

Dossier Evaluation Process - principles applied by ECHA in reviewing read-across and category approaches

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European Chemicals Agency



Background

- As part of REACH Evaluation Joint Action Plan
 - ECHA and the Commission are stepping up actions to identify substances for data generation
 - Current focus is registrations with tonnage band over 100 tpa
- Companies with large portfolios and Industry associations are in a position to optimise testing strategies
 - A cooperation agreement with CEFIC is an action under the Action Plan
 - Workshops organised by ECHA and CEFIC identified learnings on how to improve compliance for groups of substances
- Registrants may proactively wish to submit testing strategies and testing proposals to address deficiencies in their registrations
- This presentation aims to clarify the general expectations for the submission of testing strategies under dossier evaluation for groups of substances

Compliance check versus Testing Proposal

Compliance Check

- ECHA requires information to bring the dossier into compliance
- If read-across adaptation fails, ECHA rejects the approach and requests resulting data gaps for each substance
- Limited possibility to consider refined/new testing strategy during the process

Testing Proposals

- Possibility to incorporate a testing strategy with the submitted Testing Proposals
 - Sequence of tests for a substance, and within a category

Main reasons for non-compliance

- Waiving of data requirements not correctly justified
- Adaptations (**read-across**, QSAR, WoE) failing due to lack of solid scientific justification or documentation – leading to data gaps for higher tier information requirements
- Documentation insufficient - e.g. insufficient level of detail in robust study summaries to allow for an independent assessment
- Check: <https://echa.europa.eu/recommendations-to-registrants>



Why *read-across* fails – most common deficiencies observed



Read-across approach Analogue or category

Structural similarity
(Analogue approach)

Category definition
(Category approach)

Hypothesis: basis why a **property** can be predicted

Justification: **supporting evidence** to verify the basis for the **prediction**

Data: source study(ies) and results serving as the basis for the prediction
The effects observed characterise the property of the **source** substance(s)

Read-across as a **technique** to predict



Outcome: prediction of the property under consideration for the **target** substance(s)

Read-across assessment framework

- Registrants can use it to improve their read-across adaptations
- Structures and codifies expert judgement of complex scientific questions on the critical aspects of read-across
- Covers Human Health and Environment; separate consideration for UVCBs



Please see <https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across>



How to support read-across

Type and amount of information needed depends on the read-across hypothesis and the information requirement to be read across

The RAAF defines two general read-across hypotheses:

1. (Bio)transformation into a common toxicant
 - Toxicokinetic information may support the approach
2. Different compounds have the same type of effects
 - Toxicodynamic information may support the approach

RAAF assessment – What’s the problem?

Assessment element	Examples of typical issues identified
Formation common compound	No information provided, not rapid/complete metabolism
Common underlying mechanisms	Cannot assess – no data on target, different effects in different types of studies
Consistency effects in matrix	Cannot assess – no data on target, different effects in different types of studies, clear different effects
Impact parent compound	Not complete/rapid metabolism, no data on parent compound
Formation/impact non-common compounds (NCC)	No info ID of NCC., no tox data on NCC
Occurrence of other effects than predicted	Cannot assess – no data on target, different effects in different types of studies, clear different effects
Structural similarity/differences in category	No info on applicability domain of the category, missing info on ID and composition of substances
Substance characterisation (source/cat members)	Missing information on ID and composition



Frequent deficiencies (1)

- Insufficient characterisation of the source and target substances: identifiers, structure, composition
 - Does not allow comparison of structural similarity between the source and target substance(s). Similarity not established
- Unreliable data for the source substance
 - Data provided for the source substance is not reliable and/or summary does not allow independent assessment
 - Example of read-across results from 90-day study from substance X to substance Y.
 - But 90-day study with substance X is non-compliant as it does not cover all necessary investigations; therefore, no adequate basis for prediction



Frequent deficiencies (2)

- **Missing read-across hypothesis**
 - Absence of scientific justification linking structural similarity with prediction of properties
 - No explanation why it is possible to read-across from substance X to substance Y. Structural similarity alone is not enough
- **Missing considerations on impact of structural differences**
 - Example of read-across from linear to branched compounds with no consideration on the impact branching may have on toxicological properties
 - A 'small' difference in structure can lead to different properties
- **Inconsistencies in the toxicological profiles**
 - No explanation provided on the reasons for different effects and why the issue is disregarded/not relevant for read-across



Frequent deficiencies (3)

- Absence of supporting information on key aspects to substantiate the hypothesis
 - Example 1 – read across from substance X to substance Y because substance X has higher toxicity (“worst case scenario”) – but there is no data to confirm
 - Example 2 – read-across from substance X to substance Y because substance Y hydrolyses fast to substance X – but no hydrolysis data to prove the rate of hydrolysis for the substance
 - Example 3 – read-across from substance X to substance Y because they have similar effects – but there is no data (bridging studies or other information) for both substances to demonstrate similar effects



Frequent deficiencies (4) - categories

- Category definition
 - Applicability domain of the category not identified: Borders not specified, absence of clear inclusion and exclusion criteria, e.g. range carbon chain length, linear/branching, type and number of functional groups, range of specific physico-chemical properties
- Data density within the category
 - Low data density within the category, often limited to a single data point (e.g. source study): generally insufficient to address the structural variations across the category
 - Waiving of all higher tier data or too small number of tests proposed
 - Lower tier data inconsistent with the hypothesis



**How to improve compliance –
stepping up efforts**

**Benefits of Testing
Strategies**



Testing proposals

- Testing proposals can incorporate a strategy – e.g. in a category approach
 - To support the approach, some tests could be initiated immediately (e.g. Annex VII & VIII information requirements, toxicokinetics)
 - Testing proposals are made for the higher tier tests for selected substances as part of a testing strategy to cover the whole category of substances
 - Commitment and need for realism with regard to how compliance could be achieved within reasonable timelines
- Submitting testing proposals as part of a well founded read across testing strategy can save costs and reduce the number of required animal tests

Organisational Issues for Registrants

- Consortia management, in particular aligning on the decisions to be taken, is of paramount importance
 - Large groups can present logistical challenges
- Timely availability of laboratory capacity can create some constraints
- Registrants should consider updating their dossiers before starting to work on establishing a testing strategy to further improve the data quality of the dossier
- Registrants need to demonstrate a clear commitment towards their proposed testing strategy and defined timelines (e.g. via Testing Proposals). Acknowledging that deviations may occur, if properly justified

Category definition

- The category domain with clear boundaries needs to be provided
- Describe which substances are part of the category
- Provide details on their identity and purity/impurity profiles

Substance identity

- Clear description of the composition of the substance is a prerequisite for the application of read-across
 - Unknown impurities' to be reported (individually or as groups)
 - Sufficient analysis of the compositions to be included)
 - Manufacturing process adequately described (e.g. UVCBs)
- Align compositions of all co-registrants with the Boundary Composition for the registered substance

Test material

- Registrants need to ensure that the test material is representative of the boundary composition
- Describe the composition of test material
 - Detailed information on the amount, variation and identity of constituents

Data gap analysis

- Must be realistic

Read-across hypothesis (1)

- Hypothesis generation
 - Responsibility of Registrants
 - Generate data so that hypothesis has support
 - Initial hypothesis may fail
 - Requires detailed knowledge of substances and scientific area
- Read-across hypothesis
 - Essential to guide the testing strategy
 - Must have support from data so that there is a realistic basis ('plausible') for undertaking the planned testing
 - ECHA evaluates at this standard
- Early generation of (Annex VII/VIII) data is strongly recommended

Read-across hypothesis (2)

- Hypothesis based on biotransformation might be plausible (e.g. read across from data on a metabolite of the substance)
 - Often the biotransformation hypothesis is more challenging: reliant on detailed information on TK including (multistep) metabolism or degradation
 - ECHA cannot require TK studies under Dossier Evaluation
 - Responsibility is on the registrants to make the case and generate non-standard information
- More usually, the hypothesis is that there is a trend within a category, i.e. similar structures have similar effects
 - This hypothesis will require considerable supporting data
 - Large groups can introduce greater variety of structural dissimilarities which need to be addressed by the hypothesis and supporting data

Annex VII/VIII information

- Data fulfilling Annex VII/VIII standard information requirements, can inform on higher testing needs (e.g. Annex IX/X requirements) and support the read across
 - Generate a data matrix
 - Consider gaps in Annex IX/X information requirements, taking into account triggers for testing & waiving opportunities & information needed for e.g. (v)P(v)BT assessment
 - Note that the OECD TG 422 provides screening level properties information on both reproductive and repeated dose toxicity and may provide useful supporting ('bridging') information
- Such data generation does not require Testing Proposal
- In general, ECHA would normally expect a complete set of Annex VII/VIII information
 - Taking account of adaptation possibilities, allowance for large categories if justified

Annex IX/X information

- For a category of mainly Annex IX/X substances, experience shows that a proportion of 30-50% higher tier studies with data from the registered substances is needed to support the read across hypothesis
- Deviations from these percentages are possible with the proper justification (e.g. worst case, very similar compositions)
- If higher tier studies are required for your strategy you will need to submit Testing Proposals to generate the data

Testing Proposals

- The specific higher-tier tests, and the substances to be tested, must be unambiguously specified
- The proposed testing strategy should cover all endpoints targeted and decision points must be clear
 - e.g. for PNDT: *“we will do 1st and 2nd species PNDTs for specific substances, on the basis of a read-across hypothesis”*- potentially acceptable
 - *“we will do 1st species PNDTs, then evaluate the need for 2nd species PNDT”* - not acceptable
- EOGRTS TPs will only be processed once the results of 90-day studies are known
- Possible to include in the strategy the option of changing substances to be tested for the submitted TPs based on the results of e.g. expected OECD 422 screening studies, if adequately justified

Testing Strategy

- Pay attention to justifying your strategy
- Testing strategies either fail or succeed
- Negotiation of a new strategy is not possible during the course of a dossier evaluation process
- Failure of a strategy (for read-across) leads to testing requests for all data gaps for all substances

Summary

- Be realistic in your data gap analysis and testing strategy
- Clear understanding of substance ID is a prerequisite
- Need clarity on substances in the group and their regulatory status
 - Avoid too large/too small groups
 - Make use of the information in the chemical universe on ECHA's website
- Availability/generation of Annex VII/VIII tests is usually necessary (no Testing Proposals needed)
- Strategy can be tiered but would need to show commitment for doing higher-tier testing to fill the gaps e.g. through submission of TPs
- Start preparing your testing strategies and generating supporting data as early as possible
- Responsibility remains with the registrants to make the case

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