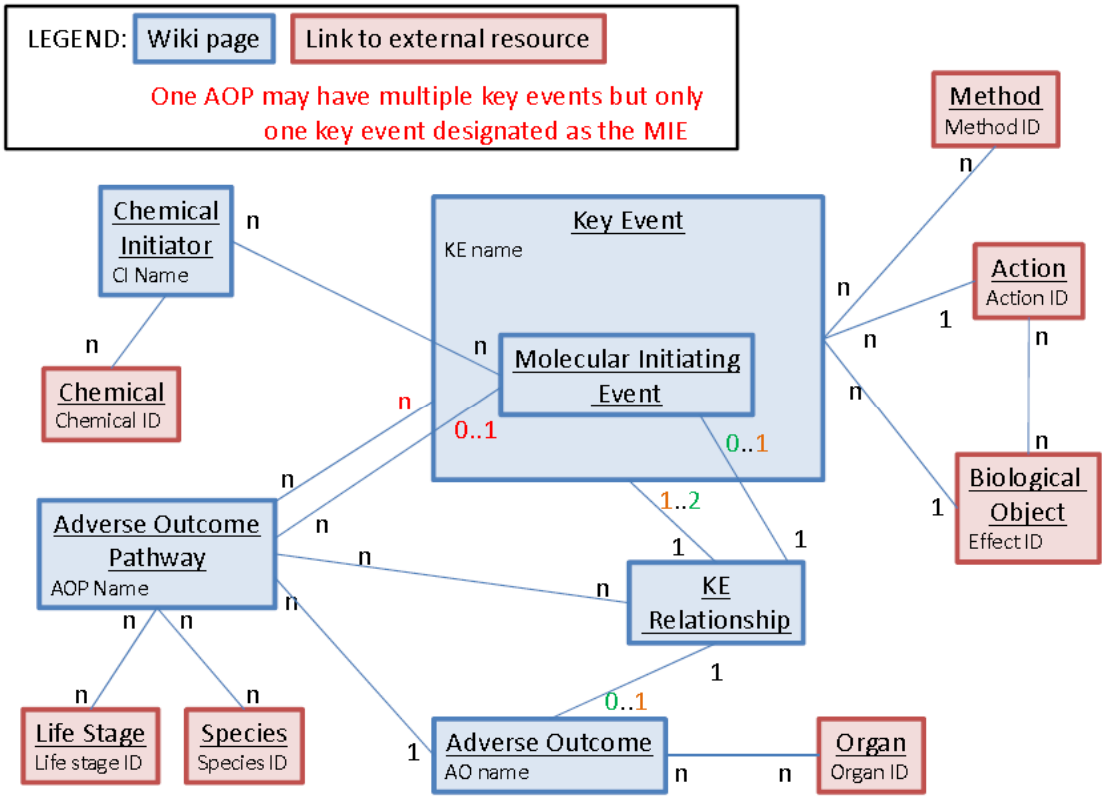
Summary: /* Introduction */

This is a minor edit ☑ Watch this page

Use this check box to stay informed about edits to this page

Save page | Show preview | Show changes | Cancel | Editing help (opens in new window)

AOPWiki Article categories



5 Categories of Wiki Pages

1. Chemical initiator
2. Key event (including MIE; node)
3. KE Relationship (linkage; edge)
4. Adverse Outcome
5. AOP