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

Increased low-digestible carbohydrates in the colon leading to Leydig cell tumor

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 Increased low-digestible carbohydrates in the colon leading to Leydig cell tumor and we propose to develop the AOP.

In the rat, increase in colorectal low-digestible carbohydrates lowers pH, enhances calcium absorption and induces hypercalcemia [1]. Hypercalcemia stimulates thyroid c-cells to increase the secretion of calcitonin. Calcitonin inhibits the secretion of prolactin (PRL) as well as reduces blood calcium level [2,3]. Increased serum PRL downregulates LH receptor on Leydig cells and subsequently decreases testosterone production. To compensate decreased testosterone level, LH secretion increases and eventually results in Leydig cell hyperplasia and Leydig cell tumor.

The risk of low-digestible carbohydrates-induced Leydig cell tumor development in human deems to be low compared with rodents considering the following difference between rats and humans. Calcium absorption is not affected in human treated with slowly digestible or poorly absorbable carbohydrates [4]. Cook et al. suggested that the Leydig cell tumor is common spontaneous tumor and often induced in response to some chemicals, whereas quite rare tumor in humans (0.00004%). Leydig cell in rats has more receptors for GnRH, PRL and LH and is more sensitive to increased levels of gonadotropin than that in humans [5].

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 of Dr. Kumiko Ogawa (National Institute of Health Sciences).

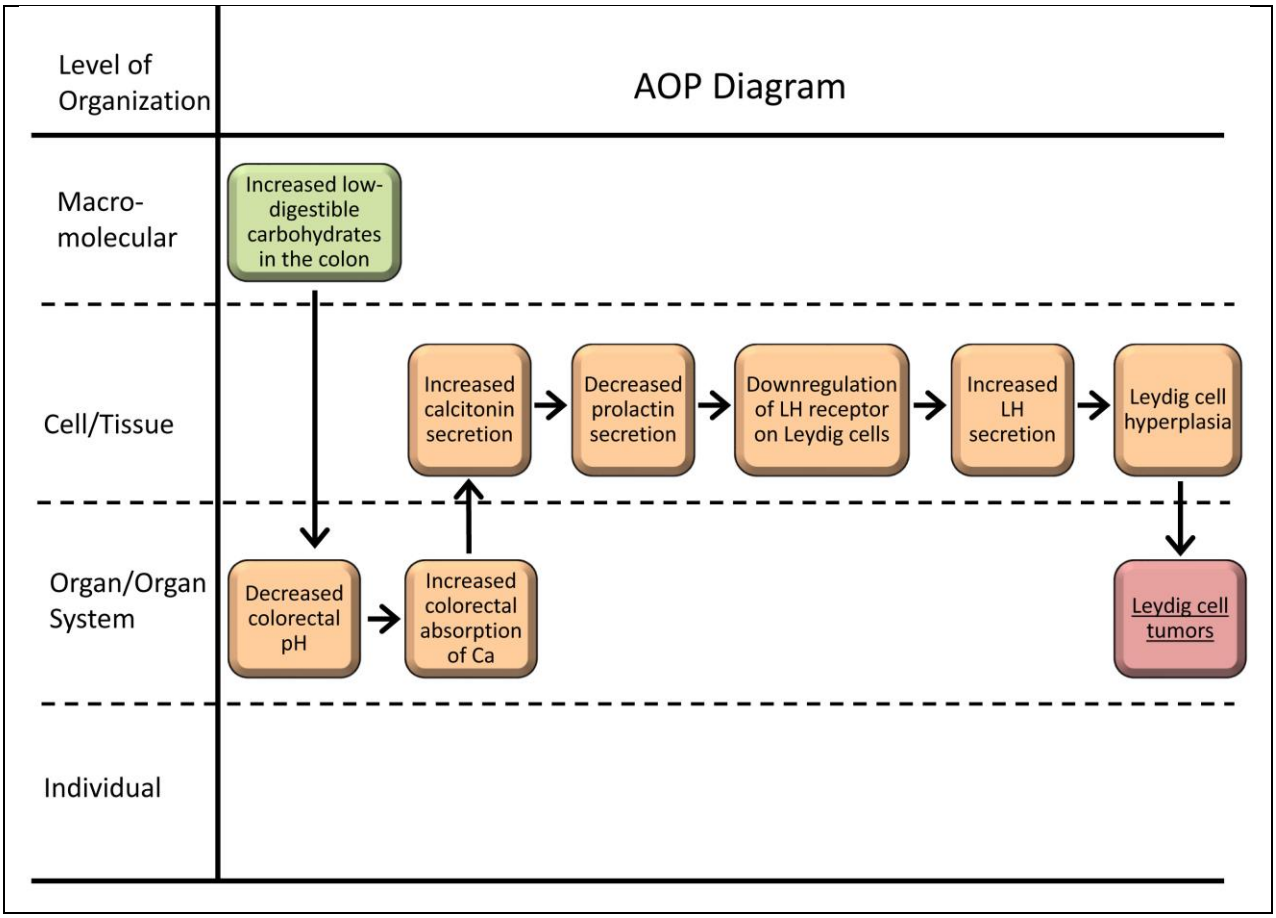
The timeline of the development of the present AOP is as follows:

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. de Groot AP, Lina BA, Hagenaars AJ, Hollanders VM, Andringa M, Feron VJ (1995), Effects of a dietary load of acid or base on changes induced by lactose in rats. Food Chem Toxicol 33:1-14.
2. Tohei A, VandeGarde B, Arbogast LA, Voogt JL (2000), Calcitonin inhibition of prolactin secretion in lactating rats: mechanism of action. Neuroendocrinology. 71(5):327-32.
3. Ren Y, Sun YP, Shah GV (2003), Calcitonin inhibits prolactin promoter activity in rat pituitary GGH3 cells: evidence for involvement of p42/44 mitogen-activated protein kinase in calcitonin action. Endocrine. 20(1-2):13-22.
4. Bar A (1992), Significance of Leydig cell neoplasia in rats fed lactitol or lactose. J Am Coll Toxicol. 11:189-207.
5. Cook JC, Klinefelter GR, Hardisty JF, Sharpe RM, Foster PM (1999), Rodent Leydig cell tumorigenesis: a review of the physiology, pathology, mechanisms, and relevance to humans. Crit Rev Toxicol. 29(2):169-261.