

Use of analogues and read-across in risk assessment

Fact sheet series: Topics in risk assessment of substances under the *Canadian Environmental Protection Act, 1999* (CEPA)

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Addressing data needs through read-across

Read-across is one approach frequently used in the risk assessment of substances that lack information on their physical-chemical or toxicological properties, or their environmental fate. For more information, refer to the [Approaches for addressing data needs in risk assessment](#) fact sheet. It involves using experimental or model data from structurally similar substances (analogues) to predict the behaviour of a substance being assessed (the target substance). The approach is based on the assumption that substances which are structurally similar will have reasonably similar physical-chemical properties, behave similarly, and elicit similar toxic effects.

Most commonly, read-across is used to fill data needs when particular information is lacking for the target substance. However, it can also be useful as another line of evidence for verifying or validating experimental data that are available. When planning research on substances, consideration of which substances are suitable analogues for the target substance can help in prioritizing and streamlining testing strategies.

Read-across approach

In the read-across approach, information on a given property or endpoint for one or more analogues is used to predict (read-across) the property or endpoint for the target substance under assessment that is lacking this information. Different analogues may be selected for read-across to different properties of the same target substance. Read-across is most frequently used to estimate toxicity of a substance, but may also be used

to provide estimates for bioaccumulation, degradation, physical-chemical properties, or to identify potential uses of the target substance.

It is also possible to use a category approach, in which data sets from one or multiple analogue substances are used for read-across within a substance's structural or functional category. A structural substance category consists of multiple target substances that are structurally similar and have been grouped for assessment because their toxicological and physical-chemical properties are reasonably similar or follow a regular pattern. A functional substance category consists of substances that may be dissimilar in terms of structure but have a similar mode of action (meaning that they affect a cell or organism in the same way). The properties of individual substances within a category that are missing information are assessed on the basis of the evaluation of the category as a whole .

Selection of analogues

The identification of suitable analogues for read-across of information requires a number of considerations including similarity in structural features, physical-chemical properties, and if available, reactivity, kinetics (absorption, distribution, metabolism, excretion), and information from other endpoints or routes. Determining what constitutes sufficient similarity is important, as small changes in the structure of a substance may cause significant changes in behaviour.

When selecting an analogue, consideration needs to be given to the specific property or endpoint for which it will be used. For example, a good analogue for degradation may not be an acceptable analogue for toxicity. As another example, an analogue that is acceptable for an acute toxicity endpoint (such as mortality) may not be suitable for a chronic effect (such as carcinogenicity).

There are several steps that are typically followed when selecting analogues for use in an assessment.

1. **Search for potential analogues:** Databases may be searched based on structural similarity to the target substance (or substance category) to identify potential analogues for which experimental data are available.
2. **Compare structures:** Potential analogues are then closely compared to the target substance to determine if they have similar molecular weights and common functional groups, elements, or fragments, and what influence these may exert on the endpoint of interest.
3. **Compare physical-chemical properties:** If the analogue is proposed for toxicity endpoints or environmental fate properties, the next step is to compare any known physical-chemical properties of the analogue and target substance such as water solubility and vapour pressure. These properties influence the fate and bioavailability of a substance in the environment and within organisms, and as such can also be important in determining whether 2 substances are likely to have similar toxic effects.

4. **Consider metabolism / degradation pathways:** Comparison of any available information on the metabolic or degradation pathways is also helpful in selecting analogues. Examining the rates of absorption, distribution, metabolism and excretion can also indicate whether 2 substances are likely to have similar toxicity.
5. **Compare toxicity, degradation and bioaccumulation:** A comparison of any other available toxicity and environmental fate information should also be made between a prospective analogue and the target substance. This may include a comparison of data generated through models or in vitro tests for toxicity, degradation or bioaccumulation. For experimental data, consideration should be given to whether the route of exposure (such as through ingestion or contact with the skin) used in the analogue study is relevant for the target substance.
6. **Accept or reject analogue:** Taking into account all of the above comparisons and considerations, one or more analogues that are suitable for read-across for a specific property or endpoint(s) are selected.
7. **Apply read-across for accepted analogue:** Once 1 or more analogues are selected, the next step is to apply the read-across data to fill the data need. The read-across information may be qualitative or quantitative. For example, qualitative read-across could be a yes or no indication as to whether the target substance is expected to elicit a particular effect, as observed with the analogue(s). With quantitative read-across, a numerical value is obtained for a particular property or endpoint based on information available for the analogue(s). This may be done through direct read-across, where the endpoint value for the analogue (or the average from several analogues) is assumed to be the same for the target substance. Alternatively, a value for the target substance may be calculated by scaling the experimental values for similar analogues based on trends seen over the range of chemical structures. For example, the toxicity of a substance with a particular chain length might be estimated to fall in between those of an analogue with a slightly shorter chain length and another analogue with a slightly longer chain length.
8. **Document uncertainties:** When a read-across approach is used in a risk assessment, any uncertainties concerning the suitability of the analogue(s) are considered in the weight of evidence and are clearly documented in the assessment report. Using the steps outlined above, multiple lines of comparison are considered in selecting an analogue. This leads to greater certainty in the read-across and in the overall assessment conclusions.

In summary, the use of read-across information contributes to the weight of evidence and reduces uncertainty in an assessment. It can also provide verification or validation of other data and potentially identify where there are needs for further testing.