scaht
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Framework for the SCAHT Research Programme 2021-2024

"Advancing pathway-based toxicology for future human health risk assessment"

The purpose of this document is to provide a framework for guiding project formulation in order to increase the relevance of research output of SCAHT-funded research to regulatory science and future decision-making. The starting point of project formulation should be the desired output and formulating the research questions should result from this.

Goals and objectives of the SCAHT Research Programme

The strategic research programme is focused on toxicological issues relevant to human health protection and addresses important data gaps in the human safety assessment of chemicals from all regulatory sectors.

The 2021 – 2024 research programme comprises 5 core projects looking at steroid alteration and male fertility, occupational exposure to endocrine disruptors, xenobiotics disrupting the corticosteroid-androgen balance, neurotoxicity of solvents, and bioanalytical & metabolomic readouts for toxicology.

To complement its existing research competences and to broaden its scientific network, the SCAHT is making funds available for specific research projects which represent a meaningful enhancement of the existing core research areas of the 2021 – 2024 research programme. Thematically, project proposals should fit into one of the following categories: Toxicology and female-specific diseases, Developmental Neurotoxicity (DNT), mixtures, substances of concern and their replacement.

Conceptual model

Projects should be **anchored in human adverse outcomes on topics of relevance to future regulation** and this could be conceptualized by organizing the activity along one or more of three principal lines of inquiries. The first line has a shorter-term perspective by focusing on generating data fit for use in human health risk assessment. The two other lines support the advancement of next generation risk assessment[1] by contributing to the OECDs adverse outcome pathways (AOP) framework for future regulatory use, in the medium to long-term perspective:

1. **Investigation of toxicodynamic dose-effect relationships of chemicals of concern to human health**

   The purpose is to conduct targeted investigations into dose-effect relationships of potentially harmful chemicals and use modeling tools to link biological effects with internal and external exposure levels. *In vitro* concentrations that trigger a response should be compared to a biologically effective dose at an *in vivo* target by applying modeling tools. Projects should address the kinetics of selected compounds, including first pass metabolism, as well as the

[1] Next Generation Risk Assessment (NGRA) can be defined as an exposure-led, hypothesis-driven risk assessment approach that integrates in silico, in chemico and in vitro approaches. For background information please refer to Krewski D, et al. A framework for the next generation of risk science. Environ Health Perspect. 2014 Aug;122(8):796-805. doi: 10.1289/ehp.1307260.

dynamic biological effects of the compounds (and their relevant metabolites) in potential target tissues.

Output: Tools (e.g. fit-for-purpose in vitro models, PBTK/IVIVE models) that allow evaluation of biological effects in relation to exposure levels.

Better integration of exposure and toxicity by providing an understanding of doses relevant to potential effects on human health.

2. **Advancing the quantitative understanding of existing adverse outcome pathways (AOP)**

The scope is to develop tools allowing quantitative understanding of (already endorsed) AOPs. Focus should lie on building an understanding of the thresholds required for a pathway to progress from one key event (KE) to the next, moving the understanding from a qualitative to a quantitative level. This would require the use of relevant and reliable test systems (*in vitro* or *in vivo*) and, as in *line of inquiries n°1*, including modeling expertise at the core of the project.

Output: Advancement of the AOP-framework (Effectopedia) for future quantitative risk assessment.

3. **Elucidating toxicity pathways and generating data in support of AOP development.**

The aim is to advance the development of AOPs and elucidate mechanisms of toxicity leading to specific human adverse outcomes. Projects should in a focused way apply state-of-the-art technologies to elucidate the dynamic effects on biological systems. Inquiries should either focus on further description of KEs and KE Relationships (KERs), or apply tools to discover toxicity pathways/mechanisms of action of data-poor compounds (potential synergies with the compounds chosen in *line of inquiries n°1* should be explored). The data generated should support the improvement of existing, or the development of new qualitative AOPs (AOP Wiki).

Output: Expansion and development of the qualitative AOP framework through pathway discovery.

Disease-based focus areas

All projects should seek **anchoring in a potential human adverse outcome** related to a disease area. The two-following disease-based areas were identified of interest by the SCAHT: effects on reproduction, and effects on the nervous system.