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

D2 receptor antagonism leading to pituitary 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 D2 receptor antagonism leading to pituitary tumors and we propose to develop the AOP.

The antipsychotic drugs having Dopamine D2 antagonistic potential, such as haloperidol and risperidone, induce pituitary adenoma (carcinogenesis: regulatory toxicological endpoint) in mice [1,2]. Following AOP can be proposed for the pituitary tumor development by Dopamine D2 antagonism in mice.

The lactotroph secreting prolactin in the pituitary is subjected to negative regulation of dopamine through D2-receptor [3,4,5] and positive regulation of thyrotropin releasing hormone (TRH)[6], oxytocin [7] and vasoactive intestinal peptide (VIP)[8]. These mediators are tonically secreted from the hypothalamus. In addition, the lactotroph is stimulated continually by estrogen secreted mainly from the ovaries [9]. The antagonism of D2-receptor blinded by D2-antagonists (MIE) [10] and inhibits the dopamine's negative signal (KE1). The positive mediators including TRH, oxytocin, VIP and estrogen bind to their receptors on the lactotroph and stimulate cyclic AMP (cAMP) production (KE2). cAMP is a stimulator for proliferation of the lactotroph (KE3) [11]. Without negative input of dopamine, the proliferation of the lactotroph is not controlled and then exaggerated (hyperplasia) so that the lactotroph is transformed to malignant cell (AO) [12].

The human relevance of MOA of the pituitary adenoma in mice is not neglected because of no information of species difference between human and mouse on pituitary dopamine regulation and the signal of pituitary neoplasm development reported using WHO database[13].

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).

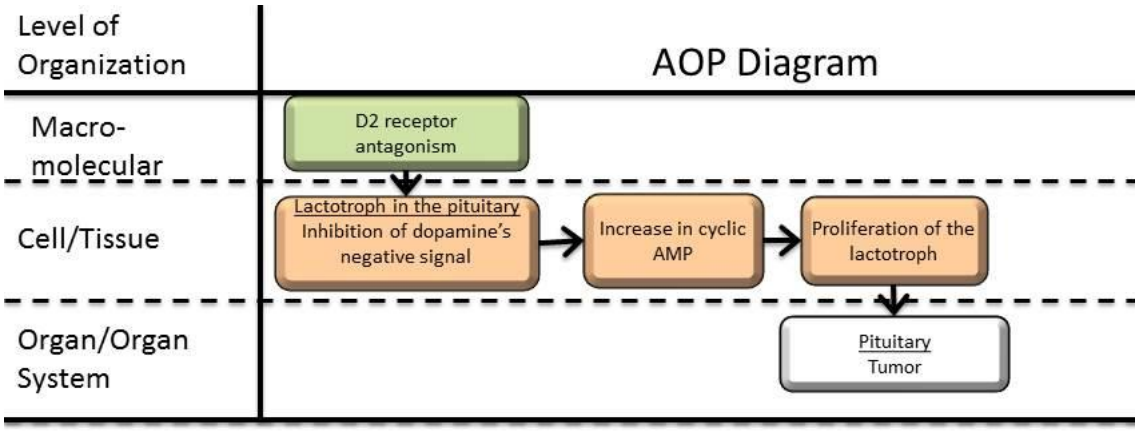
The timeline of the development of the present AOP is as follows:

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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