Project proposal, 15–30 hp

**Development of an Adverse Outcome Pathway (AOP) Framework for Monofunctional Alkylating Compounds**

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**Project description**

An Adverse Outcome Pathway (AOP) is a conceptual framework designed to support chemical risk assessment based on mechanistic understanding. The AOP builds a linkage between a chemical interacting with a biological molecule or process, a molecular initiating event, and an adverse health effect. Understanding and mapping of AOPs is important to make systematic use of vast chemical and toxicological data available in the literature, which will aid in risk assessment procedures and regulatory decisions. Data for constructing AOPs can be used from animal experiments, *in vitro* studies, as well as computational approaches, bringing together synthetic knowledge on how chemicals lead to adverse effects and in connecting the key events.

For alkylating chemicals, considered as cancer-risk increasing compounds, amongst the different biological processes that lead to mutation, covalent binding to DNA is regarded as the molecular initiating event. Understanding the reactivity for formation of DNA adducts is therefore one of the key aspects of predicting a possible genotoxic effect. The aim of this project is to summarize literature data and other information that will support the construction of an AOP framework for potentially genotoxic compounds. The focus will be on low molecular weight (˂ 200 g/mol) and monofunctional alkylating compounds. Data will be gathered to provide a relationship between chemical properties, *in vivo* exposure and the key event at the point of biomolecule interaction that is also the molecular initiating event, which will in turn be correlated to relative cancer risk.

*Selected references*:

1. Ankley G.T. et al., 2010, *Environ. Toxicol. Chem.*, 29, 730-441

2. Enoch S.J. and Cronin M.T.D, 2010, *Crit. Rev. Toxicol.*, 40, 728-748

3. OECD (The Organisation for Economic Co-operation and Development), http://www.oecd.org/chemicalsafety/launch-adverse-outcome-pathways-knowledge-base.htm (*2016-02-16*)

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