

Read-Across Assessment Framework (RAAF)



Disclaimer

This document is not to be considered as guidance on REACH. Grouping of substances and read-across can be used as an adaptation of the standard information requirements under REACH and they are further explained in the relevant Guidance documents by the European Chemicals Agency (ECHA). This document is intended to provide an overview of the Read-Across Assessment Framework (RAAF) used by ECHA to assess read-across approaches when encountered in registration dossiers with respect to documentation and scientific justification. However, readers are reminded that the text of the REACH Regulation is the only authentic legal reference and that the information in this document does not constitute legal advice. ECHA does not accept any liability with regard to the contents of this document.

Read-Across Assessment Framework (RAAF)

Reference: ECHA-15-R-07-EN
Cat. number: ED-04-15-203-EN-N
ISBN: 978-92-9247-361-7
Dol: 10.2823/546436
Date: May 2015
Language: English

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1. Introduction

'Read-across and grouping', or 'read-across', is one of the most commonly used alternative approaches for data gap filling in registrations submitted under the REACH Regulation. Read-across entails the use of relevant information from analogous substances (the 'source' information) to predict properties for the 'target' substance(s) under consideration.

The conditions under which 'Read-across and grouping' can be used to adapt the standard testing regime are listed in Annex XI, 1.5 of the REACH Regulation. It has to be ensured that prediction of a property based on read-across is reliable, can be used for risk assessment and/or classification and labelling, and complies in general with the provisions in REACH for the substance under consideration.

Registrants are obligated to consider and, where they can, use appropriate alternative approaches to fulfil applicable REACH information requirements concerning vertebrate animal studies. If read-across which meets the information requirements is applied, unnecessary animal testing may be avoided as there will be no need to carry out one-by-one testing of all their substances to fulfil the information requirements.

Methods for building read-across cases are already described in ECHA guidance and other publications. The present document describes, for the first time, a systematic method to assess whether such cases are compliant under REACH.

ECHA is therefore in the process of codifying a systematic approach to assessing those read-across cases that are encountered in its dossier evaluation activities. This systematic approach is called 'The Read-Across Assessment Framework', or RAAF. The RAAF provides a framework and guidance for consistent evaluation of the scientific aspects of a proposed read-across case, resulting in an output which is suitable for subsequent regulatory consideration of the read-across case. The approach reflects both a need to consider toxicological principles underpinning the application of read-across and experience gained from dossier evaluation in the context of the REACH information requirements. As such, the scientific principles it contains are already being applied to cases under evaluation. In developing this approach, ECHA also sought to accommodate a wide range of views and expertise from stakeholders at workshops held in 2012 and 2014.

This resulting document now describes publicly, for the first time, the RAAF when applied to the REACH information requirements concerning human health. In this context, different read-across approaches are described in the form of "scenarios". The scenarios thereby categorise the type of read-across approach used to allow a systematic assessment of the crucial scientific aspects. Each 'scenario' comprises different 'assessment elements', which address different scientific considerations deemed crucial to judge the validity and the reliability of read-across. A read-across case is appraised against each of the respective assessment elements. The appraisal is then used to inform decision-making.

The RAAF is primarily designed for use by experts in ECHA to facilitate consistent assessment of read-across encountered during dossier evaluation. It is however also made available publicly to facilitate improvements in the use of read-across by experts developing read-across cases and alternative approaches aimed at fulfilling the requirements of the REACH Regulation.

Further improvement of the RAAF as well as further extension to other areas are foreseen. From the experience gained from its application in decision making under the REACH Regulation, use of the RAAF approach for environmental properties, as well as specific considerations in the assessment of UVCBs/multi-constituent substances are currently under development.

2. Scope of the document

This document describes the first version of the Read Across Assessment Framework (RAAF) developed by ECHA as an internal tool for the examination of predictions, based on read-across, of the human health properties of chemical substances in the context of the REACH Regulation. The aim of this document is to present the concept and principles underpinning the RAAF.

The RAAF provides a framework and principles for the scientific examination of a read-across case, as well as setting out the critical scientific elements of a read-across case to be assessed. However, the RAAF does not cover all scientific issues or cases, and expert judgement must be used when applying this framework. It is emphasised here that the RAAF focuses on the scientific aspects of the examination of read-across approaches and is intended to be used by experts.

It is not a purpose of this document to address the way the 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.

3. Background and definitions

The practice of predicting properties of chemicals is established in regulatory science, and improved techniques are evolving as scientific knowledge develops and is applied to this field. In view of the widespread use of the term read-across in different regulatory schemes and for different purposes, there is a need to clarify what read-across means under REACH.

Therefore, this section explains concepts and terminology for grouping of substances and read-across under REACH. Please note that the context of this scientific examination is set out by the REACH legal text, particularly Annex XI, 1.5, and that the following background and definitions serve to explain the approach followed in the RAAF.

3.1 WHAT IS GROUPING OF SUBSTANCES?

Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or 'category' of substances. Structural similarity is a pre-requisite for any grouping and read-across approach under REACH. These similarities may be due to a number of factors:

- Common functional group (i.e. chemical similarity within the group),
- Common precursors and/or likelihood of common breakdown products via physical and/or biological processes which result in structurally-similar degradation products (i.e. similarity through (bio)transformation), or
- A constant pattern in the changing of the potency of the properties across the group (i.e. of physico-chemical and/or biological properties).

3.2 WHAT IS READ-ACROSS?

The application of the grouping concept described above means that REACH information requirements for physicochemical, human health and/or environmental properties may be predicted from information

from tests conducted on reference substance(s) within the group, referred to in this document as source substance(s), by interpolation to other substances in the group, referred to as target substance(s), and this is called read-across.

Thus, in principle, read-across is regarded as a technique for predicting endpoint information for one substance (target substance), by using data from the same endpoint from (an)other substance(s), (source substance(s)). The word “endpoint” has different meanings depending on the context in which it is used and so can lead to misunderstandings. In the context of the REACH information requirements, endpoints are listed in column 1 of the standard information requirements (Annex VI to X) and are described either as a property itself (e.g. skin irritation) and/or as a type of study (e.g. carcinogenicity study).

Other hazardous properties of a substance partially/not covered by the column 1 information requirements (e.g. immunotoxicity) may also be relevant to understanding the hazards and risks a substance may present. Due to the different complexities (e.g. key parameters, biological targets) of each endpoint, a read-across must be specific to the endpoint or property under consideration. In the context of this document, preference is given to the term “property”, which is used to describe the outcome of a relevant study used to fulfil a REACH information requirement.

The term ‘analogue approach’ is used when read-across is employed between a small number of structurally-similar substances; there is no trend or regular pattern on the properties. As a result of the structural similarity, a given toxicological property of one substance (the source) is used to predict the same property for another substance (the target) to fulfil a REACH information requirement. The outcome of a study conducted with the source substance is read-across for all investigated parameters to the target substance. A worst-case approach may also be used. In the context of the RAAF as describe in this document, the simplest case of an analogue approach is considered: read-across from a single source substance to a target substance. If an analogue approach uses more than one source or target substance, the assessment of the read-across approach has to be repeated for each source and/or target substance.

The term category approach is used when read-across is employed between several substances that have structural similarity. These substances are grouped together on the basis of defined structural similarity and differences between the substances. As a result of the structural similarity, the toxicological properties will either all be similar or follow a regular pattern. Predictions should cover all parameters as required in the respective REACH information requirements. It may be possible to make predictions within the group for the target substance(s) on the basis of a demonstrable regular pattern. Alternatively, whenever there is more than one source substance in the category and no regular pattern is demonstrated for the property under consideration, the prediction may be based on a read-across from a category member with relevant information in a conservative manner (worst case). The basis for the prediction must be explicit.

In the context of read-across, a worst-case approach means that the strength of effect(s) in the target substance is actually expected to be lower than the strength of effect(s) observed for the source substance; hence using the value obtained from the source substance, the prediction constitutes a worst case that will not lead to an underestimation of the effect(s) that would be observed in a study with the target substance if it were to be conducted. Scientific explanations for such situations may be based on kinetic considerations (e.g. evidence for differences in bioavailability) or on potency considerations (e.g. evidence that structural features lead to a higher potency for the source substance).

Under REACH, any read-across approach must be based on structural similarity between the source and target substances. However, structural similarity alone is not sufficient to justify the possibility to predict property(ies) of the target substance by read-across. A read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological property is possible and should be based on recognition of the structural aspects the chemical structures have in common and the differences between

the structures of the source and target substances. The possibility for predictions of similar properties should be linked to the common structural aspects. The differences in the chemical structures should not influence the toxicological properties or do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Under REACH, registrants are required to submit a complete dossier with specific information complying with REACH information requirements. For each information requirement, registrants must indicate explicitly whether they are making an adaptation using read-across, and they must provide a comprehensive justification for the use of a read-across approach.

The justification for read-across which is provided in the dossier is the documentation that will be assessed using the RAAF. ECHA evaluates the documentation which is provided in the dossier, and does not undertake extra analysis or research to further develop the scientific justification that would be insufficient or the supporting documentation that would be incomplete.

4. The Read-Across Assessment Framework

4.1 OVERVIEW OF THE RAAF

The RAAF has been developed by ECHA as an internal tool providing a framework for a consistent and structured assessment of grouping and read-across approaches under REACH.

The RAAF, as presented in this document, is designed to assess read-across approaches used to predict REACH-relevant properties related to human health hazard identification for mono-constituent substances. While the RAAF was designed to encompass the approaches most frequently encountered during the evaluation of registrations submitted to ECHA, each read-across case is unique. Therefore, the RAAF is intended to be understood as a living framework for analysis, rather than a series of steps to be followed mechanically. Deviations from the indicative framework are possible depending on the case being analysed. Note that there are a number of circumstances where the RAAF does not apply, e.g. for UVCBs. Nonetheless, the RAAF sets out a framework for analysis which may be applied in an analogous manner in such cases.

Use of the RAAF ensures that crucial scientific aspects of the read-across are evaluated. Application of the RAAF results in a structured assessment, which recognises the strengths of the read-across and identifies possible shortcomings in documentation, scientific reasoning and/or supporting evidence. The outcome of the assessment is a conclusion on whether the read-across is scientifically acceptable or not.

Under the RAAF, the assessment of read-across approaches is conducted through the use of scenarios, assessment elements and assessment options. To support assessment, detailed explanations of each scenario are supported with examples and these are provided in the scenario specific sections.

The initial examination of a prediction based on read-across is performed in a preparatory assessment followed by a detailed scientific assessment.

The scientific assessment according to the RAAF is divided into scenarios to account for the most frequently applied read-across approaches observed in REACH registration dossiers. Different scenarios are designed to distinguish analogue approaches from category approaches and are based on the types of read-across hypotheses typically submitted to ECHA.

It is necessary to select the most appropriate scenario to be used for the assessment as each scenario comprises a series of dedicated assessment elements (AEs) which represent crucial scientific aspects of the individual scenarios to be addressed during the assessment. The RAAF therefore leads the assessing expert to judge on the scientific validity of the approach for each AE of the selected scenario. To indicate their conclusion on the adequacy and scientific robustness of the information provided in the dossier for the AE under consideration the assessing expert selects one of a predefined set of assessment options (AOs). The reasons for selecting the AO needs a justification from the assessing expert.

The outcome of the read-across assessment is established on the basis of the conclusions derived for all of the AEs.

A separate assessment should be conducted for each information requirement intended to be fulfilled by the read-across approach.

4.2 PREPARATORY ASSESSMENT

The preparatory assessment addresses pre-conditions that have to be considered before the scientific assessment of the read-across under the RAAF can be conducted.

The pre-conditions covered in the preparatory assessment are:

- Substance identity of the registered substance

A fundamental aspect of read-across is structural similarity. Chemical composition, including structural information should be well defined. In addition, other constituents of a substance (e.g. impurities) can have a significant impact on the hazard of a substance. Unambiguous substance identity both for the target and the source substances is therefore a prerequisite for read-across assessment. In the preparatory assessment, the identity of the registered substance (i.e. the target substance of the read across approach) is checked against the requirements on substance identity as defined under REACH Annex VI. If the requirements on substance identity are not met, the identity of the target substance needs to be clarified before the assessment of the read-across can be conducted; and

- Documentation of the read-across

The documentation provided needs to be sufficient to allow a scientific assessment. The ECHA Guidance on information requirements and chemical safety assessment Chapter R.6 – QSARs and grouping of chemicals lists the elements that need to be included in the documentation of read-across approaches. Unless comprehensive documentation has been provided, the scientific assessment is not possible and this is a basis to reject the read-across.

4.3 DESCRIPTION AND SELECTION OF THE SCENARIOS

4.3.1 Description on the scenarios

Once the pre-conditions presented above are satisfied, the most appropriate “scenario” used as the basis for assessment needs to be selected to address the appropriate scientific aspects of the case. The scenarios differ as they reflect different types of read-across approaches¹.

Firstly, there is a need to distinguish whether it is an analogue or category approach (see section 3.2 above).

Secondly, to identify the correct scenario there is a need to identify the basis of the read-across hypothesis. Two options are foreseen and are described as follows:

1. (Bio)transformation to common compound(s):

The read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed. The common compound may be the unchanged form of one of the parent substances and the (bio)transformation product of the other substance. The common compound may also be a (bio)transformation product formed from both substances. The common compound(s) solely determine the type of effect (qualitative) as well as its strength (quantitative) observed in the study(ies) with the source substance(s) and predicted for the target substance(s). A prerequisite of this explanation

¹ Some read-across explanations may use multiple different scenarios to justify the read-across; in this case, each of the different scenarios must be analysed.

is that non-common compound(s) (e.g. parent substance, impurities, other metabolites that are formed) do not have an impact on the prediction of the toxicological property. This read-across hypothesis can also be used to predict the absence of effects.

2. Different compounds have the same type of effect(s):

The read-across hypothesis is that the organism is not exposed to common compounds but rather, as a result of structural similarity, that different compounds cause the same type of effects. These compounds may be the source and target substances themselves or one or more of their (bio) transformation products. It is explained, on a mechanistic level, why the same type of effects are expected although the test organism is exposed to different compounds. This read-across hypothesis can also be used to predict the absence of effects.

Thirdly, for a category approach, there is a need to further take account of whether or not quantitative variations in the effects are observed among the category members. Hence, this document describes a total of six scenarios: two for analogue approaches and four for category approaches. A description of each scenario is provided below and summarised in table 1. These broad descriptions are explained further with examples in the scenario-specific sections of this document.

Scenario 1

This scenario covers the analogue approach for which the read-across hypothesis is based on (bio) transformation to common compound(s). For the REACH information requirement under consideration, the effects obtained in a study conducted with one source substance are used to predict the effects that would be observed in a study with the target substance if it were to be conducted. The same type of effect(s) or absence of effect is predicted. The predicted strength of the effects may be similar or based on a worst case.

Scenario 2

This scenario covers the analogue approach for which the read-across hypothesis is based on different compounds which have the same type of effect(s). For the REACH information requirement under consideration, the effects obtained in a study conducted with one source substance are used to predict the effects that would be observed in a study with the target substance if it were to be conducted. The same type of effect(s) or absence of effect is predicted. The predicted strength of the effects may be similar or based on a worst case.

Scenario 3

This scenario covers the category approach for which the read-across hypothesis is based on (bio) transformation to common compound(s). For the REACH information requirement under consideration, the effects obtained in studies conducted with different source substances are used to predict the effects that would be observed in a study with the target substance if it were to be conducted. The same type of effect(s) are observed for the different source substances; this may include absence of effects for some members of the category. There are differences in strength of the effect(s) forming a regular pattern. The prediction is based either on this regular pattern within the category, when the members are ordered by a variable related to the structural differences in the category, or on a worst-case approach. The scientific explanation has to include the reason why differences in strengths of effects are observed/predicted.

Scenario 4

This scenario covers the category approach for which the read-across hypothesis is based on different

compounds which have the same type of effect(s). For the REACH information requirement under consideration, the effects obtained in studies conducted with different source substances are used to predict the effects that would be observed in a study with the target substance if it were to be conducted. The same type of effect(s), are observed for the different source substances; this may include absence of effects for some members of the category. There are differences in strength of the effect(s) and they may form a regular pattern. The prediction is based on the regular pattern within the category, when the members are ordered by a variable related to the structural differences in the category, or on a worst-case approach. The scientific explanation has to include the reason why differences in strengths of effects are observed/predicted.

Scenario 5

This scenario covers the category approach for which the read-across hypothesis is based on (bio) transformation to common compound(s). For the REACH information requirement under consideration, the effects obtained in studies conducted with different source substances are used to predict the effects that would be observed in a study with the target substance if it were to be conducted. The same type of effect(s), are observed for the different source substances; this may include absence of effects for every member of the category. No relevant differences in strengths of effect(s) are observed for several source substances.

Scenario 6

This scenario covers the category approach for which the read-across hypothesis is based on different compounds which have the same type of effect(s). For the REACH information requirement under consideration, the effects obtained in studies conducted with different source substances are used to predict the effects that would be observed in a study with the target substance if it were to be conducted. The same type of effect(s) are observed for the different source substances; this may include absence of effects for every member of the category. No relevant differences in strengths of effect(s) are observed for several source substances.

Note: Scenarios 3 and 5 are based on the same category hypothesis, i.e. (bio)transformation to common compound(s), but differ in the way the strength of the predicted effect(s) is related to the strength of the effects described for the source substances. The regular pattern observed for the source substances which is used for the prediction may be based on variations in the strength of the effects (scenario 3) or in the absence of such variations (scenario 5). The approach taken in the assessment of the scientific aspects addressed in the AEs slightly differs to account for the presence or absence of variation in the strength of the predicted effect(s) and warranted the distinction of these situations in two scenarios. Similar considerations apply to scenarios 4 and 6. The need for distinguishing these scenarios may be re-assessed in the future.

Table 1: 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.

4.3.2 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. The diagram below illustrates the scenario selection.

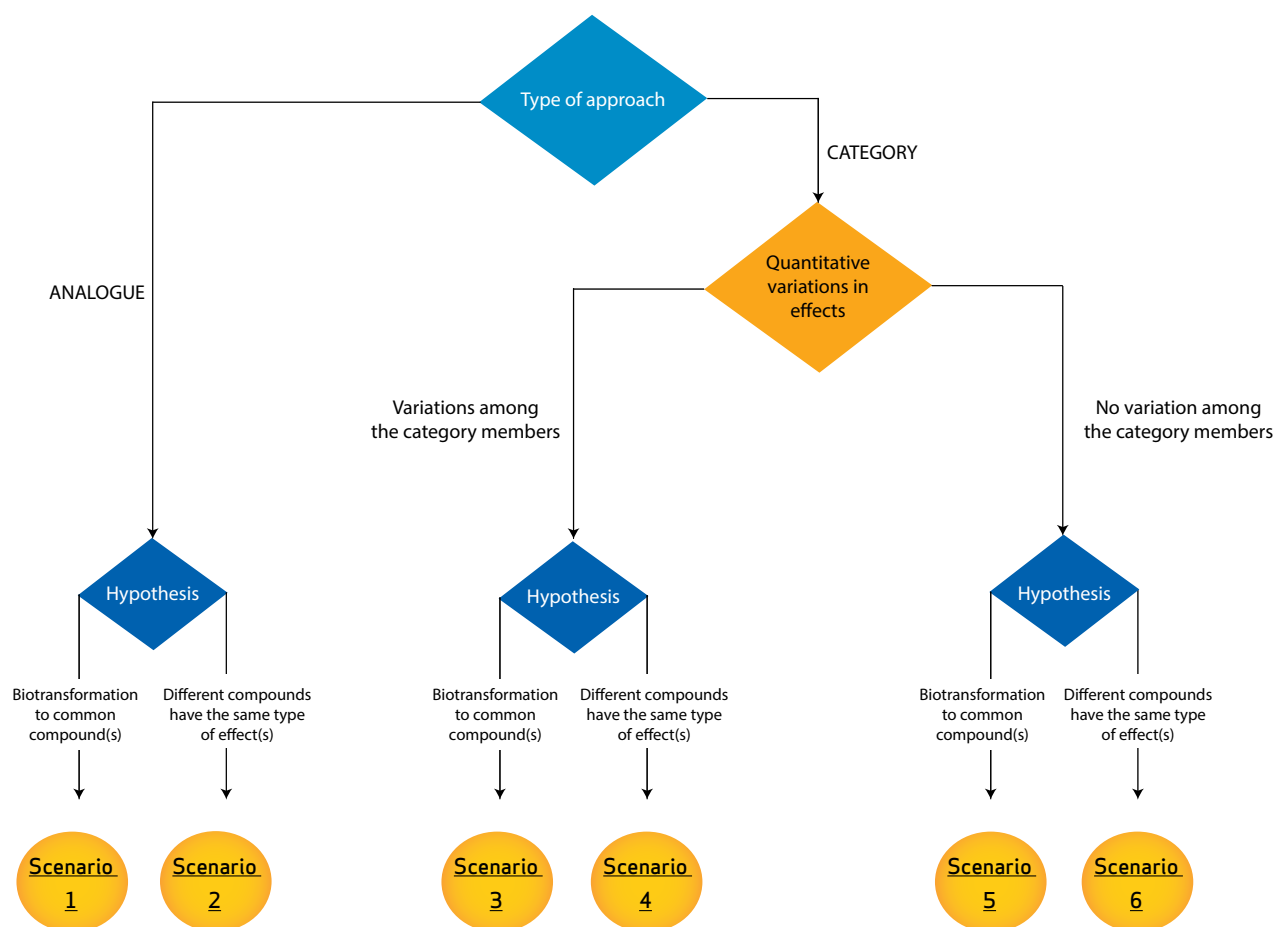


Figure 1: Schematic presentation of the scenario selection

4.4 SCIENTIFIC ASSESSMENT

4.4.1 General considerations

4.4.1.1 Assessment elements and assessment options

Each scenario consists of a pre-defined set of assessment elements (AEs) that, when taken together, cover all of the essential scientific aspects that need to be addressed in the read-across approach for a particular scenario.

It therefore follows that all AEs allocated to the scenario must be considered when assessing a read-across approach under the RAAF. The AEs have also been formulated in such a way that the assessment does not stop if, for one AE, it is concluded that the information provided is not acceptable or not sufficient. All AEs assigned to the scenario are assessed for each scenario. It may be noted also that within the AEs some are common to either analogue approaches or category approaches.

Each AE reflects a critical scientific aspect of a read-across to be assessed and consists of a number of questions to be answered. To understand how AEs are formulated, and before describing these more fully

below, it is helpful to first understand the possible outcomes of the consideration of the read-across against an AE.

After examination using the questions posed in the AE, the conclusion on the adequacy and scientific robustness of the information provided in the dossier for the AE is reflected by the selection of one assessment option (AO) from a predefined set of assessment options. The set of AOs is presented in Table 2 below. The selection of a specific AO for a given AE needs to be justified by the assessing expert.

For specific cases, some AE might not apply. Then the outcome of the assessment of this specific scientific issue will be recorded as “*not relevant*”.

Table 2: Overview of Assessment Options (AOs)

SCORES	AOs	MEANING OF THE AOs
5	Acceptable with high confidence	Acceptance without reservations in the scientific explanation and documentation addressing the scientific aspects of the AE.
4	Acceptable with medium confidence	Acceptance with minor reservations about the scientific explanation and documentation addressing the scientific aspects of the AE.
3	Acceptable with just sufficient confidence	Acceptance with notable reservations. Minimum level of confidence in the scientific explanation provided in the documentation and addressing the scientific aspects of the AE.
2	Not acceptable in its current form	Acceptance for the AE under consideration may become possible if improved explanations and/or supporting evidence is made available by the registrant.
1	Not acceptable	A major flaw in the approach for the AE under consideration which is not expected to be resolved by the addition of supporting information.

The general structure of the decision logic used in most of the AEs is similar and is based on two principal questions:

1. has the scientific aspect of the AE been addressed in the documentation?
2. has supporting evidence been provided?

Each AE is accompanied by technical explanatory information and examples illustrating the theme of the AE to further support the assessment. The full set of AEs and accompanying information is presented in annexes A to F.

An AE starts with the yes or no answer to the question on whether the scientific aspect of the AE has been addressed. If the answer to that first question is yes, an assessment of the adequacy and robustness of the scientific reasoning and of the supporting evidence provided is carried out. Where the combination of the

scientific explanation and supporting evidence sufficiently addresses the scientific aspect addressed in the AE, the assessing expert indicates their conclusion by selecting one of the following AOs: “Acceptable with high confidence”, “Acceptable with medium confidence” or “Acceptable with just sufficient confidence”.

The outcome “Acceptable with just sufficient confidence” is reached if the evidence provided does not adequately address all of the aspects covered by the AE. The possible reasons for this are:

- a) only a few data, but considered acceptable on the basis of available theoretical reasons
- b) experimental data appear strong, but available theoretical reasons leads to doubts
- c) experimental data only partially support the read-across hypothesis but do not contradict it.

If the supporting evidence is insufficient, not provided or is regarded as contradicting the read-across hypothesis, the scientific aspect of this AE is regarded as being not sufficiently addressed in the read-across justification. This situation leads to the evaluation of possibilities for improvement and ends in the selection of the AOs “not acceptable in its current form” or “not acceptable”.

A negative answer to the first question leads to a negative outcome for this AE. Nevertheless, a decision can be made on whether the approach may be improved, leading to the selection of the AO “not acceptable in its current form”, or whether improvement is considered not possible and the AO selected for the AE is “not acceptable”.

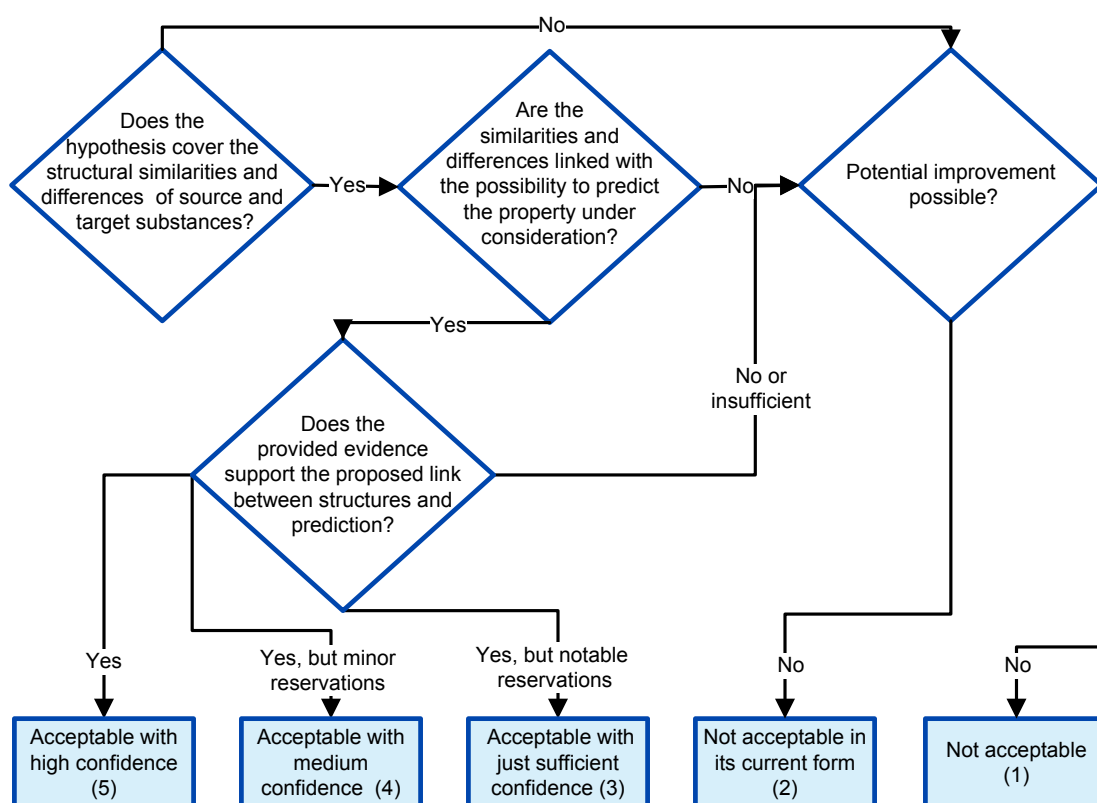


Figure 2: Example of the decision logic within an AE – Extracted from AE 1.1 Formation of common (identical) compound(s)

The outcome of a read-across assessment performed according to the RAAF is a conclusion on whether the read-across approach is scientifically acceptable. This proposal is reached by considering the set of individual AOs obtained for each of the AEs in the applied scenario and results in an overall conclusion. All AEs for a scenario are regarded as critical and all of the resulting AOs have to be taken into account. In general, for a read-across approach to be acceptable, all of the AEs for the applied scenario will require an AO of “Acceptable with high confidence”, “Acceptable with medium confidence”, or “Acceptable with just sufficient confidence”. The overall assessment is expressed in a conclusion identifying the strengths and weaknesses of the read-across approach and includes an opinion on whether the read-across approach is scientifically acceptable.

4.4.1.2 Prediction of absence of effects

In principle, it is possible to predict the presence or absence of a property/effect by applying the read-across approach. For a prediction of the absence of effects, typically there will be no mechanistic insight available which would support such a claim. The absence of effect(s) may however be explained by the absence of exposure of the biological target(s) or the lack of biological interaction leading to an adverse outcome. These situations need to be addressed in the read-across hypothesis and read-across justification in the case of a prediction of the absence of effects.

The RAAF, as currently designed, applies to both the prediction of effects or prediction of absence of effects by means of read-across by using identical sets of assessment elements and options. The RAAF highlights aspects of particular relevance to the themes of the different AEs when assessing a prediction of absence of effects.

4.4.1.3 Supporting evidence

The supporting evidence is considered as an essential part of the read-across justification. Due to the diversity of cases, the toxicological property under consideration and the range of possible explanations, it is not possible to provide rules for the type of supporting evidence which would be required to support a particular read-across hypothesis.

Supporting evidence may range from theoretical considerations or expert systems, to results from in vivo or in vitro studies. For many cases, toxicokinetic data constitute valuable supporting evidence. Often quantitative information is needed.

In vitro, in chemico and in silico studies (e.g. computational tools such as Derek, Meteor, OECD QSAR Toolbox) may increase the robustness of a case, but are not usually sufficient as stand-alone information.

If potency differences are proposed to be the reason for observed differences in strength of effects, quantitative data explaining the mechanism are valuable. The data matrix also constitutes a source of supporting evidence. Even in the simplest case, such as when two analogues are considered, a data matrix can be constructed to outline consistency of information within a given scenario.

Consistency does not necessarily mean absence of quantitative variations in the effects (or absence of effect(s)) for all substances and for all properties. The analysis of the information presented in the data matrix should support the read-across hypothesis. Contradictions should be absent. Anchor studies for the target substance are of specific importance. For instance, to predict the effects of, for example, a pre-natal developmental toxicity study, the availability of a reproductive/repeat dose toxicity screening study conducted with the target substance is valuable. The same applies for predictions of effects in other repeated dose toxicity studies.

Each of the AEs of the RAAF also assesses whether evidence supporting the read-across hypothesis for the aspect under consideration has been provided. All types of supporting evidence provided are considered when conducting an assessment according to the RAAF. A property-specific read-across hypothesis is always required. Information on other properties than the one to be predicted (i.e. derived from the data matrix) is not sufficient to justify a read-across approach without a property-specific read-across hypothesis.

4.4.1.4 Weight of evidence approaches

Annex XI, section 1.2 of the REACH Regulation provides the possibility to use a weight of evidence approach to adapt the standard information requirements under REACH. In contrast, read-across is an alternative method for the identification of hazards and the fulfilment of standard information requirements. The RAAF therefore is not concerned with the examination of weight of evidence approaches relying on Annex XI 1.2.

However, a read-across approach may be included as one line of evidence in a weight of evidence argumentation. In this case, the prediction based on read-across is assessed according to the RAAF. The result of the assessment is then used together with the assessment of the other weight of evidence arguments in determining whether the adaptation complies with the requirements of Annex XI 1.2.

4.4.1.5 Bias

Bias may be introduced in read-across by, for example, incorrect/incomplete selection of source substance(s) or due to a particular selection of source study(ies). Bias may be important if it would materially affect the prediction.

To increase the transparency in this regard, it is useful if it is clear from the documentation how the source substance(s) have been chosen, for example, what methods/tools have been used to map the field of potential source substance(s), which other substances have been considered and why they have been discarded.

The RAAF contains a dedicated assessment element to consider such potential bias. The bias may be apparent from the supporting documentation or it may be apparent from additional information that the assessing expert may have which may contradict the prediction.

4.4.2 Analogue approach

In the context of the framework described in this document, the simplest case of the analogue approach was considered: read-across from a single source substance to a single structurally similar target substance. This essential one-to-one character of analogue-approach read-across means that the prediction of properties relies essentially on the structural similarity between the source and target substances and on the read-across hypothesis.

4.4.2.1 Common assessment elements for analogue approaches

ECHA has identified AEs which apply to both types of analogue approach irrespective of the read-across hypothesis which is used and which must be addressed i.e. they are the same when applied to either scenarios 1 or 2. These AEs address the following aspects of the analogue approach and are presented in detail in annexes A and B. The list below contains the purpose of the AE and does not reflect all aspects considered in a specific AE.

AE A.1 Identity and characterisation of the source substance

Structural similarity is a pre-requisite for any prediction based on read-across under REACH. To assess the structural similarity between the source and the target substances, the identity and characterisation of both substances needs to be clear. Assessment of the substance characterisation of the target substance has been addressed already at the preparatory assessment step described in section 4.2. This AE investigates whether the identification and characterisation of the source substance, including its impurity profile, are sufficient for a scientific assessment of the read-across approach.

AE A.2 Link of structural similarities and differences with the proposed prediction

This AE checks whether the read-across hypothesis and justification establish the structural similarities and differences of the source and target substances and whether these similarities and differences are linked with the possibility to predict similar properties.

AE A.3 Reliability and adequacy of the source study

The source study needs to comply with the default REACH requirements for any key study in terms of adequacy and reliability. This AE addresses the adequacy and reliability of the study design for the source study to fulfil the information requirement, investigates whether the test material used represents the source substance as described in the read-across hypothesis, e.g. in terms of purity and impurities and whether the study results are adequate for the purpose of classification and labelling and/or risk assessment.

AE A.4 Bias that influences the prediction

The selection of the source substance is a critical aspect in an analogue approach and may introduce bias in the prediction of the property under consideration for the target substance.

This AE assesses the extent to which it is clear from the documentation how other structurally similar substances have been considered as potential source substances and generally whether other structurally similar substances could be used as alternative source substances. The AE addresses whether information available on these substances would result in a difference in the prediction of the properties under consideration for the target substance.

This AE also assesses whether the source study used as the basis for the prediction corresponds to the study giving rise to the highest concern for the property under consideration.

Table 3: Overview of the analogue common AEs (scenarios 1 and 2)

AE A.1	Identity and characterisation of the source substance
AE A.2	Link of structural similarities and differences with the proposed prediction
AE A.3	Reliability and adequacy of the source study
AE A.4	Bias that influences the prediction

4.4.2.2 Scenario 1

Description

This scenario covers the analogue approach for which the read-across hypothesis is based on (bio) transformation to common compound(s). For the REACH information requirement under consideration, the effects obtained in a study conducted with one source substance are used to predict the effects that would be observed in a study with the target substance if it were to be conducted. The same type of effect(s) or absence of effect is predicted. The predicted strength of the effects may be similar or based on a worst-case approach.

Examples

Disclaimer: The examples provided below are intended to provide high level illustrations of situations corresponding to this scenario. They do not provide the comprehensive set of circumstances and supporting evidence required to adequately document a read-across approach.

Example 1 - The common (identical) compound formed from both the target and source substances.

The source substance AY and the target substance AZ are structurally similar substances which are rapidly and extensively absorbed after administration. Both substances are (bio)transformed in the same tissue/organ to the common compound A and to the non-common compounds Y and Z.

The common compound A is solely responsible for the (absence of) effects. The (bio)transformation of the parent substances is rapid and extensive and therefore, only no/negligible systemic exposure to them occurs. Exposure to the non-common compounds Y and Z does not influence the prediction of the property under consideration. The effects of the target substance AZ are predicted to be equal to the effects of the source substance AY for the property under consideration.

	PARENT SUBSTANCES	(BIO)TRANSFORMATION	COMMON COMPOUND	NON-COMMON COMPOUNDS
SOURCE	AY	AY → A + Y	A	Y
TARGET	AZ	AZ → A + Z	A	Z

Example 2 - The common compound is the unchanged form of the source substance and a (bio)transformation product of the target substance.

The source substance A and the target substance B are structurally similar substances which are rapidly and extensively absorbed after administration. Substance A is not (bio)transformed. Substance B is rapidly and extensively (bio)transformed to substance A, and therefore no/negligible systemic exposure to substance B occurs. The source substance A is the common compound in this analogue approach. The common compound A is solely responsible for the (absence of) effects. The effects of the target substance B are predicted to be equal to the effects of the source substance A for the property under consideration.

	PARENT SUBSTANCES	(BIO)TRANSFORMATION	COMMON COMPOUND	NON-COMMON COMPOUNDS
SOURCE	A	A -> not transformed	A	-
TARGET	B	B -> A	A	-

Scenario 1 specific assessment elements

The scientific aspects addressed in the scenario 1 specific AEs are presented below. The complete set of information attached to each AE is presented in Annex A. The list below contains the purpose of the AE and does not reflect all aspects considered in a specific AE.

AE 1.1 Formation of common (identical) compound(s)

In this scenario, the common (bio)transformation compound(s) are claimed to influence the considered property alone. This AE covers only the formation of the common compound(s), irrespective of their effects. The focus of the AE is on the scientific explanation and documentation on how the (bio)transformation from source and target substances to the common compound(s) occur.

AE 1.2 The biological targets for the common compound(s)

The read-across hypothesis under scenario 1 claims that the common compound(s) have the same biological target(s) and hence cause the same effects.

This AE investigates how the (bio)transformation of source and target substances to the common compound(s) results in the exposure of the same biological target(s) and whether the same type of effects are caused in the same biological targets by the common compound(s).

AE 1.3 Exposure of the biological target(s) to the common compound(s)

Under this scenario, it is expected that the exposure of the biological targets to the common compound(s) is similar for source and target substances.

This AE focuses on whether the justification with regard to the similar exposure of the biological targets to the common compound(s) is established.

AE 1.4 The impact of parent compounds

(Bio)transformation of parent compounds, i.e. target and source substances, may not be immediate and/or complete. As a result, exposure of possible biological targets to the parent compounds may occur for source and/or target substances. Similarly, exposure to impurities of the source and/or target substances may occur.

This AE investigates whether the systemic availability (for local targets the exposure at the site of contact

has to be considered) of the parent compounds as well as of their impurities has been assessed and whether their impact on the prediction of the property under consideration has been addressed.

AE 1.5 Formation and impact of non-common compounds

The formation of common compound(s) often goes together with the formation of non-common compound(s) and/or potential intermediates during the formation of the common compound(s). Source and/or target substances can also be (bio)transformed by other pathways than the one involved in the formation of the common compound(s), leading to additional non-common compounds.

This AE examines whether non-common compounds (including possible intermediates) are formed by the common (bio)transformation pathway or other pathways and whether their possible impact on the property under consideration have been considered.

Table 4: Overview of the Scenario 1 - specific AEs

AE 1.1	Formation of common (identical) compound(s)
AE 1.2	The biological targets for the common compound(s)
AE 1.3	Exposure of the biological target(s) to the common compound(s)
AE 1.4	The impact of parent compounds
AE 1.5	Formation and impact of non-common compounds

4.4.2.3 Scenario 2

Description

This scenario covers the analogue approach for which the hypothesis is based on different compounds which have the same type of effect(s). For the REACH information requirement under consideration, the effects obtained in a study conducted with one source substance are used to predict the effects that would be observed in a study with the target substance if it were to be conducted. The same type of effect(s) or absence of effect is predicted. The predicted strength of the effects may be similar or based on a worst-case approach.

Examples

Disclaimer: The examples provided below are intended to provide high level illustrations of situations corresponding to this scenario. They do not provide the comprehensive set of circumstances and supporting evidence required to adequately document a read-across approach.

Example 1 - Exposure to different compounds cause the same effects via common underlying mechanism.

The source substance A and the target substance B are structurally similar substances which are rapidly and extensively absorbed after administration and not (bio)transformed. The exposure to A and B causes same

types of (absence of) effects via a common mechanism. The strength of effects of the target substance B are predicted to be similar to the effects of the source substance A for the property under consideration.

	PARENT SUBSTANCES	(BIO)TRANSFORMATION	COMMON COMPOUND	NON-COMMON COMPOUNDS
SOURCE	A	A -> not transformed	A	-
TARGET	B	B -> not transformed	B	-

Example 2 - Exposure to different compounds, which are (bio)transformed and cause the same effects via common underlying mechanism.

The source substance A and the target substance B are structurally similar substances which are rapidly and extensively absorbed after administration and (bio)transformed to substances A1 and A2 and B1, respectively. Due to rapid and extensive (bio)transformation, only no/negligible systemic exposure to parent compounds A and B occurs. The exposure to A1 and to B1 causes the same type of (or absence of) effects via a common mechanism. Exposure to A2 does not influence the prediction of the property under consideration. The effects of target substance B are predicted to be equal to the effects of source substance A for the property under consideration.

	PARENT SUBSTANCES	(BIO)TRANSFORMATION	COMMON COMPOUND	NON-COMMON COMPOUNDS
SOURCE	A	A -> A1 + A2	A1	A2
TARGET	B	B -> B1	B1	-

Scenario 2 specific assessment elements

The scientific aspects addressed in the Scenario 2 specific AEs are presented below. The complete set of information attached to each AE is presented in Annex B. The list below contains the purpose of the AE and does not reflect all aspects considered in a specific AE.

AE 2.1 Compounds the test organism is exposed to

Under Scenario 2, it is claimed that exposure to different compounds causes the same effects or absence of effects for the property under consideration.

This AE examines whether the compounds to which the test organism is exposed after administration of the

source and the target substances have been identified.

AE 2.2 Common underlying mechanism, qualitative aspects

The read-across hypothesis should explain how exposure to different compounds causes the same effects or absence of effects. A common mechanism linking the presence of the compounds driving the effects with the prediction needs to be identified, and should also link the structures of the compounds under consideration with the possibility to predict qualitatively similar effects for the target substance.

This AE examines whether a common underlying mechanism is established and if this allows the prediction of a similar type of effects, qualitatively.

AE 2.3 Common underlying mechanism, quantitative aspects

Under this scenario, no quantitative differences of biological significance should be observed for the effects caused through the common underlying mechanism.

This AE investigates whether it has been established that the common underlying mechanism leads to the same quantitative outcome for source and target substances with regard to the prediction of the property under consideration.

AE 2.4 Exposure to other compounds than to those linked to the prediction

Other compounds than those linked to the prediction in the read-across hypothesis may be formed via other (bio)transformation pathways or may be intermediates/metabolites of the identified pathway. Exposure to impurities of the source and/or target substance may also occur. Exposure to these compounds has to be considered in the justification.

This AE investigates the possibility that compounds other than those linked to the prediction are formed (e.g. via other (bio)transformation pathway, as intermediates or as impurities of the source/target substance). It is also assessed whether indications are available that such compounds could influence the prediction of the property under consideration.

AE 2.5 Occurrence of other effects than covered by the hypothesis and justification

Besides the common mechanism claimed to drive the toxicity, other mechanism(s) than addressed by the read-across hypothesis may be acting.

This AE investigates whether different effects described in the toxicological profiles of source and/or target substances would suggest the presence of other acting mechanism(s). This AE also examines the doses at which the effects triggered by these other mechanisms occur and whether their impact on the prediction is addressed sufficiently in the read-across justification.

Table 5: Overview of the Scenario 2 - specific AEs

AE 2.1	Compounds the test organism is exposed to
AE 2.2	Common underlying mechanism, qualitative aspects
AE 2.3	Common underlying mechanism, quantitative aspects
AE 2.4	Exposure to other compounds than to those linked to the prediction
AE 2.5	Occurrence of other effects than covered by the hypothesis and justification

4.4.3 Category approach

In a category approach, read-across is used among a number of structurally similar substances. Within this category, as a result of the structural similarity, the physico-chemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern.

A category approach with several data points for one specific property should increase the confidence in the prediction of this property for one member of the category compared to a prediction based on one source substance alone. Within a category, different prediction models can be used: a prediction can be based on the observation of a regular pattern (i.e. quantitative variation of the predicted effect(s) in a predictable manner) for the property under consideration or all group members can be predicted to have the same (absence of) effects. A worst-case approach may also be used to predict properties of category members. It is to be noted that different prediction models may be used to predict different properties within a category.

The basis for forming a category should be established using the similarity rules specified in Annex XI of the REACH Regulation and further elaborated in Chapter R.6 of the REACH Guidance on information requirements and chemical safety assessment.

The category definition should define what characteristics a chemical should have to belong to the category and should outline the substance exclusion rules. The category definition should also include a category hypothesis presenting the rationale according to which the human health properties of the target substance may be predicted from data for reference substance(s) within the category by interpolation.

4.4.3.1 Common assessment elements for category approaches

The assessment of category approaches in the context of the RAAF examines the rationale for forming the category. It also investigates the robustness and adequacy of the category hypothesis. A set of AEs applicable to all category approaches, i.e. category common AEs, ensures a consistent assessment of such category approaches. AEs focusing on specific aspects of the category hypothesis are applied in addition to the category common AEs to assess the robustness and the validity of the category hypothesis. In principle, each prediction of a property for a single target within a category requires a separate assessment.

These category common AEs are presented below. The complete set of information attached to each AE is

presented in annexes C to F. The list below contains the purpose of the AE and does not reflect all aspects considered in a specific AE.

AE C.1 Substance characterisation

The substances which are grouped in a category need to be clearly identified and characterised.

This AE assesses whether the chemical identity and the impurity profile of each category member are sufficiently detailed for a scientific assessment of the category approach.

AE C.2 Structural similarity and differences within the category

There should be no doubts on the aspects of the chemical structure shared by all the category members and on the aspects of the chemical structures for which differences are allowed.

This AE verifies that the structural similarities among all category members are identified and that the structural differences allowed within the category are described. This AE confirms that all category members fulfil the criteria on required structural similarity and allowed structural differences detailed in the category definition.

AE C.3 Link of structural similarities and structural differences with the proposed regular pattern

Whenever category approach read-across is used, properties of target substances are predicted from properties of source substances within the category. The category hypothesis should apply in an unambiguous manner to all the category members. Only category members that are covered by the category hypothesis can be involved in the read-across.

This AE assesses whether a category hypothesis has been provided and whether it applies to all the category members.

AE C.4 Consistency of effects in the data matrix

The category justification should include a comparison of the existing experimental data for the category members and a clear data matrix.

This AE investigates whether a comparison of experimental data has been provided, preferably in the form of a data matrix. This AE further assesses whether the available data show that properties of the group members across the data matrix are consistent. Consideration is given to the nature and range of effects reported in the study(ies) to be read-across and in related properties identified in studies with the category members. This AE also checks whether effects differ in strength across the category members and whether this difference is characterised.

AE C.5 Reliability and adequacy of the source study(ies)

Whenever read-across is used for purposes of data gap filling under REACH, the source study(ies) need to match the default REACH requirements for any key study in terms of adequacy and reliability.

This AE addresses the adequacy and reliability of the study design of the source study(ies) used to fulfil the information requirement. The AE investigates whether the test material(s) used correctly represent the source substance(s) in terms of purity and impurities and whether the study results are adequate for the purpose of classification and labelling and/or risk assessment.

AE C.6 Bias that influences the prediction

The selection of the category members is a critical aspect in a category approach and may introduce bias in the prediction of the properties under consideration for the target substance.

This AE assesses the extent to which it is clear from the documentation how other structurally similar substances have been considered as potential category members and generally whether other structurally similar substances could be used as additional category members. The AE addresses whether information available on these substances would result in a difference in the prediction of the properties under consideration for the target substance.

This AE also addresses whether the source study(ies) used as the basis for the prediction correspond(s) to the reliable study(ies) giving rise to the highest concern for the properties under consideration.

Table 6: Overview of the category common AEs (scenarios 3 to 6)

AE C.1	Substance characterisation
AE C.2	Structural similarity and differences within the category
AE C.3	Link of structural similarities and structural differences with the proposed regular pattern
AE C.4	Consistency of effects in the data matrix
AE C.5	Reliability and adequacy of the source study(ies)
AE C.6	Bias that influences the prediction

4.4.3.2 Scenarios 3 and 5

As described in section 4.3, scenarios 3 and 5 are based on the same category hypothesis, i.e. (bio) transformation to common compound(s), but differ in the presence of quantitative variations in the predicted effect(s) according to a regular pattern (scenario 3) or in the absence of quantitative variations in the predicted effect(s) (scenario 5).

The scenario-specific AEs for these scenarios address the same scientific aspects and are presented below. However, the approach taken in the assessment of the aspects addressed by some AEs requires adaptations to account for the presence or absence of variation in the strength of the effect(s) observed for the source substances.

Descriptions

Scenario 3

This scenario covers the category approach for which the hypothesis is based on (bio)transformation to common compound(s). For the REACH information requirement under consideration, the effects obtained in studies conducted with different source substances are used to predict the effects that would be observed

in a study with the target substance if it were to be conducted. The same type of effect(s), are observed for the different source substances; this may include absence of effects for some members of the category. There are differences in strength of the effect(s) forming a regular pattern. The prediction is based either on this regular pattern within the category, when the members are ordered by a variable related to the structural differences in the category, or is based on a worst-case approach. The hypothesis has to include the reason why differences in strengths of effects are observed/predicted.

Scenario 5

This scenario covers the category approach for which the hypothesis is based on (bio)transformation to common compound(s). For the REACH information requirement under consideration, the effects obtained in studies conducted with different source substances are used to predict the effects that would be observed in a study with the target substance if it were to be conducted. The same type of effect(s), are observed for the different source substances; this may include absence of effects for every member of the category. No relevant differences in strengths of effect(s) are observed for several source substances.

Examples

Disclaimer: The examples provided below are intended to provide high level illustrations of situations corresponding to this scenario. They do not provide the comprehensive set of circumstances and supporting evidence required to adequately document a read-across approach.

Scenario 3 - Qualitatively similar effects are caused by a common compound, which is formed from all category members, but the strength of the effects vary in a predictable manner throughout the category.

Substances A, B, C and D are structurally similar substances. All substances have information on oral absorption rates and extent, which identify a pattern of regularly decreasing absorption from A to D (Oral absorption $A > B > C > D$). The differences in absorption rates are clearly related to differences in a structural feature.

After absorption, substances A, B, C and D are (bio)transformed rapidly and completely to the common compound Z. The common compound Z is the only determining factor in the toxicity of substances A, B, C and D and is known to cause kidney toxicity.

As a result of the differences in oral absorption of the substances A, B, C and D, the area under the curve and C_{max} in the blood of the common compound Z show a decreasing pattern: $A > B > C > D$. This difference is assumed to influence the level of exposure of the kidneys to the common compound Z after oral administration of substances A, B, C or D.

The same type of effect was observed in the kidney in 28-day repeated-dose toxicity studies conducted with substances A, B and D. The strength of this effects was: $A > B > D$.

The kidney toxicity for C is predicted using trend analysis

Scenario 5 - Qualitatively and quantitatively similar effects are caused by a common compound, which is formed from all category members.

Substances AZ, BZ, CZ and DZ are different inorganic salts of a common acid. They dissociate rapidly in the test organism to the common anion Z and to their different counter ions. The counter ions do not influence the solubility and the toxicity of the category members. In the repeated-dose toxicity studies, the exposure to AZ, BZ, and DZ causes similar type of effects both qualitatively and quantitatively, i.e. the same severity/

degree of the effects is observed at similar doses. The effects of the target substance CZ are predicted to be equal to the effects of the source substances AZ, BZ and DZ for the property under consideration.

	PARENT SUBSTANCES	(BIO)TRANSFORMATION	COMMON COMPOUND	NON-COMMON COMPOUNDS
SOURCE	AZ	AZ → A + Z	Z	A
SOURCE	BZ	BZ → B + Z	Z	B
TARGET	CZ	CZ → C + Z	Z	C
SOURCE	DZ	DZ → D + Z	Z	D

Scenarios 3 and 5 specific assessment elements

The scientific aspects addressed in the AEs developed for the assessment of the category hypothesis of scenarios 3 and 5 are presented below. The complete set of information attached to each AE is presented in annexes C (scenario 3) and E (scenario 5). The list below contains the purpose of the AE and does not reflect all aspects considered in a specific AE.

AEs 3.1 and 5.1 Formation of common (identical) compound(s)

This AE covers only the formation of the common compound(s) as it is addressed in the hypothesis, irrespective of their effects. Convincing evidence has to be provided that the common compound(s) are formed from the category members. If the scientific explanation for the formation of the common compound(s) is missing for one or more category members, it has to be assessed whether this has any impact on the prediction of the properties under consideration.

AE 3.2 and 5.2 The biological target(s) for the common compound(s)

The category hypothesis claims that the common compound(s) have the same biological target(s) and hence cause the same type of effects.

This AE investigates how the (bio)transformation of source and target substances to the common compound(s) results in the exposure of the same biological target(s) and whether the same type of effects are induced in the same biological targets by the common compound(s) throughout the category.

AE 3.3 and 5.3 Exposure of the biological target(s) to the common compound(s)

Under scenario 3, it is expected that the quantitative exposure of the biological targets to the common compound(s) derived from the source substances may vary in a predictable manner and that this explains differences in strength of effects for all or some category members. If at equivalent doses, the kinetics

of the (bio)transformation to the common compound(s) differ among the category members, the internal exposure to the common compound may differ and may explain the observed differences in effects.

This AE checks whether it is established that exposure of the biological targets to the common compound(s) varies in a predictable manner. The AE further assesses whether the prediction is derived from the observation of a regular pattern between the property under consideration and an independent variable defining an order within the category or whether the prediction is based on a worst-case approach within the category.

Under scenario 5, it is expected that the quantitative exposure of the same biological target(s) to the common compound(s) derived from the source and target substances is similar, causing effects of similar strength for all category members.

This AE focuses on whether the similarity in the exposure of the biological targets to the common compound(s) is established. If the justification did not establish similar exposure of the biological target for one or more category members, it has to be assessed whether this has any impact on the prediction of the properties under consideration.

AE 3.4 and 5.4 The impact of parent compounds

The (bio)transformation of the target and source substances may not be immediate and/or complete. As a result, exposure of possible biological targets to the parent compounds may occur for source and/or target substances. Exposure to impurities from the source and/or target substances may also occur.

This AE investigates whether the systemic availability of the parent compounds and of their impurities have been addressed and its impact on the prediction of the property under consideration has been assessed. For local biological targets, the exposure to the parent compounds at the site of contact has to be considered.

AE 3.5 and 5.5 Formation and impact of non-common compounds

The formation of common compound(s) often goes together with the formation of non-common compound(s) and possible intermediates which form the common compound(s). Source and/or target substances can also be (bio)transformed via other pathways than that leading to the formation of the common product(s), and which generate additional non-common compounds.

This AE examines whether the formation of non-common compounds (including possible intermediates) formed via such other pathways and their possible impact on the prediction of the property under consideration have been considered.

Table 7: Overview of the scenario 3 and 5 - specific AEs

SCENARIO 3	SCENARIO 5	ASSESSMENT ELEMENT TITLE
AE 3.1	AE 5.1	Formation of common (identical) compound(s)
AE 3.2	AE 5.2	The biological target(s) for the common compound(s)
AE 3.3	AE 5.3	Exposure of the biological target(s) to the common compound(s)
AE 3.4	AE 5.4	The impact of parent compounds
AE 3.5	AE 5.5	Formation and impact of non-common compounds

4.4.3.3 Scenarios 4 and 6

As described in section 4.3, scenarios 4 and 6 are based on the same category hypothesis, i.e. different compounds have the same type of effect(s), but differ in the presence of variations in the strength of the predicted effect(s) according a regular pattern (scenario 4) or in the absence of variations in the strength of the predicted effect(s) (scenario 6). The scenario-specific AEs for these scenarios address the same scientific aspects and are presented below. However, the approach taken in the assessment of the aspects addressed by some AEs requires adaptations to account for the presence or absence of variation in the strength of the effect(s) observed for the source substances.

Descriptions

Scenario 4

This scenario covers the category approach for which the hypothesis is based on different compounds which have the same type of effect(s). For the REACH information requirement under consideration, the effects obtained in studies conducted with different source substances are used to predict the effects that would be observed in a study with the target substance if it were to be conducted. The same type of effect(s), are observed for the different source substances; this may include absence of effects for some members of the category. There are differences in strength of the effect(s) and they may form a regular pattern. The prediction is based on the regular pattern within the category, when the members are ordered by a variable related to the structural differences in the category, or on a worst-case approach. The hypothesis has to include the reason why differences in strengths of effects are observed/predicted.

Scenario 6

This scenario covers the category approach for which the hypothesis is based on different compounds which have the same type of effect(s). For the REACH information requirement under consideration, the effects obtained in studies conducted with different source substances are used to predict the effects that would be observed in a study with the target substance if it were to be conducted. The same type of effect(s), are observed for the different source substances; this may include absence of effects for every member of the category. No relevant differences in strengths of effect(s) are observed for several source substances.

Examples

Disclaimer: The examples provided below are intended to provide high level illustrations of situations corresponding to this scenario. They do not provide the comprehensive set of circumstances and supporting evidence required to adequately document a read-across approach.

Scenario 4 - Exposure to different substances causes qualitatively similar effects via a common mechanism, but the strength of the effect varies in a predictable manner throughout the category.

Substances A, B, C and D are structurally similar substances. Their structures differ only in the number of functional groups X. All four substances are absorbed at similar rates and extent and are not further (bio)transformed. Substances A, B, C and D are known to be agonists of receptor Z. In vitro data indicates that their potency towards Z increases with the number of functional groups X. The information on other properties reported in the data matrix presents an overall consistent quantitative pattern throughout the category. In the repeated dose toxicity studies, similar effects were observed at increasing doses after exposure to A, B and D, i.e. the same effect was observed at a high dose of A, medium dose of B and low dose of D, which constitutes a regular pattern. The effects of the target substance C are predicted based on the effects of the source substances A, B and D for the property under consideration.

SUBSTANCE	A - Source	B - Source	C - Target	D - Source
TARGET	1	2	3	4

Scenario 6 - Exposure to different substances causes qualitatively and quantitatively similar effects via a common mechanism.

Substances A, B, C and D are structurally similar substances containing one double C-bond which is metabolised to an epoxide. Their structures differ in the carbon chain length which does not impact the toxicity of the substances. Based on the data obtained from in vitro gene mutation studies in mammalian cells, the epoxides which are formed from substances A and D bind to DNA and cause mutagenicity. The information from expert systems supports the hypothesis that epoxides formed from substances B and C have similar chemical reactivity towards DNA-binding as the epoxides formed from substances A and D. Results of the mutagenicity assays conducted with A and D are used to predict the property under consideration of substances B and C.

SUBSTANCE	A - Source	B - Source	C - Target	D - Source
TARGET	3	4	5	6

Scenario 4 and 6 specific assessment elements

The scientific aspects addressed in the AEs developed for the assessment of the category hypothesis of scenarios 4 and 6 are presented below. The complete set of information attached to each AE is presented in annexes D (scenario 4) and F (scenario 6). The list below contains the purpose of the AE and does not reflect all aspects considered in a specific AE.

AE 4.1 and 6.1 Compounds the test organism is exposed to

Under this scenario, it is claimed that exposure to different compounds causes the same effects or absence of effects via a common mechanism.

This AE examines whether the compounds to which the test organism is exposed after administration of the source and the target substances have been identified.

AE 4.2 and 6.2 Common underlying mechanism, qualitative aspects

The category hypothesis should explain how exposure to different compounds causes the same effects or absence of effects. A mechanism linking the presence of the compounds driving qualitatively similar effects with the prediction needs to be identified and should be the same for the target and source substances. This mechanism should also link the structures of the compounds under consideration with the possibility to predict qualitatively similar effects for the target substance.

This AE examines whether a common underlying mechanism is established and if this allows a prediction of qualitatively similar effects.

AE 4.3 and 6.3 Common underlying mechanism, quantitative aspects

Under scenario 4, quantitative variations in the effect caused by exposure to the source and target substances via a common mechanism are expected. These variations may be caused by differences in kinetics and/or potency among the substances to which the organism is exposed after administration of the source and the target substances. The prediction needs to be supported by the scientific explanation of how kinetics and/or potency determine the quantitative variations in the type of effects observed for the property under consideration.

This AE focuses on whether predictable quantitative variation in the same effect is established among the category members. The AE assesses whether the prediction is derived from the observation of a regular pattern between the property under consideration and an independent variable defining an order within the category or whether the prediction is based on a worst-case approach within the category. The AE also examines whether the approach used to predict the property under consideration, i.e. regular pattern or worst-case approach, is consistent with the common mechanism invoked in the category hypothesis.

Under scenario 6, there should be no biologically significant quantitative differences for the effects caused by exposure to structurally similar but different compounds via the underlying mechanism.

This AE investigates whether it has been established that the common underlying mechanism leads to the same quantitative outcome for the source and target substances with regard to the prediction of the property under consideration.

AE 4.4 and 6.4 Exposure to other compounds than those linked to the prediction

Other compounds than the ones linked to the prediction in the category hypothesis may be formed via other (bio)transformation pathways or may be intermediate/metabolites of the identified pathway. Exposure to impurities of the source and/or target substances may also occur. Exposure to these compounds has to be considered in the category justification.

The AE examines the possibility that compounds other than those linked to the prediction are present or formed (e.g. via other (bio)transformation pathways, as an intermediate or as impurity of the source and/or target substance) and if so, what their influence on the prediction of the property under consideration is.

AE 4.5 and 6.5 Occurrence of other effects than covered by the hypothesis and justification

Besides the common mechanism claimed to drive the toxicity, other mechanism(s) than the ones addressed by the category hypothesis may be acting. Quantitative and qualitative evaluation of the effects which have been reported in the data matrix may be indicative of such additional mechanism(s).

This AE investigates whether different effects described in the toxicological profile of source and/or target substances would suggest the presence of other acting mechanism(s). This AE also examines the doses at which the effects triggered by the other mechanisms occur and whether their impact on the prediction is addressed sufficiently in the category justification.

Table 8: Overview of the scenarios 4 and 6 - specific AEs

SCENARIO 4	SCENARIO 6	ASSESSMENT ELEMENT TITLE
AE 4.1	AE 6.1	Compounds the test organism is exposed to
AE 4.2	AE 6.2	Common underlying mechanism, qualitative aspects
AE 4.3	AE 6.3	Common underlying mechanism, quantitative aspects
AE 4.4	AE 6.4	Exposure to other compounds than those linked to the prediction
AE 4.5	AE 6.5	Occurrence of other effects than covered by the hypothesis and justification

Glossary

ABBREVIATION/TERM	EXPLANATION/DEFINITION
AE	Assessment element. A critical scientific aspect of a read-across to be assessed. It is assessed through a number of questions to be answered. These AEs are described in data sheets which are compiled in the annex to this document.
Analogue approach	The term analogue approach is used when read-across is employed between a few very structurally similar substances for which it is not possible to establish a trend or a regular pattern. As a result of the structural similarity, a given toxicological property of one substance (the source) is used to predict the same property for another substance (the target), for which this property is not available but is needed to fulfil a REACH information requirement. The outcome of a study conducted with the source substance is read-across for all investigated parameters to the target substance. A worst-case approach may also be used.
AO	Assessment option. A verbal descriptor reflecting the opinion of the assessor on the information provided to cover the aspect addressed by an assessment element.
Applicability domain	The set of inclusion/exclusion rules that identify the ranges of values within which a reliable prediction can be made for category members.
Bias	Three types of bias are addressed in the RAAF: <ol style="list-style-type: none"> 1. Analogue substance selection. Information from (an)other suitable analogue substance(s) which is significantly different for relevant property(ies), and thereby reduce confidence in the proposed prediction. 2. Study selection. Information from other studies than the one proposed to be used as source study which give rise to a higher concern. 3. Independent variable. The results of the measurement or estimation for the independent variable which is used to describe a regular pattern are systematically and inappropriately altered in category members with certain structural features. This may have an influence on the prediction.
(Bio)transformation	A series of chemical changes in a compound as a result of enzymatic or other activity in a living organism.

Category approach	The term category approach is used when read-across is employed between several substances that have structural similarity. These substances are grouped together on the basis of defined structural similarity and differences between the substances. As a result of the structural similarity, one or more toxicological properties are proposed to be similar or to follow a regular pattern. The predictions are made within the group for the target substance(s) based on the observed regular pattern. Alternatively, the prediction is based on a read-across from a category member in a conservative manner (worst case).
Category definition	The category definition includes a category hypothesis, description of the applicability domain of the category and details on the identity and purity/impurity profiles of the category members.
Category hypothesis	Explanation as to why property(ies) of category members may be predicted from reference substances within the category. This explanation must be based on a relationship between structural similarity and the predicted property(ies).
Category justification	Reasoning and associated supporting evidence that are provided to verify the scientific validity and robustness of the category hypothesis.
Data matrix	A table that summarises all available study results of the source and target substances per REACH information requirement/endpoint and including planned studies. The data should be arranged to reflect the regular pattern identified and used in the prediction. The IUCLID dossier should contain (robust) study summaries of each study referred to in the data matrix to allow an independent assessment of the data.
Group	Under REACH, substances that are structurally similar with physicochemical, toxicological, ecotoxicological and/or environmental fate properties that are likely to be similar or to follow a regular pattern may be considered as a group of substances. Within a group of substances, a data gap might be filled by read-across, as described below.
Mono-constituent substance	A mono-constituent substance is a substance, defined by its quantitative composition, in which one main constituent is present to at least 80% (w/w).
Non-common compound	This term encompasses the structurally different compounds formed through (bio)transformation of the source and target substances, including intermediates formed during the (bio)transformation.

Order within the category	To predict a property within a category of substances, an order has to be established among the category members. As structural similarity is the basis for read-across under REACH this order has to be based on a variable directly linked to the allowed structural differences in the group (e.g. the number of carbon atoms in a side chain or a suitable physical chemical property).
Prediction	In the context of read-across, the property of target substance(s) is estimated from the property of source substance(s). The prediction may be made by means of read-across or by observation of a regular pattern.
Prediction of absence of effect(s)	This term refers to the situation where no effects have been observed in a source study and this result, i.e. absence of effect(s), is read-across to a target substance. This situation is also often referred to as “negative read-across”.
Property	In the context of this document, property is considered to refer to inherent characteristics of the substance which can be studied in a defined experimental study type. These characteristics may relate to physico-chemical or toxicological aspects. The properties of a substance can be determined from the results of experimental studies.
REACH	Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals
Read-across	Under REACH, read-across is a technique for predicting endpoint information for one substance (target substance), by using data from the same endpoint from (an)other substance(s), (source substance(s)). Consequently, the read-across approach has to be considered as property specific.
Read-across approach	A read-across approach, either analogue or category approaches, is composed of elements addressing the structural similarity, a read-across hypothesis, a read-across justification and the prediction of property(ies) of the target substance(s).
Read-across hypothesis	Hypothesis on the basis of which property(ies) of target substance(s) may be predicted from source substance(s). This hypothesis must be based on a relationship between structural similarity and the predicted property(ies) and needs to be supported by read-across justification.
Read-across justification	The reasoning and associated supporting evidence that are provided to verify the scientific validity and robustness of the read-across hypothesis.
Regular pattern	A regular pattern refers to the observation of regular behaviour in a property among the category members. This can consist of no observed differences in a property across the category or in a regular change in that property across the category.

Supporting evidence	Any scientific evidence provided to support the read-across hypothesis. Such supporting evidence may be, for example, information on the toxicokinetic properties of the substances, information from valid (Q)SARs, in vitro or in vivo experimental data addressing specific aspects of the read-across hypothesis.
Test material	The substance actually tested in the source study(ies). The identity and composition (including impurities) of this test substance should be representative of the source substance described in the read-across hypothesis.
Worst-case approach	The strength of effect(s) in the target substance is actually expected to be lower than the strength of effect(s) observed for the source substance; hence using the value obtained from the source substance, the prediction constitutes a worst case that will not lead to an underestimation of the effects that would be observed in a study with the target substance if it were to be conducted.

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ED-AH-14-001-EN-N - DoI: 10.2823/69353 - ISBN: 978-92-9244-844-8 - ISSN: 1831-7340



Publications Office