

April 2017

## OECD ADVERSE OUTCOME PATHWAY

### Project Submission Form

If you require further information please contact the OECD Secretariat  
Return completed forms to our generic account (env.tgcontact@oecd.org), and Nathalie  
Delrue (Nathalie.delrue@oecd.org)

---

#### PROJECT TITLE

Anti-dopaminergic activity leading to pancreatic islet cell tumors

#### SUBMITTED BY (Country/ European Commission / Secretariat)

Japan

#### DATE OF SUBMISSION TO THE SECRETARIAT

NOV.14<sup>th</sup>, 2018

---

#### DETAILS OF LEAD COUNTRY/CONSORTIUM

Country/Organisation:	Japan
Agency/ministry/Other:	Japan Pharmaceutical Manufacturers Association
Contact person(s):	Tatsuya Nagasawa
Mail Address:	2320-1 maki, Hotaka, Azumino, Nagano, 399-8305, Japan
Phone/fax:	+81-(0)263-83-5053
Email:	tatsuya_nagasawa@pharm.kissei.co.jp

#### 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 dopamine antagonism-induced pancreatic islet tumor formation and we propose to develop the AOP.

Dopamine by itself acts as a main prolactin inhibiting factor (PIF) with some other factors to suppress prolactin (PRL) release from the anterior pituitary [1]. In cases where serotonin-dopamine antagonists such as risperidone [2] and iloperidone [3] binds to dopamine D2 receptors for prolonged period, the dopamine-induced negative signal on prolactin secretion is suppressed with a resultant increase in blood PRL level. PRL stimulates rodent pancreatic  $\beta$ -cell proliferation via affecting cell cycle phase and polyamine metabolism [4,5]. Chronic hyperprolactinemia sustains exaggerated proliferation of islet cells, which results in pancreatic islet cell tumor formation.

The relationship between elevated blood PRL level and islet tumor formation in humans is not clearly understood at present. However, the anti-dopaminergic activity-related risks of pancreatic islet cell tumors in human deems to be low compared with rodents considering that human  $\beta$ -cells might lacks functional PRL receptors and do not proliferate in response to PRL [6,7]. So far, the relationship between long-term administration of antipsychotic drugs in humans and tumorigenesis has not been proved shown by the results of various epidemiological studies [8,9].

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).

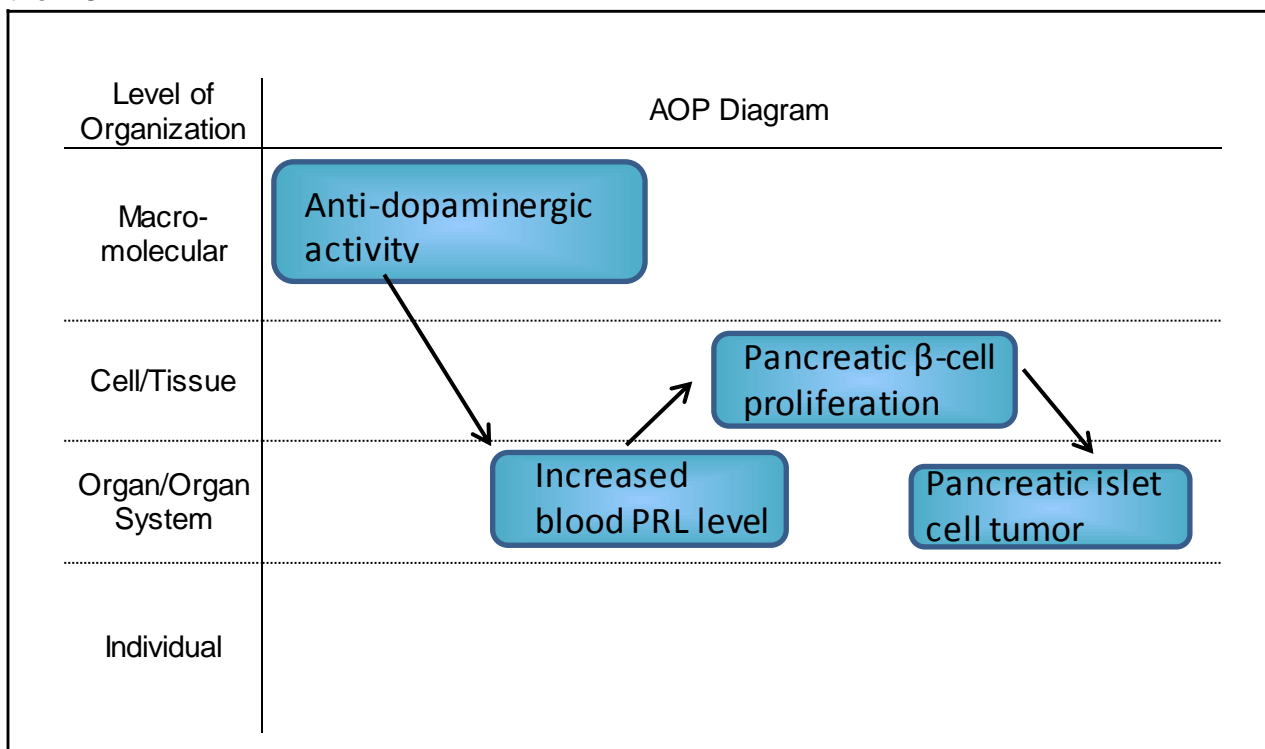
The timeline of the development of the present AOP is as follows:

Nov., 2018: to submit the AOP SPSF

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

**FLOW DIAGRAM**

In this section, please provide a flow diagram of the proposed AOP, including the ME, KEs at the various stages (molecular interaction, cellular response, organ response) and the AO.



References

1. Kim HY, Lee CK, Lee JT, Moon CS, Ha SC, Kang SG, Kim DH, Kim HD, Ahn JH, Lee SB, Kang MG. (2009) Effects of manganese exposure on dopamine and prolactin production in rat. *Neuroreport*. 20(1):69-73.
2. US Package Insert (RISPERDAL®)  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/020272S-055S-058S-061S-062lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020272S-055S-058S-061S-062lbl.pdf)
3. US package Insert (FANAPT®)  
<https://www.fanapt.com/product/pi/pdf/fanapt.pdf>
4. Brelje TC, Parsons JA, Sorenson RL. (1994) Regulation of islet beta-cell proliferation by prolactin in rat islets. *Diabetes*. 43(2): 263-73.
5. Russell DH, Larson DF, Cardon SB, Copeland JG. Cyclosporine inhibits prolactin induction of ornithine decarboxylase in rat tissues. *Mol Cell Endocrinol*. 35 (2-3): 159-66.
6. Aamodt KI and Powers AC. (2017) Signals in the pancreatic islet microenvironment influence  $\beta$ -cell proliferation. *Diabetes Obes Metab*. 19 (Suppl. 1): 124-36.
7. Chen Hainan, Kleinberger JW, Takane KK, Salim F, Fiaschi-Taesch N, Pappas K, Parsons R, Jiang J, Zhang Y, Liu H, Wang P, Bender AS, Frank SJ, Stewart AF. (2015) Augmented stat5 signaling bypasses multiple impediments to lactogen-mediated proliferation in human  $\beta$ -cells. *Diabetes*. 64: 3784-3797.
8. Mortensen PB. (1994) The occurrence of cancer in first admitted schizophrenic patients. *Schizophr Res*. 12(3):185-94.
9. Mortensen PB. (1989) The incidence of cancer in schizophrenic patients. *J Epidemiol Community Health*. 43(1):43-7.