# The Read-Across Assessment Framework and REACH

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## Introduction

**Grouping of substances and read-across approach (read-across) is an adaptation according to Annex XI, Section 1.5. of the REACH Regulation[1], and this adaptation is extensively used in REACH registration dossiers. The European Chemicals Agency's (ECHA) Guidance on read-across illustrates the potential scientific complexity of read-across[2] and ECHA must evaluate read-across cases in different processes and at different stages. ECHA has developed a Read-Across Assessment Framework (RAAF)[3] to increase transparency and consistency in evaluation of read-across.**

## Read-across

REACH provides the possibility to adapt a standard information requirement (for a test) by read-across (Annex XI, Section 1.5.). Whereas the Registrant is responsible for building the case, ECHA and the Member States are responsible for evaluation of the read-across. Article 13 provides "*In particular for human toxicity, information shall be generated whenever possible by means other than vertebrate animal tests, through the use of alternative methods, …*".

In 2014, it was reported that on the basis of the 2013 and earlier registrations, the most common and widely used alternatives are building categories and predicting properties by read-across. Up to 75% of the analysed dossiers contain read-across at least for one endpoint (2014; see Figure 1)[4].

## Read-across and Annex XI, Section 1.5.

In REACH, the legal basis for read-across is set out in Annex XI, 1.5.

- Read-across starts with structural similarity
- Common structural elements may lead to the claim that a particular property(ies) can be predicted for a target substance
- However, such a claim cannot be supported by only considering the structure(s) of source and target
    - Very similar substances can have very different effects: what about the differences in the structures?
    - Why does a particular structural similarity allow the read-across for the property under consideration?
- A mechanistic hypothesis is required that connects the structures with the toxicological basis for prediction.

A wide spectrum of possible scientific arguments and different types of data can be used to justify read-across. Consequently, a broad range of expertise is required for the assessment of such read-across cases. Experts may bring different viewpoints and the reasons for these different viewpoints needs to be transparent. The assessment needs to be organized in such a way that consistency is guaranteed for the relevant aspects of the read-across.

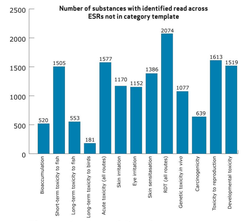




***Figure 1: Use of Read-across***

For dossiers submitted before the 2013 deadline, this shows the number of endpoint study records which have read-across by endpoint[4].


## How does the RAAF work?

The RAAF builds a structure of generic (toxicological) knowledge that is relevant for read-across; the first version of the RAAF is focussed on human health. The assessment framework is embedded in this structure. The structure directs and guides the assessing expert by posing relevant questions and suggesting possible answers. The outcome of the RAAF is whether the read-across is scientifically acceptable or not.

The RAAF defines different scenarios for different read-across approaches. The respective scenarios are selected and applied to the proposed cases (see Table 1). Each scenario is associated with particular aspects (assessment elements, AEs) that are deemed crucial to the assessment (see Table A1). Each AE poses questions which lead an assessing expert to select pre-defined conclusions (assessment options, AOs). The AO conclusion show whether there is sufficient confidence in a that particular scientific aspect.

The selected assessment options reflect the strengths and weaknesses of the read-across, and so, its acceptability. Figure 2 shows an example of the assessment options.

It is a scientific framework; it needs to be handled flexibly and to answer the questions posed may require substantial expertise. The RAAF documents do not cover how RAAF is implemented in ECHA's processes nor to describe how the shortcomings identified in the scientific assessment are evaluated in the course of dossier evaluation under REACH.

## Conclusions

**ECHA has developed a RAAF, which structures expert judgement, so that the criteria for expert opinions on which regulatory decisions are based are transparent and can be applied consistently. The RAAF increases transparency on how ECHA assesses read-across cases and provides registrants with a focus to assess and improve their cases. The RAAF will lead to an improved and consistent ECHA assessment of read-across cases.**

***Table 1: Overview for scenario selection***

To select the applicable RAAF scenario for assessment, one must identify the type of approach applied, i.e. analogue approach or category approach, identify the read-across hypothesis used and, for category approaches, consider whether quantitative variations in the effect(s) are observed among the category members.

| Overview for scenario selection | | | |
|---|---|---|---|
| **Scenario** | **Approach** | **Read-across hypothesis based on** | **Quantitative variations** |
| 1 | Analogue | (Bio)transformation to common compound(s) | Effect(s) of the target substance predicted to be quantitatively equal to those of the source substance or prediction based on a worst-case approach. |
| 2 | Analogue | Different compounds have the same type of effect(s) | Effect(s) of the target substance predicted to be quantitatively equal to those of the source substance or prediction based on a worst-case approach. |
| 3 | Category | (Bio)transformation to common compound(s) | Variations in the strength of effect(s) observed among source substances. Prediction based on a regular pattern or on a worst-case approach. |
| 4 | Category | Different compounds have the same type of effect(s) | Variations in the strength of effect(s) observed among source substances. Prediction based on a regular pattern or on a worst-case approach. |
| 5 | Category | (Bio)transformation to common compound(s) | No relevant variations in strength of effects observed among source substances and the same strength predicted for the target substance. |
| 6 | Category | Different compounds have the same type of effect(s) | No relevant variations in strength of effects observed among source substances and the same strength predicted for the target substance |

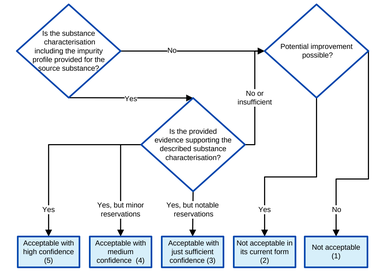
***Table A1: Assessment elements for scenario 1***

The assessment elements (AEs) for this scenario consist of four AEs common to the analogue-approach and five scenario-specific AEs which depend on the mechanistic explanation.

| ASSESSMENT ELEMENTS (AEs) FOR SCENARIO 1 | | |
|---|---|---|
| **AE #** | **AE type** | **AE title** |
| AE A.1 | Common | Characterisation of source substance |
| AE A.2 | Common | Link of structural similarity and differences with the proposed prediction |
| AE A.3 | Common | Reliability and adequacy of the source study |
| AE 1.1 | Scenario-specific | Formation of common (identical) compound(s) |
| AE 1.2 | Scenario-specific | The biological targets for the common compound(s) |
| AE 1.3 | Scenario-specific | Exposure of the biological target(s) to the common compound(s) |
| AE 1.4 | Scenario-specific | The impact of parent compounds |
| AE 1.5 | Scenario-specific | Formation and impact of non-common compounds |
| AE A.4 | Common | Bias that influences the prediction |

***Figure 2: Assessment options for 'Characterisation of source substance' in Scenario 1***

The substance, which is used as the source substance , needs to have a clear substance characterisation. It has to be assessed whether (a) the chemical identity of the analogue is sufficiently clear for a meaningful assessment of the proposed read-across; and (b) the impurity profile is clear. The current AE only looks at the basic information, which allows the comparison of chemical structures to start.




## References

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