Example of a metal category, cobalt compounds

MISA

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General introduction(1)

- ECHA mostly examines the categories under compliance check
- If the read-across adaptation, which based on a category fails, all the missing data is requested for all the category members
- This could be avoided in case such data is generated, which shows the similarity or trend in the category, and an adequate justification and documentation according the RAAF are given

General introduction(2)

- In regard of the read-across and categories, examination of testing proposals differs from compliance check.
- Testing programs may be means to strengthen the category. ECHA has discussed the testing program with some consortia, but our resources for that are limited.
- Metals and metal compounds differ from the organic substances, the example will show how

Introduction to the Cobalt case

- The consortia/registrants propose that with read-across, the higher tier toxicity of several cobalt compounds could be predicted.
- The prediction is based e.g. on existing studies of some well-characterised cobalt compounds and on a trend of bioavailability, and sub-grouping.
- The evaluation of this case and our advice to you are based on the Read Across Assessment Framework RAAF published by ECHA

1. Category definition, category domain

- According to REACH Annex XI, Section 1.5., it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group by interpolation to other substances in the group (read-across approach).
- Based on the above, a group or “category“ needs to defined in such a manner that the boundaries of the group are clearly indicated.

Provided in the dossier or in updated documents

Members of the category are the Annex IX and Annex X metal compounds.

"The substances are characterised by the same physico-chemical characteristics considered relevant for this assessment:

- all represent inorganic salts, oxides/hydroxides or elemental cobalt
- all liberate divalent cobalt cations upon dissolution in biological media, which is the toxicologically relevant species
- anionic species liberated upon dissolution are considered to contribute to a much lesser extent to the overall toxicity compared to the cobalt cation."

List of substances that belong to each of the three sub-groups is given.

ECHAs evaluation:

- The category definition has been improved, sub-categories are clearly set out.
- Not yet clear how the low tonnage Cobalt can be covered by the read-across.
- For the lower tonnage cobalt compounds, certain read-across adaptations (e.g. for 90 day, EOGRTS and PNDT) will not be necessary.

2. Substance characterisation AE C.1

- RAAF: The substances that are grouped in a category need to be clearly identified and characterised.
- The REG should provide data on the chemical identity and the impurity profile of each category member that are sufficiently detailed for a scientific assessment of the category approach.

Provided in the dossier

- Inorganic members of the category are mono-constituent substances.
- Some of the cobalt “carboxylates” are UVCBs.
- The relevant SID information is provided.

ECHAs evaluation

- Concerning the inorganic cobalt compounds, SID the information is considered sufficient.

3. Structural similarity and differences within the category AE C.2

- RAAF: 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.
- The REG needs to make sure that the structural similarities among all category members are identified and that the structural differences allowed within the category are described.

Provided in the dossiers

- The common characteristic of the source and target substances is that all substances liberate cobalt cations as the same toxic entity upon dissolution in aqueous biological media...
- There are quantitative differences in the dissolution rate in different aqueous biological media
- Impurity profiles are addressed shortly

ECHAs evaluation

- ECHA did not question the structural/chemical similarity in the final decision on the testing proposals.

4. Link of structural similarities with the proposed regular pattern of toxicity AE C.3

- RAAF: In read-across, 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.
- Thus REG needs to provide a category hypothesis and demonstrate that it applies to all the category members.
- The hypothesis can also be seen as a **method of prediction**. The hypothesis explains why and how the unknown toxicity of the target substances can be predicted using the toxicity and other data on the sources substance(s).

Provided in the report dated 18/09/2018:

- The common characteristic of the source and target substances is that they liberate cobalt cations as the same toxic entity upon dissolution in aqueous biological media…
- There are quantitative differences in the dissolution rate in different aqueous biological media, thus an assumed difference in systemic toxicity which is predicted to correlate with the ability of the substance to release cobalt cations (dissolution kinetics)
- …the systemic toxicity of the dissolved cobalt substance can be interpolated by assessing the toxicity of cobalt as toxicological relevant unit.

ECHAs preliminary evaluation of the report

- In general the hypothesis is plausible
- It appears that a quantitative prediction is not made per substance, but will be based on data on selected member of a sub-group.
- However, it is not clear how exactly the prediction for the RDT properties will be made.
- In the worst case approach, only the most bioaccessible member of a group could represent the repeated dose toxicity of all members of that sub-group.

Take home message - Solutions

- The possible effects of the counter-ion, especially on the absorption needs to be addressed.
- “Bioavailability” studies may be useful, when a trend within the category is demonstrated/documented.
- However, bioavailability (uptake) *in vivo* is a dynamic process and a non-animal test methods may underestimate the actual uptake and systemic dose of the metal.
- Therefore, *in vitro* bioaccessibility should be used for grouping, but not for risk assessment purposes.
- Bridging studies, i.e. sub-acute studies or reproductive toxicity screening studies are useful tools in bringing confidence that the category holds.

5. Consistency of effects in the data matrix, (toxicological similarity) AE C.4

- You should demonstrate that the category members have similar toxic properties.
- The category justification should include a comparison of the existing experimental data for the category members
- This comparison should be provided preferably in the form of a data matrix.
- The available data should show that properties of the group members across the data matrix are consistent.

Provided in the report dated 18/09/2018

- The bioaccessibility data was put into relation to the effect levels of oral repeated dose toxicity studies, by plotting the NOAEL values against the bioelution data.
- The data cover the full spectrum from readily to poorly bioaccessible cobalt substances."
- The in vivo NOAELs confirm the expected low toxicity of the less bioaccessible substances *tricobalt tetraoxide and cobalt sulphide*, and conversely the expected high toxicity of *cobalt dichloride and cobalt metal powder.*
- Also new *in vivo* toxicokinetic studies have been reported.
- Three sub-groups are presented.

ECHAs preliminary evaluation of the report

- The correlation between bioaccessibility and toxicity data per group appears to support the relevance of the bioaccessibility data.
- The mismatch that concerns the *organic* cobalt compounds has been adequately addressed.

Take home message – Solutions

- A matrix that shows the consistency and inconsistencies among the category members is a very useful tool in read-across, both for the registrants and for ECHA.
- A matrix will show e.g. whether the bioelution/bioaccessibility data matches with the toxicity studies.
- In case only few substances have adequate higher tier toxicity data, it will be difficult to confirm the category hypothesis and predict the toxicity of the target substances.

Example of a data matrix: Toxicity of ethylene glycols

Category Member	EG	DEG	TEG	tetraEG	pentaEG
Acute oral toxicity (rat)	LD_{50}: 4000 – 13000 mg/kg	LD_{50}: 253000 mg/kg	LD_{50}: 17000-22000 mg/kg	LD_{50}: 34700 mg/kg	LD_{50}: > 16000 mg/kg
Acute inhalation toxicity (rat)	6800 mg/m3/h (TOPKAT 6.1 prediction)*	0/10 deaths at substantially saturated vapour	0/10 deaths at 50 mg/L (aerosol)	0/6 deaths at substantially saturated vapour	0/12 deaths at 2516 mg/m^3 aerosol
Skin irritation (human)	Some evidence of irritation (humans)	Minimal irritation (humans)	Minimal irritation (humans)	Minimal irritation (humans)	Minor irritation (rabbit)
Eye irritation	Minimal irritation	Minimal irritation	Minimal irritation	Minor transient irritation	Minor transient irritation
Skin sensitization	Non-sensitizing (GPMT)	Non sensitizing (GPMT)	Non sensitizing (GPMT)	Non-sensitizing (GPMT)	Non sensitizing (read-across from other members of the category)
Reproductive toxicity (oral)	Two generation study (mice; drinking water): 0, 410, 840, 1640 mg/kg/d P (NOEL): 1640 mg/kg/d F1 (NOAEL): 840 mg/kg/d; F1 (LOEL): 1640 mg/kg/d (lower number of live pups/litter, unusual facial features, skeletal defects);	RACB test (mice; drinking water): 0, 610, 3060, 6130 mg/kg/d P (NOEL): 3060 mg/kg/d F1 (NOEL): 3060 mg/kg/d F1 (LOAEL): 6130 me/kg/d (decreased number of litters per fertile pair)	RACB (mice; drinking water): 0, 590, 3300, 6780 mg/kg/d P (NOAEL): > 6780 mg/kg/d F1 (NOAEL): > 6780 mg/kg/d	NOAEL (mice): > 6000 mg/kg/d (read-across from TEG)	NOAEL (mice): >6000 mg/kg/d (read-across from TEG)

What does the example show

- In a data matrix, you can see consistency and inconsistency or individual endpoints - and across the endpoints
- You can assess, whether there seems to be enough data to demonstrate similarity or a trend
- You can consider your “method of prediction”: e.g.
  - similarity across the category,
  - trend, or
  - read-across from the closing analogue
- When a category is “data rich” you might want to choose one study per item in the matrix

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

- RAAF: the source study(ies) need to match the default REACH requirements in terms of adequacy and reliability.
- Adequacy and reliability of the study design of the source study(ies) should be addressed.
- The test material(s) should represent the source substance(s) in terms of purity and impurities.
- Study results should be adequate for classification and labelling and/or risk assessment.

Provided in the dossiers

The key studies on repeated dose toxicity, genotoxicity, reproductive toxicity (screening studies), and developmental toxicity are mostly rated with reliability 1, and are recently made.

ECHAs evaluation

ECHA did not question the quality of the source studies in the final decision on the testing proposals.

Take home message - Solutions

- The studies made with the source substance of the read-across must be of sufficient quality and reliability.
- In case Klimisch score 1 or 2 can be allocated to those studies, they are normally adequate.
- Adherence to the GLP and to the OECD test guidelines are indicators of adequate quality.