April 2017

OECD ADVERSE OUTCOME PATHWAY

Project Submission Form

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

PROJECT TITLE

Decreased Trypsin activity leading to pancreatic acinar cell tumor formation

SUBMITTED BY (Country / European Commission / Secretariat)

Japan

DATE OF SUBMISSION TO THE SECRETARIAT

Nov. 14th, 2018

DETAILS OF LEAD COUNTRY/CONSORTIUM

Country/Organisation:	Japan
Agency/ministry/Other:	Japan Pharmaceutical Manufacturers Association
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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.

During the decades of drug development with rodent carcinogenicity studies, some classes of pharmaceuticals are known to induce tumors with non-genotoxic mechanisms based on their on-target or off-target pharmacology as well as toxicity; some are mostly common in rodents and the others might be extrapolated to humans. One of these non-genotoxic carcinogenesis is trypsin inhibition-induced pancreatic acinar cell tumors and we propose to develop the AOP.

In rodents, exocrine secretion of pancreatic acinar cells is at least in part controlled by cholecystokinin (CCK) secreted from I cells in the duodenal mucosa. On an empty stomach, trypsin degrades monitor peptides secreted from the pancreas to be kept at low level within the intestine; however, when food enters into the duodenum, the level of monitor peptides escaped from digestion is increased to stimulate CCK secretion from I cells [1,2]. The resultant increase in the serum level of CCK stimulates the secretion by pancreatic acinar cells mediated by CCK-1 receptors [3].

In cases where trypsin is continuously inactivated by trypsin inhibitors such as soybean contents and protease inhibitor camostat, the intestinal concentration of monitor peptides is increased [4,5], which stimulates pancreatic acinar cells to secret and proliferate through increased serum level of CCK [6]. Prolonged CCK receptor-mediated stimulation of pancreatic acinar cells to proliferate results in pancreatic acinar cell tumor formation [7,8,9].

There are species differences in the mechanism of regulation for exocrine secretion. Contribution of CCK receptors expressed on human pancreatic acinar cells to exocrine secretion is low compare with rodents, and the secretion is mainly stimulated by vagal nerves with CCK-1 receptors with minimum effect on acinar cell proliferation [10,11,12].

Therefore, the risk of trypsin inhibition-induced pancreatic acinar cell tumor formation deems to be low compared with rodents considering these species differences.

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.

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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.

The Japanese Pharmaceutical Manufacturers Association (JPMA) will develop several AOPs for non-genotoxic carcinogenesis based on our survey on the pharmacology-induced modes of action of carcinogenesis in the next four years under the cooperation with Dr. Kumiko Ogawa (National Institute of Health Sciences).

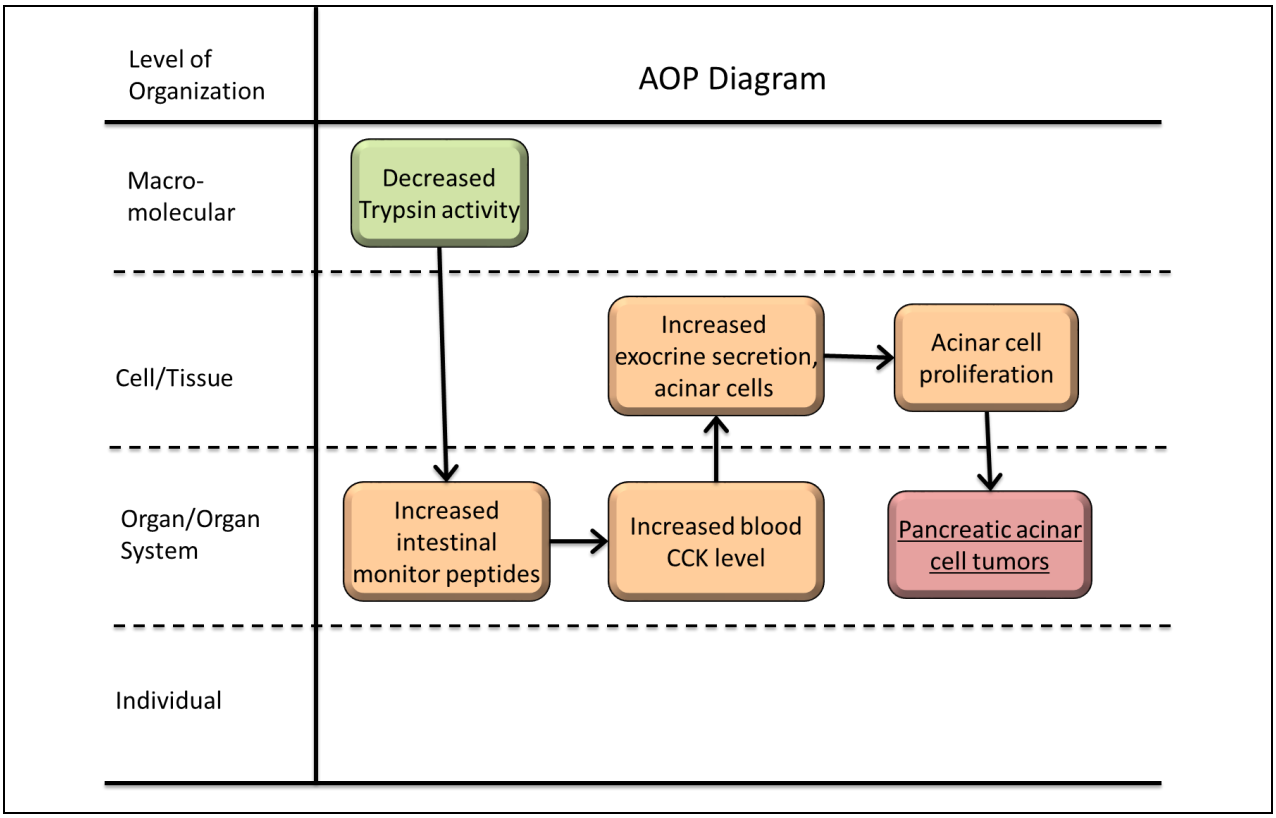
The timeline of the development of the present AOP is as follows:

Nov., 2018: to submit the AOP SPSF

Jun., 2019: to complete AOP Wiki input and wiki input and request an internal review by EAGMST

FLOW DIAGRAM

n 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.



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