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# INTEGRATING QSAR AND READ ACROSS FOR ENVIRONMENTAL ASSESSMENT

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Read across and QSAR have different traditions. Recently these approaches have been often discussed together. They are called non-testing methods, and are more and more used within regulatory frameworks. There are two main issues to be addressed: 1) how to take advantage of the results of both approaches, to reinforce relative results? 2) how to solve the issue of the subjectivity of the evaluation of the results, which may be particularly critical for read across, but may have a role also for the QSAR assessment?

Several of the modern QSAR programs include tools to visualize chemicals in the training and/or test sets, in order to evaluate the model's reliability. Since they show the most similar compounds, they can be also used for read across.

The approach of the QSAR model starts from a large population of chemicals, and the assessment can focus on the target chemical. The presence of similar chemicals with property values close to those predicted by the model can support the final assessment of the result.

The read across approach is the opposite. The assessment is focused on the few substances similar to the target compound. The strength and the limitation of read across rely on this: if the quality and quantity of data on similar chemicals is enough, this will represent a very sound basis; if this is not the case, there is the risk of wrong results, or read across is not applicable. Indeed, a major risk in the case of read across is that the quality of the property data of the similar compounds may be low.

Another risk is the poor standardization in the definition of "similarity". There is a high level of subjectivity in the definition of similarity, because different "reasons" to screen chemicals may be applied. Ideally, the logical process to identify the similar compounds should be transparent and explained. The choice should be done on the basis of the different possibilities and reasons explained. Inspired by the principles of high transparency and reproducibility, a new program for read across, called ToxRead, has been developed and made freely available (www.toxgate.eu). This program lists rules applicable to the target chemical, indicates the statistical characteristics of these rules, and shows the most similar chemicals which obey to that rule. A graph represents the rules, the similar compounds and their links. This provides a clear way to the expert to make reasoning, take decisions, and explain their basis. An interlaboratory exercise on the use of the programs for read across demonstrated that users gave highly reproducible answers assessing the same chemicals.

This opens the way to a deeper integration between the results of QSAR models and read across. Indeed, there are three different levels of the possible integration of these two approaches.

1) The first level is the extent of agreement between the results. Of course, if there is good agreement, it is easy to get a decision, but problems may arise in case of conflicting results.
2) The transparency, and documentation which some modern programs offer can provide valid support useful to evaluate the reliability of the individual results, and thus to take a decision in case of conflicting results. The weight assigned to each result can be established on that basis. This increases the flexibility in the integration of the results of the two approaches.
3) Besides the evaluation of the individual result, some modern programs open new ways to reciprocally support the results from QSAR and read across. QSAR is often criticized as a black-box approach, since it operates at the abstract level of descriptors, not always easily related to simple reasoning. However, linking read across to QSAR provides the practical examples of chemicals obeying to the QSAR algorithms. Conversely, the visualization of rules in the case of read across allows reaching an abstraction level which generalizes the examples of the individual chemicals.

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