- **Definition of ontology:** An ontology is a kind of controlled vocabulary of well-defined terms with specified relationships between those terms, capable of interpretation by both humans and computers. (National Center for Biomedical Ontology (NCBO) (https://www.bioontology.org/community/learning-about-ontologies). **Biomedical ontologies** can provide terms descriptive of biological entities useful for computationally representing AOPs.
- **Why incorporate ontology terms in the AOP-Wiki:**
    - Improve query of existing KEs, and provide more flexibility for authors in creating and naming new KEs.
    - Encourage reuse of KEs or KERs and reduce redundancy.
    - Ontologies enable a computer reasoner to make inferences and discover additional connections among KEs and AOPs.
    - The ability to explicitly attach scientific evidence in support of the AOP, including assays and biomarkers linked to KEs. In future, incorporation of ontologies covering the domain of experiments, for example BioAssay Ontology (BAO) and Experimental Factor Ontology (EFO), will allow for the development of tools that integrate and display these data in the context of an AOP.
    - Enable information sharing and integration across species and knowledge domains computationally, which supports the evaluation of taxonomic relevance of KEs.
    - Speed up the development of quantitative AOPs (qAOPs) by providing explicit biological entities underlying the KEs and a better understanding of how AOPs interact with one another to form AOP networks.
- **Annotating AOP KEs using Ontology Terms:** The use of ontology-based information to describe AOP Key Events will play a key role in promoting the systematic reuse of AOP elements to streamline multi-party AOPs development and enhance AOP network interoperability
  (Edwards SW *et al*, J Pharmacol Exp Ther. 2016; Oki NO *et al*, Curr Environ Health Rep. 2016; Kleinstreuer NC *et al*, Regul Toxicol Pharmacol. 2016). The AOP-KB ontology working group is carrying out a project to introduce ontology terms to annotate or "tag" AOP Wiki Key Events with terms from standardized ontologies and controlled vocabularies.

- **Introducing the Event Component concept:**

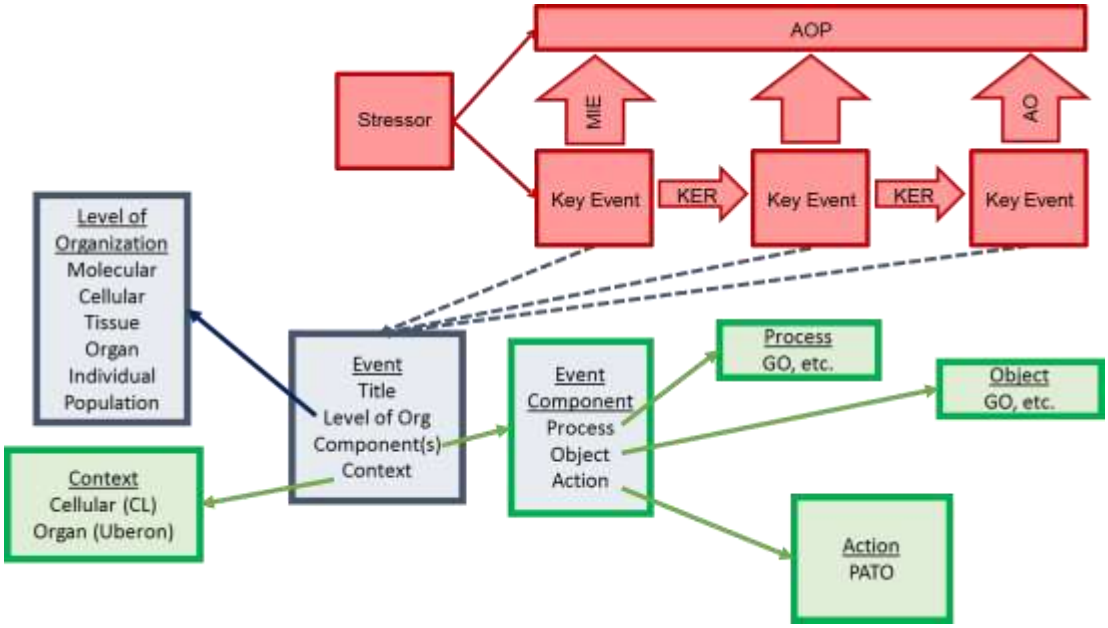


Figure. Schematic for how the Event Component data model extends the AOP Ontology. Components contained in the existing AOP-Ontology are in red. The data model provides Process, Object, Action, and Context (green), which are external but linked to AOP Ontology via the annotation of KE's. Entities in blue are part of the AOP-Wiki application. CL, Uberon, and GO represent examples of ontologies that these data fields will import from.

  - The existing **AOP-Ontology** (https://github.com/DataSciBurgoon/aop-ontology) provides a conceptualization of AOPs and AOP associated information.
  - Definitions: The concept of an **Event Component** was introduced to allow for ontology-based annotations of Key Events in the AOP-Wiki. Each Event Component was defined via a Process, an Object, and an Action term.
  - The **Process** represents the dynamics of the underlying biological system (e.g. receptor signaling).
  - The **Object** was the subject of the perturbation, for example, a specific biological receptor that is activated or inhibited. Ideally, the Process and the Object represent the normal biology that is perturbed as part of the AOP, and not the perturbation itself. This represents the perturbation of this system described by the other two terms that results in this key event (e.g. 'decreased' in the case a receptor is inhibited to indicate a decrease in the signaling by that receptor).
  - The **Action** represents the perturbation of this system described by the other two terms that results in this key event (e.g. 'decreased' in the case of a receptor is inhibited to indicate a decrease in the signaling by that receptor).
  - A fourth and separate term, the **Context**, was incorporated to represent the location or biological environment in which the KE took place. The Context term

was tied to the level of biological organization as described by authors in the AOP-Wiki.

- For KEs with molecular or cellular level of biological organization, the KE was assigned a Cellular or Organ context.
- For KEs at the tissue or organ level of biological organization, the KE was assigned an Organ context.
- At the individual or population levels of biological organization KEs were not assigned a Context, as their biological context was represented by the existing "Taxonomy," "Sex," and "Life Stage" of applicability terms in the AOP-Wiki.
- Where a KE took place in multiple biological contexts, the KE was assigned only one Cellular or Organ Context, usually representing the most specific compartment where the KE occurred. For instance, a KE that takes place in both 'eukaryotic cell' and 'hepatocyte' was assigned a Cell Context of 'hepatocyte.'

- **List of Ontologies and Controlled Vocabularies for annotating Key Events:**

		Level of Biological Organization*						
Data Source	**Domain**	**M**	**C**	**T**	**O**	**I**	**P**	**# of classes**
	OBO Foundry							
Gene Ontology (GO)	biology	Y	Y	Y	Y	Y	?	260
Chemical Entities of Biological Interest (CHEBI)	biochemistry	Y	X	X	X	X	X	67
Protein Ontology (PRO)	proteins	Y	X	X	X	X	X	140
Protein-protein interaction (MI)	experiments	Y	X	X	X	X	X	5
Cell Ontology (CL)	cells	X	Y	X	X	X	X	70
Uber Anatomy Ontology (UBERON)	anatomy	?	Y	Y	Y	?	?	80
Foundational Model of Anatomy (FMA)	anatomy	Y	Y	Y	Y	X	X	7
Vertebrate Trait (VT)	vertebrate trait	X	X	Y	Y	Y	X	7
Human Phenotype Ontology (HP)	phenotype	X	Y	Y	Y	Y	X	5
Mammalian Phenotype Ontology (MP)	phenotype	X	Y	Y	Y	Y	X	55
Neuro Behavior Ontology (NBO)	behavioral phenotypes	X	X	X	X	Y	X	7
Phenotypic Quality Ontology (PATO)	phenotype	Y	Y	Y	Y	Y	Y	N/A
Population and Community Ontology (PCO)	populations and communities	X	X	X	X	X	Y	3
	Controlled Vocabulary							
UMLS/Medical Subject Headings (MeSH)	biomedical information	Y	Y	Y	Y	Y	Y	71
		Total						777

*Molecular, Cellular, Tissue, Organ, Individual,
Y = definitely covers this level of organization.
X = definitely doesn't covers this level of organ
?=maybe

Table: List of ontologies used for annotating key events.

- Ontology terms derived from this list, chosen based on literature review of ontologies and controlled vocabularies primarily from the Open Biological

Ontologies (OBO) Foundry (http://www.obofoundry.org/) based on those containing at a level of biological organization applicable to AOPs. One controlled vocabulary, Medical Subject Headings (MeSH), was selected due to its widespread use in the medical domain, even though it is not a formal ontology.

- **How to annotate AOP Key Events:**
  - KEs from the AOP-Wiki were mapped to classes from the chosen ontologies in **Table 1**. KE titles and text on individual KE Wiki pages were manually reviewed for text phrases representative of KEs. Query text phrases were entered into three ontology browser sites: Ontobee (http://www.ontobee.org/), NCBO Bioportal (http://bioportal.bioontology.org/), and the EMBL-EBI Ontology Lookup Service (https://www.ebi.ac.uk/ols/index). From the browser's list of output "hits," ontology terms or classes were reviewed in order to find the appropriate matching class for annotation. Classes were selected based on the appropriateness of the definition in capturing the biology occurring in the KE description, and choice from the ontology tree of the most specific class or target node available that matched the level of detail provided in the KE description, as well as a set of formalized conventions defining KE annotation in order to ensure accuracy and reproducibility.

- **Conventions defining annotation of KEs via the event component model:**

One or more event components can be used to describe a KE.
KE can have a Process and/or Object term. Action is a required term.
Chemicals and experiments are excluded; except when a chemical is endogenous.
In most cases, the most specific ontology term should be chosen to represent the KE.
The PATO ontology was used as a basis for deriving a set of Action terms: increased, decreased, morphological change, functional change, occurrence, disrupted, arrested, delayed, premature, abnormal, and pathological.
Optional Cell or Organ Context.

- **Examples of Event Component annotations of KEs in the AOP-Wiki:**

1. KE component showing annotation of the KE, “Reduction, 17beta-estradiol synthesis by ovarian granulosa cells” with a Process, Object, and an Action term.

Event: 3

Key Event Title

Reduction, 17beta-estradiol synthesis by ovarian granulosa cells

Short name

Reduction, 17beta-estradiol synthesis by ovarian granulosa cells

Key Event Component

Process	Object	Action
estrogen biosynthetic process	17beta-estradiol	decreased

2. On the KE page, the Cell Term which is tied to a Cellular Level of Biological Organization.

Level of Biological Organization

Biological Organization
Cellular

Cell term

Cell term
granulosa cell

Organ term

3. KE component showing annotation of the KE, “Reduction, Plasma 17beta-estradiol concentrations” with only an Object and an Action term.

Key Event Component

Process	Object	Action
	17beta-estradiol	decreased

4. Annotation of the KE, “Reduction, Vitellogenin accumulation into oocytes and oocyte growth/development” with multiple KE components.

Key Event Component

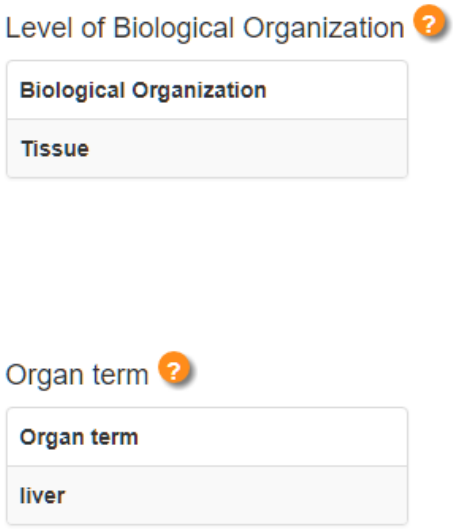
Process	Object	Action
receptor-mediated endocytosis	vitellogenins	decreased
oocyte growth		decreased
oocyte development		decreased

5. KE component showing annotation of the KE, “Decrease, Population trajectory,” with only a Process and an Action term.

Key Event Component

Process	Object	Action
population growth rate		decreased

6. On the KE page, the Organ Term which is tied to a Tissue Level of Biological Organization.



7. On the KE page, showing a KE at the Cellular Level of Biological Organization having both a Cell term and an Organ term.