

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

Reduced binding of TH to THR in developing brain cells leads to mental retardation due to alterations in white matter.

SUBMITTED BY (Country / European Commission / Secretariat)

Germany/ Ellen Fritsche

DATE OF SUBMISSION TO THE SECRETARIAT

20.3.2019

DETAILS OF LEAD COUNTRY/CONSORTIUM

Country/Organisation:	Germany/IUF - Leibniz Institute for Environmental Medicine
Agency/ministry/Other:	
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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.

This novel AOP is based on published results on TH promoting maturation of human oligodendrocytes that were differentiated from human neural progenitor cells (NPC; Dach et al. Sci Rep 2017). Co-treatment of maturing mixed cultures with TH and the TH receptor antagonist NH-3 antagonises TH-related oligodendrocyte maturation. Oligodendrocyte maturation was studied by gene expression of myelin basic protein (MBP) upon treatment with TH. It is suggested that TH exerts a direct transcriptional effect on MBP gene expression because a TRE was identified within the MBP promoter (Farsetti et al. JBC 1991). In the Dach et al. (2017) paper, also species and molecular aspects were studied by using NPC from TH receptor deficient animals. Linking this cellular response in vitro to the cell and organ level observed in intracerebral hypothyroid patients in vivo, decreased myelin and alterations in the white matter are amongst the histopathological findings. These children suffer from severe mental retardation showing the functional effect of the disturbed myelination on the organism level. Reduced binding of TH to TH receptors in developing brains can have multiple causes, which would be individual MIEs. Besides competitive antagonism at the TH receptor level, inhibited TH transport across cell membranes involving blockage of TH transporters or disturbed intracellular TH metabolism by interference with deiodinases could be possible MIEs with the common KE of reduced binding of TH to TH receptor in developing brain cells. This putative AOP is related to endocrine disruption (ED) on the developing brain. It concerns developmental toxicity as well as ED.

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.

This project will start immediately. The putative AOP can be filled into the AOP Wiki. Ongoing work uses a recently developed test method (Dach et al. 2017) to assess chemicals' effects on the endpoint TH-dependent human oligodendrocyte maturation, which is probably a common KE from several AOPs. This testing is part of the OECD/EFSA screening project for DNT in vitro. Therefore, the putative AOP is supposed to be recognized in the OECD guidance document on DNT in vitro that is currently prepared by the OECD in collaboration with EFSA, the JRC, Health Canada and the US-/DK-EPA as well as collaborators from academia and industry. With the amount of testing data, the AOP will become stronger. The testing work will end in the 1st quarter of 2020. However, the entry of the putative AOP into the AOP Wiki will be finished within 2019.

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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.

