MISA 1 workshop
Human Health Endpoint information requirements

Brussels – 2 October 2018

Executive Summary

The first MISA workshop, focusing on the human health information requirements/adaptations/read-across, was attended by about 50 participants and was structured in sessions discussing the following themes: read-across, Extended One Generation Reproductive Toxicity studies, routes of exposure and mutagenicity.
In preparation of the workshop consortia had been invited to carry out an assessment of their registration files for the endpoints of interest, using a self-assessment tool developed by Eurometaux (SAT-HH).
The results of these self-assessments allowed to a) provide an overview of the situation of the dossier when it comes to data/strengths, b) give indications where work may be needed, and c) identify recurrent questions/elements around which to structure the workshop.

The workshop started with a presentation by Jos Mossink (ECHA), who recalled that by 2020, ECHA wants to know for all substances > 100 tons whether they are of (potential) concern, or if there is a need for more (hazard) information and if these substances need to be addressed through regulatory risk management action or can labelled as currently of low priority. This however requires good data and registration dossiers are vital in this perspective to demonstrate that industry knows its portfolio, that all necessary information is available, that the chemical safety assessment is appropriate and convincing and that all customers are informed adequately on how the substance must be safely used.

The workshop used a format of plenary and breakouts discussions, with examples and case studies so as, to as much as possible, achieve clear agreements on how to address the regulatory requirements and/or identify issues where technical support would be needed.

In follow-up of the workshop, industry was expected to complete a workplan and submit it to ECHA.

A detailed report of the workshop, reporting in detail the discussions held on 2 October was prepared and reviewed by ECHA/Eurometaux. It is available for the MISA participating metals/inorganics. The key learning lessons are reported below by topic addressed during the workshop.

1. Read-across

The case studies discussed in plenary (presented by ECHA and by industry) allowed to explain how to provide/build an adequate justification and documentation according to the Read Across Assessment Framework (RAAF) elements. Key aspects are recalled below but the workshop participants were referred both to the RAAF as well as to the two case studies for more details.

- **Category definition and the category domain**. A group or "category" needs to be defined in such a manner that the boundaries of the group are clearly indicated.
- **Substance characterisation Assessment Element**: Substances that are grouped in a category need to be clearly identified and characterised by the registrant. Data should cover the chemical identity and the impurity profile of each category member, so as to allow a scientific assessment of the category approach. Substance Identification (SID) is the starting point of the assessment.
- **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." The registration dossier should therefore contain an explanation to ensure that the structural similarities among all category members are identified and that the structural differences allowed within the category are well described.
- **Link of the structural similarities with the proposed regular pattern of toxicity:** The registrant needs to provide a category hypothesis and demonstrate that it applies to all the category members. The hypothesis explains why and how the unknown toxicity of the target substances can be predicted using the toxicity and other data on the source substance(s) used in REACH.

  Important notes in this context:
  - the possible effects of the counter-ion, especially on absorption, need to be addressed
  - *in vitro* bioaccessibility can be used for grouping and assess trends, but under certain conditions. A base set of in vivo data is required for each category.
  - bridging studies (sub-acute or reproductive screening studies) are useful tools to show that the category holds.

- **Consistency of effects in the data matrix:**
  The registrant should demonstrate that as a result of structural similarity the category members have similar toxic properties or the properties follow a regular pattern. The category justification should include a comparison of the existing experimental data for the category members. This comparison should be preferably provided in the form of a data matrix, which allows at a glance to see the consistency and inconsistency of individual endpoints and across the endpoints.
- **Reliability and adequacy of the source study(ies):**
  The source study(ies) need to match the default REACH requirements in terms of adequacy and reliability. The adequacy and reliability of the source study(ies) should be evaluated and reported in detail. Test material(s) should represent the source substance(s) in terms of purity and impurities.

A number of items were discussed more in depth in the breakouts and key messages of the discussions were summarised in the boxes below.

Data density: when is there enough data? When to split a category in subgroups? What for lower tonnages?

In a nutshell

- *Categories are based on similarity or trend scenarios*
- *(Sub)Grouping and scenarios are endpoint dependent!*
- *The justification for the category scenarios (one category or subgroup) needs to be provided*
- *Bioaccessibility data should not be used in isolation to justify a category. Supportive data should be provided to demonstrate the predictivity of the bioaccessibility data (e.g. bridging studies), making the link between in vitro and in vivo*
- *Lower tonnage substances should be included in grouping approach. They can be proposed for testing for higher tier endpoints as representative for the sub-category, but this is rarely done in practice in view of the uncertainty of the acceptance of the read-across*

Do we need different read-across for different exposure routes?

In a nutshell

- *The more data on different routes of exposure the better, but…*
- *Typically, the oral route is selected as the most relevant*
- *Read-across is route-dependent*

Mode of action vs. predictivity: useful or needed?

In a nutshell

- *Mode of action is not a data requirement as such*
- *It can be useful for justification of the read-across hypothesis*
- *This type of data is often not an element of standard OECD Guidelines tests*
- *Triggers which bridging studies to develop (in justification of the read-across)*

Can we do read-across from bioavailability alone?

In a nutshell

- *Not to use as stand-alone but in combination with toxicity data*
- *Helps to build the categories/subgroups*
- *Need for guidance on boundaries and streamlining of terminology*

Counterion: what do we do with it?

In a nutshell

- *Need to demonstrate that it does not add to the toxic effects and that it does not affect the bioavailability of the metal*
- *For organic anions: check degradation products*
- *Proposal: generate data set on common counterion*

Weight-of-evidence: what is a good WoE report?

In a nutshell, need to assess/report

- *Reliability (of all data used)*
- *Relevance for the endpoint*
- *Consistency of the data*

- *Coverage and Adequacy (covered parameters for the endpoints, key element for ECHA!)*
- *Validity*

Proposed actions:

- ***Have a compilation of examples of bridging studies***
- ***Prepare files on the counterions***
- ***Use a key event reasoning***
- ***Clarify role bioelution and terminology in a note/guide***

2. Extended One Generation Reproductive Toxicity Study

The starting point for the discussion were ECHA's expectations on this endpoint and industry's presentation on a case study. The summary of recommendations is reported in the box below.

In a nutshell:

- *If a 2-generation study initiated before 13 March 2015 is available (and is GLP and in accordance with OECD TG 416), it can be used to fulfil the EOGRTS (as column 1, "standard information requirements") BUT this requires checking the concern for DNT or DIT by using the same triggers as for EOGRTS cohorts (check ECHA Guidance)*
- *Follow-up tests: for DIT, still unclear, but for DNT, the OECD TG 426 may be considered*
- *A recent Board of Appeal case has confirmed that under Annex VIII an EOGRTS can be requested by ECHA when there is "serious concern"*
- *Pre-mating period: 10 weeks by default (if no F2). It can be shortened to 2 weeks. This duration is often relevant for metals, but most consortia considered 10 weeks to ensure acceptance of the data in other jurisdictions (this should be indicated in the justification/proposal)*
- *It is important to include a justification in the dossiers why F2, DNT, DIT or EOGRTS are not needed*
- *It is recommended to include explanation on the other study design parameters as well e.g. species; route, pre-mating exposure duration*

3. Elements to consider for the selection of the most appropriate route of administration for RDT studies.

Starting point for the discussion were the legal requirements under Annex VIII and Annex IX and a case study presented by industry.

In practice, there are three elements to consider for the selection of the most appropriate route of administration for RDT studies.

1. Is human exposure via inhalation likely?
2. Are local effects via the inhalation route already addressed?
3. Is there a concern e.g. route specific systemic toxicity that requires testing by the inhalation route?

The summary of recommendations is reported in the box below**.**

In a nutshell:

- *PROCs drive the assessment for the need to choose either the inhalation or oral route for systemic toxicity (repeated dose toxicity)*
- *There are some criteria to help with the selection/justification of the route of exposure: e.g. for dust.*
- *There is a trend for testing the inhalation route for 28 days in case of nano or spray coating (in additional to the oral 28 days)*
- *Local effects might drive an additional assessment route, however in case of irritation or sensitisation properties the inhalation route might be out of scope.*
- *It should be reminded that all registered forms of a substance have to be covered by the data*

4. Mutagenicity

The summary of recommendations is included in the box below:

In a nutshell:

- A weight-of-evidence approach is often applied for metals given they are often data- rich but one needs to ensure to:

- *differentiate high vs. low quality (Klimisch 1-2 in matrix vs 3 in separate document, to be provided as well)*
- *balance between scientific arguments and legal requirements*
- *that the scientific review is done on primary data*
- *stress data reliability: low relevance of Ames and cytogenicity tests for metals*

- IUCLID reporting:

- *Always link target and source substances when read-across*
- *If WoE is used, then it is difficult to report all individual data by specific endpoint. It is proposed to report data matrix and endpoint summary in pdf (e.g. in section 13) to facilitate assessor to get global overview. A reference to this document can be added under the endpoints as well*
- *There is a need to clarify when enough data is sufficient (question for the implementing Act)*