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

Disrupted laminin-beta1-integrin interaction leading to developmental neurotoxicity

SUBMITTED BY (Country / European Commission / Secretariat)

Germany/ Ellen Fritsche & Spain/Marta Barenys

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:

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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 interference of a compound with laminin thereby disturbing binding of human neural progenitor cells (NPC) via their β1-Integrin receptors to the extracellular matrix protein laminin that causes disturbances of NPC adhesion and thus migration and radial glia cell orientation (Barenys et al. Arch Toxicol 2017). This work also contains species comparisons with rat NPC (rNPC). Recent work confirmed migration effects with the same compound in rNPC of a different strain and tested a variety of the compound's analogues (Kühne et al. Food Chem Toxicol 2019). Studies in conditional β1-integrin deficient (CNS-(nestin-Cre)-b1-integrin-deficient) mice display chaotic radial glia orientation and a deficiency of radial glia to anchor to the pia surface (Graus-Porta et al. Neuron 2001). The phenotype of chaotic glia processes is still maintained ex vivo when nestin-Cre-b1-integrin-deficient cells are transferred into a culture dish (Belvindrah et al. J Neurosci 2007). On the organ level, CNS-(nestin-Cre)-b1-integrin-deficient mice present 'less tightly packed' cells in cortical layers (Graus-Porta et al. Neuron 2001). For the adverse outcome, mice wiht b1-integrin lacking in excitatory neurons show impairment of hippocampus-dependent learning (Warren et al. J Neurosci 2012). These Nex-Cre (itgb1flox/flox Nex-Cre+) mice display a behavioral phenotype; they fail to discriminate between novel and familiar objects in a hippocampus-dependent novel object recognition task (Warren et al. J Neurosci 2012). This hypothetical AOP was previously published as part of a review on AOPs generated from a session at the International Neuroscience Association Meeting in Montreal (Bal-Price et al. 2016).

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 immeditately. The putative AOP can be filled into the AOP Wiki. Ongoing work uses the radial glia migration assay(NPC2, Bal-Price et al. ALTEX 2018) as a test method to assess chemicals' effects on the endpoint migration, 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.