April 2019

OECD ADVERSE OUTCOME PATHWAY

Project Submission Form

If you require further information, please contact the OECD Secretariat
Return completed forms to our generic account (env.tgcontact@oecd.org), and Nathalie Delrue (Nathalie.delrue@oecd.org)

PROJECT TITLE

Inhibition of 5α-reductase leading to impaired fertility in female fish

SUBMITTED BY (Country / European Commission / Secretariat)

South Korea

DATE OF SUBMISSION TO THE SECRETARIAT

DETAILS OF LEAD COUNTRY/CONSORTIUM

Country/Organisation:	South Korea
Agency/ministry/Other:	KIST Europe
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PROJECT CATEGORY

☒ Development of an AOP - applicable to a chemical category

Select the development tool to be used
☒ AOP-Wiki ☐ Effectopedia

☐ Guidance document related to AOP development including its evaluation

☐ Knowledge management tool for supporting AOP development including its evaluation

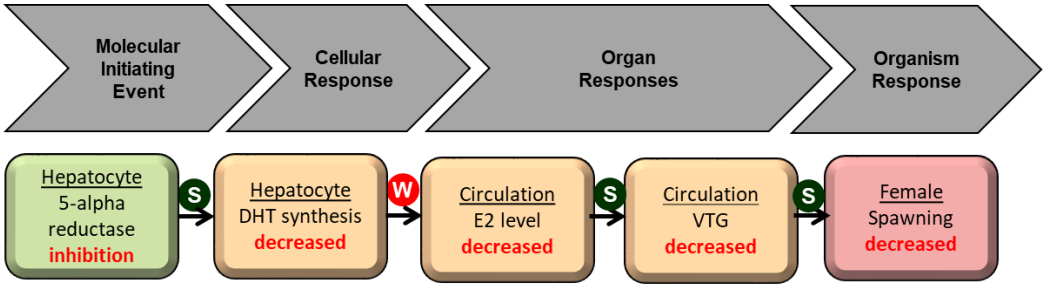
☐ Other, please specify below

If other category, please specify:

PROJECT DESCRIPTION

Please provide sufficient information to facilitate the review of the project submission by the OECD secretariat and the Extended Advisory Group with respect to its suitability to be included in the workplan of the AOP programme.

This AOP describes an adverse outcome that results from the inhibition of 5α-reductase (3-Oxo-5α-steroid 4-dehydrogenase) in female fish. 5α-reductase catalyzes a 3-oxo-5α-steroid to a 3-oxo-Δ4-steroid. Major reaction is the conversion of testosterone to 5α-dihydrotestosterone (DHT) which is a strong endogenous androgen receptor agonist. Inhibition of 5α-reductase can be caused by chemical inhibitors such as finasteride, dutasteride, epristeride, and etc. 5α-reductase inhibition (KE 790), the MIE for this AOP, results in decreasing levels of DHT and possibly 3β-androstanediol (3β-diol, agonist of estrogen receptor β), metabolite of DHT, followed by increasing of the level of testosterone in female fish (L.Mariotta-Calsaluci et al., 2013 Aquatic Toxicol). Whereas inhibition of 5α-reductase leads to decrease in the level of 17β-estradiol (E2) (KE 219) in a female by the unknown mechanism, which corresponds to decreased egg production and spawning. There have been a few studies on the evaluation of the inhibition of 5α-reductase in fish (L.Mariotta-Calsaluci et al., 2013 Aquatic Toxicol.;García-García et al. 2017 J Steroid Biochem Mol Biol) and these studies did not clarify the mechanism of the inhibition of 5α-reductase to decrease 17β-estradiol (E2) in female fish. Ornostay et al. (2016) reported DHT increased the level of E2 and steroidogenesis gene expression in fathead minnow ovary. The level of E2 is highly correlated with the synthesis of vitellogenin (VTG), having significant roles in reproduction. Reduced VTG (KE 221) in fish has been used as an endpoint for adverse effects on fertility and reproduction (Toxicol Sci, 2013. 132(2):284-297; Environ Toxicol Chem, 2016. 35(8): 2117-2224; Environ Toxicol, 2017. 32(7):1869-1877; Aquat Toxicol, 2018. 200:206-216). Additionally, possible KE is the inhibition of 5α-reductase affects the level of the other endogenous substrate steroids such as androstenedione, progesterone, cortisol, and aldosterone. The physiological responses of the reduction of these steroids and the inhibition of 5α-reductase are not fully understood (Azzouni et al. 2012). Furthermore, key event relationship (KER) to the levels of reduced aromatase (expression/activity) or reduced VTG by the inhibition of 5α-reductase was not well defined. Cumulative fertility is the major endpoint for the evaluation of reproductive toxicity caused by endocrine disruption with the exposure to endocrine disrupting chemicals (Ecotoxicol Environ Saf, 2018. 162:438-445; Environ Pollut, 2018. 240:403-411; J Appl Toxicol, 2018.38(4):544-551).



Weight of evidence [WoE]

S **Strong**

W **Weak**

This AOP is designed to detect changes in cumulative fecundity and spawning resulted from the inhibition of 5α-reductases by 5α-reductase inhibitors. Alteration of fecundity and spawning in fish is the critical endpoint for reproductive toxicity caused by endocrine disruption. This endpoint is essential and useful for screening of the potential endocrine disrupting chemicals and/or risk assessment for the possible contaminated sites by these chemicals. Therefore, this AOP can be applied to the prediction of reproductive toxicity caused by the inhibition of 5α-reductase .

Note: For AOP Development projects please indicate the extent of the pathway to be described (i.e. the anchor points), the intermediate events that are likely to be addressed, the state of current development**,** the degree to which this pathway is already understood and described in the literature, and the expectation on the availability of evidence to support the AOP. Proposers should also indicate if and how the AOP is associated to any regulatory toxicological endpoints (e.g. acute or chronic toxicity, toxicity to reproduction etc.) Please provide references, links or attachments for supplementary information.

PROJECT PLANNING

In this section, please provide an indication of when the project is likely to commence and the expected duration. Please also make reference to any particular milestones or external factors that will influence project planning, and if the project is linked to programmes of particular organisations or consortia.

This AOP is under development supported by the National Research Council of Science & Technology (NST) grant by the Korea government (MSIP) (No. CAP-17-01-KIST Europe).

To do		Expected duration
Building the AOP frame	Development of KEs	3 month
	Production of experimental data	18 month
Overall assessment of the AOP	Biological domain of applicability	3 month
	Essentiality of all KEs	3 month
	Evidence supporting all KERs	5 month
	Quantitative WoE considerations	5 month
	Quantitative understanding for each KER	6 month

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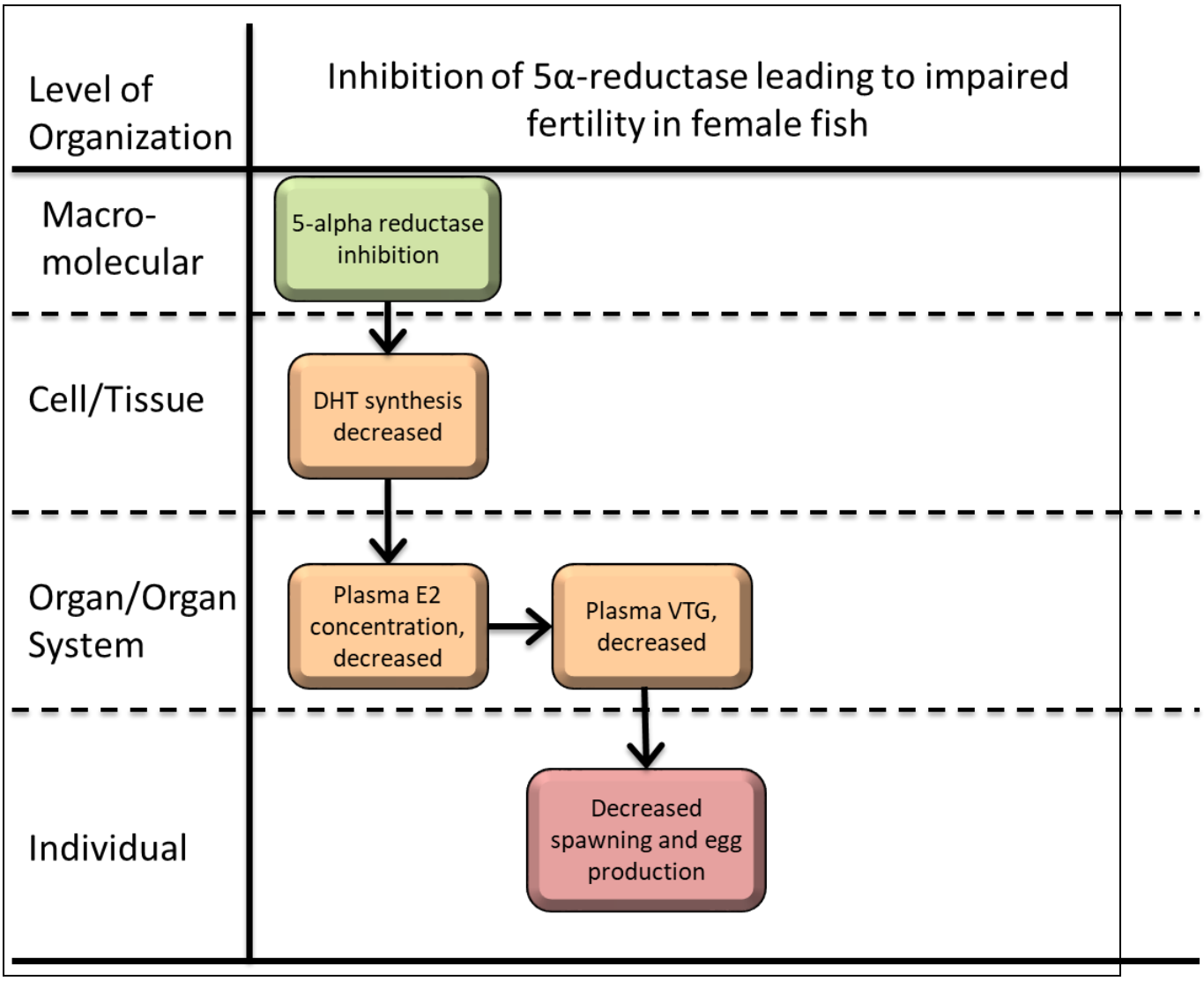
DIAGRAM

In this section, please provide a flow diagram of the proposed AOP, including the MIE, KEs at the various stages (molecular interaction, cellular response, organ response) and the AO.



COORDINATION OF OECD ACTIVITIES

AOP developers who submit a new AOP project proposal are invited to inform their National Coordinator of the Test Guidelines Programme.

National Coordinators' contact details are available at the following URL on the OECD public website:
http://www.oecd.org/env/ehs/testing/national-coordinators-test-guidelines-programme.htm