EU-ToxRisk workshop – "NAM-Supported Read-Across: From Case Studies to Regulatory Guidance in Safety Assessment"

Executive Summary & Objectives

Depending on regulatory field or purpose, like for instance screening or prioritization, risk assessment involves the use of hazard and exposure information. Specific risk assessment strategies for cosmetics, chemicals, pesticides, or biocides are necessary to account for suitability and limitations of test systems, models, and hazard assessment methods.

Read-across (RAX) is a valuable means to fill data gaps for complex toxicological endpoints without the use of test animals. Toxicological data from compounds with certain structural / physicochemical properties can be used to help predict toxicological endpoints from similar compounds that lack these data. But for RAX to be reliable, biological similarity has to be accounted for as well. New approach methods that describe toxicokinetic and toxicodynamic properties can be deployed to establish scientifically reliable and robust read-across.

The **overall aim** of the workshop is to collect expert scientific and regulatory feedback on various read-across scenarios to serve as input to a regulatory guidance document for NAM-supported RAX for the broader toxicology community, containing guidance on applications in different regulatory contexts.

To facilitate discussion, the EU-ToxRisk consortium will provide **a draft outline** of a guidance document. This outline will contain the main elements of a typical read-across workflow and pinpoint where in the workflow NAMs may support the RAX argument.

The **modus operandi** of the workshop is, through plenary and parallel case study breakout discussions, to identify where and how NAMs can support a RAX problem formulation, identify areas that contain data-gaps, and suggest how these gaps can be filled.

To ensure a common understanding of key concepts, EU-ToxRisk proposes the following terminology:

New Approach Methods (NAMs) encompass novel *in vitro* methodologies, like for example high-throughput screening and high-content imaging methods, along with *in silico* methods, like QSAR and PBPK modelling, that are used not only for data generation, but also data interpretation and integration.

Read-across (RAX) describes a category or analogue approach as defined in the Read-Across Assessment Framework (RAAF) (ECHA, 2015).

Compounds with relevant *in vivo* data are named **source compounds**, whereas the compounds that lack *in vivo* data are named **target compounds**.

Category approach refers to a grouping in which data from many source compounds are used to predict the hazard of one target compound ("many-to-one read-across") or many target compounds (many-to-many read-across). Properties of compounds within such category may follow a consistent trend. **Analogue approach** refers to the prediction from one-to-one or one-to-many target compounds.

Within a read-across problem formulation, endpoint data of source compounds are used to estimate the same endpoint for the target compound in a qualitative and quantitative way.

This project has received funding from the European Union's Horizon 2020 Research and Innovation programme under Grant Agreement no. 681002.