Position paper on « read across » by FRANCOPA

In recent years, the EU REACH regulation on chemicals and the EU regulation 1223/2009 on cosmetics have brought to the forefront the prediction of toxicity from chemical structure and properties and prompted the implementation of free dedicated tools such as the OECD (Q)SAR Toolbox and the QSAR platform VEGA. Among all the possible predictive methods that are based on structural analogies, the use of read-across to fill data gaps is an approach that is explicitly cited by the Annex XI of the REACH regulation and that has been used in other regulatory frameworks.

The "read-across approach" assumes that human health effects and environmental effects can be predicted as a function (usually by interpolation) of the experimental toxicities that characterise chemicals that are deemed to be similar to the chemical with known structure but unknown toxicity.

The data analysis performed by ECHA after the first registration deadline (30th of November 2010) confirmed the established role of read-across predictions as an alternative to experimental testing. Indeed, data gap filling by read-across was the most common method adopted by registrants in order to fulfil data requirements. Because of the regulatory relevance of the use of read-across, FRANCOPA (the French platform dedicated to the development, validation, and dissemination of alternative methods in animal testing.), the SPTC ("Société de Pharmaco-Toxicologie Cellulaire") and the SFT (« Société Française de Toxicologie ») co-organized a conference dedicated to the use of read-across on the 15th of November 2013 in Paris. Presentations were performed by international experts on "read across": Steven Enoch (John Moore Liverpool University); Tatiana Netzeva (ECHA); Enrico Mombelli (INERIS); Emilio Benfenati (Istituto di Ricerche Farmacologiche Mario Negri) and users of "read across" in different contexts (food regulation, pesticides, chemicals) (Isabelle Gaou, ARKEMA; Georges Kass, EFSA; Antony Fastier, ANSES). The day ended with a round table discussion at the end of which the following conclusions were reached:

- Substantiating read-across predictions is more time-consuming than usually expected. Indeed, most observers and FRANCOPA consider that, among all the methods that are based on structural analogies (e.g. statistically validated Quantitative Structure Activity Relationships), read-across approaches have to be especially supported by a mechanistic rationale that justifies the adopted criteria for similarity; They also have to be supported by toxicokinetics assessment that would identify both analogous metabolites likely to cause adverse effects and similar fates in the organism, especially when systemic effects are cosidered. The work on skin sensitization carried out by the FRANCOPA research working group showed that, once read-across is correctly substantiated (i.e. identification of pertinent structural analogs thanks to similarity and mechanistic considerations), it becomes particularly relevant.

- Usually, QSAR tools are used when a sufficient number of substances can enable their calibration and validation whereas the use of read-across is used to resolve cases when there are a few substances only with a substantial amount of information per substance. The possible synergy between these two methods tends to be overlooked. Nevertheless, it is worth noting that the use of read-across can provide a critical assessment of the reasoning that underlies the algorithm of QSAR models thanks to a visual inspection of the structural analogs that determine the predictions. Moreover, the parallel application of read-across permits a local and specific inspection of the chemical space that surrounds the chemical of interest and such an inspection could reveal local inconsistencies of QSAR

models. Finally, it also important to point out that the possibility of carrying out a visual inspection of the structural analogs identified by QSAR models, facilitate exchanges between QSAR modelers and non-specialists. For this reason, FRANCOPA supports initiatives such as the European project CALEIDOS, coordinated by Emilio Benfenati, that targets an enhanced understanding and regulatory acceptance of QSAR models while providing fully transparent QSAR models that facilitate the parallel assessment of read-across and QSAR predictions.

As a conclusion, read across remains a relevant approach. Criticisms arose from a use that has been too intensive and not rigorous enough. In response to these criticisms, FRANCOPA both supports the emergence of guidelines and clear rules of acceptance, especially through the efforts of clarification and help by ECHA, so as the initiatives to enhance the read-across approaches through a synergy with other methods.