AOP ID and Title:

SNAPSHOT

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AOP 29: Estrogen receptor agonism leading to reproductive dysfunction

Short Title: Estrogen receptor agonism leading to reproductive dysfunction

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Status

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Abstract

This AOP describes the linkages between agonism of the estrogen receptor (ER) and population relevant impacts on reproductive function in a range of oviparous vertebrates including amphibia, birds and fish. The information in this AOP for ER agonism does not apply to mammalian species and also not to invertebrates.

Amphibians are sensitive to ER agonists during the transformation from larval tadpole to juvenile frog as these include critical periods of metamorphic development and sex differentiation that may be particularly sensitive to endocrine disruption. Larvae exposed to ER agonists during mid-metamorphosis show developmental effects, a subsequent strong female-biased sex ratio which suggests that transient early life-stage exposure to ER agonists can produce effects on the reproductive organs that persist into the beginning of adult life-stages. Birds are also known to be vulnerable to ER agonists causing disruption of estrogen-regulated functions such as sexual differentiation and sexual behaviour. Model species such as the Japanese quail have been widely used as a model for studying various long-term effects after embryonic exposure to ER agonists. In terms of teleost fish, exposure to ER agonists leads to a suite of adverse outcomes depending upon whether exposures occur during or beyond the larval, juvenile and adult life-stages. For example, aquatic exposure to potent ER agonists during the larval and juvenile life-stages may leads to gonadal and renal pathology and skewed-sex ratios in adult fish (potentially 100% females). Larval, juvenile and adult male fish exposed to the same ER agonists display abnormal plasma or whole body levels of vitellogenin (VTG). Cumulative fecundity in adult populations is also adversely affected by ER agonists and this is an important endpoint in the OECD Test Guideline 229 Fish Short Term Reproduction Assay. In summary, this AOP has utility in supporting the application of test methods for detecting ER agonists, or in silico predictions of the ability of chemicals to act as ER agonists and cause impaired sexual development and reproductive dysfunction.

Summary of the AOP

Events

Molecular Initiating Events (MIE), Key Events (KE), Adverse Outcomes (AO)

Sequence	Type	Event ID	Title	Short name
1	MIE	111	Agonism, Estrogen receptor (https://aopwiki.org/events/111)	Agonism, Estrogen receptor
2	KE	78	Reduction, Cumulative fecundity and spawning (https://aopwiki.org/events/78)	Reduction, Cumulative fecundity and spawning
3	KE	220	Increase, Plasma vitellogenin concentrations (https://aopwiki.org/events/220)	Increase, Plasma vitellogenin concentrations

Sequence	Type	Event ID	Title	Short name
4	KE	307	Increase, Vitellogenin synthesis in liver (https://aopwiki.org/events/307)	Increase, Vitellogenin synthesis in liver
5	KE	252	Increase, Renal pathology due to VTG deposition (https://aopwiki.org/events/252)	Increase, Renal pathology due to VTG deposition
6	AO	360	Decrease, Population trajectory (https://aopwiki.org/events/360)	Decrease, Population trajectory
7	AO	363	Altered, Reproductive behaviour (https://aopwiki.org/events/363)	Altered, Reproductive behaviour
8	AO	339	Altered, Larval development (https://aopwiki.org/events/339)	Altered, Larval development
9	AO	364	Impaired development of, Reproductive organs (https://aopwiki.org/events/364)	Impaired development of, Reproductive organs

Key Event Relationships

Upstream Event	Relationship Type	Downstream Event	Evidence	Quantitative Understanding
Agonism, Estrogen receptor (https://aopwiki.org/relationships/127)	adjacent	Impaired development of, Reproductive organs	High	
Increase, Renal pathology due to VTG deposition (https://aopwiki.org/relationships/280)	adjacent	Altered, Larval development	High	
Agonism, Estrogen receptor (https://aopwiki.org/relationships/128)	adjacent	Increase, Vitellogenin synthesis in liver	High	
Increase, Plasma vitellogenin concentrations (https://aopwiki.org/relationships/254)	adjacent	Increase, Renal pathology due to VTG deposition	High	
Agonism, Estrogen receptor (https://aopwiki.org/relationships/126)	adjacent	Altered, Reproductive behaviour	High	
Increase, Vitellogenin synthesis in liver (https://aopwiki.org/relationships/336)	adjacent	Increase, Plasma vitellogenin concentrations	High	

Overall Assessment of the AOP

In terms of the criteria associated with Key Events in this AOP, the following observations have been made as shown in parentheses []:

1. concordance of dose-response relationships?; [There is strong dose-response relationship concordance over a wide range of experimental studies using ER agonists in well-defined animals models, including amphibians, birds and fish];

2. temporal concordance among the key events and adverse effect?; [There is strong temporal concordance from partial and full life-cycle studies using ER agonists in well-defined animals models];

3. strength, consistency, and specificity of association of adverse effect and initiating event?; [In fish, there is a strong and consistent association between ER agonist exposure, disruption of sexual development and reproductive dysfunction. The same is true for amphibians and birds although the published studies are less numerous.];

4. biological plausibility, coherence, and consistency of the experimental evidence?; [For the oviparous species frequently studied to date, there is a high level of biological plausibility, coherence, and consistency across the published experimental evidence];

5. alternative mechanisms that logically present themselves and the extent to which they may distract from the postulated AOP?; [Other mechanisms of relevance to estrogen-mediated sexual development include the disruption of the steroidogenic pathways (eg see the AOP for aromatase inhibition in fish) and this alterative AOP should be considered alongside ER agonism in the context of elevated plasma VTG levels, disrupted sexual development of reproductive dysfunction. The possibility of other AOPs arisign should be kept in mind through critical analysis of the updated pree-reviewed literature];

6. uncertainties, inconsistencies and data gaps?; [An important aspect of uncertainty is quantifying the degree to which disrupted sexual development leads to a population-relevant impact via reproductive dysfunction. Experimental and validated population modelling is a key need to address this data gap and uncertainty. In the author's view, there are no major scientific inconsistencies with regard to the ER agonism AOP and associated Key Events].

Domain of Applicability

Life Stage Applicability

Life Stage	Evidence
Juvenile	High
Embryo	High

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
fathead minnow	Pimephales promelas	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=90988)
Japanese quail	Coturnix japonica	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=93934)
northern leopard frog	Rana pipiens	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=8404)
medaka	Oryzias latipes	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=8090)
zebrafish	Danio rerio	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=7955)

Sex Applicability

Sex	Evidence
Male	High

Life Stage Applicability, Taxonomic Applicability, Sex Applicability
In terms of the taxonomic domains of applicability, exposure to ER agonists is capable of disrupting sexual development and causing reproductive dysfunction in oviparous species suchas amphibians, birds and fish (see examples of peer-revised literature cited below).

References

Dang, Z., Traas, T., Vermeire, T. (2011) Evaluation of the fish short term reproduction assay for detecting endocrine disrupters. Chemosphere 85: 1592-1603

Halldin, K., Axelsson, J., Brunström, B., (2005) Effects of endocrine modulators on sexual differentiation and reproductive function in male Japanese quail. Brain Research Bulletin 65: 211-218

Hogan, N.S., Duarte, P., Wade, M.G., Lean, D.R.S., Trudeau, V.L. (2008) Estrogenic exposure affects metamorphosis and alters sex ratios in the northern leopard frog (Rana pipiens): Identifying critically vulnerable periods of development. General and Comparative Endocrinology 156: 515-523

Hutchinson T.H. (2002) Impacts of endocrine disrupters on fish development: opportunities for adapting OECD Test Guideline 210. Environmental Sciences 9: 439-450

Länge R., Hutchinson T.H., Croudace C.P., Siegmund F., Schweinfurth H., Hampe P., Panter G.H., Sumpter J.P. (2001) Effects of the synthetic oestrogen 17 -ethinylestradiol over the life-cycle of the fathead minnow. Environmental Toxicology and Chemistry 20: 1216–1227

Leino, R.L., Jensen,K.M., Ankley, G.T. (2005) Gonadal histology and characteristic histopathology associated with endocrine disruption in the adult fathead minnow (Pimephales promelas). Environmental Toxicology and Pharmacology 19: 85-98

Ottinger, M.N., Carro, T., Bohannon, M., Baltos,L., Marcell, A.M., McKernan, M., Dean, K.M., Lavoie, E., Abdelnabi, M. (2013) Assessing effects of environmental chemicals on neuroendocrine systems: Potential mechanisms and functional outcomes. General and Comparative Endocrinology 190: 194-202

Appendix 1

List of MIEs in this AOP

Event: 111: Agonism, Estrogen receptor (https://aopwiki.org/events/111)

Short Name: Agonism, Estrogen receptor

Key Event Component

Process	Object	Action
estrogen receptor activity	estrogen receptor	increased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:29 - Estrogen receptor agonism leading to reproductive dysfunction (https://aopwiki.org/aops/29)	MolecularInitiatingEvent
Aop:52 - ER agonism leading to skewed sex ratios due to altered sexual differentiation in males (https://aopwiki.org/aops/52)	MolecularInitiatingEvent
Aop:53 - ER agonism leading to reduced survival due to renal failure (https://aopwiki.org/aops/53)	MolecularInitiatingEvent

Biological Context

Level of Biological Organization
Molecular

Cell term

Cell term
hepatocyte

List of Key Events in the AOP

Event: 78: Reduction, Cumulative fecundity and spawning (https://aopwiki.org/events/78)

Short Name: Reduction, Cumulative fecundity and spawning

Key Event Component

Process	Object	Action
egg quantity		decreased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:29 - Estrogen receptor agonism leading to reproductive dysfunction (https://aopwiki.org/aops/29)	KeyEvent
Aop:25 - Aromatase inhibition leading to reproductive dysfunction (https://aopwiki.org/aops/25)	KeyEvent
Aop:23 - Androgen receptor agonism leading to reproductive dysfunction (in repeat-spawning fish) (https://aopwiki.org/aops/23)	KeyEvent
Aop:30 - Estrogen receptor antagonism leading to reproductive dysfunction (https://aopwiki.org/aops/30)	KeyEvent

AOP ID and Name	Event Type
Aop:122 - Prolyl hydroxylase inhibition leading to reproductive dysfunction via increased HIF1 heterodimer formation (https://aopwiki.org/aops/122)	AdverseOutcome
Aop:123 - Unknown MIE leading to reproductive dysfunction via increased HIF-1alpha transcription (https://aopwiki.org/aops/123)	AdverseOutcome
Aop:271 - Inhibition of thyroid peroxidase leading to impaired fertility in fish (https://aopwiki.org/aops/271)	AdverseOutcome

Stressors

Name
Tris(1,3-dichloropropyl)phosphate - TDCPP

Biological Context

Level of Biological Organization
Individual

Evidence for Perturbation by Stressor

Tris(1,3-dichloropropyl)phosphate - TDCPP

Reduction of cumulative fecundity and spawning following exposure to low levels of TDCIPP (15, 46 and 90 nM) has been reported in 3 different zebrafish studies (Liu et al., 2013; Wang et al., 2015a; Zhu et al., 2015).

Domain of Applicability

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
fathead minnow	Pimephales promelas	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=90988)
Fundulus heteroclitus	Fundulus heteroclitus	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=8078)
Oryzias latipes	Oryzias latipes	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=8090)

Life Stage Applicability

Life Stage	Evidence
Adult, reproductively mature	High

Sex Applicability

Sex	Evidence
Female	High

Cumulative fecundity and spawning can, in theory, be evaluated for any egg laying animal.

Key Event Description

Spawning refers to the release of eggs. Cumulative fecundity refers to the total number of eggs deposited by a female, or group of females over a specified period of time.

How it is Measured or Detected

In laboratory-based reproduction assays (e.g., OECD Test No. 229; OECD Test No. 240), spawning and cumulative fecundity can be directly measured through daily observation of egg deposition and egg counts.

In some cases, fecundity may be estimated based on gonado-somatic index (OECD 2008 (http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2008)22&doclanguage=en)).

Regulatory Significance of the AO

Cumulative fecundity is the most apical endpoint considered in the OECD 229 Fish Short Term Reproduction Assay. The OECD 229 assay serves as screening assay for endocrine disruption and associated reproductive impairment (OECD 2012 (http://www.oecd-ilibrary.org/environment/test-no-229-fish-short-term-reproduction-assay_9789264185265-en)). Fecundity is also an important apical endpoint in the Medaka Extended One Generation Reproduction Test (MEOGRT; OECD Test Guideline 240 (http://www.oecd-ilibrary.org/environment/test-no-240-medaka-extended-one-generation-reproduction-test-meogrt_9789264242258-en); OECD 2015).

A variety of fish life cycle tests also include cumulative fecundity as an endpoint (OECD 2008 (http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2008)22&doclanguage=en)).

References

- OECD 2008. Series on testing and assessment, Number 95. Detailed Review Paper on Fish Life-cycle Tests. OECD Publishing, Paris. ENV/JM/MONO(2008)22.
- OECD (2015), *Test No. 240: Medaka Extended One Generation Reproduction Test (MEOGRT)*, OECD Publishing, Paris. DOI: http://dx.doi.org/10.1787/9789264242258-en (http://dx.doi.org/10.1787/9789264242258-en)
- OECD. 2012a. Test no. 229: Fish short term reproduction assay. Paris, France:Organization for Economic Cooperation and Development.

Event: 220: Increase, Plasma vitellogenin concentrations (https://aopwiki.org/events/220)

Short Name: Increase, Plasma vitellogenin concentrations

Key Event Component

Process	Object	Action
	vitellogenins	increased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:29 - Estrogen receptor agonism leading to reproductive dysfunction (https://aopwiki.org/aops/29)	KeyEvent
Aop:53 - ER agonism leading to reduced survival due to renal failure (https://aopwiki.org/aops/53)	KeyEvent

Biological Context

Level of Biological Organization
Organ

Organ term

Organ term
blood plasma

Event: 307: Increase, Vitellogenin synthesis in liver (https://aopwiki.org/events/307)

Short Name: Increase, Vitellogenin synthesis in liver

Key Event Component

Process	Object	Action
gene expression	vitellogenins	increased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:29 - Estrogen receptor agonism leading to reproductive dysfunction (https://aopwiki.org/aops/29)	KeyEvent

Biological Context

Level of Biological Organization
Tissue

Organ term

Organ term
liver

Event: 252: Increase, Renal pathology due to VTG deposition (https://aopwiki.org/events/252)

Short Name: Increase, Renal pathology due to VTG deposition

Key Event Component

Process	Object	Action
Kidney Diseases		increased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:29 - Estrogen receptor agonism leading to reproductive dysfunction (https://aopwiki.org/aops/29)	KeyEvent

Biological Context

Level of Biological Organization
Organ

Organ term

Organ term
kidney

List of Adverse Outcomes in this AOP

Event: 360: Decrease, Population trajectory (https://aopwiki.org/events/360)

Short Name: Decrease, Population trajectory

Key Event Component

Process	Object	Action
population growth rate		decreased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:23 - Androgen receptor agonism leading to reproductive dysfunction (in repeat-spawning fish) (https://aopwiki.org/aops/23)	AdverseOutcome
Aop:25 - Aromatase inhibition leading to reproductive dysfunction (https://aopwiki.org/aops/25)	AdverseOutcome
Aop:29 - Estrogen receptor agonism leading to reproductive dysfunction (https://aopwiki.org/aops/29)	AdverseOutcome
Aop:30 - Estrogen receptor antagonism leading to reproductive dysfunction (https://aopwiki.org/aops/30)	AdverseOutcome
Aop:100 - Cyclooxygenase inhibition leading to reproductive dysfunction via inhibition of female spawning behavior (https://aopwiki.org/aops/100)	AdverseOutcome
Aop:122 - Prolyl hydroxylase inhibition leading to reproductive dysfunction via increased HIF1 heterodimer formation (https://aopwiki.org/aops/122)	AdverseOutcome
Aop:123 - Unknown MIE leading to reproductive dysfunction via increased HIF-1alpha transcription (https://aopwiki.org/aops/123)	AdverseOutcome
Aop:155 - Deiodinase 2 inhibition leading to reduced young of year survival via posterior swim bladder inflation (https://aopwiki.org/aops/155)	AdverseOutcome
Aop:156 - Deiodinase 2 inhibition leading to reduced young of year survival via anterior swim bladder inflation (https://aopwiki.org/aops/156)	AdverseOutcome
Aop:157 - Deiodinase 1 inhibition leading to reduced young of year survival via posterior swim bladder inflation (https://aopwiki.org/aops/157)	AdverseOutcome
Aop:158 - Deiodinase 1 inhibition leading to reduced young of year survival via anterior swim bladder inflation (https://aopwiki.org/aops/158)	AdverseOutcome
Aop:159 - Thyroperoxidase inhibition leading to reduced young of year survival via anterior swim bladder inflation (https://aopwiki.org/aops/159)	AdverseOutcome
Aop:101 - Cyclooxygenase inhibition leading to reproductive dysfunction via inhibition of pheromone release (https://aopwiki.org/aops/101)	AdverseOutcome
Aop:102 - Cyclooxygenase inhibition leading to reproductive dysfunction via interference with meiotic prophase I /metaphase I transition (https://aopwiki.org/aops/102)	AdverseOutcome
Aop:63 - Cyclooxygenase inhibition leading to reproductive dysfunction (https://aopwiki.org/aops/63)	AdverseOutcome
Aop:103 - Cyclooxygenase inhibition leading to reproductive dysfunction via interference with spindle assembly checkpoint (https://aopwiki.org/aops/103)	AdverseOutcome

Biological Context

Level of Biological Organization
Population

Domain of Applicability

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
all species	all species		NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=0)

Life Stage Applicability

Life Stage	Evidence
All life stages	Not Specified

Sex Applicability

Sex	Evidence
Unspecific	Not Specified

Consideration of population size and changes in population size over time is potentially relevant to all living organisms.

Key Event Description

Maintenance of sustainable fish and wildlife populations (i.e., adequate to ensure long-term delivery of valued ecosystem services) is an accepted regulatory goal upon which risk assessments and risk management decisions are based.

How it is Measured or Detected

Population trajectories, either hypothetical or site specific, can be estimated via population modeling based on measurements of vital rates or reasonable surrogates measured in laboratory studies. As an example, Miller and Ankley 2004 used measures of cumulative fecundity from laboratory studies with repeat spawning fish species to predict population-level consequences of continuous exposure.

Regulatory Significance of the AO

Maintenance of sustainable fish and wildlife populations (i.e., adequate to ensure long-term delivery of valued ecosystem services) is a widely accepted regulatory goal upon which risk assessments and risk management decisions are based.

References

- Miller DH, Ankley GT. 2004. Modeling impacts on populations: fathead minnow (Pimephales promelas) exposure to the endocrine disruptor 17ß-trenbolone as a case study. Ecotoxicology and Environmental Safety 59: 1-9.

Event: 363: Altered, Reproductive behaviour (https://aopwiki.org/events/363)

Short Name: Altered, Reproductive behaviour

Key Event Component

Process	Object	Action
reproductive behavior		abnormal

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:29 - Estrogen receptor agonism leading to reproductive dysfunction (https://aopwiki.org/aops/29)	AdverseOutcome

Biological Context

Level of Biological Organization
Individual

Event: 339: Altered, Larval development (https://aopwiki.org/events/339)

Short Name: Altered, Larval development

Key Event Component

Process	Object	Action

Process	Object	Action
larval development		abnormal

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:29 - Estrogen receptor agonism leading to reproductive dysfunction (https://aopwiki.org/aops/29)	AdverseOutcome

Biological Context

Level of Biological Organization
Individual

Event: 364: Impaired development of, Reproductive organs (https://aopwiki.org/events/364)

Short Name: Impaired development of, Reproductive organs

Key Event Component

Process	Object	Action
developmental process	reproductive organ	abnormal

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:29 - Estrogen receptor agonism leading to reproductive dysfunction (https://aopwiki.org/aops/29)	AdverseOutcome

Biological Context

Level of Biological Organization
Individual

Appendix 2

List of Key Event Relationships in the AOP

List of Adjacent Key Event Relationships

Relationship: 127: Agonism, Estrogen receptor leads to Impaired development of, Reproductive organs (https://aopwiki.org/relationships/127)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
Estrogen receptor agonism leading to reproductive dysfunction (https://aopwiki.org/aops/29)	**adjacent**	**High**	

Relationship: 280: Increase, Renal pathology due to VTG deposition leads to Altered, Larval development (https://aopwiki.org/relationships/280)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
Estrogen receptor agonism leading to reproductive dysfunction (https://aopwiki.org/aops/29)	**adjacent**	**High**	

Relationship: 128: Agonism, Estrogen receptor leads to Increase, Vitellogenin synthesis in liver (https://aopwiki.org/relationships/128)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
Estrogen receptor agonism leading to reproductive dysfunction (https://aopwiki.org/aops/29)	**adjacent**	**High**	

Evidence Supporting Applicability of this Relationship

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
zebrafish	Danio rerio	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=7955)
fathead minnow	Pimephales promelas	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=90988)

Evidence Supporting this KER

Biological Plausibility

High degree of plausibility in fathead minnow, zebrafish and other cyprinid species.

Empirical Evidence

A wide range of studies using adult fish show that induction of plasma vitellogenin (VTG) occurs within 21 days in vivo aquatic exposure to estrogen receptor agonists (eg 17beta-estradiol and 4-tert pentylphenol) as shown during the successful validation of the OECD Test Guideline 229 and related protocols. A smaller number of experiment studies with fish have shown that within the OECD Test Guideline 2010, larval fish can also show induction of whole body VTG levels within 21 days aquatic exposure to estrogen receptor agonists.

Uncertainties and Inconsistencies

There are generally few inconsistencies for experimental studies using model fish species dervied from pathogen-free laboratory cultures. However, there can some uncertainties where wild fish have been used for experimental purposes.

References

Navas, J.M., Segner, H. (2006) Vitellogenin synthesis in primary cultures of fish liver cells as endpoint for in vitro screening of the (anti)estrogenic activity of chemical substances. Aquatic Toxicology 80: 1-22

Thorpe, K.L., Benstead, R., Hutchinson, T.H., Tyler, C.R. (2007). Associations between altered vitellogenin concentrations and adverse health effects in fathead minnow (Pimephales promelas). Aquatic Toxicology 85: 176-183

Relationship: 254: Increase, Plasma vitellogenin concentrations leads to Increase, Renal pathology due to VTG deposition (https://aopwiki.org/relationships/254)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
Estrogen receptor agonism leading to reproductive dysfunction (https://aopwiki.org/aops/29)	**adjacent**	**High**	

Evidence Supporting Applicability of this Relationship

Publish studies specifically relate to fish, although it is plausible that the same response may occur in the aquatic life-stages of amphibians.

Evidence Supporting this KER

Biological Plausibility
High level of biological plausibility in fish.

Empirical Evidence
Laboratory in vivo aquatic exposures of fish (fathead minnow) to 17alpha-ethinylestradiol led to renal pathology within 16 weeks, concomitant with macroscopic evidence of osmoregulatory dysfunction and morbidity (Laenge et al., 2001).

Uncertainties and Inconsistencies
None that the author of this entry is aware of.

References

Herman, R.L., Kincaid, H.L. (1988) Pathological effects of orally administered 17beta-estradiol to rainbow trout. Aquaculture 72:165–172

Länge, R., Hutchinson, T.H., Croudace, C.P., Siegmund, F., Schweinfurth, H., Hampe, P., Panter, G.H., Sumpter, J.P. (2001) Effects of the synthetic estrogen 17 alpha-ethinylestradiol on the life-cycle of the fathead minnow (Pimephales promelas). Environ Toxicol Chem 20:1216-1227

Relationship: 126: Agonism, Estrogen receptor leads to Altered, Reproductive behaviour (https://aopwiki.org/relationships/126)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
Estrogen receptor agonism leading to reproductive dysfunction (https://aopwiki.org/aops/29)	**adjacent**	**High**	

Relationship: 336: Increase, Vitellogenin synthesis in liver leads to Increase, Plasma vitellogenin concentrations (https://aopwiki.org/relationships/336)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
Estrogen receptor agonism leading to reproductive dysfunction (https://aopwiki.org/aops/29)	**adjacent**	**High**	

Evidence Supporting this KER

Biological Plausibility
High level of physiological plausibility in fish.