May 2019

OECD ADVERSE OUTCOME PATHWAY

Project Submission Form

(Revised 14 October 2014: the Secretariat information to send the form was modified)
If you require further information please contact the OECD Secretariat
Return completed forms to Lisa Savary (Lisa.SAVARY@oecd.org) and Camilla Francis (Camilla.FRANCIS@oecd.org)

PROJECT TITLE

Inhibition of retinaldehyde dehydrogenase leads to population decline

SUBMITTED BY (Country / European Commission / Secretariat)

South Korea

DATE OF SUBMISSION TO THE SECRETARIAT

21/05/2019

DETAILS OF LEAD COUNTRY/CONSORTIUM

Country/Organisation:	South Korea/Korea Institute of Science and Technology
Agency/ministry/Other:	KIST Europe
Contact person(s):	Kim,Young Jun
Mail Address:	Environmental Safety Group, Korea Institute of Science and Technology (KIST) Europe, Campus E 7.1, Saarbruecken, Germany
Phone/fax:	+49-681-9382-327/049-681-9382-109
Email:	kichul.cho@kist-europe.de, changryu@kist-europe.de, baeckkyoung@gmail.com, sbaik@kist-europe.de, youngjunkim@kist-europe.de

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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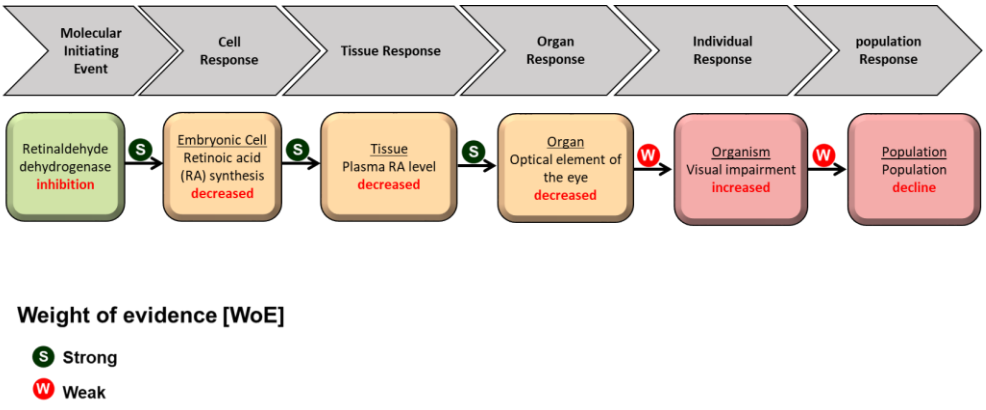
PROJECT DESCRIPTION

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 adverse outcome pathway (AOP) represents the potential causative adverse outcomes (AOs) by inhibition of retinaldehyde dehydrogenase (RALDH), which is one of the crucial enzymes participating in retinol metabolism. The role of RALDH in retinol metabolism is to catalyze the chemical reaction converting retinal to retinoic acid (RA). The synthesized RA is associated with the cellular RA-binding protein (CRABP) and enters into the nucleus, and then bind to retinoic acid receptors (RARs) along with retinoid X receptors (RXRs) (Vilhais-Neto and Pourquié, 2008). The activated RARs and RXRs can act as target gene transcription factors regulating embryonic development in fishes (Perz-Edwards et al., 2011). Inhibition of RALDH can be caused by chemical inhibitors such as Disulphiram, Citral, Paclobutrazol, Diethylaminobenzaldehyde, Nitrofen, 4-biphenyl carboxylic acid, Bisdiamine, SB-210661 and etc. (Marsh-Armstrong et al., 1994; Chawla et al., 2018; Wang et al., 2017; Le et al., 2012; Mey et al., 2003). RALDH inhibition, the molecular initiating event (MIE) for this AOP, leads to decreased RA synthesis blocking the reaction converting retinal to RA in embryonic cells (Hyatt and Dowling, 1997; Molotkov et al., 2002; Le et al., 2012; Duester, 2009). Since RA is an essential activator for the RARs and RXRs-mediated gene transcription, low level of plasma RA leads to abnormal development in embryonic cells. A number of previous studies well-elucidated the abnormal developments by RA inhibition including visual function and eye development (Duester et al., 2009; Hyatt and Dowling, 1997; Hyatt et al., 1996; Kam et al., 2012; Le et al., 2012; Luo et al., 2006; Marsh-Armstrong et al., 1994; Matt et al., 2005; Wang et al., 2017), intestinal development (Nadauld et al., 2005), brain patterning and neurogenesis (Begemann et al., 2004; Niederreither and Dollé, 2008; Samarut et al., 2015), and heart development (Niederreither and Dollé, 2008; Samarut et al., 2015). The development of early embryonic cells of fishes plays an essential role in the organism's young of year survival and adaptation in fluctuated environmental condition. The impact of the development of the optical elements of the eye by RALDH inhibition in fish population trajectory has not been clarified yet, although the importance of the visual function of fishes previously mentioned by previous studies (Fernald, 1984; Sandström, 1999).



The present AOP is designed to estimate potential AO of fishes results from the RALDH inhibition. Visual impairment results from eye development of an embryonic cell might lead to population decline which is the potential endpoint. This AOP will provide a useful risk assessment tool for the toxic assessment of chemicals. Furthermore, this AOP can be applied to the prediction of eco-toxicity caused by the inhibition of RALDH.

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

References

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