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

Sodium glucose cotransporter (SGLT1) inhibition leading to adrenal pheochromocytoma 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 sodium glucose cotransporter (SGLT1) inhibition leading to adrenal pheochromocytoma formation and we propose to develop the AOP.

The agents that induce hypercalcemia or impaired calcium homeostasis are reported to promote pheochromocytoma formation in the adrenal medulla of the rat [1]. One of these agents is SGLT2 inhibiters [2]. Most of the SGLT2 inhibiters, which suppress the reabsorption of glucose from proximal tubules, also suppress SGLT1. SGLT1 is expressed in the intestinal mucosa to mediate glucose absorption from the intestine, and its inhibition increases the luminal content of glucose. Then, accumulated glucose is fermented by colorectal microbes to lower luminal pH [3]. The acidic condition of the colorectal lumen increases Ca^{2+} uptake from the colon into the blood stream with resultant hypercalcemia or impaired calcium homeostasis such as increased urinary excretion [3].

Hypercalcemic condition like this might directly or indirectly enhance the proliferation of adrenomedullary cells (chromaffin cells) as well as enhancing synthesis and release of catecholamines (CAs) in the rat [3,4,5,6]. The continued enhancement of chromaffin cell proliferation leads to the formation of nodular hyperplasia and following pheochromocytomas [4].

Hypercalcemic condition might increase the influx of Ca^{2+} into chromaffin cells, which deems to be the same outcome as that of sympathetic nerve stimulation. Chromaffin cells promote the synthesis and release of CAs after sympathetic nerve stimulation. In addition, rat chromaffin cells continue to proliferate even in the adult age, and sympathetic nerve stimulation enhances the proliferation of chromaffin cells as well as the synthesis and release of CAs [7, 8].

There is species differences in the reactivity of chromaffin cells to nerve stimulation, in that, in vitro stimulation of chromaffin cells from rats with nerve growth factors induces proliferation but does not from humans [8]. Therefore, neurogenic factors are less mitogenic to human chromaffin cells and then, hypercalcemia-induced chromaffin cell proliferation in the rat is not applicable to human.

Furthermore, the clinical trials showed that SGLT2 inhibitors did not induce symptoms of carbohydrate malabsorption such as changes in urinary excretion of calcium, PTH and 1,25-hydroxyvitamin D [9].

Consequently, the risk of SGLT1 inhibition-induced pheochromocytoma formation in human 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.

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:

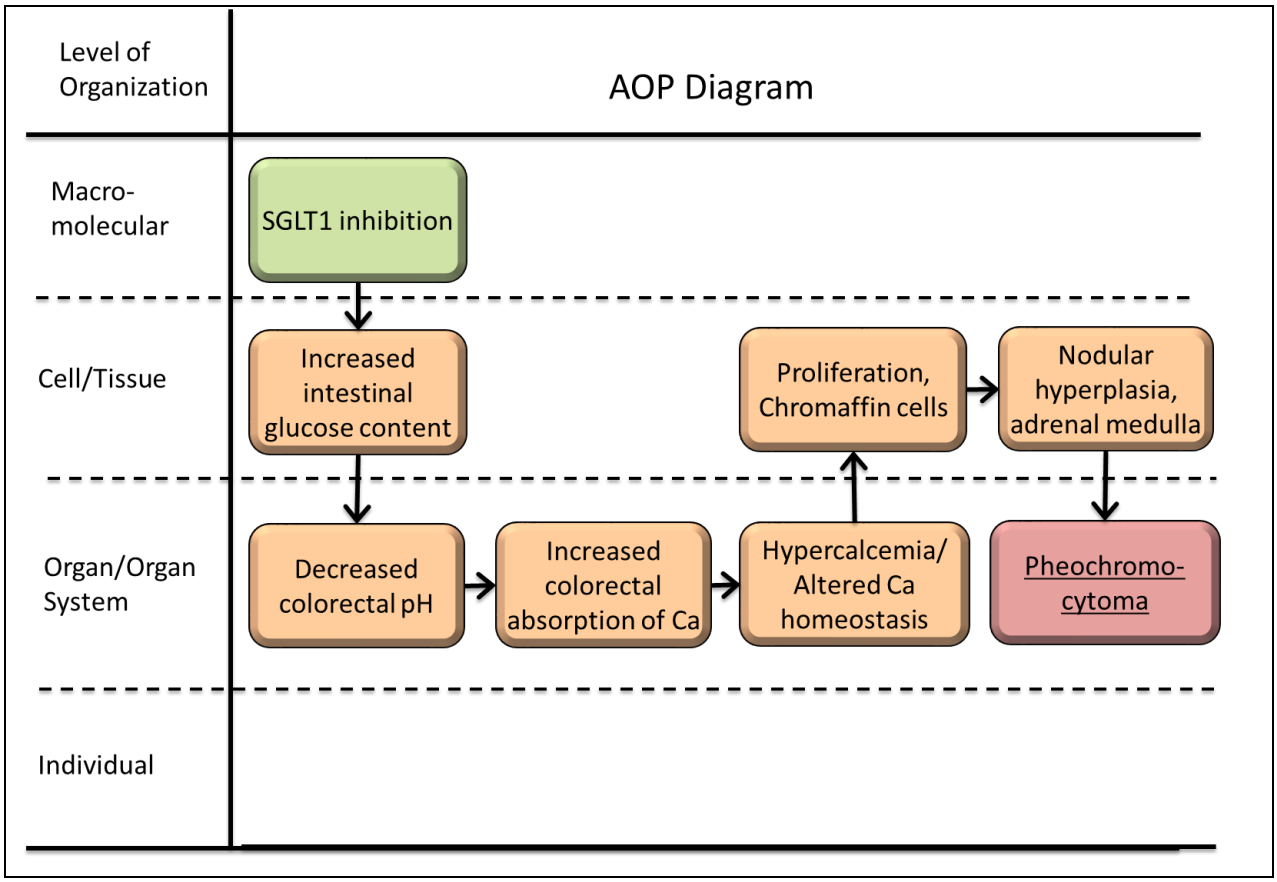
Nov., 2018: to submit the AOP SPSF

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

April 2017

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.



References

1. Greim H, Hartwig A, Reuter U, Richter-Reichhelm HB, Thielmann HW (2009), Chemically induced pheochromocytomas in rats: mechanisms and relevance for human risk assessment. Crit Rev Toxicol 39:695-718.4.

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 the SGLT2 inhibitor canagliflozin. Chem Biol Interact. 2014 Dec 5;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. De Jonghe S, Johnson MD, Mamidi RNVS, Vinken P, Feyen B, Lammens G, Proctor J (2017), Renal tubular and adrenal medullary tumors in the 2-year rat study with canagliflozin confirmed

to be secondary to carbohydrate (glucose) malabsorption in the 15-month mechanistic rat study. Chem Biol Interact 277:85-90.

5. Isobe K, Ito T, Komatsu S, Asanuma K, Fujii E, Kato C, Adachi K, Kato A, Sugimoto T, Suzuki M (2012), Stimulation of adrenal chromaffin cell proliferation by hypercalcemia induced by intravenous infusion of calcium gluconate in rats. J Toxicol Pathol 25:281-285.
6. Yoshida M, Ishibashi S, Nakazawa M, Tamura H, Uchimoto H, Kawaguchi K, Yoshikawa K, Hamasu Y, Sumi N (1995), The mechanism of lactitol (NS-4) in inducing adrenomedullary proliferative lesion in rats. J Toxicol Sci 20 Suppl 1:37-45.
7. Tischler AS, McClain RM, Childers H, Downing J (1991), Neurogenic signals regulate chromaffin cell proliferation and mediate the mitogenic effect of reserpine in the adult rat adrenal medulla. Lab Invest 65:374-376.
8. Tischler AS, Riseberg JC (1993), Different responses to mitogenic agents by adult rat and human chromaffin cells in vitro. Endocr Pathol 4:15-19.
9. Ways K, Johnson MD, Mamidi RN, Proctor J, De Jonghe S, Louden C (2015), Successful integration of nonclinical and clinical findings in interpreting the clinical relevance of rodent neoplasia with a new chemical entity. Toxicol Pathol 43:48-56.