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

Inhibition of vesicular monoamine transporter (VMAT) 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 inhibition of vesicular monoamine transporter (VMAT) leading to adrenal pheochromocytoma formation and we propose to develop the AOP.

Adrenal medullary cells (chromaffin cells) promote the synthesis and release of catecholamines (CAs) after sympathetic nerve stimulation. In addition, rat chromaffin cells continue to proliferate even in the adult age, and sympathetic nerve stimulation enhance the proliferation of chromaffin cells as well as the synthesis and release of CAs [1, 2].

Some sympathetic blockers deplete monoamines such as norepinephrine and dopamine from sympathetic nerve ending by the inhibition of VMAT. Reserpine is one of such agents; the anti-adrenergic drug induces compensatory response of sympathetic nerves in response to monoamine depletion, which induces proliferation of chromaffin cells in rats [3, 4, 5]. Denervation of the adrenal glands prevents the reserpine-induced chromaffin cell proliferation in the rat [5]. Prolonged proliferation of rat chromaffin cells, in turn, leads to the formation of nodular hyperplasia and following pheochromocytomas [6].

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 so much from humans, showing that neurogenic factors are less mitogenic to human chromaffin cells [7]. There is no epidemiological/clinical studies proving reserpine prescription-related increase in the incidence of pheochromocytomas.

Therefore, the risk of VMTA inhibition-induced pheochromocytoma formation in humans 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.

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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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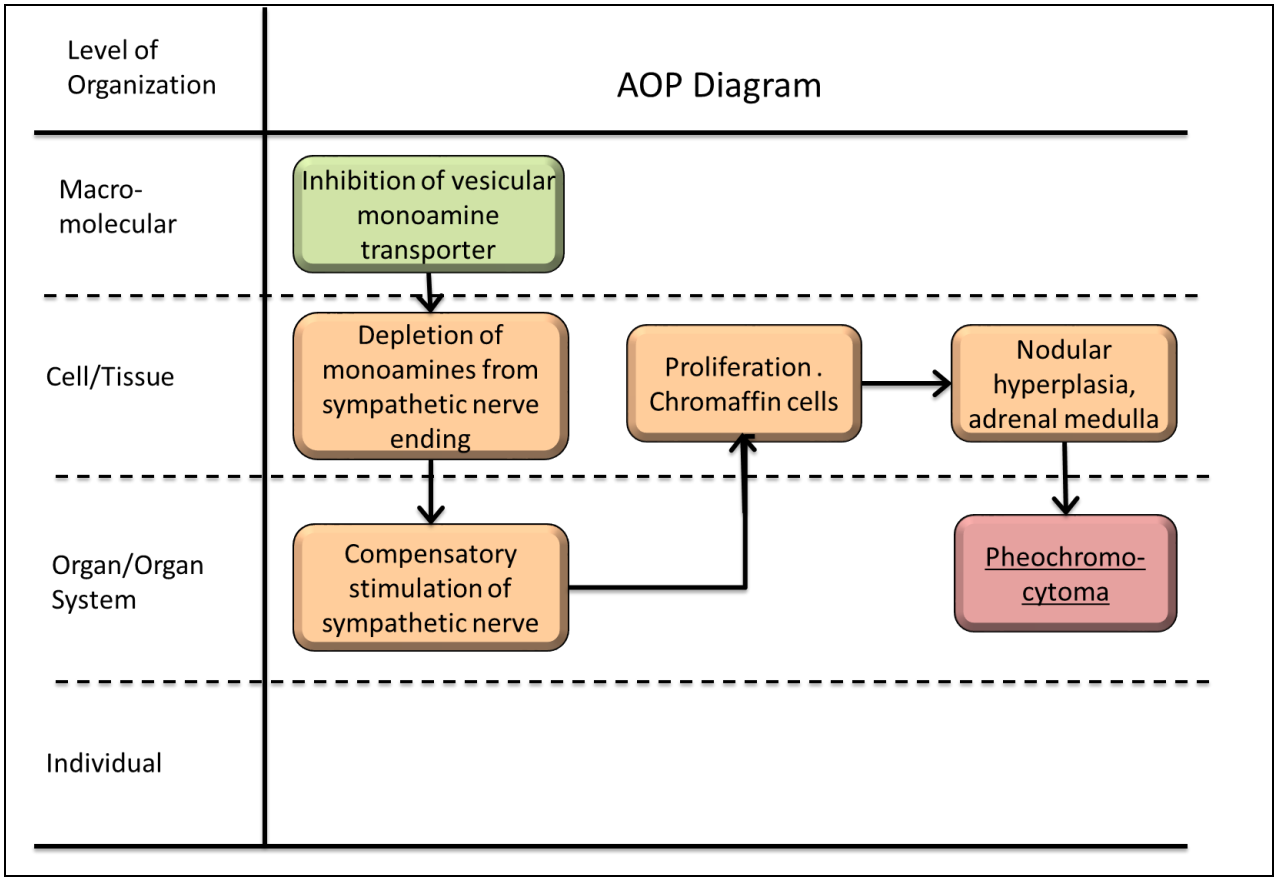


## References


1. 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.
2. Tischler AS, Riseberg JC (1993), Different responses to mitogenic agents by adult rat and human chromaffin cells in vitro. Endocr Pathol 4:15-19.
3. Tischler AS, DeLellis RA, Nunnemacher G, Wolfe HJ (1988), Acute stimulation of chromaffin cell proliferation in the adult rat adrenal medulla. Lab Invest 58:733-735.
4. Tischler AS, Ziar J, Downing JC, McClain RM (1995), Sustained stimulation of rat adrenal chromaffin cell proliferation by reserpine. Toxicol Appl Pharmacol 135:254-257.
5. 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.
6. Natl Toxicol Program Tech Rep Ser 193:1-123 (1982), Bioassay of reserpine for possible carcinogenicity (CAS No. 50-55-5).
7. Tischler AS, Riseberg JC (1993), Different responses to mitogenic agents by adult rat and human chromaffin cells in vitro. Endocr Pathol 4:15-19.