

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

Wnt ligand stimulation and Wnt signalling activation lead to cancer malignancy

SUBMITTED BY (Country / European Commission / Secretariat)

Japan

DATE OF SUBMISSION TO THE SECRETARIAT

DETAILS OF LEAD COUNTRY/CONSORTIUM

Country/Organisation:	Japan
Agency/ministry/Other:	National Institute of Health Sciences
Contact person(s):	Shihori Tanabe
Mail Address:	3-25-26, Tonomachi, Kawasaki-ku, Kawasaki, 210-9501, Japan
Phone/fax:	+81-44-270-6686/+81-44-270-6703
Email:	stanabe@nihs.go.jp

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.

Wnt (*Wingless* and *INT-1*) ligands stimulate Frizzled receptors and activate WNT signaling leading to cancer malignancy. This AOP workplan entitled “Wnt ligand stimulation and Wnt signaling activation lead to cancer malignancy” is suitable for the AOP programme in terms of revealing cancer signaling with the molecular signaling cascades induced by Wnt ligands. The current AOP includes MIE as Wnt ligand stimulation, KE1 as Frizzled activation, KE2 as GSK3beta inactivation, KE3 as beta-catenin activation, KE4 as Snail, Zeb, Twist1 activation, KE5 as epithelial-mesenchymal transition (EMT) and AO as cancer malignancy. The current AOP would be associated to the prediction of the cancer malignancy, which would be the regulatory toxicological endpoint, by chemicals or molecules activating Wnt signaling. The Wnt/beta-catenin signaling is well understood in terms of development and cancer. The relationship between EMT and cancer malignancy has recently been investigated in many research fields such as molecular signatures of cells. References: 1. Tanabe S et al (2016) “Gene expression and pathway analysis of CTNNB1 in cancer and stem cells” *World J Stem Cells*, 8, 384-395. 2. Tanabe S et al (2016) “Regulation of CTNNB1 signaling in gastric cancer and stem cells” *World J Gastrointestinal Oncol* 8, 592-598. 3. Tanabe S (2017) “Molecular markers and networks for cancer and stem cells” *J Embryol Stem Cell Res* 1, 1. 4. Tanabe S (2017) “Networking the Signaling Pathways in Stem Cells and Cancer” *J Clinical Epigenetics* 3, 28. 5. Tanabe S (2018) “Molecular Network and Cancer” *Research J Oncol* 2, 3. 6. Clevers H (2006) “Wnt/beta-catenin signaling in development and disease” *Cell* 127, 469-480.

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.

January 2019: the development of the AOP starts.

June 2019: the AOP explanation at OECD EAGMST meeting

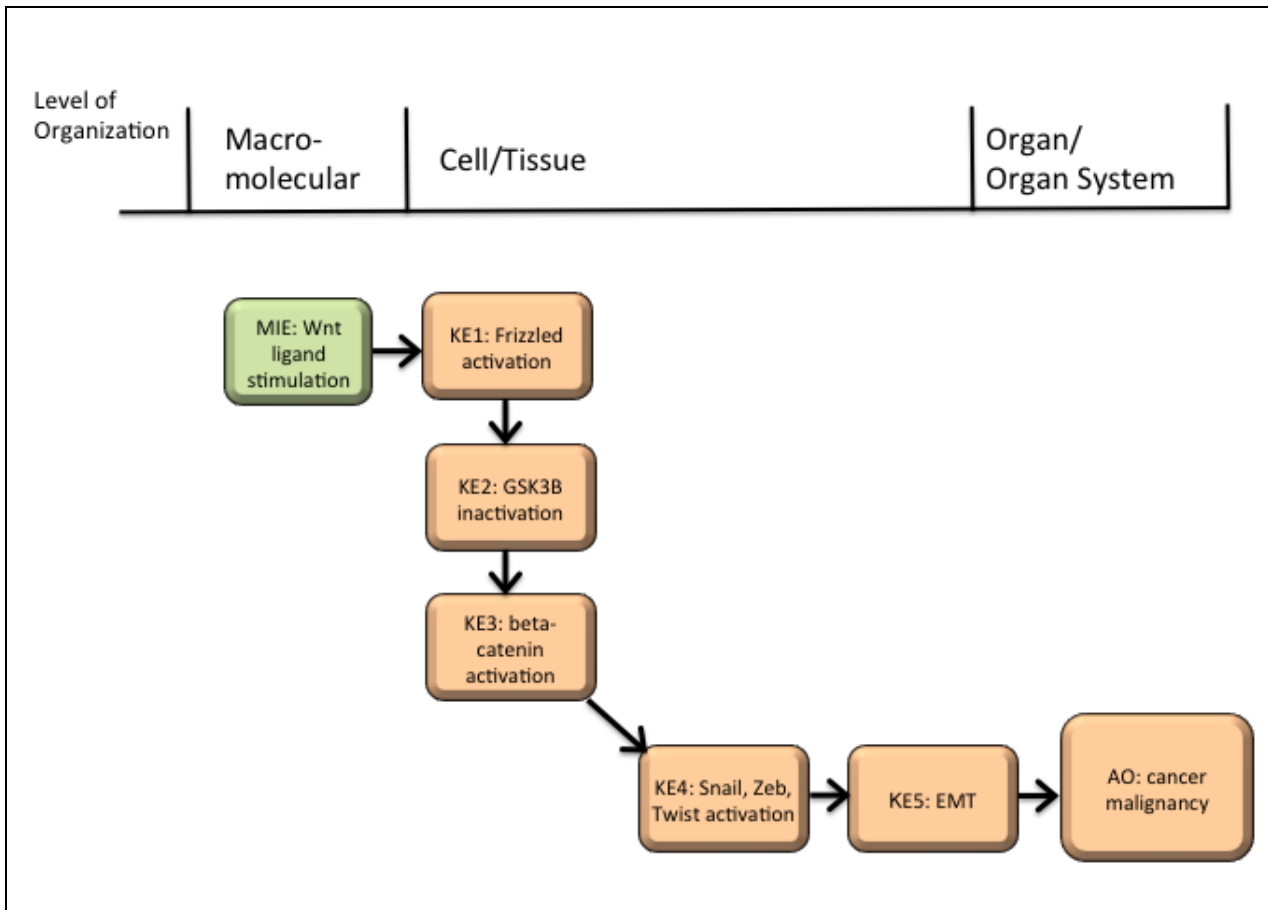
2019-2020: the reviewing processes proceed*

June 2020: the adoption at OECD EAGMST meeting

*It depends on the revision of the reviewing process at OECD EAGMST from current 2-step system that includes both internal review and external review into potential revised 1-step system with internal and external reviewers at the same time.

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>