Master thesis project (30 – 60 hp)

Development of risk assessment procedures for genotoxic compounds using methods with potential to reduce animal experiments

Approaches using biological chemistry are being developed in our group to aid in a paradigm shift from animal testing for cancer risk assessment of genotoxic compounds.[1,2] This can be assisted by the Adverse Outcome Pathway (AOP) framework that is conceptually constructed to portray existing knowledge relevant to risk assessment.[3] The proposed project focuses on genotoxic or cancer-risk increasing compounds, which humans are exposed to via, e.g., occupational exposure (1,3-butadiene) and food (ethyl vinyl ketone), and endogenous sources (ethylene oxide). The project addresses some key features of the AOP that will add useful information for toxicity testing, and has the potential to reduce animal cancer assays. Two cornerstones of the project are the estimation of in vivo dose and prediction of genotoxic potency of the studied compounds. A case study structure to validate the use of the generated data (cf. Specific aims below) in a biological read across setting will be used, so that the approaches can be applied going forward for new structures where no in vivo data is available.

The student will obtain experience in biochemical methods, mass spectrometry, in vitro metabolism using liver homogenate and risk assessment principles. The project is in collaboration with Swetox, Södertälje.

Specific aims:

i. To obtain in vitro metabolic rates of some potentially genotoxic compounds in rodent and human.

ii. To estimate the in vivo dose of genotoxic compounds from the metabolic parameters and pharmacokinetic modelling.

iii. To estimate genotoxic potencies of the concerned compounds relative to a well-studied genotoxic compound, e.g. ethylene oxide, by reaction-kinetic characterization and by structure activity relationship studies.

References

1. Motwani HV, Törnqvist M, 2014, Toxicol. Appl. Pharmacol., 281, 276-284.

2. Silvari V, Haglund J, Jenssen D, Golding BT, Ehrenberg L, Törnqvist M., 2005, Mutat. Res., 580, 91-101.

3. OECD Environment, Health and Safety Publications, 2013; Series on testing and Assessment No. 184. Guidance document on developing and assessing adverse outcome pathways.

Supervisors

Hitesh Motwani (hitesh.motwani@aces.su.se) and Daniel Mucs (daniel.mucs@swetox.se)