

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

Activation of TLR 7 leading to psoriatic skin disease

SUBMITTED BY (Country / European Commission / Secretariat)

Japan

DATE OF SUBMISSION TO THE SECRETARIAT

Nov. 30 , 2018

DETAILS OF LEAD COUNTRY/CONSORTIUM

Country/Organisation:	Japan
Agency/ministry/Other:	AOP Working Group, Testing Methodology Committee, The Japanese Society of Immunotoxicology
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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**

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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.

Psoriatic skin disease can occur following the binding of an inducing agent, such as antiviral drugs, to Toll-like receptors (TLR), e.g. binding to TLR7 in the dendritic cells. Activation of TLR7 in dendritic cells (Molecular Initiating Event: MIE) results in dendritic cell maturation and the secretion of IL-23 (Key Event 1: KE 1). IL-23 plays a role in the differentiation of Th17 cells and the secretion IL-22 and IL-17 by these cells (KE 2), which promotes epidermal keratinocyte proliferation (KE 3) and the production inflammatory cytokines leading to psoriatic skin disease (Adverse Outcome: AO). Thus, the IL-23 /IL-17 pathway plays an important role in the disease.

Application of antiviral drugs that stimulate TLRs in mice causes overexpression of IL-22 which results in psoriatic skin disease with epidermal hyperplasia. In patients with psoriasis, IL-22 levels have been reported to be markedly elevated in both the psoriatic lesions and blood. In vitro, human keratinocytes treated with IL-22 undergo hyperproliferation that is accompanied by abnormal terminal differentiation.

We propose an AOP relating to the IL-23 / IL-17 pathway starting from TLR activation and ending to the psoriatic skin disease.

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.

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AOP Working Group of Testing Methodology Committee in the Japanese Society of Immunotoxicology will develop several AOPs for immunotoxicology in the next three years.

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

Nov., 2018: to submit the AOP development

Jun., 2019: to complete AOP Wiki input and submit internal review of the AOP

Dec., 2019: EAGMST review

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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.

