November 2017

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

TPO inhibition leading to impaired fertility in 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:	Korea Institute of Toxicology
Contact person(s):	June-Woo Park
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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:

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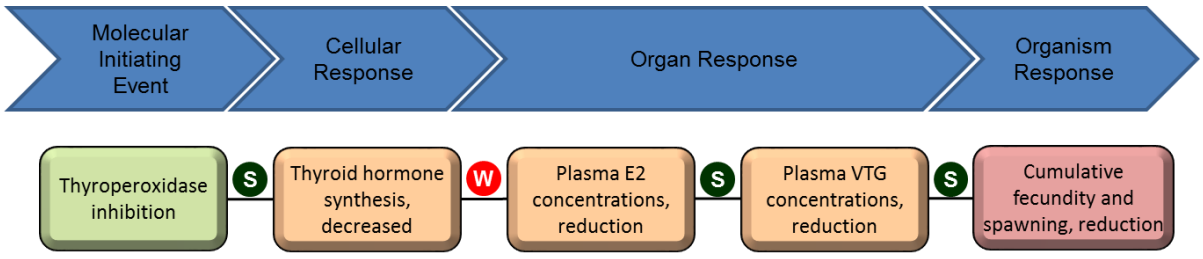
PROJECT DESCRIPTION

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 may result from the inhibition of thyroid peroxidase (TPO). TPO is the key enzyme that catalyses thyroid hormone biosynthesis. Chemical inhibition of TPO, the molecular-initiating event (MIE), results in decreased thyroid hormone (TH) synthesis. Reduction of TH induces the decline of E2 and VTG, which leads to decreased cumulative fecundity and spawning. Although there are several studies on reduction of thyroid hormone (TH) biosynthesis caused by TPO inhibition (Endocrinology, 1996. 113(3):921-8; Toxicol Appl Pharmacol. 2012 260(1):81-8), it is lacking in fish. At the molecular level, estrogen receptor (ER) and thyroid receptor (TR) share a common consensus half-site sequence (5'-AGGTCA-3'), and it has been shown that TR can bind to and activate an estrogen responsive element (ERE). Several studies show that TH disruption leads to alteration of estrogens and/or vitellogenin at molecular level in fish (Gen Comp Endocrinol, 2012. 175(1):19-26; Mol Cell Endocrinol, 2016. 436:259-67). The synthesis of vitellogenin (VTG) is primarily under the control of circulating estrogens, well known for their roles in reproduction. Alteration of VTG in fish has been used as a biomarker for endocrine disrupting chemicals and is associated with 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). Cumulative fertility is major endpoint for evaluation of reproductive toxicity caused by endocrine disruption following 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 reduction of thyroid hormone synthesis by TPO inhibition. Alteration of fecundity and spawning in fish is critical endpoint of reproductive toxicity caused by endocrine disruption. Its endpoint is important/useful for screening the potential endocrine disrupting chemicals and/or environmental risk assessment in endocrine disrupting chemicals contaminated site. Therefore, this AOP would be applied to prediction of reproductive toxicity caused by thyroid disrupting, screening of thyroid disrupting chemical, and/or environmental monitoring in thyroid disrupting-contaminated area.

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

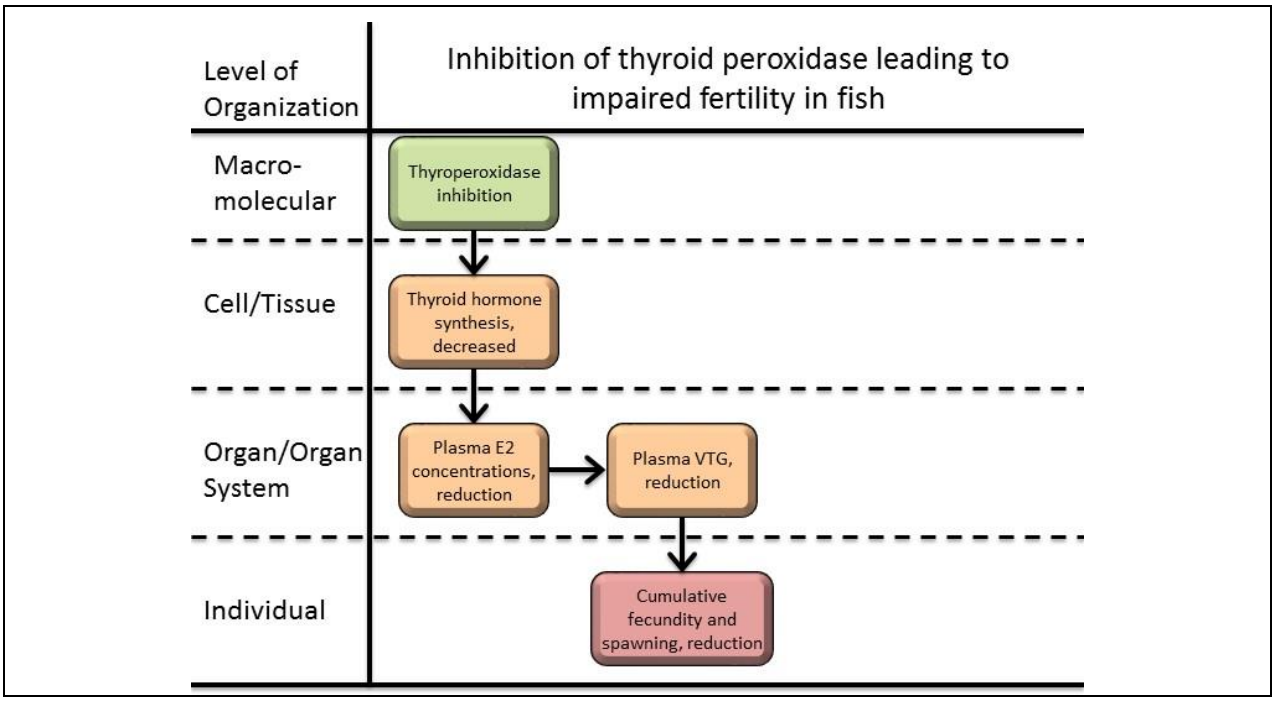
In this section, please provide an indication of when the project is likely to commence and the expected duration. Please also make reference to any particular milestones or external factors that will influence project planning, and if the project is linked to programmes of particular organisations or 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	12 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	5 month

FLOW 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