Assessment of Read-Across in ECHA

Under construction

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- Introduction & background
- Legal requirements
- Assessment of a prediction
- Outline of a possible approach

Introduction & background

Intelligent approach to property evaluation in REACH

- **New animal studies are a last resort** for REACH registration.

- **Data sharing** obligations for registrants of the same substance to avoid duplicate testing.

- Registrants must first **collect and assess all existing data**, then **identify data gaps** and consider whether **data waivers** apply or if gaps can be filled by **non-standard data** before deciding on new studies.

- **Annex XI 'adaptation'** of the standard information requirements.

- Information from structurally-related substances, i.e. '**read-across' and 'chemical categories/grouping'**.

Conditions for non-standard data for REACH

- Results must be **adequate for classification**.

- Results must enable **adequate risk assessment**.

- **Key parameters from the standard study** are addressed, e.g. adequate exposure duration & route for toxicology data.

- Thoroughly-documented **scientific explanation** to justify the non-standard methods, e.g. a hypothesis for why the properties of a substance can be 'read across' with supporting evidence.

What is a good read-across case?

Discussions on read-across mostly focus on how a good case can and should be built by industry.

The definition of "good" is the problem in these discussions.

In a sense, these discussions are open-ended. They hardly address the criteria for "good" in terms of "acceptance by the evaluator".

Clear and explicit criteria for regulatory acceptance are not formulated. Possibly because such criteria cannot be defined.

Assessment is about acceptance

The assessment of read-across cases by the regulatory authority is not described in a guidance. For the regulatory assessor the question is:

"When is a case acceptable for a certain purpose?"

Assessment is about uncertainty

When a case is accepted by a regulatory authority for a certain purpose, the second question is:

> **"How should the extra uncertainty be dealt with, which is inevitably associated with read-across, as it is, after all, a prediction."**

A standardized approach is necessary for the assessment

REACH offers the facility of read-across as an alternative to standard tests. Hence the pre-occupation of ECHA experts with these questions. In other words, we have to deal with your proposals.

This presentation is on how ECHA tries to get a grip on the assessment of read-across, including our attempts to develop a consistent, transparent and structured internal assessment approach.

ECHA read-across framework (RAAF): a work in progress

- For ECHA use in examining read-across cases in dossier evaluation (CCHs & TPEs);

- An outcome from September 2010 ECHA workshop on non-test methods

- Scope of RAAF being developed: human health studies that are read-across/grouping from tested 'source' substance(s) to 'target' substance(s) to fulfil REACH registration information requirements.

Tier I. A screening phase.

- Sift out clearly inadequate cases, identify 'obvious' cases & which to pass to Tier II for thorough scientific scrutiny.

Tier II. Scientific evaluation phase (in development)

- This phase covers the scientific core of the assessment using expert judgement in a structured manner to score the read-across hypothesis to conclude on the acceptability of the case & the associated uncertainty.

Legal requirements

Read-Across under REACH

ANNEX XI

GENERAL RULES FOR ADAPTATION OF THE STANDARD TESTING REGIME SET OUT IN ANNEXES VII TO X

1.5 Grouping of substances and read-across approach

Guidance on information requirements and chemical safety assessment

Volume 3: Collection, evaluation, adaptation and generation of information

Chapter R.6: QSARs and grouping of chemicals

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ANNEX XI, 1.5

Grouping of substances and read-across approach

Substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern **as a result of structural similarity** may be considered as a group, or 'category' of substances.

Application of the group concept requires that physicochemical properties, human health effects and environmental effects or environmental fate **may be predicted** from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach). …..

ANNEX XI, 1.5

The similarities **may** be based on:

(1) a common functional group;

(2) the common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals; or

(3) a constant pattern in the changing of the potency of the properties across the category.

ANNEX XI, 1.5

If the group concept is applied, substances shall be classified and labelled on this basis.

In all cases results should:

— be adequate for the purpose of classification and labelling and/or risk assessment,

— have adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3),

— cover an exposure duration comparable to or longer than the corresponding test method referred to in Article 13(3) if exposure duration is a relevant parameter, and

— **adequate and reliable documentation of the applied method shall be provided.**

Under REACH it is essential that:

- Meeting an information requirement by means of read-across should not lead to an underestimation of hazard for the considered toxicological endpoint.

- *I.e.*, an underestimation compared to the estimation of this hazard based on a standard study.

- The data-gap should be filled in such a way by read-across that the result can be used as a starting point for the normal REACH hazard and risk assessment for the endpoint, *e.g.*, DNEL derivation.

- An overestimation of hazard is sometimes accepted, as long as the hazard and risk assessment remains meaningful.

Assessment of a Prediction

Assessment of a Prediction

Information requirement under REACH can be met by means of the **standard study** or a comparable study.

The relevant property is then **measured** for the test substance by means of a method that is accepted beforehand.

Information requirement can also be met by means of **read-across**.

The relevant property is then **predicted** starting from a **measurement** of that property for another substance (the source).

Assessment of a Prediction

If the **correct test and measurement** is carried out (according to the guidelines and under GLP), the information requirement is met.

Assessment: Check whether the correct test conditions and measurements were indeed applied.

Even if **read-across** is carried out in an **perfect way**, it still has to be decided during the assessment whether the case is convincing enough to accept the prediction and, if so, under what conditions.

Assessment: Experts have to form an opinion; assessment is ultimately based on expert judgement.

Assessment of a Prediction

Explicit criteria for the acceptance or rejection of a read-across case do not exist.

There is a gradual scale from "**not at all credible**" to "**immediately evident**".

The acceptance of read-across cases made according to the rules, still requires that the evaluator is convinced based on theory and supporting data.

Read-across cases that follow all the rules are **NOT per definition, i.e., automatically, acceptable**.

Read-across = measurement + prediction

"Prediction" implies that for well-made cases:

- It is difficult to imply explicit criteria in the assessment;

- The outcome of the assessment always contains terms as "convincing", "plausible", "likely", etc.;

- The assessment is always ultimately based on "expert judgement";

- There is always residual uncertainty.

Assessment of a Prediction

The registrant has to **convince** the assessor that the property of the target substance can indeed with a sufficient level of confidence be predicted based on results obtained with the source.

This means that this prediction should not result in an underestimation of the hazard in comparison to such an estimation when it is based on a measurement by means of a standard study.

Assessment of a Prediction

Ultimately it is not possible to **prove** that the test with the target can be replaced. It can "only" be made scientifically credible on the basis of theory and supporting data.

The registrant has to deal with the **residual uncertainty**. This means that in many cases the result obtained with the source substance cannot be used as such for the target. Uncertainty has to be compensated for.

PREDICTION AND UNCERTAINTY

Annex I, Section 1.4

Section 1.4 of Annex I, where it is stated:

When establishing the DNEL, the following factors shall, inter alia, be taken into account:

(a) the uncertainty arising, among other factors, from the variability in the experimental information and from intra- and inter-species variation;

(b) the nature and severity of the effect;

(c) the sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies.

PREDICTION AND UNCERTAINTY

The REACH guidance (R.8.4.3) stipulates the following.

Special consideration should also be given to alternative data, e.g. in vitro data, (Q)SAR, **read across** *or chemical categories. The use of alternative data is stimulated under REACH and preferred above performing additional animal studies, if considered justified. However, using these data in a quantitative way (if at all possible) might be associated with some additional uncertainty in the dose descriptor derived (see Chapter R.7 and general guidance on (Q)SARs and grouping of chemicals (Chapter R.6)).* **This should be accounted for.**

Table R. 8-6 Default assessment factors

Assessment factor – accounting for differences in:		Default value systemic effects	Default value local effects
Interspecies	- correction for differences in metabolic rate per body weight	$AS^{a, b}$	–
	- remaining differences	2.5	1^f 2.5^g
Intraspecies	- worker	5	5
	- general population	10^c	10^c
Exposure duration	- subacute to sub-chronic	3	3^h
	- sub-chronic to chronic	2	2^h
	- subacute to chronic	6	6^h
Dose-response	- issues related to reliability of the dose-response, incl. LOAEL/NAEL extrapolation and severity of effect	1^d	1^d
Quality of whole database	- issues related to completeness and consistency of the available data	1^d	1^d
	- issues related to reliability of the alternative data	1^e	1^e

[a] AS = factor for allometric scaling (see Table R. 8-3)

[b] Caution should be taken when the starting point is an inhalation or diet study

[c] Not always covering for very young children; see text for deviations from default

[d] See text for deviations from default

[e] Special consideration needed on a case-by-case basis

[f] for effects on skin, eye and GI tract via simple destruction of membranes

[g] for effects on skin, eye and GI tract via local metabolism; for effects on respiratory tract

Models versus case-by-case

Read-across is **prediction on a case-to-case basis**. Every case needs its own theory (explanation why it is possible to read-across) and supporting data, generic and/or substance-specific. And every case needs to be assessed individually.

Prediction in toxicology can also be based in some cases on **models**, which are expected to predict relevant properties in a certain applicability domain. Then the assessment is focussed on the model and its domain, and if combination of both is acceptable, the predictions are in principle accepted.

Building Quality and Certainty

The "building quality" of a read-across proposal determines our insight in the:

→ **Effect that the target substance would have in the replaced test**. ←

The "100%-certainty" level can in theory be approached by means of a large supporting-research effort.

However, such an effort can show with 100% certainty that read-across is impossible.

Higher certainty does not imply **higher acceptability**.

Lower certainty implies a **higher risk of underestimation**.

Expert judgement

Expert judgement

The assessment of read-across is characterized by:

- The absence of explicit standard criteria for the assessment;
- The fact that read-across is a case-by-case prediction;
- The freedom of the registrant to come with whatever theory and whatever data to build and support his case.

Conclusion: the assessment has to rely strongly on the personal judgement of the expert.

Expert judgement

Experts are needed for the assessment, who can deal with (aspects of) the various types of explanations (read-across hypotheses) and supporting data.

These experts decide whether a read-across case can be **accepted**. If they accept a case, they have to indicate a level of **confidence**, and, thereby the **residual uncertainty**.

Expert judgement in a regulatory context should be characterized by:

- Transparency;
- Consistency;
- Clear explanation;
- Traceability.

Outline of an approach

Outline of an approach

ECHA's assessment approach addresses the following questions.

- Is the read-across really necessary or should it be deemed redundant and set aside?
- Should it be rejected for administrative, legal or technical shortcomings?
- Should it be accepted or rejected for obvious scientific reasons?
- Should it be accepted or rejected on the basis of expert judgement?
- How to deal with uncertainty after acceptance?

Outline of an approach

Assessment by ECHA is done at two levels:

Tier I → A screening level, aimed at weeding out and addressing the obvious cases; see the first three bullet points of the previous slide.

Tier II → An expert-judgement level, addressing the well built cases that are not set-aside, accepted or rejected during Tier I.
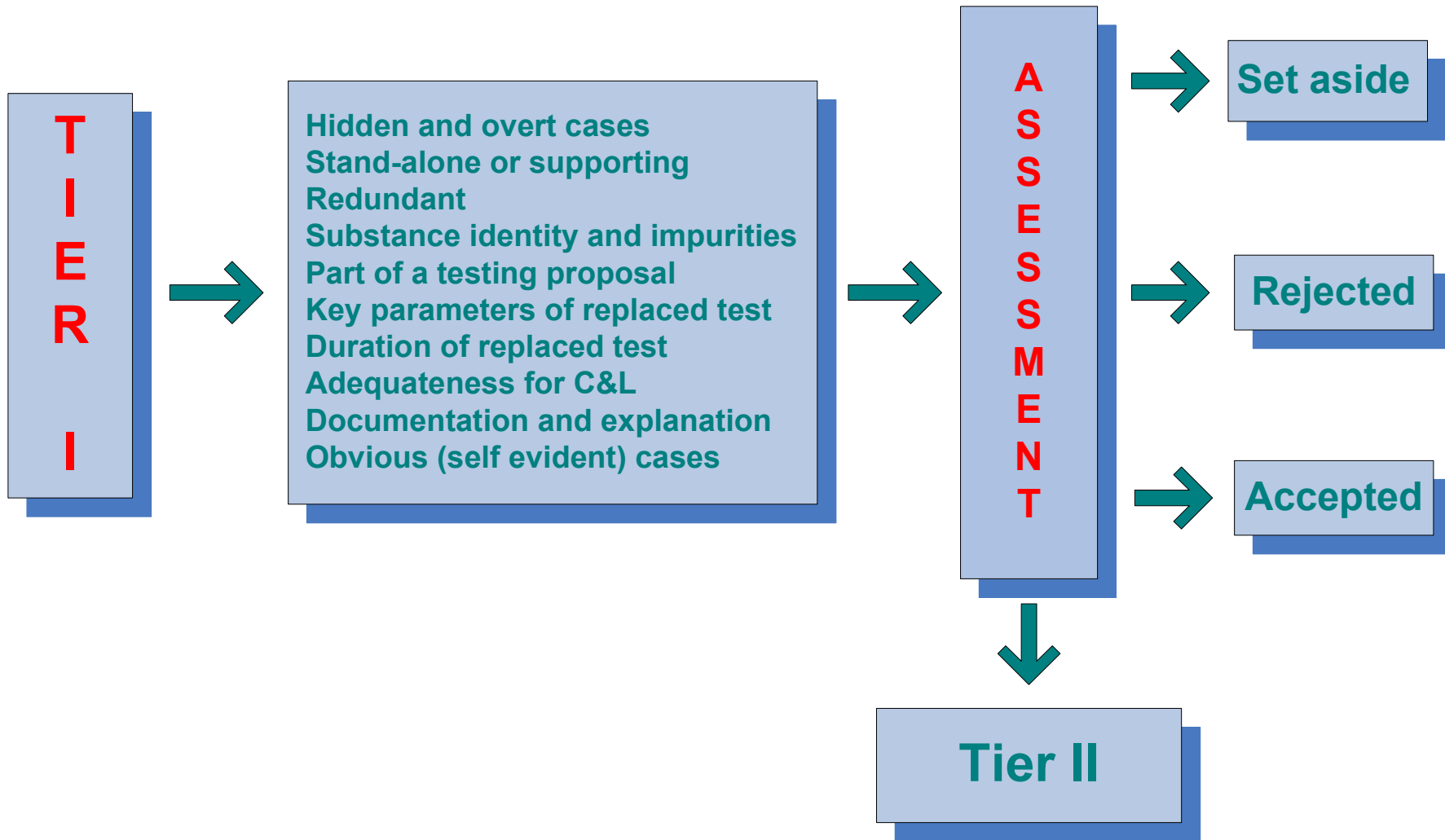
Outline of an approach

Acceptance in Tier I:

Only with the highest level of confidence

Uncertainty needs not to be addressed.

Acceptance in Tier II:

Three different levels of confidence

Uncertainty to be compensated for the lowest and the middle level of confidence

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T I E R I

Hidden and overt cases
Stand-alone or supporting
Redundant
Substance identity and impurities
Part of a testing proposal
Key parameters of replaced test
Duration of replaced test
Adequateness for C&L
Documentation and explanation
Obvious (self evident) cases

A S S E S S M E N T

Set aside

Rejected

Accepted

Tier II

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.
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.

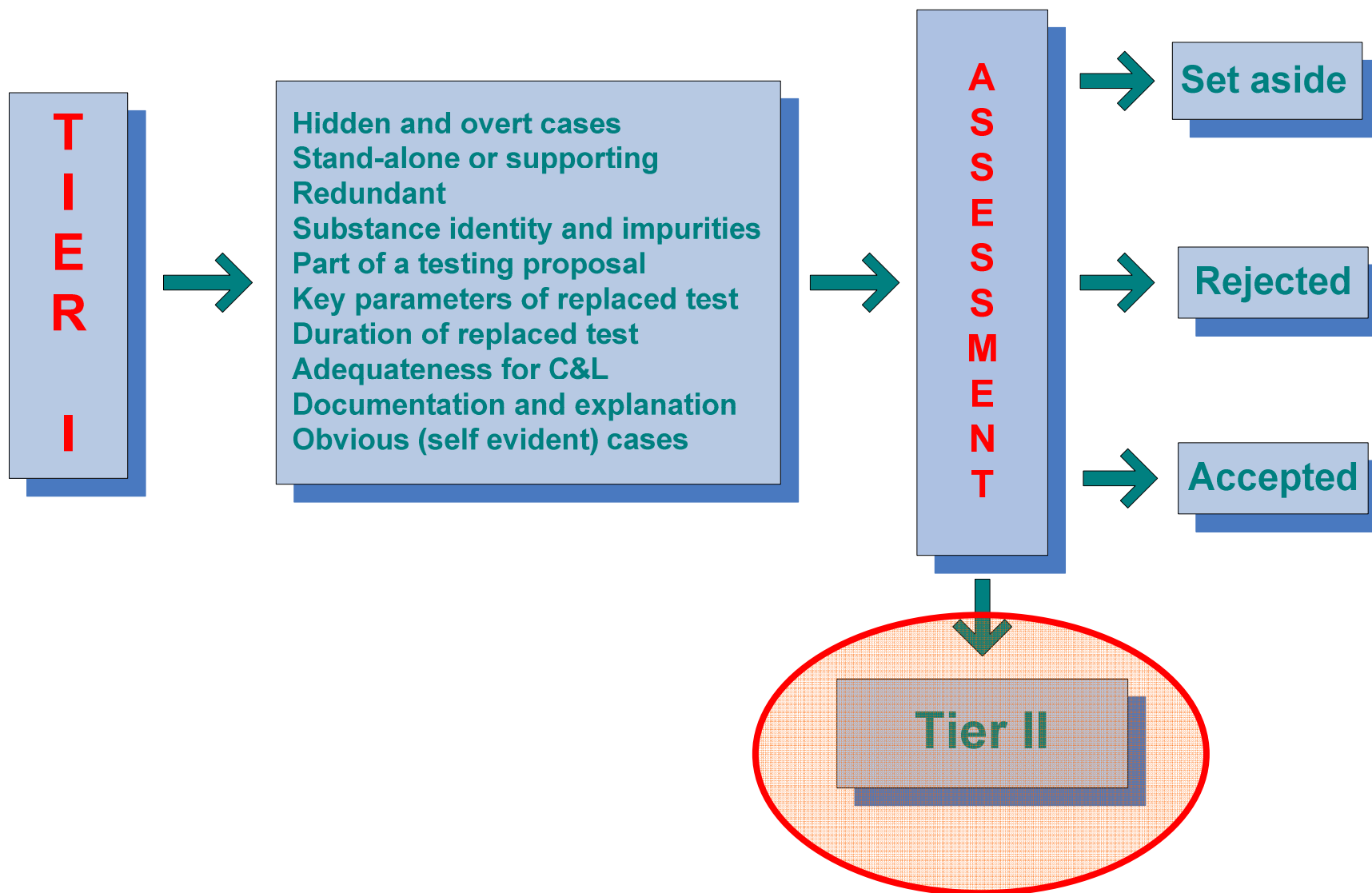| Whether it can be deemed redundant and thus needs no further evaluation	Read-across cases can be redundant, i.e. their outcome does not influence the outcome of a compliance check of the dossier or the evaluation of a testing proposal. For instance, if a read-across case is present for a 28-day repeated 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, assuming an acceptable read-across, for whatever reason, 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 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 ads the phrase: "if exposure duration is a relevant parameter".

TIER I

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	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.

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TIER I

Hidden and overt cases
Stand-alone or supporting
Redundant
Substance identity and impurities
Part of a testing proposal
Key parameters of replaced test
Duration of replaced test
Adequateness for C&L
Documentation and explanation
Obvious (self evident) cases

ASSESSMENT

Set aside

Rejected

Accepted

Tier II

Tier II → Structured Expert Judgement

Different **basic types of read-across** are defined.

Crucial or key aspects are defined for each different type of read-across. These are the aspects that are deemed to determine acceptance and the level of confidence.

Each key aspect has a number of **assessment options**, representing **levels of confidence**.

The assessment approach is tuned by the definition of the basic types of read-across, the key aspects and the assessment options.
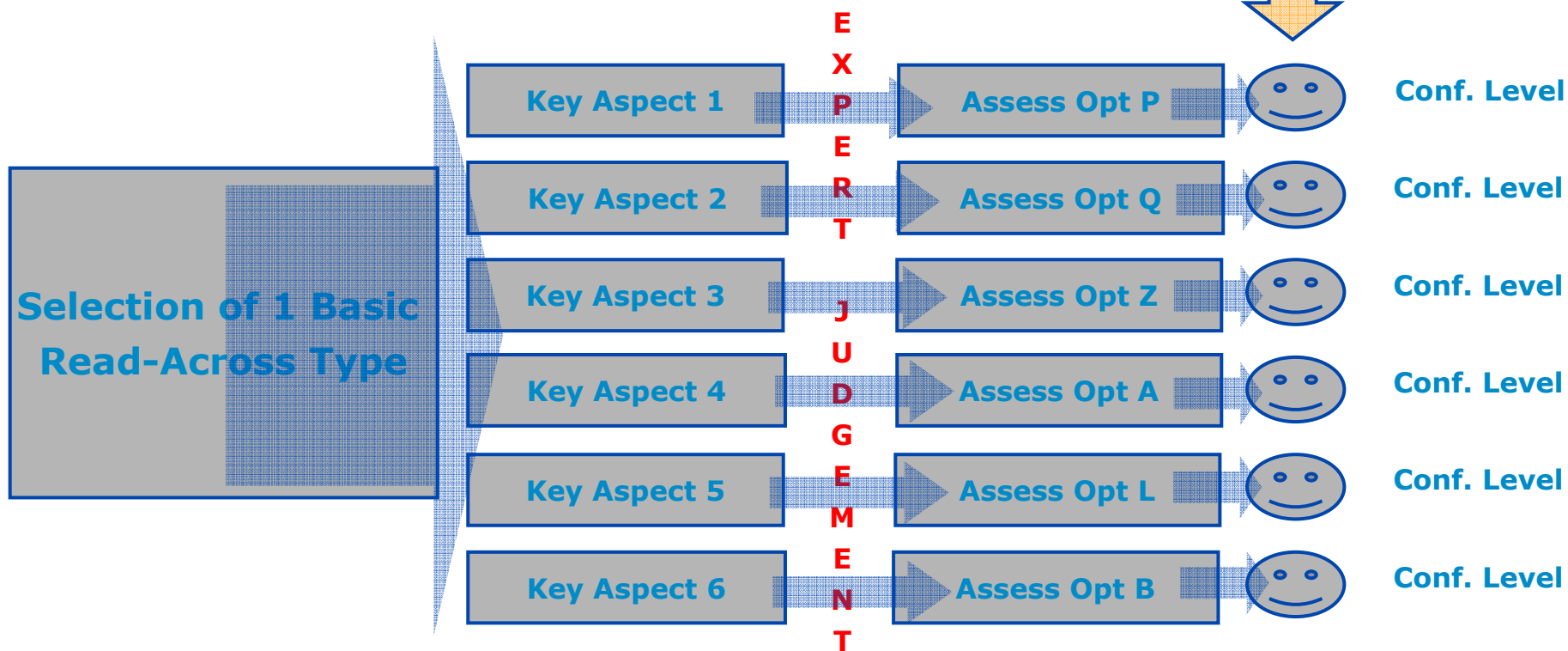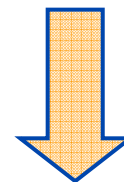
One of the assessment options has to be chosen by the evaluator for each key aspect. This choice has to be accompanied by a written explanation and opinion.

So there is a series of chosen options. The one with the lowest confidence level determines acceptance and how residual uncertainty is addressed.

Outline of an approach

Which one has the lowest confidence level?

TIER II

		Conf. Level
Key Aspect 1	Assess Opt P	Conf. Level
Key Aspect 2	Assess Opt Q	Conf. Level
Key Aspect 3	Assess Opt Z	Conf. Level
Key Aspect 4	Assess Opt A	Conf. Level
Key Aspect 5	Assess Opt L	Conf. Level
Key Aspect 6	Assess Opt B	Conf. Level

Selection of 1 Basic Read-Across Type

EXPERT JUDGEMENT

It is the weakest link that determines the strength of the read-across chain

Essential components of a read-across proposal

Core of EVERY read-across proposal consists of:

The explanation by the registrant why the read-across can be done (read-across hypothesis or theory) and generic or substance-specific data that support this explanation.

Types of Read-Across

- Analogue approach: between two or among a few substances; trends play no role;

- Category approach: among a group of substances; trends in the group play a role.

Types of read-across hypotheses

- Theoretical mechanistic explanation (read-across hypothesis) why the results with the source can indeed be used for the target. Needs in most cases generic and/or substance-specific supporting data.

- Theoretical mechanistic explanation (group justification) why group membership goes with certain properties (similar, identical, absence, regular pattern). Needs in most cases data with group members that support the group justification. Other, generic and/or substance-specific supporting data may also be required.

- Analysis of a trend within a group for the REACH relevant property under consideration. Always requires a lot of data on this property the for group members.

- Analysis of trends within a group for **other** REACH relevant properties than the one under consideration. Always requires a lot of data on these properties for group members.

Types of read-across hypotheses are already reflected by the Regulation

ANNEX XI, 1.5

The similarities **may** be based on:

(1) a common functional group;

(2) the common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals; or

(3) a constant pattern in the changing of the potency of the properties across the category.

Examples of basic 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.

Key Aspects

Every basic explanation is characterized by its own set of key aspects. These are the aspects that are dominating its predictive value. In other words, the aspects that are critical or crucial for the acceptance and reliability of the read-across case.

Possible 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

Assessment Options

The level of confidence has to be established for each key aspect. In other words, it has to be determined whether and if so, to what extent the read-across succeeds as regards the key aspect under consideration.

To this end specific assessment options are defined for each key aspect. The assessor has to select one option for each key aspect. The options are linked to a pre-defined level of confidence.

Example 2: Different ultimate toxicants

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 addresses 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.

Assessment Options 1

Key Aspect "Biotransformation" of Example 2

The evaluator has to select one of these options for this key aspect

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.

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Assessment Options 2

Key Aspect "Biotransformation" of Example 2

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 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.
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.

Sensitivity of the Approach

The sensitivity of the assessment to accept a read-across proposal is strongly determined by the definition of the basic read-across hypotheses, the key aspects, and the assessment options and the link of these with confidence levels.

Future RA cases

- RAAF is a concept that helps decision making for evaluators;

- RAAF is not a ready made solution for ideal RA building but helps to understand the "base-line" quality aspects;

- RAAF is work in progress;

- Feedback from MSCA expert – see next presentation.

Thank You.

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