April 2017

αOECD 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

Alpha-glucosidase inhibition leading to renal tubular tumors

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 α-glucosidase inhibition-induced renal tubule tumors and we propose to develop the AOP.

α-glucosidase located in the microvilli of mucosal lining cells of the small intestine regulates carbohydrate metabolism. Inhibition of α-glucosidase activity reduces the degradation of carbohydrates to glucose, which increases intestinal content of carbohydrates. Increased carbohydrates are fermented by colorectal microbes with the resultant decrease in the intestinal pH, and the acidic condition increases solubility and absorbability of calcium in the colon. Such disturbance of calcium homeostasis enhances the urinary excretion of calcium, which deems to induce tubular cell injury and following regenerative proliferation. Sustained proliferation of tubular cells promotes renal tumor formation. This type of renal tumor formation is reported in the 2-year rat carcinogenicity study of an α-glucosidase inhibitor, acarbose [1] as well as sodium glucose cotransporter-2 inhibitors [2,3].

The risk of the renal tumor formation by α-glucosidase inhibition in humans deems to be low compared with rodents considering that the degree of calcium homeostasis disturbance through α-glucosidase inhibiter therapy in humans might be much less than that in rodents [4].

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).

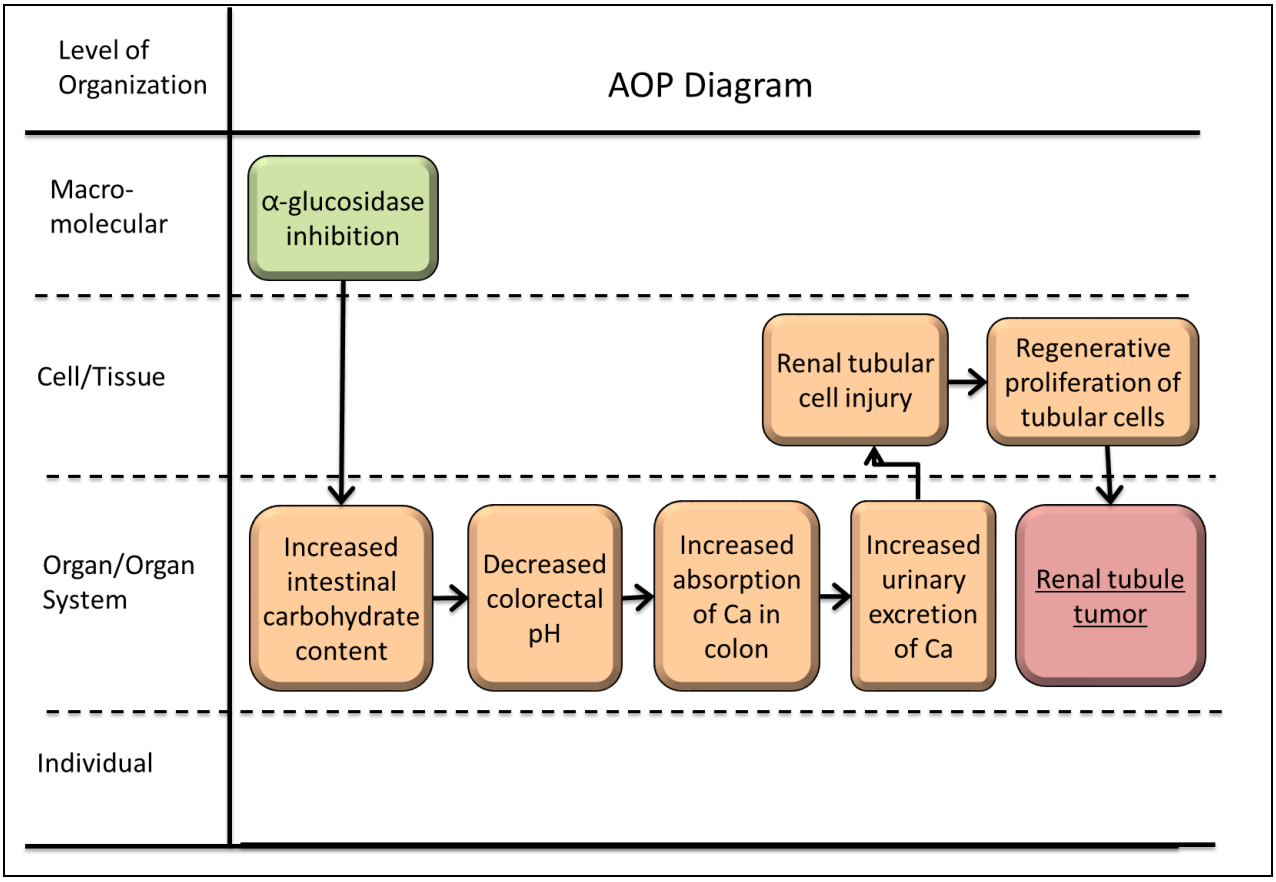
The timeline of the development of the present AOP is as follows:

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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References

1. Schluter G. (1988) Toxicology of Acarbose, with special reference to long-term carcinogenicity studies. In:Creutzfeldt W, editor. Acarbose for the treatment of diabetes mellitus. 2nd International Symposium on Acarbose.New York. Springer-Verlag.:5-14.
2. De Jonghe S, Proctor J, Vinken P, Feyen B, Wynant I, Marien D, Geys H, Mamidi RN, Johnson MD. (2014) Carcinogenicity in rats of SGLT2 inhibitor canagliflozin. Chem Biol Interact. 224:1-12.
3. Mamidi RN, Proctor J, De Jonghe S, , Feyen B, Moesen E, Vinken P, Ma JY, Bryant S, Snook S, Louden C, Lammens G, Ways K, Kelley MF, Johnson MD. (2014) Carbohydrate malabsorption mechanism for tumor formation in rats treated with the SGLT2 inhibitor canagliflozin. Chem Biol Interact. 221:109-118.
4. Hollander P. (1992) Safety profile of acarbose, an alpha-glucosidase inhibitor. Drugs. 44 Suppl 2:47-53.