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

Histamine receptor 2 blockade leading to gastric carcinoid 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 Histamine H2 receptor blockade-induced gastric carcinoid tumor formation and we propose to develop the AOP.

Histamine H2 receptor antagonists (H2 blockers), competitively bind to the histamine H2 receptors of the parietal cells, and inhibit acid secretion from parietal cells in oxyntic mucosa [1]. H2 blockers reversibly bind to H2 receptor and so that the effect is short acting and less potent in general. On the other hand, long-acting type H2 blockers have been developed, and the potency and duration of their pharmacologic action are comparable to those of proton pump inhibitors (PPIs). Inhibition of gastric acid secretion by the long-acting H2 blockers lead to elevated gastric luminal pH and, secondarily, to release of gastrin from G-cells (gastrin secreting cells) in pyloric antrum into the blood stream [2]. Gastrin has a trophic effect to stomach tissue [3], and thus causes both hypertrophy of the oxyntic mucosa, and hypertrophy [4] and hyperplasia [5] of the enterochromaffin-like (ECL) cells, one of neuroendocrine cells in the oxyntic mucosa. Sustained hypergastrinemia caused by prolonged inhibition of gastric acid secretion results in ECL cell carcinoid tumor development in rats [4, 6-9].

The risk of histamine receptor 2 blockade -induced gastric neuroendocrine cell tumor formation in humans deems to be low compared with rodents considering that the degree of increase in circulating gastrin and the trophic effect of gastrin to ECL cells in human is much less than those observed in rodents [10,11,12].

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

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.

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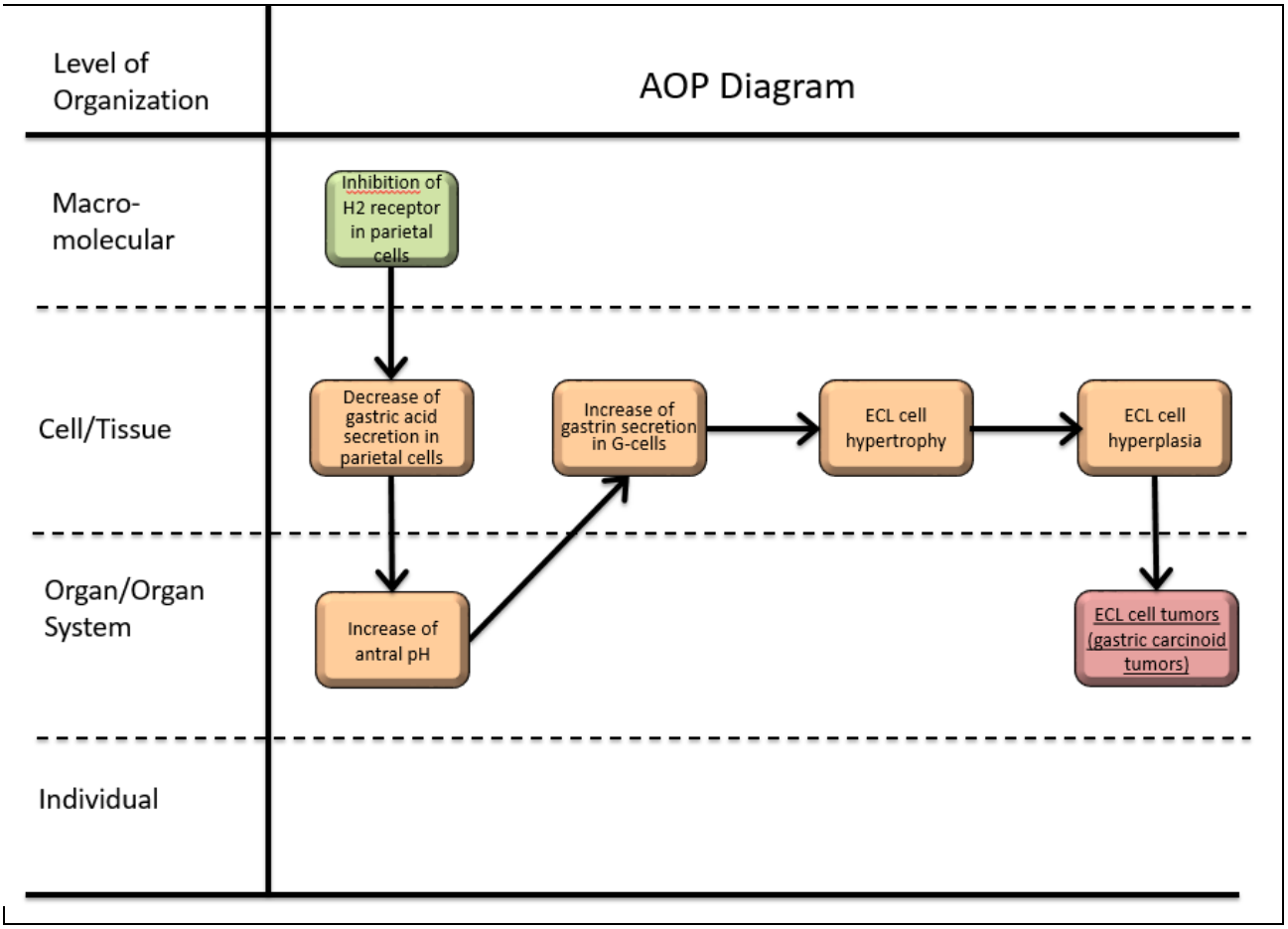
Level of Organization
AOP Diagram
Macro-molecular
Cell/Tissue
Organ/Organ System
Individual
Inhibition of H2 receptor in parietal cells
Decrease of gastric acid secretion in parietal cells
Increase of gastrin secretion in G-cells
ECL cell hypertrophy
ECL cell hyperplasia
Increase of antral pH
ECL cell tumors (gastric carcinoid tumors)

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