ECHA
EUROPEAN CHEMICALS AGENCY

Read-Across Assessment Framework (RAAF)

Disclaimer

This document aims to assist users in complying with their obligations under theREACH Regulation. However, users 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. Usage of the information remains under the sole responsibility of the user. The European Chemicals Agency does not accept any liability with regard to the use that may be made of the information contained in this document.

Read-Across Assessment Framework (RAAF)

Reference: ECHA-17-R-01-EN
Cat. number: ED-02-17-140-EN-N
ISBN: 978-92-9495-758-0
DoI: 10.2823/619212
Date: March 2017
Language: English

If you have questions or comments in relation to this document please send them (quoting the reference and issue date) using the information request form. The form can be accessed via the 'Contact ECHA' page at: http://echa.europa.eu/contact

European Chemicals Agency

Mailing address: P.O. Box 400, FI-00121 Helsinki, Finland
Visiting address: Annankatu 18, Helsinki, Finland

Table of contents

1. INTRODUCTION 4

2. SCOPE OF THE DOCUMENT 5

3. BACKGROUND AND DEFINITIONS 6

3.1 What is grouping of substances? 6

3.2 What is read-across? 6

4. THE READ-ACROSS ASSESSMENT FRAMEWORK 9

4.1 Overview of the RAAF 9

4.2 Preparatory assessment 10

4.3 Description and selection of the scenarios 11

4.3.1 Description of the scenarios 11

4.3.2 Scenario selection 13

4.4 Scientific assessment of human health effects 15

4.4.1 General considerations 15

4.4.2 Analogue approaches 19

4.4.3 Category approach 25

4.5 Scientific assessment of environmental fate and effects 34

4.5.1 General considerations 34

4.5.2 Analogue approach 39

4.5.3 Category approach 46

GLOSSARY 56

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 involves the use of relevant information from analogous substance(s) (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 to the REACH Regulation. It has to be ensured that the 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. This 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, ecotoxicological and fate 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 for the main principles with an emphasis on human health.

This resulting document now describes publicly, for the first time, the RAAF when applied to the REACH information requirements concerning human health, environmental fate and environmental hazards. 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 systematically assess 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 help consistently assess the read-across encountered during dossier evaluation. It is however also made available publicly to improve 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 is foreseen based on the experience gained from its application in decision making.

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 examining predictions, based on read-across, of the human health, environmental fate and environmental hazard 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 scientifically examining 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.

This document does not address the way the RAAF is implemented in ECHA's processes nor does it describe how the shortcomings identified in the scientific assessment are evaluated in the course of dossier evaluation under REACH.

3. Background and definitions

Predicting properties of chemicals is an established practice 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 the concepts and terminology used for grouping 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 that have physicochemical, toxicological and ecotoxicological properties that 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 through physical and/or biological processes which result in structurally-similar degradation products (i.e. similarity through (bio) transformation).

- 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?

Applying 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). 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, long-term toxicity to sediment organisms) and/or as a type of study (e.g. carcinogenicity study, fish early life stage test).

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 (eco)toxicological or fate 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 described 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, ecotoxicological and/or environmental fate 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. 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, ecotoxicological or environmental fate 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, ecotoxicological or environmental fate 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 provided in the dossier is the documentation that will be assessed using the RAAF. ECHA evaluates the documentation 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, environmental hazard identification and environmental fate for mono-constituent substances. While the RAAF is 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. Nonetheless, the RAAF sets out a framework for analysis that 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, scenarios, assessment elements and assessment options are used to assess read-across approaches. 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 based on 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 or fate of a substance. Unambiguous substance identity for both 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 read-across can be assessed; 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 of 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 approaches.hh[1] The scenarios are developed for evaluating read-across predictions of 'properties'. A 'property' refers to toxicological effects (human health), ecotoxicological effects or environmental fate properties.

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 property (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 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 (eco) toxicological or fate 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 have similar (eco)toxicological and fate properties. 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 similar properties 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 take further account of whether or not quantitative variations in the properties 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

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.

property investigated in a study conducted with one source substance is used to predict the properties that would be observed in a study with the target substance if it were to be conducted. Similar properties or absence of effect are predicted. The predicted property may be similar or based on a worst-case approach.

Scenario 2
This scenario covers the analogue approach for which the read-across hypothesis is based on different compounds with qualitatively similar properties. For the REACH information requirement under consideration, the property investigated in a study conducted with one source substance is used to predict properties that would be observed in a study with the target substance if it were to be conducted. Qualitatively similar properties or absence of effect are predicted. The predicted property may be similar or based on a worst-case approach.

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 property investigated in studies conducted with different source substances is used to predict the property that would be observed in a study with the target substance if it were to be conducted. Similar properties are observed for the different source substances; this may include absence of effects for some members of the category. There are quantitative differences in the predicted property(ies) 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 predicted properties are observed/predicted.

Scenario 4
This scenario covers the category approach for which the read-across hypothesis is based on different compounds with qualitatively similar properties. For the REACH information requirement under consideration, the properties investigated in studies conducted with different source substances are used to predict the properties that would be observed in a study with the target substance if it were to be conducted. Qualitatively similar properties are observed for the different source substances; this may include absence of effects for some members of the category. There are quantitative differences in predicted properties 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 predicted properties 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 property investigated in studies conducted with different source substances is used to predict the property that would be observed in a study with the target substance if it were to be conducted. Similar properties are observed for the different source substances; this may include absence of effects for every member of the category. No relevant differences in predicted properties 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 with qualitatively similar properties. For the REACH information requirement under consideration, the properties investigated in studies conducted with different source substances are used to predict the properties that would be observed in a study with the target substance if it were to be conducted. Qualitatively similar properties are observed for the different source substances; this may include absence of effects for every member of the category. No relevant quantitative differences in predicted properties 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 predicted property is related quantitatively to the properties 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 properties (Scenario 3) or in the absence of such variations (Scenario 5). The approach taken when assessing the scientific aspects addressed in the AEs slightly differs to account for the presence or absence of variation in the predicted properties 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)	Property 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 qualitatively similar properties	Properties 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 properties observed among source substances. Prediction based on a regular pattern or on a worst-case approach.
4	Category	Different compounds have qualitatively similar properties	Variations in the properties 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 properties observed among source substances and the same strength predicted for the target substance.
6	Category	Different compounds have qualitatively similar properties	No relevant variations in properties 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, the type of approach applied, i.e. analogue approach or category approach, and the read-across hypothesis used must be identified. In addition, for category approaches, whether quantitative variations in the properties are observed among the category members must be considered. Figure 1 below illustrates the scenario selection.

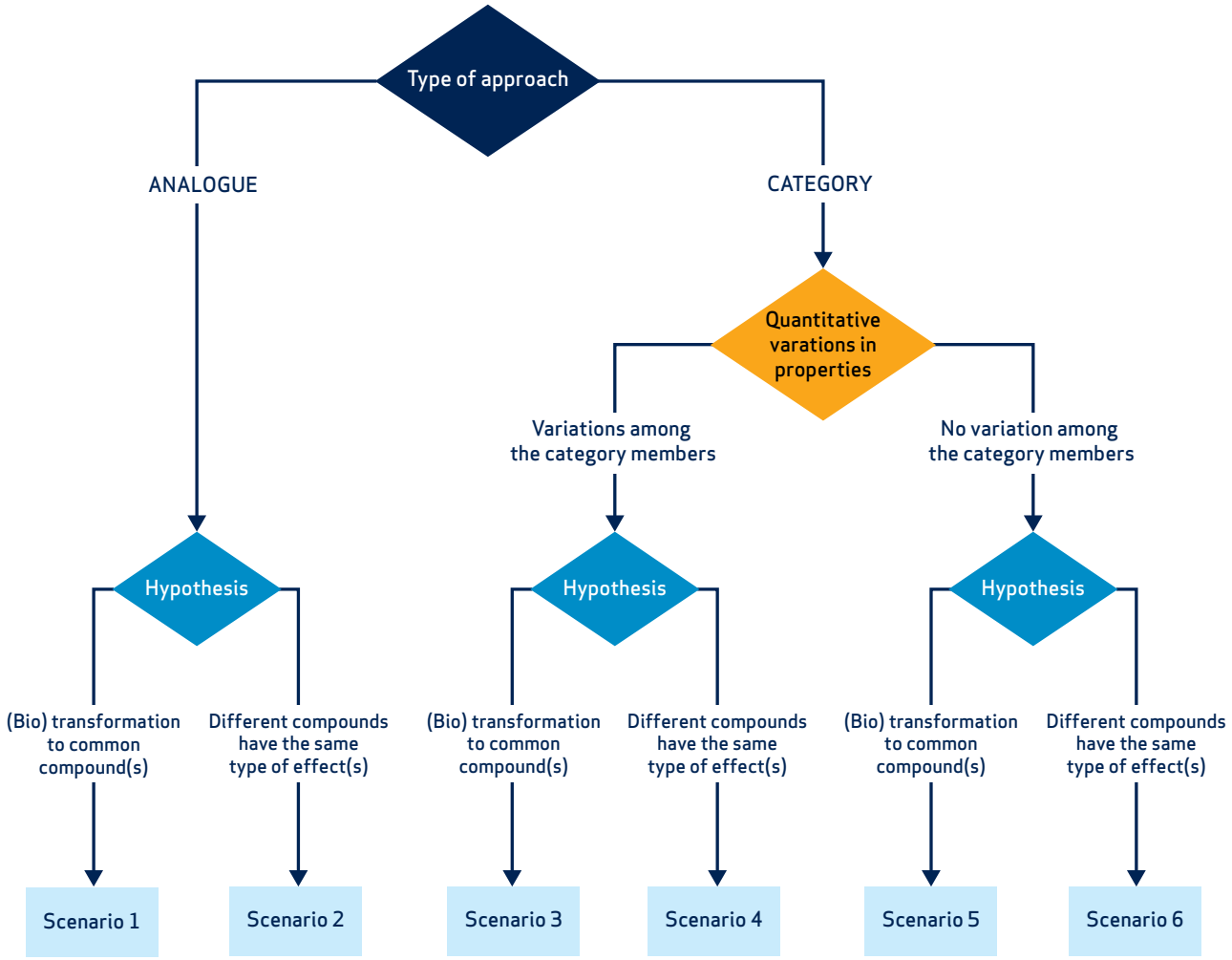

Figure 1 – Schematic presentation of the scenario selection

4.4 SCIENTIFIC ASSESSMENT OF HUMAN HEALTH EFFECTS

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 AEs might not apply. Then, the outcome of the assessment of this specific scientific issue will be recorded as "*Not relevant*".

Table 2 -Overview of the 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 a 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 lead 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".

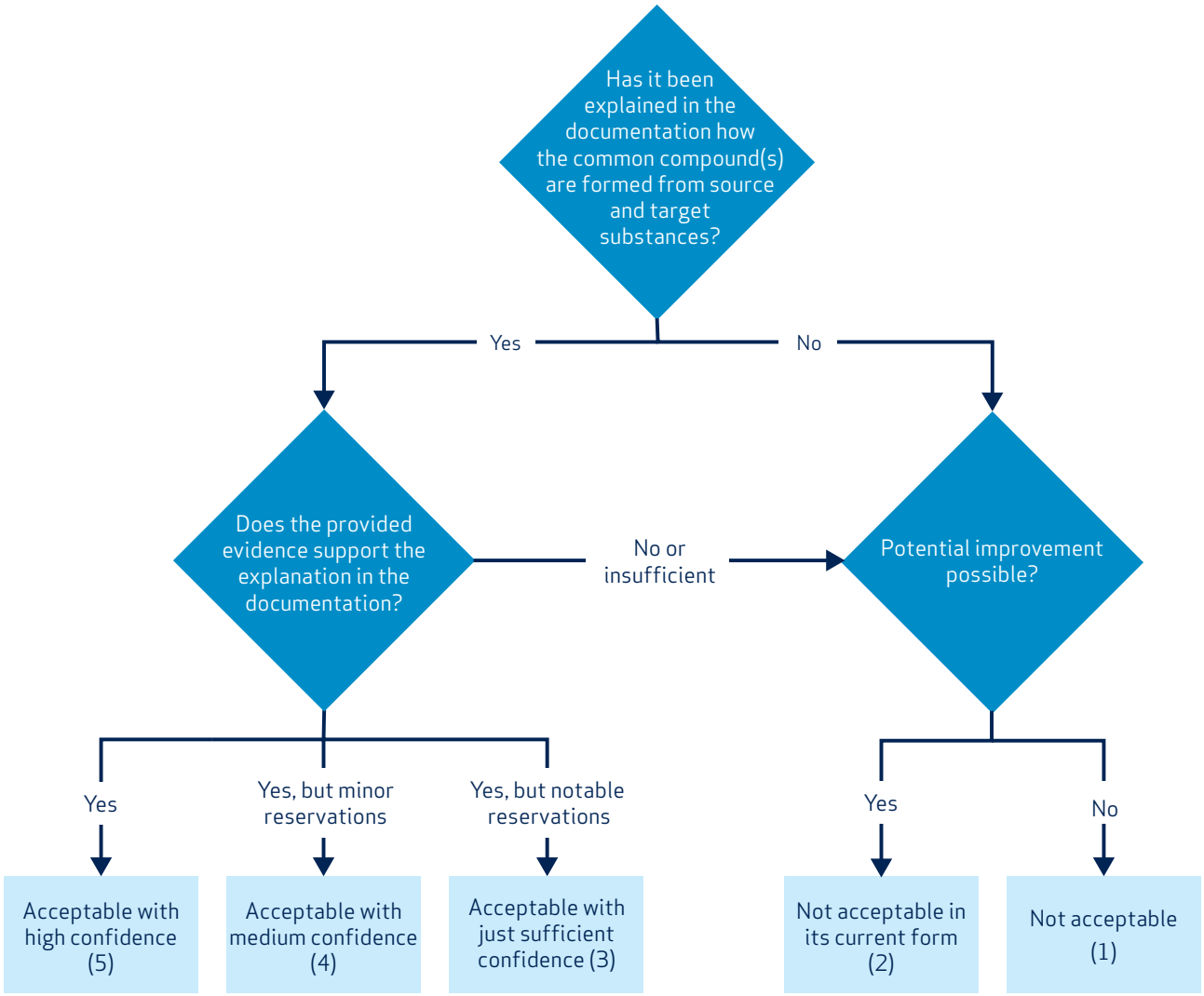

Figure 2: Example of the decision logic within an AE – Extracted from AE 1.1 Formation of common (identical) compound(s)

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 and 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 and the OECD QSAR Toolbox) may increase the robustness of a case, but are not usually sufficient as standalone 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 to 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 identifying hazards and fulfilling standard information requirements. The RAAF therefore is not concerned with examining 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 approaches

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 a 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 COMPOUNDS	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 therefore 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 with 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 a 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 through a 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 the same types of (absence of) effects through 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 transfromed	A	-
TARGET	B	B → not transfromed	B	-

Example 2 - Exposure to different compounds, which are (bio)transformed and cause the same effects through a 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 through 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 similar types of effect, 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 through 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. through other (bio)transformation pathways, 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 mechanisms than those 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 mechanisms. 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 to 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 common AEs for category approaches 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 that 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 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 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 assessing 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 a 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 Cmax 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 assessing 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 therefore 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 through 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 through 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 to 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 assessing 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 that 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 that 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 a 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 through 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 extents 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
NUMBER OF FUNCTIONAL GROUPS X	1	2	3	4

Scenario 6 - *Exposure to different substances causes qualitatively and quantitatively similar effects through 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
NUMBER OF C IN THE SIDE CHAIN	3	4	5	6

Scenario 4 and 6-specific assessment elements

The scientific aspects addressed in the AEs developed for assessing 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 through 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 through 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 a 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 through 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 those linked to the prediction in the category hypothesis may be formed through 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. through 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 mechanisms than those 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 mechanisms.

This AE investigates whether different effects described in the toxicological profile of source and/or target substances would suggest the presence of other acting mechanisms. 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

4.5 SCIENTIFIC ASSESSMENT OF ENVIRONMENTAL FATE AND EFFECTS

4.5.1 General considerations

4.5.1.1 Assessment elements and assessment options

As an initial remark, the environmental part of the RAAF has been developed for mono-constituent substances[2] to predict properties of hydrolysis, biodegradation, bioaccumulation, aquatic and sediment toxicity. Nonetheless, the RAAF sets out a framework for analysis which may be applied in an analogous manner for toxicity endpoints that are not explicitly covered (e.g. terrestrial toxicity endpoints).

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.

Therefore, 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 normally continues even 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 addressed. To understand how AEs are formulated, and before describing these more in detail below, it is helpful to first understand the possible outcomes of the consideration of the read-across against an 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 9 below. The selection of a specific AO for a given AE needs to be justified by the assessing expert.

For specific cases, some AEs might not apply. Then the outcome of the assessment of this specific scientific issue will be recorded as "*Not relevant*".

2 Although initially developed for organic substances, the RAAF principles can also be applied to inorganic substances, including metals and metal compounds. However, this requires some caution and different definitions/interpretations for terms such as structural similarity, transformation or fate. Metals can be differentiated from their total elemental composition into different redox species, metal compounds, complexes, or precipitates/minerals - each species of a specific element having different chemical and physical properties, and differences in mobility, bioavailability, and/or toxicity. Therefore, the read-across hypothesis should cover speciation of the metal and its influence on the mobility and predicted properties. The read-across hypothesis may be based on the rate and extent to which metals and sparingly soluble metal compounds can produce soluble available ionic and other metal-bearing species in aqueous media (see OECD Series on Testing and Assessment, number 29, ENV/JM/MONO(2001)9). Therefore, the hypothesis for metals may often rely more on the same metal ion being (bio)available than on a strict interpretation of structural similarity and therefore many such cases would fall under the read-across hypothesis "transformation to common compounds", i.e. scenarios 1-3-5. Similarly, transformation as presented in the current RAAF (hydrolysis, dissociation, (bio)degradation) is better characterised by speciation for metals/metal compounds, which also determines the environmental behaviour, fate/bioavailability of metals and exchanges between environmental compartments. For metals and inorganic substances bioaccumulation and biomagnification endpoints require special considerations, since organisms can regulate uptake of some metal ions within a given margin. This means that the BCF is sometimes inversely related to the exposure concentration making read-across assumptions for bioaccumulation and biomagnification difficult if not impossible to prove. Further, certain (parts of) assessment elements might need adaptation or are not applicable for specific cases.

Table 9: Overview of the 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 ENV-A to ENV-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 experts indicate 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. 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".

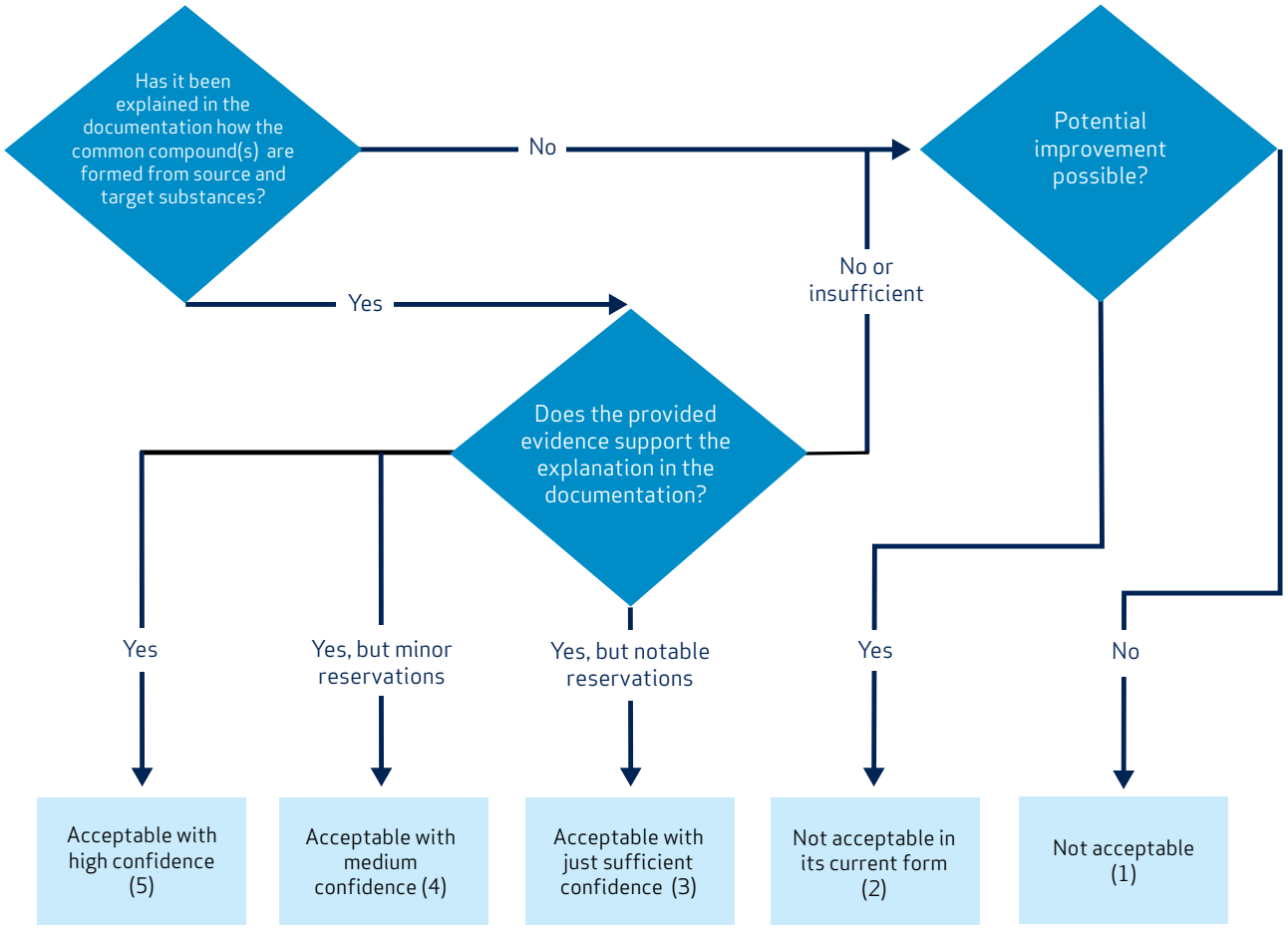

Figure 3: Example of the decision logic within an AE – Extracted from AE 1.1 Formation of common (identical) compound(s)

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".

If an AE is considered "Not acceptable in its current form", the read-across may become acceptable for the

AE under consideration if further improved with scientific explanations and/or supporting evidence is made available by the registrant. 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.

4.5.1.2 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 that would support such a claim. The absence of effect(s) may however be explained by the absence of exposure of the biological target(s) (e.g. due to a very low bioavailability, leading to very low internal concentrations) 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 for a prediction of the absence of effects. Lack of environmental exposure (low emissions, low predicted environmental concentrations) are usually *not* part of such evidence.

The RAAF, as currently designed, applies to both the prediction of effects and the 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.

4.5.1.3 Supporting evidence

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

However, in general, supporting evidence may range from theoretical considerations or expert systems, to results from *in vivo* or *in vitro* studies. Data from other interrelated endpoints (degradation, bioaccumulation, environmental effects) constitute valuable supporting evidence. Often quantitative information is needed.

In vitro, *in chemico* and *in silico* studies (e.g. computational tools such as OECD QSAR Toolbox, EPI Suite, ECOSAR, VEGA, T.E.S.T, Catalogic) may increase the robustness of a case.

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 properties 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 and source substances are specifically important. For instance, to predict ecotoxicological effects the availability of information on the degradation potential and the uptake/bioaccumulation potential is essential, but other toxicity studies with e.g. different test durations, test design or with other trophic levels may also confirm the similarity in toxicity levels.

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.

4.5.1.4 Weight-of-evidence approaches

Annex XI, Section 1.2 to 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 identifying hazards and fulfilling standard information requirements. Therefore, the RAAF is not concerned with examining 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.

4.5.1.5 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 affect the prediction.

To increase the transparency in this regard, it is useful if the documentation clearly shows 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 and which may contradict the prediction.

4.5.1.6 Special considerations in read-across assessment of environmental fate and effects

The same general principles apply to the read-across assessment of human health hazards and environmental hazard and fate properties. The general considerations described here are almost identical to those described in Section 4.4 Scientific assessment of human health effects.

Furthermore, the common AEs are mostly similar for read-across assessment of human health and environmental properties. However, there are some deviations from the human health read-across assessment especially in the specific assessment elements that need to be taken into account when assessing read-across in environmental properties:

- Interrelated nature of environmental fate and effect properties

  Assessing environmental effect data normally requires consideration of environmental fate information. Especially in terms of assessment of read-across and grouping, it is necessary to establish a scientifically-valid causal link between the fate of the substance in the test media (e.g. degradation processes), its availability for uptake, the potential to accumulate in organisms (bioaccumulation potential) and the effects. Such a link for the source substance(s) is essential and should be compared to similar considerations for the target substance, i.e. if the same test would be performed with the target substance. Thus, the evaluation of information for one environmental property usually requires evaluation of other related properties.

- Influence of physicochemical properties

  Key physicochemical properties also determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Physicochemical properties influence the environmental properties and should therefore be considered in read-across assessments. This implies that the use of information on physicochemical properties can underpin the basis for read-across in predicting environmental fate and effects.

4.5.2 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, on the read-across hypothesis and data available for both source and target substances (e.g. anchor studies).

4.5.2.1 Common assessment elements for analogue approaches

ECHA has identified AEs that apply to both types of analogue approach irrespective of the read-across hypothesis that is used, i.e. they are the same when applied to either Scenarios 1 or 2 (Table 10). These AEs address the following aspects of the analogue approach and are presented in detail in Annexes ENV-A and ENV-B. The list below indicates the purpose of the AE and does not reflect all aspects considered in a specific AE.

AE A.1 Characterisation of source and target substances
Structural similarity is a prerequisite 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. This AE investigates whether the identification and characterisation of the source and target substances, including their impurity profiles, are sufficient for a scientific assessment of the read-across approach.

AE A.2 Link of structural similarities and structural differences with the proposed prediction (presence of hypothesis)
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 are linked with the possibility to predict similar properties.

AE A.3 Impact of impurities on the prediction
This AE checks whether the read-across justification accounts for the impurities associated with the source and target substances and their impacts on the prediction.

AE A.4 Consistency of properties in the data matrix
The read-across justification should include a comparison of the existing reliable experimental data for the source and target substances 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 substances across the data matrix are consistent. Consideration is given to similarity in the properties reported in the study(ies) to be read-across and in related properties identified in studies with the source and target substances. This AE also checks whether the properties of source and target substances are the same or

similar or a worst-case prediction is provided.

AE A.5 Reliability and adequacy of the source data
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.6 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 10 - Overview of the analogue common AEs (scenarios 1 and 2)

AE A.1	Characterisation of source and target substances
AE A.2	Link of structural similarities and structural differences with the proposed prediction (presence of hypothesis)
AE A.3	Impact of impurities on the prediction
AE A.4	Consistency of properties in the data matrix
AE A.5	Reliability and adequacy of the source data
AE A.6	Bias that influences the prediction

4.5.2.2 Scenario 1

Description

This scenario covers the analogue approach for which the read-across hypothesis is based on transformation to common compound(s). For the REACH information requirement under consideration, the results obtained in a study conducted with one source substance are used to predict the properties that would be observed in a study with the target substance if it were to be conducted. Similar properties are predicted in this scenario. The predicted strength of the effects/properties 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 and, for the sake of simplicity, they present only examples where ecotoxicological effects are predicted. They do not provide a 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, both (bio)available for the transformation to occur. Both substances are transformed to the common compound A and to the non-common compounds Y and Z.

The common compound A is solely responsible for the effects to be predicted. The transformation of the parent substances is rapid and extensive and therefore, only negligible exposure to the parent substances 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	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 transformation product of the target substance.

The source substance A and the target substance B are structurally similar substances that are both (bio)available for the transformation to occur. Substance A is not transformed. Substance B is rapidly transformed to substance A and non-common compound Z, and therefore only negligible exposure to substance B occurs. Compound Z does not contribute to the observe effects. The source substance A is the common compound in this analogue approach. The common compound A is solely responsible for the effects to be predicted. 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	TRANSFORMATION	COMMON COMPOUND	NON-COMMON COMPOUNDS
SOURCE	A	A -> not transformed	A	-
TARGET	B	B -> A	A	Z

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 ENV-A. The list below indicates the purpose of the AE and does not reflect all aspects considered in a specific AE.

AE 1.1 Formation of common (identical) and non-common compounds
In this scenario, the common transformation compound(s) are claimed to influence the considered property alone. This AE covers the formation of the common and non-common compound(s). The focus of the AE is on the scientific explanation and documentation on how the transformation from source and target substances to the common compound(s) occurs, and at which rate. If the rate of formation to common compounds is different between the source and target substances, this AE assesses the justification regarding the potential impact of that difference in the predicted property. In contrast, the influence of the non-common compounds on the predicted property is assessed in AEs 1.2-1.4.

AE 1.2 Degradation of non-common compounds
This AE addresses abiotic and biotic degradation processes of non-common compounds that can occur in the course of testing.

It has to be assessed whether the justification addresses the potential (further) degradation of the non-common compounds during the test. Persistency of the non-common compounds should be considered and explained, especially for PBT assessment. If the persistency of the non-common compounds differ, a worst-case approach may be still acceptable (i.e. hypothesis and evidence provided to show lower persistency of the non-common compound(s) of the target substance). If bioaccumulation or environmental effects are being predicted, information on potential further degradation of the non-common compounds is required to understand to which non-common compounds the organisms are exposed in a bioaccumulation or (eco) toxicity test.

AE 1.3 Bioaccumulation potential of non-common compounds
This AE addresses the uptake and bioaccumulation potential of the non-common compounds (from AE 1.1) and any of their potential degradation products (from AE 1.2), both when bioaccumulation potential is predicted and when environmental effects are predicted (a difference in bioaccumulation potential may affect the strength of effects).

Transformation of parent compounds, i.e. target and source substances, may not be immediate and/or complete and, in this case, the parent compounds have to be considered regarding their bioaccumulation potential. In addition, the formation of common compound(s) may go together with the formation of non-common compound(s) and/or potential intermediates during the formation of the common compound(s). Therefore, this AE examines whether the hypothesis provided accounts for bioaccumulation of non-common compounds, such as the parent and non-common degradation products.

The assessment should use the information collected in the earlier assessment elements on the transformation rate of the parent compounds, rate of formation of the non-common compounds and (further) transformation of those compounds. In addition, the characteristics of all non-common compounds should be considered as they may influence the predicted property. For example, related properties such as bioavailability, uptake potential, adsorption, water solubility and lipophilicity may be used. If the bioaccumulation potential of the non-common compounds differ, a worst-case approach may still be acceptable (i.e. hypothesis and evidence provided to show lower bioaccumulation potential of the non-common compound(s) for the target substance).

Bioaccumulation potential of non-common compounds also needs to be considered when environmental effects are predicted. The AE investigates if relevant data on bioconcentration and/or bioaccumulation potential have been considered in the prediction.

AE 1.4 Impact of non-common compounds
This AE addresses the environmental effects of the non-common compounds and is applicable only when environmental effects are predicted.

This AE examines whether the hypothesis provided accounts for toxicity of non-common compounds, such as the parent and non-common degradation products. The assessment should use the information collected in the earlier assessment elements on the transformation rate of the parent compounds, rate of formation of the non-common degradation products, further transformation of those compounds, and bioaccumulation potential of all the non-common compounds.

These assessment elements reflect potential differences that the compounds may have regarding bioavailability and uptake, which in turn will affect how much of the non-common compound is present at the

target sites of toxic action and may cause effects. In addition to potential differences in bioaccumulation, differences in the mechanism of action between the non-common compounds of the target and source substances should be considered in the documentation.

If the toxic potential of the non-common compounds differ, a worst-case approach may be still acceptable. For example, hypothesis and evidence may be provided to show low bioaccumulation potential of the (narcotic) non-common compounds of the target leading to low toxic potential.

Table 11 - Overview of the Scenario 1-specific AEs

AE 1.1	Formation of common (identical) and non-common compounds
AE 1.2	Degradation of non-common compounds
AE 1.3	Bioaccumulation potential of non-common compounds
AE 1.4	Impact of non-common compounds

4.5.2.3 Scenario 2

Description
This scenario covers the analogue approach for which the hypothesis is based on different compounds with the same type of environmental effect and/or fate properties. For the REACH information requirement under consideration, the information obtained in a study conducted with one source substance is used to predict the property that would be observed in a study with the target substance if it were to be conducted. The predicted property 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 and, for the sake of simplicity, they present only examples where ecotoxicological effects are predicted. They do not provide a 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 through a common underlying mechanism.

The source substance A and the target substance B are structurally similar substances which have similar bioavailabilities (e.g. water solubility, adsorption, lipophilicity, volatility, no transformation). The exposure to A and B causes same types of (absence of) effects through 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	TRANSFORMATION	SIMILAR COMPOUND	BREAK-DOWN PRODUCTS
SOURCE	A	A -> not transformed	A	-
TARGET	B	B -> not transformed	B	-

Example 2 - Exposure to different compounds, which are transformed and cause the same effects through a common underlying mechanism.

The source substance A and the target substance B are structurally similar substances which have similar bioavailabilities (e.g. water solubility, adsorption, lipophilicity, volatility) and are transformed to substances A1 and A2 and B1, respectively.

Due to rapid and extensive transformation, only negligible exposure to parent compounds A and B occurs. The exposure to A1 and to B1 causes the same type of (or absence of) effects through 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	TRANSFORMATION	SIMILAR COMPOUND	BREAK-DOWN PRODUCTS
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 ENV-B. The list below contains the purpose of the AE and does not reflect all aspects considered in a specific AE.

AE 2.1 Degradation
This AE addresses abiotic and biotic degradation processes and the purpose is two-fold:

1. address the link between structure and property if degradation is to be predicted;

2. address the degradation processes that can occur in the course of testing and alter the test material identity if the prediction is for bioaccumulation or environmental effect properties.

If abiotic or biotic degradation are being predicted, it must be assessed from the documentation whether the source and target substances may be transformed (degraded) similarly based on their structures and, if yes, whether the transformation occurs at the same rate or to the same extent.

If the degradation potential is likely to differ, the implications this has on the read-across should be explained. A worst-case approach may still be acceptable, if a scientifically-valid hypothesis and evidence are provided to show that the property is not underestimated (e.g. lower persistency of the target substance). Furthermore, if persistency of a compound is predicted, the read-across should address the persistency of potential degradation products.

If bioaccumulation potential or environmental effects are being predicted, the justification has to be assessed to see whether it addresses the potential degradation of the target and source compounds during the test. This is required to understand which compounds the organisms are exposed to in a bioaccumulation or (eco)toxicity test and to what extent.

AE 2.2 Bioaccumulation potential

This AE examines the bioaccumulation potential of the target and source substances and whether they are likely to be the same, based on structural similarity and relevant (physicochemical and fate) properties that can be linked to bioaccumulation potential. The AE is applicable to predictions of bioaccumulation potential and environmental effects (a difference in bioaccumulation potential may affect the strength of effects).

This AE should use the information collected in the earlier assessment elements on degradation, as well as related properties such as bioavailability and the uptake potential of substances (e.g. adsorption, water solubility, lipophilicity).

If related properties differ, the implications this has on the predicted property should be explained. A worst-case approach may be still acceptable if a scientifically-valid hypothesis and evidence are provided to show that the property is not underestimated.

If environmental effects are predicted, the justification has to be assessed to see if it addresses the bioaccumulation of the compounds during the ecotoxicity test. Whether those differences are reflected in the documentation regarding the quantitative aspect of predicting environmental effects of the target substance (AE 2.4) should also be assessed. This is required to understand the extent to which the compounds are accumulated and cause toxic effects during an ecotoxicity test.

AE 2.3 Common underlying mechanism, qualitative aspects

This AE addresses qualitative aspects of the toxic potential of the target and source substances and is applicable to predictions of environmental effects.

The read-across hypothesis should explain how exposure to different compounds causes the same effects or absence of effects. A mechanism needs to be identified and should 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 (mode or mechanism of action) is established and if this allows the prediction of a similar type of effects, qualitatively.

AE 2.4 Common underlying mechanism, quantitative aspects

This AE addresses quantitative aspects of the toxic potential of the target and source substance, and is only applicable to predictions of environmental effects.

This AE investigates whether it has been established that the common underlying mechanism assessed in AE 2.3 leads to the same quantitative outcome for source and target substances with regard to the prediction of the environmental effects (hypothesis verification). No quantitative differences of biological significance should be observed for the predicted property or the differences should not be underestimated (i.e. a worst-case approach should be applied).

The AE should use the information collected in the earlier assessment elements on degradation and bioaccumulation potential of the source and the target compounds. These assessment elements reflect potential differences that the compounds may have regarding bioavailability and uptake, which in turn determine the concentration of the compound that reaches the target sites of toxic action and can cause the effects. If the toxicity of the compounds is likely to be different, a worst-case approach may still be acceptable. For example, a hypothesis and supporting evidence may be provided to show the same (or lower) bioaccumulation potential of the target, leading to the same (or lower) strength of effects of the target substance.

Table 12 - Overview of the Scenario 2-specific AEs

AE 2.1	Degradation
AE 2.2	Bioaccumulation potential
AE 2.3	Common underlying mechanism, qualitative aspects
AE 2.4	Common underlying mechanism, quantitative aspects

4.5.3 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, environmental effect and fate properties are likely to be similar or follow a regular pattern.

In a category approach usually several data points are available for one specific property. This generally increases the confidence in the prediction of this property for one member of the category compared to a prediction based on one source substance alone (analogue approach).

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 property(ies) in a predictable manner) or all group members can be predicted to have quantitatively same/similar properties. A worst-case approach may also be used to predict properties of category members.

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

The category definition includes the category description and the hypothesis. The category description needs to define what characteristics a chemical has to have in order to belong to the category and should outline the substance exclusion rules. The hypothesis should present the rationale according to which the environmental properties of the target substance may be predicted from data for reference substance(s) within the category by interpolation.

4.5.3.1 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 (Table 13), ensures a consistent assessment of such category approaches. 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.

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 ENV-C to ENV-F. The list below indicates the purpose of the AE and does not reflect all aspects considered in a specific AE.

AE C.1 Characterisation of source and target substances
The substances that 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 dissimilarity within the category (category description)
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 description.

AE C.3 Link of structural similarities and structural differences with the proposed regular pattern (presence of hypothesis)
Whenever category approach read-across is used, properties of a target substance 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 Impact of impurities on the prediction
This AE checks whether the read-across justification accounts for the impurities associated with the category members and their impacts on the prediction.

AE C.5 Consistency of properties in the data matrix
The category justification should include a comparison of the existing reliable 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 or follow a regular pattern.

Consideration is given to similarity or range of properties 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 the properties are the same or similar or quantitatively vary across the category members and whether this difference is characterised.

AE C.6 Reliability and adequacy of the source data
Whenever read-across is used for 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 classification and labelling and/or risk assessment.

AE C.7 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 13: Overview of the category approach common AEs (scenarios 3 to 6)

AE C.1	Characterisation of source and target substances
AE C.2	Structural similarity and dissimilarity within the category (category description)
AE C.3	Link of structural similarities and structural differences with the proposed regular pattern (presence of hypothesis)
AE C.4	Impact of impurities on the prediction
AE C.5	Consistency of properties in the data matrix
AE C.6	Reliability and adequacy of the source data
AEC.7	Bias that influences the prediction

4.5.3.2 Scenarios 3 and 5

As described in Section 4.3 Description and selection of the scenarios, Scenarios 3 and 5 are based on the same category hypothesis, i.e. transformation to common compound(s), but differ in the presence of quantitative variations in the predicted property according to a regular pattern (Scenario 3) or in the absence of quantitative variations in the predicted property (Scenario 5).

For the REACH information requirement under consideration, the results obtained in studies conducted with different source substances are used to predict the property that would be observed in a study with the target substance if it were to be conducted.

The scenario-specific AEs for these scenarios address the same scientific aspects and are presented below.

However, the approach taken when assessing the aspects addressed by some AEs requires adaptations to account for the presence or absence of variation in the property(ies) observed for the source substances.

Descriptions
Scenario 3
There are quantitative differences in the predicted property 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 the predicted properties are observed/predicted.

Scenario 5
No relevant quantitative differences in the predicted property are observed for several source substances. The prediction is based either on a similar property(ies) or on a worst-case approach. The hypothesis has to include the reason why the observed structural differences, and potential differences in related properties, do not produce differences in the predicted properties.

Examples
Disclaimer: The examples provided below are intended to provide high-level illustrations of situations corresponding to this scenario and, for the sake of simplicity, they present only examples where ecotoxicological effects are predicted. They do not provide a 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 AZ, BZ, CZ and DZ are structurally similar substances. All substances have information on water solubility, adsorptivity, and lipophilicity, which identify a pattern of regularly decreasing adsorptivity from AZ to DZ (logKoc AZ > BZ > CZ > DZ). The differences in logKoc are clearly related to differences in a structural feature.

When applied to sediment, substances AZ, BZ, CZ and DZ are transformed completely to the common compound Z, however, the rate is dependent on the availability of the substance to transformation in sediment and thus on logKoc. The common compound Z is the only determining factor in the toxicity of substances AZ, BZ, CZ and DZ (all non-common compounds including parent and non-common transformation products).

As a result of the differences in adsorptivity and transformation rate of the substances AZ, BZ, CZ and DZ in sediment, the exposure to the common toxic transformation product Z shows a decreasing pattern: DZ > CZ > BZ > AZ. The same type of pattern was observed in the sediment toxicity for substances AZ, BZ and DZ. The strength of this effect was: DZ > BZ > AZ.

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 medium to the common anion Z and to their different counter ions. The counter ions A, B, C and D do not influence the solubility and the toxicity of the category members.

In the aquatic 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 concentrations. 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	TRANSFORMATION (DISSOCIATION)	COMMON COMPOUND (ANION)	NON-COMMON COMPOUNDS (COUNTER ION)
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 assessing the category hypothesis of Scenarios 3 and 5 are presented below. The complete set of information attached to each AE is presented in Annexes ENV-C (Scenario 3) and ENV-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) and non-common compound(s)
This AE covers only the formation of the common and non-common compound(s) as it is addressed in the hypothesis. Convincing evidence has to be provided that the common compound(s) are formed from the category members, and at which rate.

If the scientific explanation for the formation of the common compound(s) is missing for one or more category members, any impact on the prediction of the properties under consideration has to be assessed.

If the rate of formation to common compounds is different between the source and target substances, this AE assesses the justification regarding the potential impact of that difference in the predicted property. In contrast, the influence of the non-common compounds on the predicted property is assessed in AEs 3.2-3.4 and 5.2-5.4.

AEs 3.2 and 5.2 Degradation of non-common compounds
This AE addresses abiotic and biotic degradation processes that can occur in the course of testing.

Whether the justification addresses the potential (further) degradation of the non-common compounds during the test has to be assessed. Persistency of the non-common compounds should be considered and explained, especially for PBT assessment. If the persistency of the non-common compounds differ, a worst-case approach may be still acceptable (i.e. hypothesis and evidence provided to show lower persistency of the non-common compound(s) of the target substance). If bioaccumulation or environmental effects are being predicted, information on potential further degradation of the non-common compounds is required to understand to which non-common compounds the organisms are exposed in a bioaccumulation or ecotoxicity test.

AE 3.3 and 5.3 Bioaccumulation potential of non-common compounds
This AE addresses the uptake and bioaccumulation potential of the non-common compounds (from AE 3.1 and 5.1) and any of their potential degradation products (from AE 3.2 and 5.2) both when bioaccumulation potential is predicted and when environmental effects are predicted (a difference in bioaccumulation potential may affect the toxicity).

Transformation of parent compounds, i.e. members of the category, may not be immediate and/or complete

and, in this case, the parent compounds have to be considered regarding their bioaccumulation potential. In addition, 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). Therefore, this AE examines whether the hypothesis provided accounts for bioaccumulation of non-common compounds, such as the parent and non-common degradation products.

The assessment should use the information collected in the earlier assessment elements on the transformation rate of the parent compounds, rate of formation of the non-common compounds and (further) transformation of those compounds. In addition, the characteristics of all non-common compounds should be considered as they may influence the predicted property. For example, related properties such as bioavailability, uptake potential, adsorption, water solubility and lipophilicity may be used. If the bioaccumulation potential of the non-common compounds differ, a worst-case approach may still be acceptable (i.e. a hypothesis and evidence are provided to show lower bioaccumulation potential of the non-common compound(s) for the target substance).

Bioaccumulation potential of non-common compounds also needs to be considered when environmental effects are predicted. The AE investigates if relevant data on bioconcentration and/or bioaccumulation potential have been considered in the prediction.

AE 3.4 and 5.4 Impact of non-common compounds
This AE addresses the environmental effects of the non-common compounds, and is applicable only when environmental effects are predicted.

Furthermore, this AE examines whether the hypothesis provided accounts for toxicity of non-common compounds, such as the parent compound and non-common degradation products. The assessment should use the information collected in the earlier assessment elements on the transformation rate of the parent compounds, rate of formation of the non-common degradation products, further transformation of those compounds, and bioaccumulation potential of all the non-common compounds.

These assessment elements reflect potential differences that the compounds may have regarding bioavailability and uptake, which in turn will affect how much of the non-common compound is present at the target sites of toxic action and may cause effects. In addition to potential differences in bioaccumulation, differences in mechanism of action among the non-common compounds of the category members should be considered in the documentation.

If the toxic potential of the non-common compounds differ, a worst-case approach may still be acceptable. For example, a hypothesis and evidence may be provided to show low bioaccumulation potential of the (narcotic) non-common compounds of the target leading to low toxic potential.

Table 14: Overview of the scenario 3 and 5 - specific A

SCENARIO 3	SCENARIO 5	ASSESSMENT ELEMENT TITLE
AE 3.1	AE 5.1	Formation of common (identical) and non-common compound(s)
AE 3.2	AE 5.2	Degradation of non-common compounds
AE 3.3	AE 5.3	Bioaccumulation potential of non-common compounds
AE 3.4	AE 5.4	Impact of non-common compounds

4.5.3.3 Scenarios 4 and 6

As described in Section *4.3 Description and selection of the scenarios*, Scenarios 4 and 6 are based on the same category hypothesis, i.e. different compounds have the same type of property, but differ in the presence of quantitative variations in the predicted property according a regular pattern (Scenario 4) or in the absence of variations in the predicted property (Scenario 6).

For the REACH information requirement under consideration, the results obtained in studies conducted with different source substances are used to predict the properties that would be observed in a study with the target substance if it were to be conducted.

The scenario-specific AEs for these scenarios address the same scientific aspects and are presented below.

However, the approach taken when assessing the aspects addressed by some AEs requires adaptations to account for the presence or absence of variation in the property(ies) observed for the source substances.

Descriptions

Scenario 4

There are differences in the predicted property(ies) 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 the predicted property are observed/predicted.

Scenario 6

No relevant differences in property(ies) are observed for several source substances. The prediction is based either on similar property or on a worst-case approach. The hypothesis has to include the reason why the observed structural differences, and potential differences in related properties, do not produce differences in the predicted properties.

Examples

Disclaimer: The examples provided below are intended to provide high-level illustrations of situations corresponding to this scenario and, for the sake of simplicity, they present only examples where ecotoxicological effects are predicted. They do not provide acomprehensive set of circumstances and supporting evidence required to adequately document a read-across approach.

Scenario 4 - Exposure to different substances causes qualitatively similar effects through 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 carbon chain length, increasing from A to D. The functional groups are identical. All four substances are available to aquatic organisms to a similar extent and are not transformed.

The information on other properties reported in the data matrix presents an overall consistent quantitative pattern throughout the category. In the short-term aquatic toxicity studies, increasing strength of effects were observed from A to D. The aquatic toxicity effects of the target substance C are predicted based on the regular pattern observed in effects of the source substances A, B and D.

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

Substances A, B, C and D are structurally similar substances. Their structures differ only in the carbon chain

length, increasing from A to D. The functional groups are identical. All four substances have a high molecular weight, are lipophilic and not transformed. In the short-term aquatic toxicity studies with A, B and D, toxic effects were not observed. The absence of aquatic toxicity effects in short-term exposure are predicted for the target substance C based on the results for source substances A, B and D.

Scenario 4 and 6-specific assessment elements
The scientific aspects addressed in the AEs developed for assessing the category hypothesis of Scenarios 4 and 6 are presented below. The complete set of information attached to each AE is presented in Annexes ENV-D (Scenario 4) and ENV-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 Degradation
This AE addresses abiotic and biotic degradation processes and the purpose is two-fold:

1. to address the link between structure and property if degradation is to be predicted;

2. to address the degradation processes that can occur in the course of testing and alter the test material identity if the prediction is for bioaccumulation or environmental effect properties.

If abiotic or biotic degradation is predicted, it must be assessed from the documentation whether the members of the category may be transformed (degraded) and if yes, whether the transformation occurs at the same rate or to the same extent.

If the degradation potential is likely to differ, the implications this has on the acceptability of the read-across should be explained. Scenario 4 may apply rather than Scenario 6, and the hypothesis should explain the variation in the predicted property (regular pattern). A worst-case approach may also still be acceptable (Scenario 6), if a scientifically-valid hypothesis and evidence are provided to show that the property is not underestimated (e.g. lower persistency of the target substance). Furthermore, if persistency of a compound is predicted, the read-across should address the persistency of potential degradation products.

If bioaccumulation potential or environmental effects are being predicted, it has to be assessed whether the justification addresses the potential degradation of the target and source compounds during the test. This is required to understand to which compounds the organisms are exposed in a bioaccumulation or (eco)toxicity test and to what extent.

AE 4.2 and 6.2 Bioaccumulation potential
This AE examines the bioaccumulation potential of the category members and whether they are likely to be the same (Scenario 6) or follow a regular pattern (Scenario 4), based on structural similarity and relevant (physicochemical and fate) properties that can be linked to bioaccumulation potential. The AE is applicable to predictions of bioaccumulation potential and environmental effects (a difference in bioaccumulation potential may affect the strength of effects).

This AE should use the information collected in the earlier assessment elements on degradation, as well as related properties such as bioavailability and uptake potential of substances (e.g. adsorption, water solubility, lipophilicity). If the related properties differ, the implications this has on the predicted property should be explained.

Scenario 4 may apply rather than Scenario 6, and the hypothesis should explain the variation in the predicted property (regular pattern). A worst-case approach may also still be acceptable (Scenario 6) if a scientifically-valid hypothesis and evidence are provided to show that the property is not underestimated.

If environmental effects are predicted, the justification has to be assessed to see whether it addresses the bioaccumulation of the compounds during the ecotoxicity test. Whether those differences are reflected in the documentation regarding quantitative aspect of predicting environmental effects of the target substance (AE 4.4 and 6.4) should also be assessed. This is required to understand the extent to which the compounds are accumulated and cause toxic effects during an ecotoxicity test.

AE 4.3 and 6.3 Common underlying mechanism, qualitative aspects
This AE addresses qualitative aspects of the toxic potential of the category members and is applicable to predictions of environmental effects.

The category hypothesis should explain how exposure to different compounds causes the same effects or absence of effects. A mechanism needs to be identified and should 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 (mode or mechanism of action) is established and if this allows the prediction of a similar type of effect, qualitatively.

AE 4.4 and 6.4 Common underlying mechanism, quantitative aspects
This AE addresses quantitative aspects of the toxic potential of the category members, and is only applicable to predictions of environmental effects.

This AE investigates whether it has been established that the common underlying mechanism assessed in AE 4.3 and 6.3 leads to the same quantitative outcome (Scenario 6) or quantitative variations in the effects (Scenario 4).

Under Scenario 4, quantitative variations in the effect are expected. These variations may be caused by differences in fate and/or bioaccumulation among the category members.

The prediction needs to be supported by the scientific explanation of how the differences in fate and/or bioaccumulation potential determine the quantitative variations in the type of effects observed for the effect property under consideration (hypothesis verification).

The AE assesses whether the prediction is derived from the observation of a regular pattern between the effects 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 effect 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, no quantitative differences of biological significance should be observed for the predicted effect property or the differences should not be underestimated (i.e. as a worst-case approach). The prediction needs to be supported by a scientific explanation of how potential differences in fate and bioaccumulation do not produce quantitative variations in the type of effects observed for the effect property under consideration.

The AE should use the information collected in the earlier assessment elements on the degradation and bioaccumulation potential. These assessment elements reflect potential differences that the compounds may have regarding bioavailability and uptake, which in turn determine the concentration of the compound that reaches the target sites of toxic action and can cause the effects.

Table 15 - Overview of the Scenarios 4 and 6-specific AEs

SCENARIO 4	SCENARIO 6	ASSESSMENT ELEMENT TITLE
AE 4.1	AE 6.1	Degradation
AE 4.2	AE 6.2	Bioaccumulation potential
AE 4.3	AE 6.3	Common underlying mechanism, qualitative aspects
AE 4.4	AE 6.4	Common underlying mechanism, quantitative aspects

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 that 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 or other) 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: 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 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. The term “transformation” used for environmental endpoints refers to abiotic and biotic degradation.

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 based on defined structural similarity and differences between the substances. As a result of the structural similarity, one or more (toxicological or other) 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 (category description) and details on the identity and purity/impurity profiles of the category members.
Category description	The category description describes the applicability domain (or boundaries) of the category and clearly identifies which substances can be part of the category and which not.
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.
Fate	Distribution of a chemical in various environmental compartments (e.g. soil or sediment, water, air, biota) as a result of transport, partitioning, transformation, and degradation. In the RAAF, fate properties are used to indicate REACH standard information requirements related to fate (e.g. bioaccumulation, hydrolysis, biodegradation).
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, environmental fate or (exo)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.
Transformation	A series of chemical changes in a compound as a result of biotic or abiotic degradation.
UVCB	Substances of Unknown or Variable composition, Complex reaction products or Biological materials.
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; therefore, 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.

EUROPEAN CHEMICALS AGENCY
ANNANKATU 18, P.O. BOX 400,
FI-00121 HELSINKI, FINLAND
ECHA.EUROPA.EU

Publications Office