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

Vitamin D3 receptor activation 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 vitamin D3 receptor activation 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 vitamin D3 and its analogues [2, 3]. Vitamin D3 receptor activation by these agents stimulates calcium intake from the intestine and affect osteogenesis, which results in the state of hypercalcemia and altered calcium homeostasis such as increased urinary excretion of Ca^{2+} [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 [4, 5]. The continued enhancement of chromaffin cell proliferation leads to the formation of nodular hyperplasia and following pheochromocytomas [2, 3].

Hypercalcemic condition might increase the influx of Ca^{2+} into the 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 enhance the proliferation of chromaffin cells as well as the synthesis and release of CAs [6, 7].

There are 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 [7]. Therefore, neurogenic factors are less mitogenic to human chromaffin cells and then, hypercalcemia-induced chromaffin cell proliferation in the rat is not applicable to humans. Furthermore, there is no clinical studies showing that vitamin D3-induced hypercalcemia increases the incidence of pheochromocytomas [6].

Consequently, the risk of vitamin D3 receptor activation-induced pheochromocytoma formation in humans deems to be low compared with rodents considering these species differences.

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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).

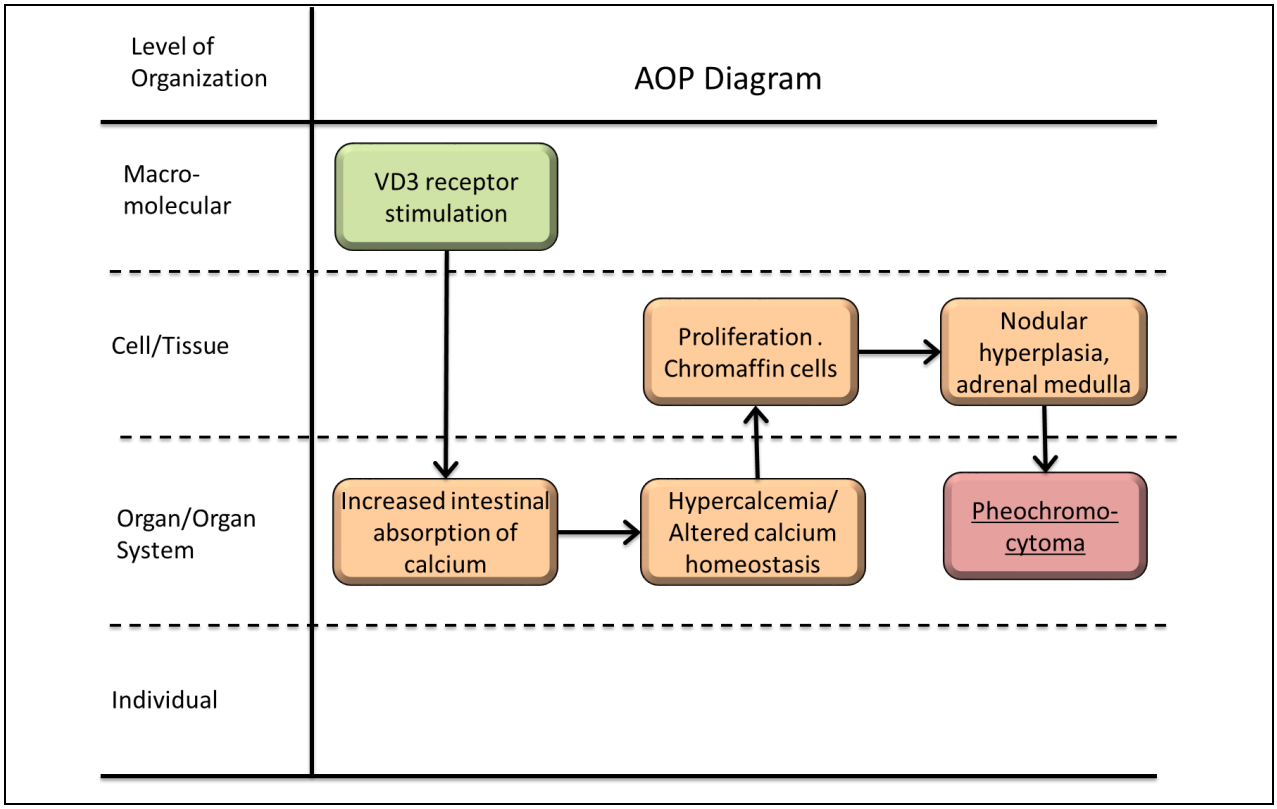
The timeline of the development of the present AOP is as follows:

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 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.
2. Tischler AS, Powers JF, Pignatello M, Tsokas P, Downing JC, McClain RM (1999), Vitamin D3-induced proliferative lesions in the rat adrenal medulla. Toxicol Sci 51:9-18.
3. Ikezaki S, Nishikawa A, Furukawa F, Tanakamaru Z, Nakamura H, Mori H, Hirose M (1999), Influences of longterm administration of 24R, 25-dihydroxyvitamin D3, a vitamin D3 derivative, in rats. J Toxicol Sci 24:133-139.
4. Tischler AS (1999), Cell Proliferation and Neoplastic Progression in the Adrenal Medulla: Insights and Questions from Immunohistochemical Studies Acta Histochemica et Cytochemica 32:121-126.
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.