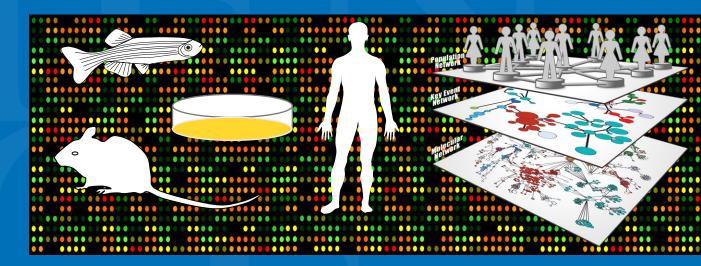


# AOP Knowledge Base/ Wiki Tool Set

Stephen W. Edwards Adverse Outcome Pathways: From Research to Regulation

This talk does not necessarily reflect the views of the Environmental Protection Agency.







- Why an AOP Knowledgebase?
- Components of the AOP Knowledgebase
- AOP-Wiki
- What's next?





- 2010 AOP development
  - relatively poorly defined ad hoc process
- 2012 Launch of OECD AOP Development Programme
  - <u>http://www.oecd.org/chemicalsafety/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm</u>
- 2013 OECD Guidance on Developing and Assessing AOPs
  - <u>http://search.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono%</u>
     <u>282013%296&doclanguage=en</u>
- 2014
  - AOP Workshops
    - Part of National Society meetings: SOT, SETAC, EMGS
    - Advancing AOPs for Integrated Toxicology and Regulatory Applications (Somma Lombardo, Italy)
    - Adverse Outcome Pathways: From Research to Regulation (Bethesda, MD)
  - Development of an OECD User Handbook as a supplement to the 2013 guidance



### **AOP-KB History**

- Effectopedia (International QSAR Foundation)
  - -Developed since 2006, alpha releases since 2010
- Chem MOA Wiki (WHO/IPCS) -> AOP Wiki
  - -EPA Fall 2012
- AOP-KB for OECD AOP Programme
  - -Joint proposals EPA, JRC, & USACE March 2013
  - -Initial Wiki beta release July 2013
  - -Formal inclusion of OECD (Effectopedia) Dec. 2013
  - -Most recent Wiki release June 2014



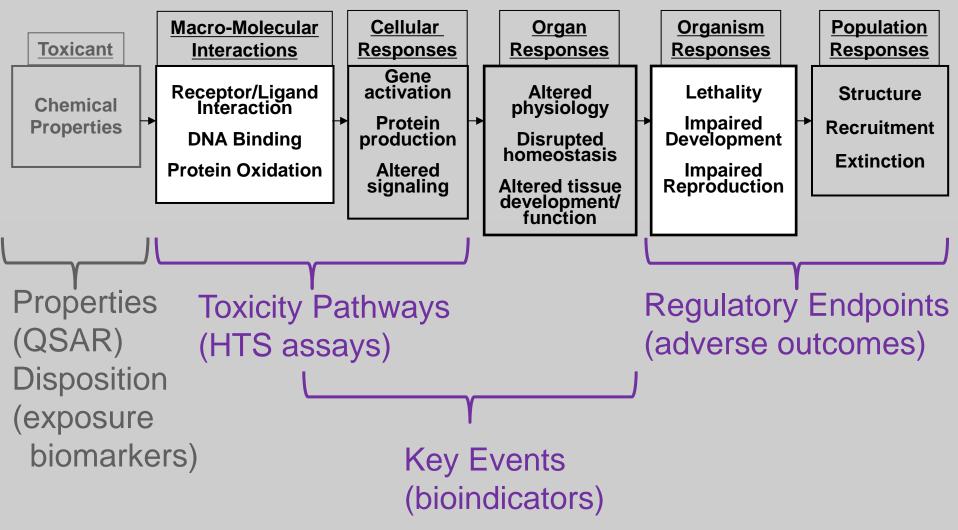


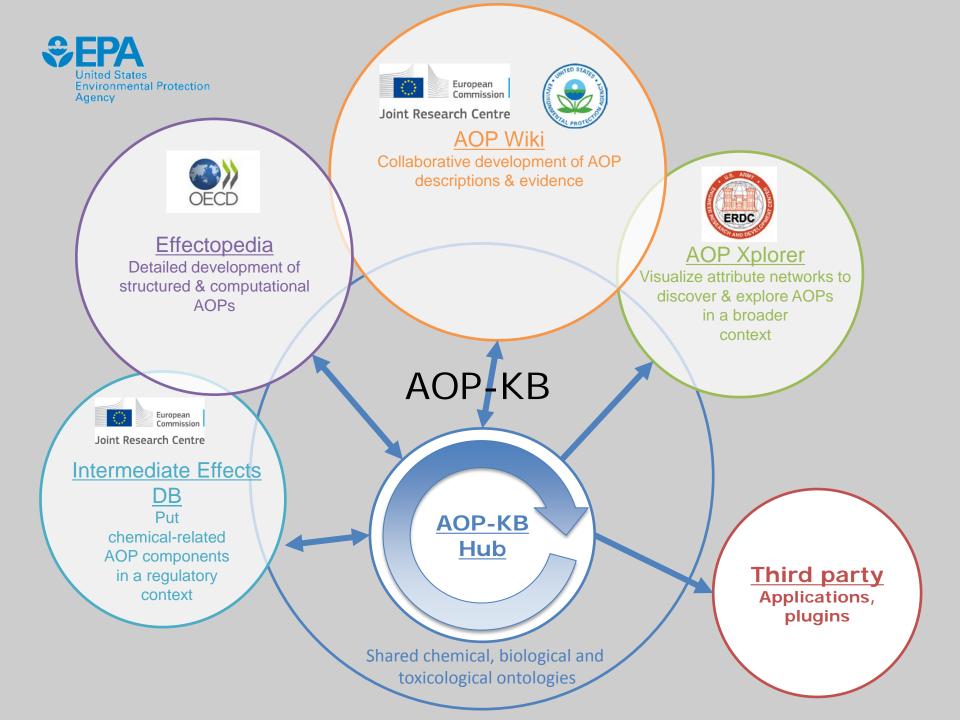
**AOP Key Concepts** 

- Organize existing knowledge
- Systematic evaluation of evidence
- Avoid duplication of the same key event
- Always expand description to include new science
- Provide a framework for utilizing 21<sup>st</sup> century toxicity testing



AOD as a Knowlades Drides







# AOP-Wiki (http://aopwiki.org)

Adverse Outcome Pathway	Page Discussion	Read	Edit	Sedwar02 View history	Prefe	Search	Contributions Log out
Wiki	Main Page						
<ul> <li>Navigation         <ul> <li>Main page</li> <li>AOP List</li> <li>Help</li> <li>FAQ</li> <li>Recent changes</li> <li>Release notes</li> </ul> </li> <li>Actions</li> </ul>	Contents [hide] 1 Announcements 2 Welcome to the Collaborative Adverse Outcome Pathway KnowledgeBase (AOP-KB) Wiki 2.1 Partners 2.2 Disclaimer 3 Main Types of Data 4 How to add a new AOP 4.1 Before You Start 4.2 To create a new AOP 4.3 To edit AOP pages 4.4 To edit other pages						

#### Welcome to the Collaborative Adverse Outcome Pathway KnowledgeBase (AOP-KB) Wiki [edit]



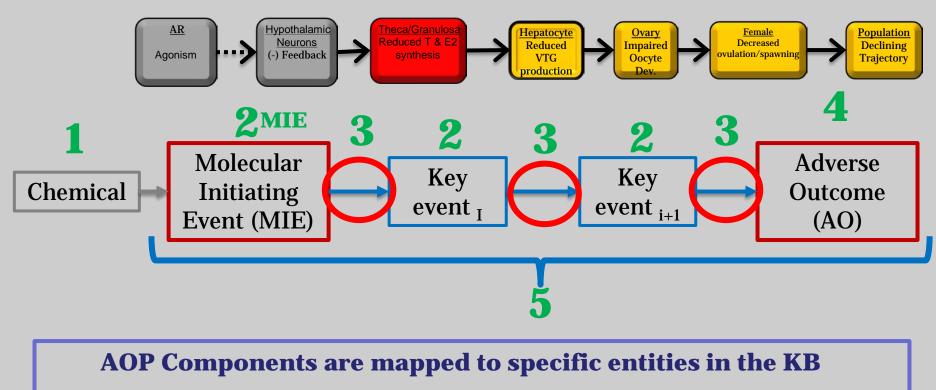
This wiki represents a joint effort between the European Commission – DG Joint Research Centre and U.S. Environmental Protection Agency. This serves as one component of a larger OECD-sponsored AOP Knowledgebase effort and represents the central repository for all AOPs developed as part of the OECD AOP Development Effort by the Extended Advisory Group on Molecular Screening and Toxicogenomics. The other major components of this knowledgebase are Effectopedia, produced by the International QSAR Foundation, and the AOP Network tool, produced by the US Army Corps of Engineers - Engineering Research and Development Center.

This wiki is based upon the Chemical Mode of Action wiki developed by the US EPA under the auspices of the WHO International Programme on Chemical Safety (IPCS) Mode of Action Steering Group.



# **Structuring and Storing AOP Information**

5. AOP



3. KE Relationship

- 1. Chemical initiator
- Key event (linkage; edge) (including MIE; node)
   Adverse Outcome

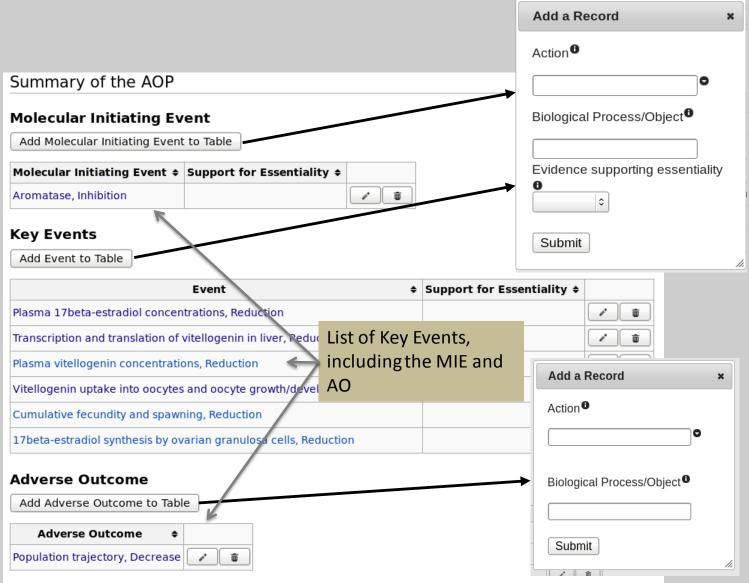
# **AOP Page in Wiki**

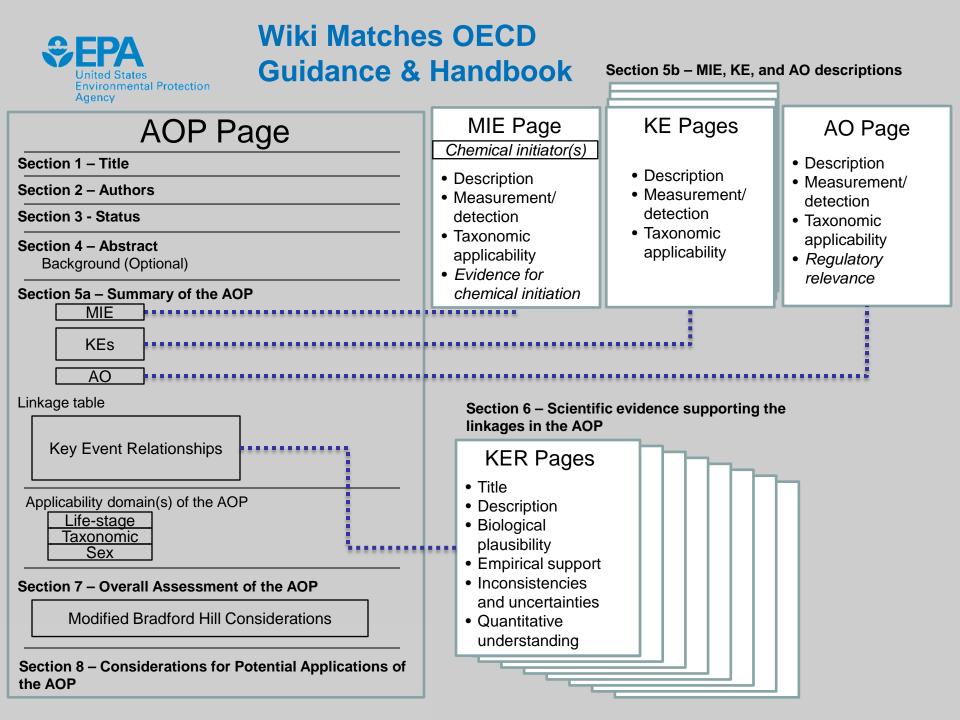
United States Environmental Protection

	Agency				
		& Sedward2 Talk Preferences Welchief Contributors Log nut		Click nodes or edges.	
dverse	Page Dacaster	Read Est Vewstadory * Search 0		Life Stage Applicability	
Pathway				Add Life Stage to table	
WIKI	Estrogen receptor agonism leading to reproductive dysfur	ction		Life Stage   Evidence   Links	Structured
VV IIVI				Juvenie Strong	
	Authors [edit]			Embryo Strong	
Navigation	Status [cdr]				Content
Main page				Taxonomic Applicability	Content
FAQ	Abstract [edit]			Add Species from list	Contont
Recent changes Release soles	This AQ <sup>3</sup> describes the triages tetriesen agentsm of the satrogen receptor (SR) and provation reterant imports information is this AQP for ER appriam does not apply to mammalian species and also not to mentebrates.	n a range at a vigance e visitoristics instructing anything, barrow and fait. The dis strategy provides of investments and search and a differentiation that is the discretion of the autobiogram of the search are referent and the second search and the second s		Name	
Actions	Amphibians are senative to ER agonists during the transformation from larval tabpole to uvenile frog as these inc	ude critical periods of metamorphic development and sex differentiation that		Fathead minnow Pimephales promelas Strong NCBI /	
Feedback	may be particularly sensitive to endocrine disruption. Larvae exposed to ER agonists during rid-instancryhosis e which suggests that transient early Hb-etage exposure to CR agonists can produce effects on the reproductive	rgara that peraid, into the beginning of adult He-stepes. Dirds are also known	-	Japanese gust Cotumix cotumix Strong NC81@	
Tools	to be uninerable to RR agoniam causing datagtion of estimpen-regulated functions such as sexual differentiation widely used as a model for studying various long-term effects after entryonic exposure to IR agoniats, in terms			Northern leopard frog Rana pipiens Strong NCBI 💋 🖌 🗉	
What links here Related changes	depending upon whether exposures occur during or beyond the larval, pulentie and adult life-stages. For example stages may leads to ponedarand renal participy and skelved-sex ratios in adult fran (potentiatly 100% females).	arvsi, svenie and aduit male tish exposed to the same ER agonists decray	/+	Medaka Oryzias latpes Strong NCBI@ 2	
Tipload file Special pages	abnormal pleams or whole body levels of vibilitization (VTG). Cumulative fecundity in adult populations is also adv Tasi Oudeline 229 Fan Short Term Reproduction Assay. In summary, this ADP has stillity in supporting the applic	really affected by ER agoniats and the is an important endpoint in the OECD to of test methods for detecting ER agoniats, or in allog predictions of the		Zebrafan Danio rerio Strong NCBr@ 🖉 🗉	
Production concerns	ability of characteria to act as 12 accelete and races intracted account development and record orbus Austraction				
Page information	Summary of the AOP			Sex Applicability	
	Molecular Initiating Event			Add a Sex to table	
	Add Molecular Initiating Event to Table			Sex      Evidence      Links	
	Molecular lutitating Event	Structure		Male Strong	
	(performed)			2 - 11 - 12	
	Key Events			Graphical Representation	
	Add Event to Table			Clos to sownows template for graphical representation 8     Link to upped graphical representation	
	Cumulative fecundity and spearning. Reduction Strong	Content		Overall Assessment of the AOP [edt]	
	Extrogen receptor, egoniam Strong 21 a			In terms of the oriteria associated with Key Events in this AOP, the following observation:	have been made as shown in parentheses Tr
	Pasna visiopern concettrations, horease Drong 2			<ol> <li>concordance of dose-response relationships?; [There is strong dose-response relation models, including amphibians, birds and fish].</li> </ol>	ship concordance over a wide range of experimental studies using ER agonists in well-defined animals
	Vitelogenn synthesis in Sver, Increase Strong 🖉 🗷		<b>Free</b>		poral concordance from partial and full life-cycle studies using ER agonists in well-defined animals
	Renal pathology due to VTG deposition, Increase Strong			models)	ent?; [In fish, there is a strong and consistent association between ER agonist exposure, disruption of
	Adverse Outcome			sexual development and reproductive dysfunction. The same is true for amphibians and b	irds athough the published studies are less numerous (;
	Add Adverse Dutcome to Table			<ol> <li>biological plausibility, coherence, and consistency of the experimental evidence?; [For too coherence, and consistency across the published experimental evidence];</li> </ol>	te oviparous species frequently studied to date, there is a high level of biological plausibility,
	Adverse Dutcome		<b>Text</b>	5. alternative mechaniams that logically present themselves and the extent to which they	may distract from the postulated AOP?; (Other mechanisms of relevance to estrogen-mediated sexual
	Population trajectory, Decrease 🖉 🕱			development include the disruption of the steroidogenic pathways (egisee the ADP for an context of elevated plasma VTG levels, disrupted sexual development of reproductive dy	onvicase inhibition in fish.) and this atterative AOP should be considered alongside ER agonism in the stunction. The possibility of other AOPs arisign should be kept in mind through critical analysis of the
	Reproductive behaviour, Altered 🖉 🛙			updated pree-reviewed iterature];	uantifying the degree to which disrupted sexual development leads to a population-relevant impact via
	Larval development, Altered			reproductive dysfunction. Experimental and validated population modeling is a key need to	
	Reproductive organa, impaired development of 🖉 🔳			inconsistencies with repard to the ER agoniam AOP and associated Key Events).	
	Key Events			Weight of Evidence Summary [edit]	
	Add Event to Table			Summary Table Provide an overall summary of the weight of evidence based on the evaluations of the in:	lividual linkapes from the Key Event Relationship pages
	Event			Essentiality of the Key Events [edit]	
	Extragen receptor, agoniam Strong VII			Nolecular Initiating Event Summary, Key Event Summary	
	Passe vielogene concentrations increase Strong			Provide an overall assessment of the essentiality for the key events in the AOP. Support adverse outcome tables above.	calls for individual key events can be included in the molecular initiating event, key event, and
	Visikgenin synthesis in Ever, increase Strong			Quantitative Considerations [edit]	
	Renal pathology sue to VTG dependent, increase Strong			Summary Table	
	Adverse Outcome				port calls for the individual relationships can be included in the Key Event Relationship table above
	Add Adverse Outcome to Table			Applicability of the AOP [edit] Life State Applicability, Textnemic Applicability, Sex Applicability	
	Adverse Dutrome			In terms of the taxonomic domains of applicability, exposure to ER agonists is capable of the	Isrupting sexual development and causing reproductive dysfunction in eviparous species such as
	Population Inspectory, Secrease 2			amphibians, birds and fish (see examples of peer-revised iterature cited below).	
	Reproductive behaviour, Altered			References [edit]	
	Larval development, Altered 🖉 🛢 Rapindu/live argane, Impaired devaluament at 🖉 🛢			Dans, Z., Trass, T., Vermeire, T. (2011) Evaluation of the fish short term reproduction ass	an Internation and and a distance of American State 1975 1975
	and the second			Haldin, K., Axelsson, J., Brunström, B., (2005) Effects of endocrine modulators on sexual	differentiation and reproductive function in male Japanese quait. Brain Research Bulletin 65: 211-218
	Relationships /mong Key Events and the Adverse Outcome			Hogan, N.S., Duarte, P., Wade, M.G., Lean, D.R.S., Trudeau, V.L. (2008) Estrogenic expor critically vulnerable periods of development. General and Comparative Endocrinology 159	ure affects metamorphosis and alters sex ratios in the northern leopard frog (Rana pipens). Identifying \$15-523
	Add record to table			Hutchinson T.H. (2002) Impacts of endocrine disrupters on fish development: opportunitie	s for adapting OECD Test Guideline 210. Environmental Sciences 9: 439-450
	Itep # Event # Description # Triggers	Vieight of Guartitative     Evidence Understanding.		Länge R., Hutchinson T.H., Croudace C.P., Slegmund F., Schweinfurth H., Hampe P., Parti of the fathead minnow. Environmental Toxicology and Chemistry 20: 1218–1227	er G.H., Sumpter J.P. (2001) Effects of the synthetic cestrogen 172-ethinylestradiol over the life-cycle
	5 Extrogen receptor, agonam Directly Lands to Reproductive organs, Impained Devel	pment of Strong		Leino, R.L., Jensen,K.M., Ankley, G.T. (2005) Gonadal histology and characteristic histopic	thology associated with endocrine disruption in the adult fathead minnow (Pimephales prometas),
					, Lavoie, E., Abdeltabi, M. (2013) Assessing effects of environmental chemicals on neuroendocrine
	a Renal pathology due to VTG deposition, Directly Leads to Larval development, Allered	Strong a		systems: Potential mechanisms and functional outcomes. General and Comparative Endoo	rinology 190: 194-202
	Extrajon receptor, aponem Directly Leads to Whitcoanh purchask in her, increas		and the second		
				Categories: Adverse Outcome Pathway   Pages with broken file links	
	2 Pasma vitelopenin concentrations, increase Directly Leads to therein pathwing due to VTG deprets	n Brong			
				This page was last modified on April 9, 2014, at 00 23.	
	Eatrogen receptor: agoniam     Orectly Leads to Reproductive behaviour, Abared	Srong .		This page has been appealed 107 times.	
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		A			1. 1 Mediciwia



### **Widgets Facilitate Data Entry**







# **AOP Snapshot from the AOP-Wiki**

#### AOP Title

#### Androgen receptor agonism leading to reproductive dysfunction

#### Authors

Dan Villeneuve, U	Key Events
Status	Event
Alert: The Weig	Gonadotropins, circulating concentrations, Rev
these tables.	Testosterone synthesis by ovarian theca cells,
Under developn	Plasma 17beta-estradiol concentrations, Redu
Abstract	Transcription and translation of vitellogenin in l
	Plasma vitellogenin concentrations, Reduction
This adverse outc reduced cumulati	Vitellogenin uptake into occytes and occyte g
Assay. The OECI	Cumulative fecundity and spawning, Reduction
variables known t receptor binding a	17beta-estradiol synthesis by ovarian granulos
Summary of	Gonadotropins, circulating conce
Molecular in	How this Key Event works
	Level of Biological Organization
Molecular Initia	Gonadotropin (luteinizing hormone [LH] and foll
Androgen recept	heterodimeric glycoproteins composed of a hor and stored in secretory vesicles. Ganadotropin
Androgen ie	of gonadotropin expression (e.g., activin, follist:
How this Key I	How it is Measured or Detected
Level of Biolog	Circulating concentrations of gonadotropins in I commercial or custom immunoassays (e.g., El
Site of action: T	(Govoroun et al. 1998; Amano et al. 2000; Kah
Responses at th	limited number of species, primarily salmonids beta subunit (fshb) tend to fluctuate in parallel i
acilitates dissoci	(Levavi-Sivan et al. 2010). Consequently, the tw
Homodimerization Claessens et al.	volumes relative to the sensitivity of the available
Tindall 2007).	Evidence Supporting Taxonomic Appli
How it is Meas	Evidence supporting faxonomic Appr
Methods that hav	Common Name Scientific Name Evidence
established in the	A functional hypothalamic-pituitary-gonadal axi
directly or indirect	taxonomic applicability of this key event is limit
Measurement/d	References
testosterone or D	Norris DO. 2007. Vertebrate Endocrinology.
based transcriptic to screen chemic	<ul> <li>Habibi HR, Huggard DL, 1998. Testosterone</li> </ul>
to acreen chemic	

ndocrinology. Habibi HR, Huggard DL. 1998. Testosterone endocrinology 119(3): 339-344. responsive proteir Trudeau VL, Spanswick D, Fraser EJ, Larivis

In fish, phenotypic fish. Biochemistry and Cell Biology 78: 241tubercles, a dors: Trudeau VL. 1997. Neuroendocrine regulation 2006; Ankley et a · Oakley AE, Clifton DK, Steiner RA, 2009, Ki activation (Raut e

Evidence Sup

Common Name Eathead minnow Medaka

Taxonomic app

Therefore, this MI

- · Amano M, ligo M, Ikuta K, Kitamura S, Yam and comparative endocrinology 120(2): 190-1 . Kah O, Pontet A, Nunez Rodriguez J, Calas
  - 41(1): 68-73 · Prat F, Sumpter JP, Tyler CR. 1996. Validatio reproductivecycle in male and female rainboy . Levavi-Sivan B, Bogerd J, Mananos EL, Gorr
  - . Sower SA, Freamat M, Kavanaugh SI. 2009. new insights from lampreys. General and co

. Cheng GF, Yuen CW, Ge W. 2007. Evidence

Govoroun M. Chyb J. Breton B. 1998. Immu

development of specific radioimmunoassays

gonadal steroids. The Journal of endocrinolog

#### Scientific evidence supporting the linkages in the AOP Event Testosterone synthesis by ovarian theca cells. Reduction Gonadotropins, circulating concentrations, Reduction

17beta-estradiol synthesis by ovarian granulosa cells, Reduction Plasma 17beta-estradiol concentrations, Reduction Transcription and translation of vitellogenin in liver. Reduction

Vitellogenin uptake into opcytes and opcyte prowth/development Reduction

Cumulative fecundity and spawning, Reduction

10 Androgen receptor, agonism

Step

2

11 Plasma vitellogenin concentrations. Reduction

#### Testosterone synthesis by ovarian theca cells, Reduction I Reduction

#### How Does This Key Event Relationship Work

#### **Biological Plausibility**

Theca cell-derived androgens (e.g., testosterone, androstenedione) are precursors are aromatized to estrogens in the ovarian granulosa cells. Consequently, reductin synthesis by the ovarian granulosa cells (Payne and Hales 2004: Miller 1988: Nac

#### Empirical Support for Linkage

- Include consideration of temporal concordance here
- . Ex vivo T production by ovary tissue collected from female fathead minnows ex exposure (Ekman et al. 2011). Reductions in ex vivo T production preceded sig · Ketoconazole is a fungicide thought to inhibit CYP11A and CYP17 (both involv
- (Villeneuve et al. 2007). Ex vivo E2 and T production were significantly reduced

#### Quantitative Understanding of the Linkage

Is it known how much change in the first event is needed to impact the second? / extrapolation approaches that help describe those relationships? At present we a indirect measure of theca cell T synthesis) and ex vivo E2 production (as an indire support the development of such a relationship. Additionally, there are a number of adaptable to support a quantitative understanding of this linkage (Breen et al. 200

#### Uncertainties or Inconsistencies

#### Evidence Supporting Taxonomic Applicability

**Common Name Scientific Name Evidence Links** 

#### References

- · Payne AH, Hales DB, 2004. Overview of steroidogenic enzymes in the pathwa Miller WL. 1988. Molecular biology of steroid hormone synthesis. Endocrine re Nagahama Y, Yoshikumi M, Yamashita M, Sakai N, Tanaka M. 1993. Molecul 3.14
- . Ekman DR, Villeneuve DL, Teng Q, Ralston-Hooper KJ, Martinovic-Weigelt D, exposure and effects assessment of the model androgen 17beta-trenbolone in · Villeneuve DL, Ankley GT, Makynen EA, Blake LS, Greene KJ, Higley EB, et assays for identifying endocrine-active chemicals. Ecotoxicol Environ Saf 68(1

#### Overall Assessment of the AOP

#### Overall Assessment of the AOP

#### **Biological Plausibility**

- The biochemistry of steroidogenesis and the predominant · Similarly, the role of E2 as the major regulator of hepatic v concentrations in the plasma and reduced uptake into opc The direct connection between reduced VTG uptake and it impaired VTG uptake limits oocyte growth and failure to re oocyte from the surrounding follicles. In at least one expervitellogenic occytes was observed (R. Johnson, personal d cumulative fecundity are best supported by the correlation initiating events (Miller et al. 2007).
- · At present, negative feedback is the most biologically place vitro exposure of fathead minnow ovary tissue to 178-trent those that produce significant responses in vivo (i.e., at no any known reports of 176-trenbolone directly inhibiting ste trenbolone caused a concentration-dependent increase in concurrent with increased transcription of CYP19 (aromata enzyme activity, negative feedback is currently the most li exact mechanisms through which an exogenous, non-aro

starting at and down-stream of reduced T synthesis. However, to dat exposure to non-endogenous AR agonists (e.g., xenobiotics, pharma

- concentrations over a range from 0.005 to 0.5 µg/L. The co indicate concentration-dependent differences in the feedba gonad stage were evident, although the concentration-resp biochemical level, concentration-dependent reductions in ( causing phenotypic masculinization in female fish.
- et al. 2006).
- showed concentration-dependent reductions that were con-· Exposure of female fathead minnows to spironolactone, a cumulative fecundity, plasma VTG and VTG mRNA express

concordance can reasonably be evaluated based on currently available

Consistency: We are aware of no cases where the pattern of key variability in the cumulative fecundity endpoint and potential comp Ekman et al. 2012) the cumulative fecundity endpoint can be les of the final adverse outcome when the other key events are obser this AOP overlap with AOPs linking other molecular initiating eve

. In general, there is a consistent body of evidence linking e and cumulative fecundity in female fish. For example, the replicated in over a dozen independent experiments (Ekm 2006: Brockmeier et al. 2013). However, relatively few exo (Lalone et al. 2013), we are not aware of the profile of resp

Uncertainties, inconsistencies, and data gaps: There are two as to the specific mechanism(s) through which AR agonism elicit data gap relative to establishing that exposure to an AR agonist I major uncertainty in this AOP relates to whether there is a direct fecundity. Plausible biological connections have been hypothesiz

#### Weight of Evidence Summary

Step	Event	Description Triggers		Weight of Evidence
2	Testosterone synthesis by ovarian theca cells, Reduction	Directly Leads to	17beta-estradiol synthesis by ovarian granulosa cells, Reduction	Strong
3	Gonadotropins, circulating concentrations, Reduction	Directly Leads to	Testosterone synthesis by ovarian theca cells, Reduction	Strong
4	17beta-estradiol synthesis by ovarian granulosa cells, Reduction	Directly Leads to	Plasma 17beta-estradiol concentrations, Reduction	Strong
5	Plasma 17beta-estradiol concentrations, Reduction	Directly Leads to	Transcription and translation of vitellogenin in liver, Reduction	Strong
6	Transcription and translation of vitellogenin in liver, Reduction	Directly Leads to	Plasma vitellogenin concentrations, Reduction	Strong
8	Vitellogenin uptake into oocytes and oocyte growth/development, Reduction	Directly Leads to	Cumulative fecundity and spawning, Reduction	Moderate
9	Cumulative fecundity and spawning, Reduction	Directly Leads to	Population trajectory, Decrease	Moderate
10	Androgen receptor, agonism	Directly Leads to	Gonadotropins, circulating concentrations, Reduction	Weak
11	Plasma vitellogenin concentrations, Reduction	Directly Leads to	Vitellogenin uptake into oocytes and oocyte growth/development, Reduction	Moderate

#### **Essentiality of the Key Events**

#### Molecular Initiating Event Support for Essentiality

Androgen receptor, agonism

Key Event	Support for Essentiality
Gonadotropins, circulating concentrations, Reduction	
Testosterone synthesis by ovarian theca cells, Reduction	
Plasma 17beta-estradiol concentrations, Reduction	
Transcription and translation of vitellogenin in liver, Reduction	
Plasma vitellogenin concentrations, Reduction	
Vitellogenin uptake into occytes and occyte growth/development, Reduction	
Cumulative fecundity and spawning, Reduction	
17beta-estradiol synthesis by ovarian granulosa cells, Reduction	

. In general, few studies have directly addressed the essentiality of the proposed sequence of key events.

- . Ekman et al. 2011 provide evidence that in fathead minnow, cessation of trenbolone exposure resulted in recovery of plasma E2 and VTG concentrations which were depressed by continuous exposure to 17beta trenbolone. This provides some support for the essentiality of these two key events
- . Essentiality of the proposed negative feedback key event is supported by experimental work that evaluated the ability of AR agonists to reduce T or E2 production in vitro. In vitro exposure of fathead minnow ovary tissue to 176-trenbolone or spironolactone does not cause reductions in T or E2 synthesis at concentrations comparable to those that produce significant responses in vivo (i.e., at non-cytotoxic concentrations; D.L. Villeneuve, unpublished data; C.A. LaLone unpublished data), nor are there any known reports of 17p-trenbolone directly inhibiting steroid biosynthesis. When tested in an in vitro steroidogenesis assay using H295R adrenal carcinoma cells, trenbolone caused a concentration-dependent increase in estradiol production, as opposed to any reductions in steroid hormone concentrations, an effect that was concurrent with increased transcription of CYP19 (aromatase) in the cell line (Gracia et al. 2007).

#### **Quantitative Considerations**

Step	Event	Description	Triggers	Quantitative Understanding
2	Testosterone synthesis by ovarian theca cells, Reduction	Directly Leads	17beta-estradiol synthesis by ovarian granulosa cells, Reduction	
I.	Conadotropins, circulating concentrations, Reduction	Directly Leads to	Testosterone synthesis by ovarian theca cells, Reduction	
4	17beta-estradiol synthesis by ovarian granulosa cells, Reduction	Directly Leads	Plasma 17beta-estradiol concentrations, Reduction	

#### Office of Research and Development Chemical Safety for Sustainability Research Program

Concordance of dose-response relationships: The dependence of Exposure of female fathead minnows to the AR agonist 17

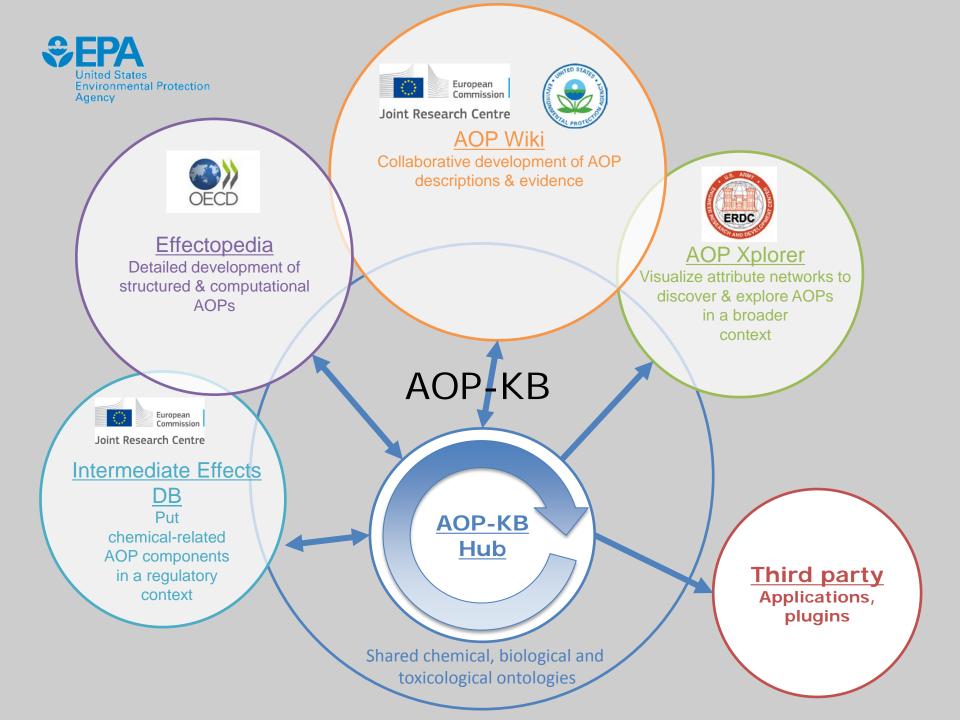
- · Jensen et al. (2006) also demonstrated concentration-dep
- In a time-course experiment in which female fathead minn
  - accumulation, and increased oocyte atresia was concentry · Exposure of female medaka to spironolactone caused cor hormone concentrations were not measured). Spironolacti

Temporal concordance among the key events and adverse negative feedback response resulting in decreased gonadotropin biosynthesis and proceeding through reductions in plasma vitello vitellogenin has not been established, in large part due to disconr reproductive toxicity testing can spawn anywhere from once daily evaluate cumulative fecundity at a time scale shorter than roughly exposure, lack of impact on cumulative fecundity before the other



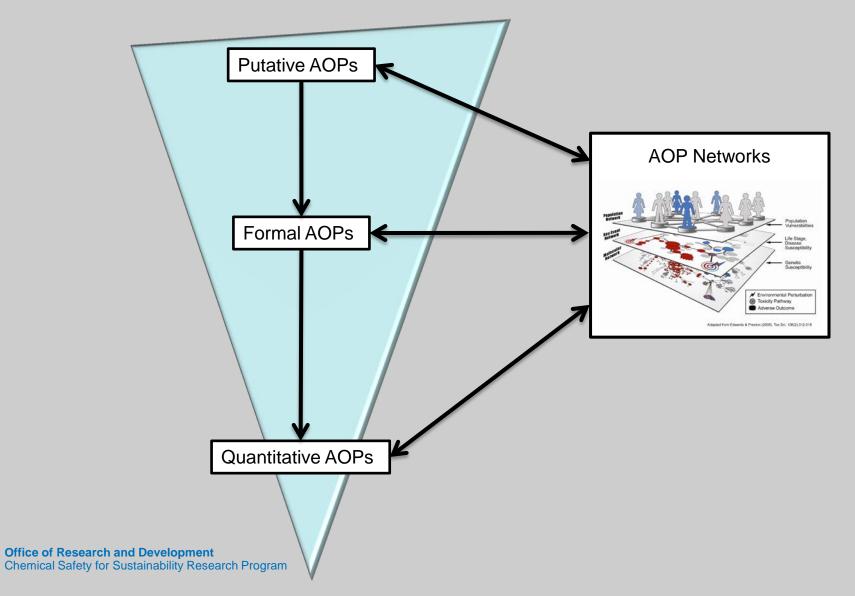
### **AOP-Wiki Status**

- 41 AOPs as of September 1, 2014
  - -8\* with documented evaluation of evidence
  - -4 with descriptions of all/most components
  - -22\* with components defined
  - -8 stubs
- New code & template release September 2014
   Will be consistent with updated AOP Handbook
- Public access starting September 25, 2014



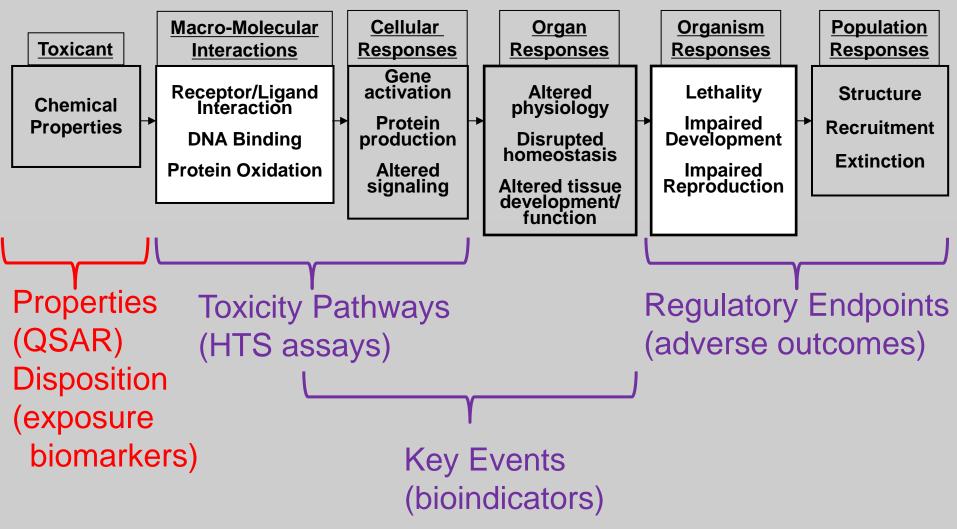


### **AOP Discovery & Development**



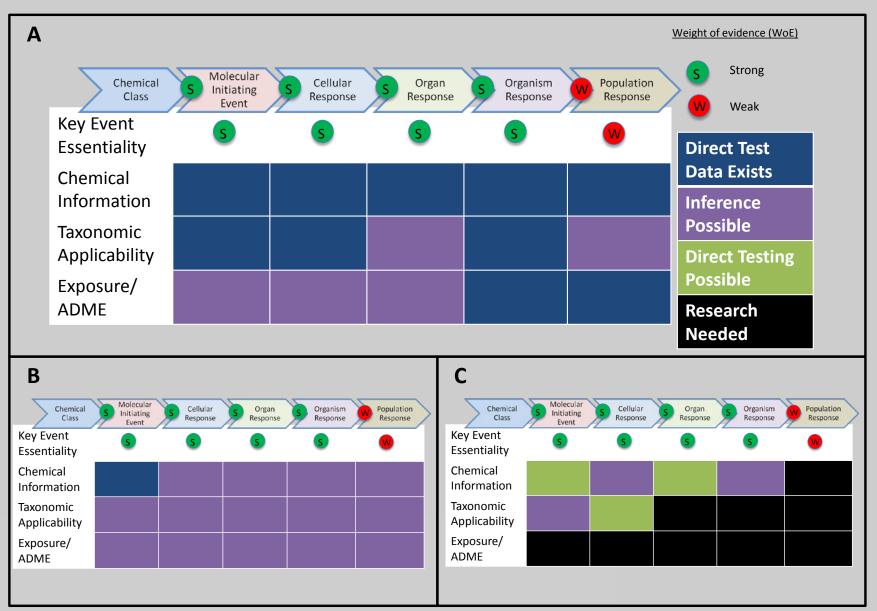


### **Using AOPs for Informed Decisions**





### AOP Confidence + Testing Data -> Regulatory Decision Making





European

Joint Research Centre

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- Clemens Wittwehr
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- Max Felsher
- Harriet Ashcroft
- Kyle Painter
- Dan Villeneuve
- Kevin Crofton
- Gary Ankley
- Lyle Burgoon
- Robert Kavlock



Hristo Aladjov
Joop DeKnecht

- Collaborative Partners
  - OECD External Advisory Group on Molecular Screening & Toxicogenomics
  - IPCS/WHO Mode of Action Steering Committee



## **Change is Good**



- Any interest in hiring a very talented scientist currently completing postdoctoral work in my group, please contact
  - -Shannon Bell, Bell.Shannon@epa.gov
- Anyone interested in a postdoctoral position in my group, please contact me (<u>Edwards.Stephen@epa.gov</u>) or see the following ad
  - -<u>http://orise.orau.gov/epa/applicants/description.aspx?JobId=14771</u>
  - -Google search: orise epa aop stephen edwards

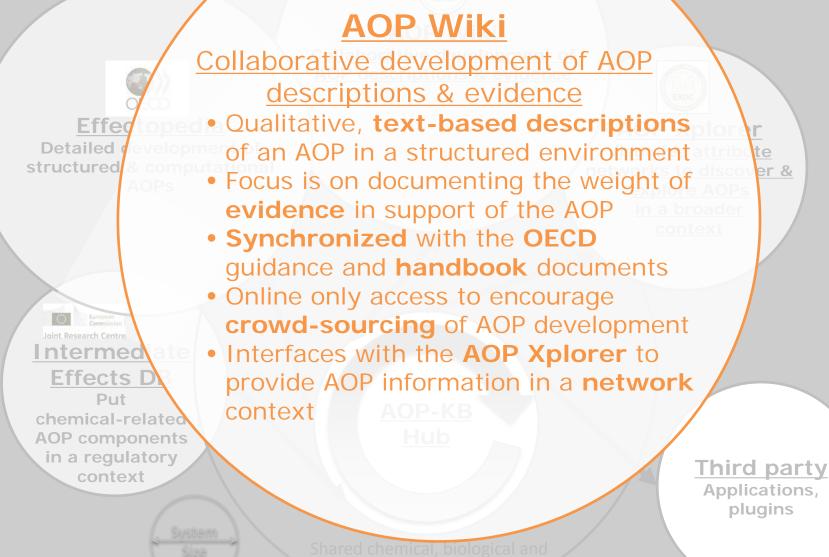
**Research Opportunity Description** 

Bioinformatics Approaches to Grouping Chemicals Using High-Throughput Screening Data Research Participation Program Office of Research and Development National Health and Environmental Effects Research Laboratory U.S. Environmental Protection Agency Research Triangle Park, NC

EPA-ORD/NHEERL-ISTD-2014-01









### **Effectopedia**

Detailed development of

- structured & computational AOPs
- Visual interface for design and collaborative editing of AOP and chemical case studies

 AOP structure guidance is embedded in the system



che AOP

in a

- Ability to store and process quantitative information, including formal description of test methods, algorithms and models along with their applicability domains and verification methods
- Provides offline editing capabilities and robust capabilities for managing data access
- Embeds the concept of AOP networks directly in the system
- Provides capabilities for sharing, discussing, and reviewing AOPs

Third party Applications, plugins

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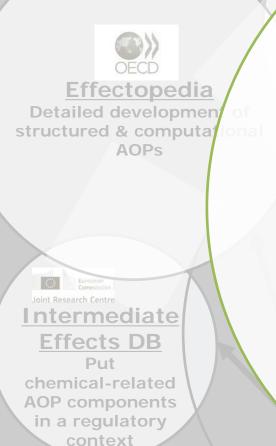


European Commission Joint Research Centre **Intermediate Effects DB** ERDC Put chemical-related AOP **P** Xplorer components in a regulatory context alize attribute str ks to discover & IUCLID repository for AOP information lore AOPs Based on OECD Harmonized a broader ontext **Templates** (OHTs) Will profit from new OHT for "Intermediate Effects" Manages observations and conclusions concerning the nature and extent to which a chemical triggers an Intermediate Effect chem Links chemical information to AOPs. AOP cc in a red Rich source of quantitative conte data for Effectopedia plugins

oxicological ontologi

Third party Applications,







### AOP Xplorer Visualize attribute networks to discover & explore AOPs in a broader context

- Allows user to explore AOPs in a network context based on shared key events
- Provides additional bioinformatics analysis tools for annotating key events and traversing the network
- Incorporates putative AOP information and facilitates AOP discovery

hir<mark>a party</mark> pplications, plugins

System Size

Shared chemical, biologies toxicological ontologies



Cognitive Dysfunction

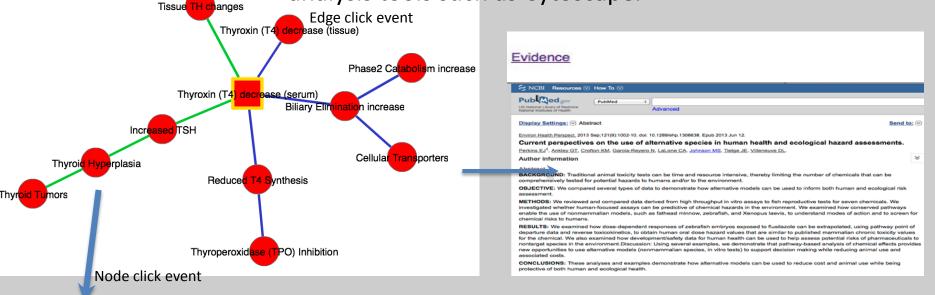
Frog metamorphosis

Altered Development



# **AOP Xplorer**

- Explore AOPs in a network context based on the shared key events.
- Search for shared key events between AOPs or chemicals.
- Nodes and edges are clickable, that displays their attributes on the same page.
- Export AOP network into feature rich visualization and analysis tools such as Cytoscape.



Title	Level of Organization	Description	Chemical	Upstream Cause	Downstream Effect	Species	Lifestages	Sex	Evidence	Genes	
Thyroxin (T4) decrease (serum)	Tissue	Large body of literature demonstrating that chemicals can reduce serum T4 in animals as well as some evidence in humans (for review, see Cooper et al., 1983).		Elimination increase;Thyroxin (T4)	Increased TSH; Tissue TH changes	rat;frog	Adult	Unknown			Cooper, D.S., Kieffer, Maloof, F., and Ridgw pharmacology in the r Endocrinology 113:92



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Interm

Effects

chemical-rel AOP compone

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context



# AOP-KB Hub

Effer • Central hub for all shared Detailed structured information among the AOP-KB

### Operates via web services for maximum flexibility in implementation of the other modules and to provide access for third party tools

Based on **established** chemical, biological and toxicological **ontologies** unified by a specifically-designed AOP ontology

> European Commission

Joint Research Centre



Third party Applications, plugins

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Size