Experts Workshop on Read-Across Assessment

with the active support of Cefic LRI

2-3 October 2012
ECHA's Conference Centre, Guido Sacconi Room, Annankatu 18, Helsinki

Background paper

An Introduction to the Assessment of Read-Across in ECHA

Introduction

Read-across data are under certain conditions accepted under the REACH Regulation as a means to meet information requirements, and many registration dossiers submitted by industry contain read-across proposals. The legal requirements for read-across under REACH are listed in Annex XI (1.5) of the REACH Regulation. The results should be 'adequate' for classification and/or risk assessment, have 'adequate and reliable' coverage of the key parameters as in the standard test method, cover a comparable or longer exposure duration, and there must be 'adequate and reliable' documentation. However, it is not explicitly indicated what is meant by 'adequate' and 'reliable' and how these qualifications relate to the 'acceptance' of read-across and how to deal with any uncertainty that is introduced. Also the relevant guidance (Chapter R6 of the 'Guidance on information requirements and chemical safety assessment') does not explicitly indicate when read-across is 'good enough' for acceptance and how the remaining uncertainty should be dealt with.

ECHA is in the process of developing a framework for the assessment of read-across cases to be used in the dossier-evaluation work: 'The Read-Across Assessment Framework', or RAAF. This framework is meant to present a structured tool for the assessment of read-across cases by the ECHA evaluators. It is thus not meant to serve as guidance for registrants, although knowledge about how read-across cases are examined by ECHA is expected to help the registrant to improve the quality of their registration dossiers. In its current form, the RAAF covers only toxicity studies for human health endpoints.

The framework is only to deal with read-across that is aimed at meeting specific information requirements for substances (i.e. studies from Annex VII to Annex X of the REACH Regulation). The starting point is a study with a 'source substance' (i.e. the 'analogue'). The core of the read-across consists of the explanation by the registrant why the result of this study can also be applied to the 'target substance', so that the prediction can be used to meet the REACH information requirement for the target substance (*i.e.* the registered substance). It should be noted that the RAAF is to assess read-across of study results, not of classifications of the source substance or of hazardous properties of the source substance predicted by non-standard methods or by means of a weight-of-evidence approach.

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

The RAAF will facilitate examination of testing proposals that involve read-across, i.e. when the registrant proposes to provide Annex IX or X toxicology information on target substance(s) by means of a new higher-tier study on the source substance.

The RAAF will also be used in compliance checks for dossiers where standard information from Annexes VII to X for the target substance is provided by read-across. The study on the source substance can be examined in the compliance check.

The REACH guidance distinguishes two types of read-across: analogue-approach read-across and grouping/category-approach read-across. The first type is concerned with read-across between two or among a few analogues, the second type involves a larger group of substances and is supported by regular patterns in this group for the endpoint that has to be read across. The RAAF covers both, analogue-approach and grouping/category-approach read-across. (The broader approach to chemical categories or grouping used in some other regulatory schemes or for other purposes should not be confused with the specific purpose for REACH information requirements examined in the RAAF.)

The RAAF consists of a two-tiered assessment scheme. Tier I, which is currently well developed, leads the evaluator through a series of key questions about the nature and the occurrence of read-across cases in a registration dossier, the compliance of these cases with the legal text and the guidance, the presentation of the cases and their basic scientific quality. Depending on the answers to these questions the outcome of Tier I can be that a read-across case is:

- Set aside as not necessary to assess;
- Rejected;
- Accepted on grounds that are immediately evident and allow for the highest level of confidence (i.e. cases that are self-evident and obviously satisfactory);
- Passed for further evaluation to the next tier (*i.e.* Tier II), when the answers from the Tier I questions fail to result in setting aside, rejecting or accepting the read-across case.

After the clear cases are 'filtered out' during Tier I, the remaining read-across cases are examined in Tier II of the RAAF. The Tier-II assessment is ultimately based on expert judgement. The Tier II, which is still in development, offers a structure and rules to facilitate consistent, explicit and transparent expert judgement of read-across cases.

Tier I

Tier I consists of a series straightforward questions on the occurrence, nature and quality of read-across cases in REACH-registration dossiers. Specific issues addressed are:

- **The presence of overt and/or hidden cases of read-across in a dossier**

  Every dossier has to be investigated for the occurrence of both 'overt' and 'hidden' cases of read-across. An overt case of read-across is identified as such by the registrant. The Tier I evaluator has to check whether it is indeed read-across. A 'hidden' case is when a registrant uses a test on a different substance, but does not specifically 'flag' that read-across is used.

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

- **Read-across in a supporting role or meant to fill an information requirement on its own**

  The purpose of read-across can be to entirely replace the results of a standard experimental study (stand-alone read-across) and hence meet mandatory information requirements for the registration tonnage (as listed in Annex VII to Annex X). In some cases it has a more supporting role. It can be part of a weight of evidence (WoE) analysis.

  The RAAF is in first instance concerned with stand-alone read-across cases. Supporting read-across cases are first judged as to their potential value for/contribution to the WoE analysis, based on their outcome. They are only assessed for their validity (acceptability) if their outcome really adds to the WoE analysis. Depending on their role in the WoE analysis, an adapted assessment may be contemplated in some cases.

- **Whether it can be deemed redundant and thus needs no further evaluation**

  Read-across cases can be redundant, i.e. their outcome does not influence the outcome of a compliance check of the dossier or the evaluation of a testing proposal. For instance, if a read-across case is present for a 28-day repeated dose toxicity (RTD) study while a valid 90-day repeated-dose toxicity study by the same route is available, the read-across case would be redundant since the presence of the 90-day study is a valid Column 2 adaptation for the 28-day study. Another example is when the read-across is presented for an information requirement for a higher-tonnage band than is required.

  In some cases it can also be decided to not assess read-across because, whatever its validity and outcome, the outcome of hazard assessment is clear and not expected to be influenced by it.

- **The substance identity and the purity of substances**

  Read-across depends on the identity of the source substance(s) and the target substance, and it is affected by the quantity and nature of impurities in both substances. Poor information on the tested source substance and, in particular, on its composition and impurity profile, can give rise to doubts as to whether the test results are informative for the proposed target substance. Multi-component substances and, in particular, UVCBs deserve special attention.

- **Read-across as part of a testing proposal**

  Some registrants include a proposal in their dossier for testing an analogue of the substance to be registered, as noted above in the Introduction. After the performance of the test, the result is to be read-across from that analogue as the source substance to the registered target substance under consideration. However, if the testing proposal on the source substance is unacceptable (e.g. the information requirement is already fulfilled), irrespective of the relevance of the read-across, the read-across is not assessed.

- **Coverage of the key parameters addressed in the test that is replaced**

  As noted in the Introduction, the study with the source substance must have adequate and reliable coverage of the key parameters as in the standard test method. Qualitative and quantitative differences in the investigated parameters should not result in an underestimation of hazard. This issue is primarily of concern in case of old studies or published data on the source substance, as a

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

study complying with the current EU method or OECD guideline will normally be adequate.

- **Exposure duration in the test with the target substance that is replaced**

  The exposure duration often strongly influences the types of effects observed and the sensitivity with which the effects are observed. Exposure duration is thus a key issue according to Annex XI, 1.5. For example, if the information requirement is for a 90-day repeated-dose toxicity study, it would normally not be possible to base read-across on a 28-day study. Annex XI, 1.5 adds the phrase: "if exposure duration is a relevant parameter".

- **The use of the result of the read-across for classification and labelling and/or risk assessment**

  Annex XI of the REACH Regulation stipulates that the result of read-across should be adequate for the classification and labelling and/or risk assessment.

- **The adequacy and reliability of the documentation provided by the registrant on the applied method, including the registrant's explanation as to why the read-across is possible and the supporting information**

  Adequate and reliable documentation of the entire read-across methodology should be submitted. This documentation should contain the following elements:

  - A detailed description of the study or studies on the source substance and their results (the source information) from which the property is read across.
  - A scientifically-credible explanation (read-across 'hypothesis') as to why the property of the source substance can be read-across to the target substance. Any limitations in the hypothesis should be described by the registrant. See Guidance (R.6.2.6) on the "Reporting formats for analogue and category evaluations".
  - The supporting evidence for the read-across hypothesis, such as scientific arguments, relevant information on other properties or other arguments.

  It is judged whether the hypothesis is clearly presented, logical, consistent and based on sound scientific principles.

- **Obvious cases that can immediately be accepted or rejected**

  Some cases are immediately obvious. An example of obvious acceptance is the immediate hydrolysis (preferably supported by experimental data) of both the source substance and the target substance into innocuous substance(s) and identical degradant toxicant(s): hence the same toxic responses can then be assumed. An example of obvious rejection is when the source and target substance are known to follow different toxicokinetic pathways resulting in markedly different distribution and/or metabolism and/or excretion; hence in spite of chemical similarity it can not be assumed there is toxicological similarity and the read-across case should be rejected. Cases can also become obvious when they are clearly contraindicated by information available to the evaluator.

If after addressing these issues no definitive decision can be taken on a read-across case, the case is to be further evaluated under Tier II.

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

Tier II

Tier II of the RAAF is concerned with read-across cases that are not rejected, set-aside or accepted during Tier I. Whereas much of the evaluation under Tier I is based on clear-cut and explicit criteria, it is not appropriate to use 'simplistic' criteria under Tier II; instead, the assessment is performed by a group of experienced experts. Tier II of the RAAF is to ensure that this expert judgement is exercised in a structured, consistent, explicit and transparent manner. In addition, Tier II allows that accepted read-across cases may have different levels of 'confidence' associated with them, and hence there is a consideration of the impact of uncertainty from the read-across test result on the hazard assessment of the target substance (for use in risk assessment and classification by the registrant).

The assessment starts under Tier II with establishing what basic type of read-across is proposed, from the explanation by the registrant why the read-across is possible (i.e. the read-across hypothesis). There are a finite number of explanation types and each of these can be characterised by a set of specific aspects that taken together are crucial for the scientific credibility and reliability of the read-across case. These key aspects thus play a central role in the assessment of the read-across case for each basic type of read-across. The expert is guided in assessing each of the key aspect into selecting from a series of defined possible assessment options. Hence the Tier-II assessment is structured in terms of basic read-across types, each with key aspects that are examined to determine the credibility and reliability of the read-across.

As noted above, it is assumed that there are a limited number of basic types of read-across explanations. These may include the following. The registrant may, for instance, argue that chemical or biological conversion results in exposure to the same toxicants, and subsequently the same effects. Another possible explanation is that two structurally different substances are still sufficiently similar in chemical structure to belong to a group of substances that cause effects *via* interaction by means of an identical mode of action with identical toxicological endpoints. Identical interactions and endpoints may imply predictability of the effects of one substance based on the effects observed with another. Read-across may in some cases also be based on purely statistical arguments. When a plot of the property under consideration on another property shows a clear trend for a group of substances, this trend alone may suffice for prediction. The explanation is sometimes also based on trends observed for other properties than the property under consideration, which are assumed to go with possibilities to predict effects.

These possible basic read-across explanation types (read-across hypotheses) are listed in Table 1 and examples of key aspects of two of these are shown in Table 2. A possible combination of a key aspect and the associated possible assessment options is given in Table 3.

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

Table 1. Examples of basic of read-across types

Type		Description
Analogue approach	Identical toxicants through biotransformation	Chemical or biological transformation results in exposure to the same toxicants, and subsequently the same effects.
	Different ultimate toxicants	Source and target are known to belong to a group of substances that cause effects by means of an identical mode of action with identical toxicological endpoints. Identical interactions and endpoints imply predictability of effects.
Category approach	Trend in the property to be read across	A plot of the property under consideration on another property shows a clear trend for a group of substances, this trend alone may suffice for prediction.
	Trend in the property to be read across plus a mechanistic explanation	A plot of the property under consideration on another property shows a trend for a group of substances; moreover, there is a mechanistic explanation why group membership goes with predictive power.
	Trend in other properties	Trends observed for other properties than the property under consideration go with possibilities to predict effects.

Table 2. Examples of key aspects of two read-across types

Example 1 Identical toxicants through (bio)transformation	Example 2 Different ultimate toxicants
Formation of common products that may cause toxic effects	(Bio)transformation
Formation of different non-toxic compounds	Structural boundaries
Existence and influence of other (bio)transformation pathways	Common modes of action
Influence of distribution and exposure	Quantitative differences in the common modes of action
Toxicity of intermediates and parent compounds	Non-common modes of action
	Exposure of target tissues and organs

The expert decides whether and, if so, to what extent the available information provided by the registrant supports the read-across case as regards each key aspect for the read-across type. In the absence of information relevant to the key aspect, the expert may be able nevertheless to reach a conclusion, based on his own expertise and knowledge; however, he cannot research the matter in detail.

The assessment of a key aspect will in many cases ultimately rely on expert judgement, i.e. there is no 'obvious' conclusion. Ultimately the expert needs to

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

balance the scientific arguments and information to give a 'best' opinion: this analysis and balancing of arguments and information is recorded, with an indication of where subjective choices were necessary, in the interests of transparency.

Table 3. A key aspect (see Table 2, Example 2) with its assessment options

Example explanation for read-across 2: Different ultimate toxicants	
Key aspect	**Assessment Option** The evaluator has to select one of these options for this key aspect
(Bio)transformation A key aspect of this example explanation of read-across is whether the ultimate toxic substances are the source and target themselves or (bio)transformation products of source and target. It also addressed the question of the influence of (bio)transformation in case source and target are postulated to be the ultimate toxic substances. In this example, a convincing coverage of the key aspect in the read-across hypothesis is deemed sufficient. In case of other possible examples, the availability of supporting data obtained with source and/or target may have a heavier weight in the assessment.	Convincingly addressed by the read-across hypothesis and available evidence
	Not convincingly addressed by the read-across hypothesis and available evidence AND Evaluator has no reasons to assume that (bio)transformation invalidates the registrant's assumption that parent compounds are the ultimate toxicants.
	Not convincingly addressed by the read-across hypothesis and available evidence AND Evaluator confident that the proposed (bio)transformation products are the ultimate toxicants.
	Not convincingly addressed by the read-across hypothesis and available evidence AND Evaluator concerned about the influence of (bio)transformation on the possibility to read across based on the assumption that the parent compounds are the ultimate toxicants. AND Concern might be alleviated by means of additional information.
	Not convincingly addressed by the read-across hypothesis and available evidence AND Evaluator concerned about the formation of the (bio)transformation product(s) that are assumed to be the ultimate toxicants. AND Concern might be alleviated by means of additional information.
	Not convincingly addressed by the read-across hypothesis and available evidence AND Evaluator concerned about the influence of (bio)transformation on the possibility to read across based on the assumption that source and target are the ultimate toxicants. AND Not expected that additional information will alleviate concern.

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

Example explanation for read-across 2: Different ultimate toxicants	
Key aspect	**Assessment Option** The evaluator has to select one of these options for this key aspect
	Not convincingly addressed by the read-across hypothesis and available evidence AND Evaluator concerned about the formation of the (bio)transformation product(s) that are assumed to be the ultimate toxicants. AND Not expected that additional information will alleviate concern.

Only one of the possible assessment options can be selected per key aspect and this assessment option indicates the credibility and reliability of the read-across hypothesis as regards that particular key aspect, i.e. it reflects the confidence of the assessor. The overall assessment of the read-across case is determined by the level of confidence for the weakest key aspect. In other words, it is the weakest "link" that determines the strength of the "read-across chain". This level of confidence determines whether the read-across proposal of the registrant can be accepted. If the proposal is accepted, the level of confidence also implies a level of uncertainty. The uncertainty in the read-across result in terms of the impact on risk assessment and classification in the registration should subsequently be accounted for. It may be appropriate to use assessment factors for this.

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu