Executive summary

Eurometaux and ECHA conducted a 4-year programme to resolve a number of technical and methodological issues that registrants of metals, metal compounds and inorganic substances (named hereafter 'metal and inorganic substances') are confronted with when improving their registration dossiers. Planning of dossier updates to improve compliance and quality was an explicit part of the programme. In total 29 industry consortia/associations, covering most of the non-ferrous metals and metal compounds signed up to the voluntary programme. In this way a continued attention for REACH registrations was obtained after the 2018 registration deadline. The COVID pandemic delayed both the technical/scientific work and several planned dossier updates.

The work focussed on improving information on human health and environment endpoint, with a focus on the use of read-across, the application of the rapid removal principle for environmental classification, registration of inorganic UVCBs and exposure.
Summaries of workshops are published on the ECHA website and Eurometaux' Metals Gateway. Detailed reports, examples, and best practices are available to participants of the programme and Member State Competent Authorities.

On each of the topics the work resulted in guidelines and a harmonised approach to key issues, taking specific properties of metals and inorganics into account. This, combined with the structured self-assessment consortia/associations performed on the quality of their registration dossier formed a good starting point for improving dossiers (see also section 1.4).

The majority of participating consortia committed to dossier updates in a workplan, which led by the end of the programme in **about 60% of the substances updated at least once, on human health and environment endpoints**, significantly more than for other non-MISA substances.
While most updates concern improvement of read-across and waivers, there is also an increase in data generation and submission of testing proposals. However, data gaps still remain for some data poor substances.

The increased insight in metal specific issues at ECHA improved the priority setting for groups of metal substances in the Integrated Regulatory Strategy. It also increased the level of scientific capacity at ECHA regarding hazard- and risk assessment.

Participating consortia/associations supported **more consistent approaches to metal specificities in registration dossiers,** such as hazard assessment of inorganic UVCBs, addressing counter-ions and classification.

Overall, a good participation from industry consortia/associations and practical outcomes of the technical and scientific work led to a positive impact on dossier updates. However, some important metal and inorganic substances were missing from the programme and filling some specific data gaps remains an issue as, data availability is still low.

1. Overview of the programme

1.1. Objectives

MISA (Metals and Inorganics Sectoral Approach) is a voluntary programme set up by ECHA and Eurometaux, to address technical and scientific issues facing the metals and inorganics sectors and to update and improve the registration dossiers in these sectors[1]. It was endorsed by metals and inorganics consortia/associations by signing a framework for cooperation document.

The agreement included a Rolling Action plan for June 2018 to end 2020, due to the COVID pandemic extended to end 2021, focussing on two equally important parallel tracks:

- Resolving outstanding technical and methodological issues to allow the improvement of the relevance of hazard information, risk assessment and risk management of metals and inorganics.
- A gradual and planned improvement of the compliance, quality and understanding of the metals/inorganics registration dossiers.

MISA stimulated **the further improvement of chemicals management by the metals and inorganics sector and thereby supports the goals of ECHA's Integrated Regulatory Strategy** by identifying substances of concern based on improved hazard and exposure information. Industry participation was also an element in the 2020 goals of SAICM[2].

Eurometaux and ECHA both recognised MISA is not a substitute for the compliance with legal REACH obligations. ECHA and Member States continued or initiated regulatory actions when necessary. On the other hand, the MISA programme was expected to reduce or prevent the need for such regulatory action in view of the increased availability of improved information on the chemicals and their risk management, as well as by resolving outstanding technical issues.

Summaries of results were made public on the ECHA and Eurometaux websites, detailed reports are available to the participants and Member State Competent Authorities.[3]

1.2. Participation

In total 29 consortia/associations joined the programme and committed themselves by signing the Framework for Cooperation to the activities agreed in the Rolling Action Plan. In the course of the programme, more than 340 metal and inorganic substances were included, covering a majority of the volume of metals and inorganic substances on the EU market. Around 450 metal and inorganic substances from similar groups were not included in MISA programme.
Most metal and inorganic substances that did not participate had either a) no responsive

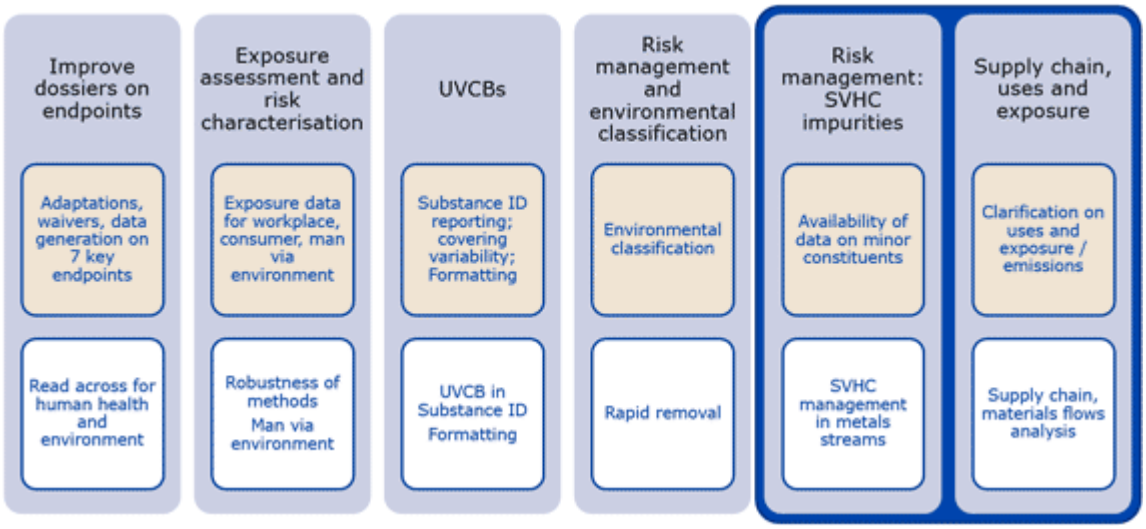
[1] The Joint Statement of ECHA and Eurometaux on the framework for cooperation is published at the ECHA website:
https://echa.europa.eu/documents/10162/3016194/jointstatement_signed_eurometaux.pdf/1d967e55-ba02-613e-17f0-4823c2078d6a
[2] See: http://www.saicm.org/Implementation/Towards2020/tabid/5499/language/en-US/Default.aspx
[3] MSCAs can find reports at the following link in S-CircaBC:
https://webgate.ec.europa.eu/s-circabc/w/browse/28d51e92-a9a2-4b52-85a3-6267b8cfdd62

consortium structure, or b) were covered by the organic sector or c) had only substances they felt not being in scope of the proposed activities. In addition, some participating consortia/associations only included some of metal compounds in their portfolio. However, it was observed that in such cases, the consortia/associations applied the learnings to all the substances they are responsible for. While the programme covered most of the important non-ferrous metals and their compounds, a few important metals groups like aluminium salts, manganese- and chromium compounds did not participate in MISA[4][5].

1.3. Structure of the programme

The MISA programme covered six priority areas of work, specified in a rolling action plan. The plan provided a description of the proposed work, formats and possible deliverables, with specified timelines and milestones[6].

Figure 1.1 Structure of the programme



1.4. General approach

For the workshops on read across for human health / environment endpoints, exposure and UVCBs, a common format was used.

In the preparation of each workshop, Eurometaux developed a specific Self-Assessment Tool (SAT) to (i) encourage consortia to review their registration dossiers and to spot possible shortcomings and (ii) identify technical and scientific issues that would need clarification during the workshops.

[4] A full list of participating consortia and substances can be found at https://echa.europa.eu/documents/10162/17228/misa_substances_consortia_rml_en.pdf/8d772c8e-9ce3-62e4-8d20-bf24603028a4

[5] These metal groups do not belong to the Eurometaux membership.

[6] The outline of the MISA programme is also explained at the Eurometaux REACH Metals Gateway: https://www.reach-metals.eu/metals-and-inorganics-sectoral-approach-misa

The self-assessments performed by the consortia ensured an in-depth and effective preparation for the participation in the MISA workshops. The self-assessments were reviewed by Eurometaux to identify commonalities as well as multi-metallic issues to be addressed. During the workshops, presentations of the key topics from the self-assessments, practical examples and discussion, were an opportunity to share good practices as well as to provide information on ECHA's expectations regarding the hazard assessment, classification and risk management. Industry participation in all workshops has been active and at a high quality.

Apart from the technical workshop on rapid removal, participation from Member State experts in the workshops has been relatively limited.
Presentations and detailed reports of the workshops were made available for the participants and to Member States. Summaries and key learnings were disseminated via the ECHA website and the Eurometaux REACH Metals Gateway and are available for a wider public.

Participating consortia and industry associations were invited to reflect the outcomes of the scientific and technical development in their work plans for dossier updates, with the findings of the self-assessment as a starting point.

ECHA did set up a regular follow-up of the work plans/updates by doing some checks and reporting the outcomes to the different consortia (e.g., in a one-pager). The MISA mailbox, set up and run by ECHA, allowed also for some specific interactions and to provide feedback when needed.

The MISA program focused on the updates and improvements of the registration dossiers as well as on the metal specific aspects of relevance. The check of quality of the updates (via compliance check or other evaluation activities) was not part of the MISA scope. However, it is expected that the use of specific examples during the workshops and publication of key learnings helped to ensure a minimum quality of the updates.

2. Technical and scientific developments

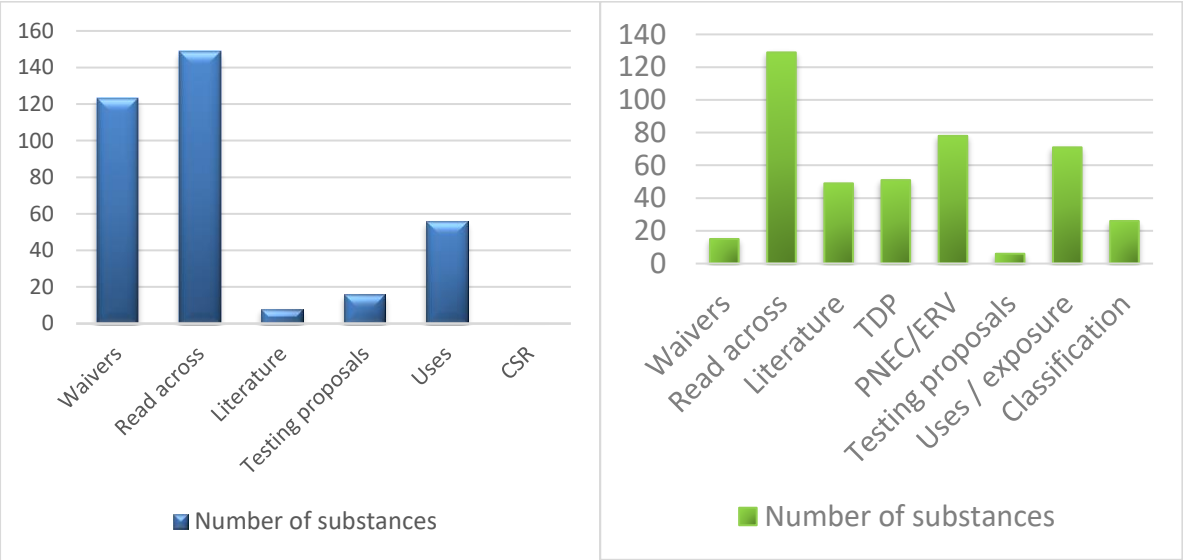
This chapter briefly summarises the key outcomes of the workshops that supported the technical and scientific developments. Summaries and key learnings are available on the ECHA and Eurometaux REACH Metals Gateway websites.

2.1. Information requirements

2.1.1. Background

It is recognised that for some endpoints, many metals, metal compounds and inorganics, the metal ion is driving the hazards. Read-across on the metal ion may therefore be a possible way to fulfil information requirements. In line with that, an analysis of the work plans and the realised dossier updates shows that for the several endpoints read-across as well as other adaptations, including waivers, are applied for many of the metal substances (see figure 2.1).

Figure 2.1 Approaches used in **updates** for human health (blue bars, left) and environment (green bars, right)



For the data-rich substances, the use of read-across is often underpinned by a sufficient data density. The quality of the updates could not be assessed in the context of the MISA work as evaluation activities were not in scope.

For data-poor substances, however, additional data generation is often needed. In addition to filling data gaps by testing proposals, studies may be needed for justifying read-across adaptations.

2.1.2. Human health endpoints

The self-assessments and the workshops enabled consortia to improve the assessments in their registration dossiers. On read-across, metal-specific considerations for strengthening justifications were made available. Guiding documents address topics such as the definition of category boundaries, identification of source/target substances, establishing structural similarity and the patterns of toxicity, the consistency and applicability of the data matrix, bio-accessibility, and the assessment of reliability of studies[7]. Case studies illustrated the practical application of the principles of ECHA's Read-

[7] A full list of recommendations is available at: https://echa.europa.eu/documents/10162/3016194/misa_1_ws_summary_en.pdf/6b668955-365c-8823-2518-78a275b56623 and https://www.reach-metals.eu/uploads/pdf/MISA%201st%20workshop%20October%202018/Executive%20Summary%20of%2020181002%20MISA%20Workshop%20on%20HH%20requirements.pdf

Across Assessment Framework.[8]

Given that additional testing is relevant for a number of metal and inorganic substances, practical considerations and recommendations on planning studies are collected enabling effective and efficient design of testing approaches. The emphasis was on the extended one-generation reprotoxicity study, the route of administration for repeated dose toxicity testing and the use of weight-of-evidence approaches on mutagenicity.

While in many cases the metal ion is assumed to be the hazard driving moiety, the counter-ion needs to be considered as well. A series of standard justifications for low hazard counter-ions and assessments of some hazardous counter-ions have been developed by industry to be used in registration dossiers.[9]

2.1.3. Environment endpoints

An extensive list of learnings from the consortia's self-assessments and cases presented at a workshop has become available, focussing on further improvement of the justifications for read-across and, expectedly on a limited scale, identifying where additional data would be needed[10].

Read-across justifications can in many cases be built on a category approach based on the release of a common metal ion where there is no variation the bio-availability of the metal-ion between category members. The transformation-dissolution protocol (T/Dp) (OECD Guidance Document 29) forms the basis for read-across on metals, soluble metal compounds and sparingly soluble metal salts. The T/Dp data is therefore an essential part of justifications, hence a required data set in a registration dossier. Examples on the effect of valence and speciation from the workshops help providing documentation on this aspect[11].

For common counter-ions, the registrants can make use of the justifications developed by industry in the MISA programme. Also the fate and toxicity of any organic fraction need to be addressed in the dossier.

A recommendation regarding Ecotoxicity Reference Values (ERV) -and Predicted No Effect Concentrations (PNEC) derivation is to follow agreed concepts for (data-rich) metals and also for transparency indicate data that is not considered (e.g., due to Klimisch score 3 or 4 or lack of relevance). Where the Species Sensitivity Distribution (SSD) approach is used to derive the PNEC, any remaining uncertainty in the HC5 derivation will need to be part of the motivation of the assessment factors applied to define the PNEC.

Specific considerations for the assessment of bioaccumulation and secondary poisoning were offered together with recommendations for substances that are difficult to test. An explicit advice is that the water accommodated fraction method is not applicable to metals/metal compounds and must not be used. To complement -the T/Dp, for instance

[8] See: https://echa.europa.eu/documents/10162/17228/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316

[9] The set of justifications for several common counter-ions are available to the participating consortia.

[10] For a full list of learnings see: https://echa.europa.eu/documents/10162/3016194/misa_2_ws_summary_en.pdf/f56c5ee6-059d-7a03-43f5-0d48815b1528 and https://www.reach-metals.eu/uploads/pdf/MISA/Executive%20Summary%20ENV%20endpoints%20-%20key%20recommendations.pdf

[11] Case studies and specific presentations have been made available to MISA participant and are open for consultation to Member State Competent Authorities.

phase diagrams and assessment of factors influencing the speciation using bioavailability models, could be useful to further strengthen read-across approaches and assessment of potential hazards to the environment in general.

2.2. Rapid Removal concept

While environmental transformation processes of metals and metal compounds to non-bioavailable forms influences classification as hazardous to the aquatic environment, questions surrounding removal from the water column and whether such mechanisms should be taken into account for aquatic hazard classification has been open for many years. However, while being recognised as useful for assessing fate and risk assessments, no consensus on the validity on the scientific concepts governing the removal of metals from the water column could previously be reached for hazard classification.

In the years preceding the MISA programme, industry developed the Unit World Model (UWM) and the Extended Transformation/Dissolution protocol (T/Dp-E) which respectively model and measure both removal and the absence of remobilisation due to resuspension, with the aim to make the concept (also known as 'rapid removal') applicable for CLP. Industry representatives presented findings of that work in an information session as preparation for further discussion[12]. Member States consistently raised concerns on both the rapid removal concept and the T/Dp-E related to the different approaches on the partitioning of metals and organic substances.

To conclude on the issue, a rapid removal workshop organised at ECHA in June 2019 discussed the relevancy and suitability of the Rapid Removal concept and T/Dp-E for use under CLP. This included discussion on:

- the consistency between metal compounds and organic substances[13],
- the (bio)availability,
- the question whether sufficient standardisation can be obtained and
- whether further adaptation of the T/Dp-E would remedy shortcomings

Member State experts participating in the workshop observed that the rapid removal concept includes sorption removal mechanisms, which are not permitted in the degradation of assessments of organics under CLP having been considered as more risk than hazard-based considerations. Consequently, it was concluded that the rapid removal concept (applied to metals) would create an unjustified inconsistency with the approach for organic substances. Furthermore, the issue of demonstrating the irreversibility of the removal from the water column (and thereby showing a lack of bioavailability) remains unresolved.

The conclusion was that Member State experts attending the workshop agreed that neither rapid removal as a concept nor the T/Dp-E method are at this stage suitable for aquatic hazard classification under CLP[14]. The potential relevance for risk assessment was recognised but for environmental classification under CLP, a generic approach using the rapid removal concept and T/Dp-E for hazard assessment was rejected until the significant issues can be addressed preferably demonstrated in a specific case. The workshop report and conclusions were presented and supported by Member State Competent Authorities at CARACAL 32. Eurometaux made the reservation that a case-by-case approach on a

[12] Papers and presentations of the information session are available for the MISA participants and authorities.
[13] Note that the metals guidance and the TDp protocol are explicitely restricted to metals and metal compounds and that the degradation concept for organics has limited or no meaning for metals.
[14] The summary of discussions and conclusions can be found at: https://echa.europa.eu/documents/10162/3016194/misa_3_ws_summary_en.pdf/14b9dcca-9067-89fc-c110-cf3012b67cea

scientific basis should be possible.

2.3. Inorganic UVCBs

There are about 65 inorganic UVCBs in the MISA programme, most of which are so called "refinables". Typical for these substances is that they generally have the same 20 to 30 elements in common, be it in often unknown speciation and with varying (most often known) concentrations. The hazard and risk assessment can be based on a constituent-based approach, though for some endpoints (for instance phys-chem) testing of the whole UVCB can be more appropriate. When a constituent-based approach is followed, all constituents and the speciation need to be considered. Detailed documentation on the actual composition (both elemental and mineralogical) and variability is essential for hazard assessment and classification.

Hazard data on the actual constituents and speciation or, if unknown, a hypothetical or worst-case speciation, would normally be obtained from studies on compounds of individual constituents. As in practice the speciation in the UVCB may differ from the registered substances, hazard data on the constituents in the UVCB are derived with a read-across. For classification, industry recommends the MeClas tool for classification (www.meclas.eu).

The key principles of the assessment of inorganic UVCBs are summarised in a brief workshop report[15]. A detailed description of a stepwise approach for hazard assessment, classification, risk assessment and reporting in the IUCLID dossier is available to the participating consortia.

2.4. Exposure

2.4.1. Environment and life cycle analysis

A specificity of the metal sector is that speciation/form may change various times over the lifecycle, leading to a new "REACH" substance to be registered. Reaction products also occur on use or in the environment. A clear life cycle tree (in the metals sector can be called mass/materials flow) is a prerequisite for exposure assessment, and recommended to be clearly documented in the CSR. The ECHA Guidance R12 on life cycle provides a good supporting tool for identifying and reporting different stages in the life cycle in IUCLID. A use corresponds to an exposure assessment/use with the contributing activities (environment & workers) resulting in contributing scenarios. Based on the conditions of use, releases and exposures of the environmental compartments/workers can be estimated (involving multiple data sets).

Practical examples showed that the Chesar tool was helpful to align use descriptions in a variety of applications. The sector also developed tools that assist in gathering downstream information taking commercial confidentiality into account, revised generic exposure scenarios, survey tools and templates for mass flow analysis.

Identifying where the life cycle ends is a critical question. The assessment shall indeed

[15] See: https://www.reach-metals.eu/uploads/pdf/MISA%203rd%20workshop%20November%202019/MISA%203%20Executive%20Summary.pdf and https://echa.europa.eu/documents/10162/3016194/misa_4_ws_summary_en.pdf/56e67ed4-e8fd-41f7-b1d4-738fade88b6c

cover all identified uses and (where relevant) the subsequent life cycle stages. So far, there is no dedicated reporting structure in IUCLID for recycling operations and "second life" (if different from first), however dismantling or recycling operations regarding articles can be reported under service life and identified with a suitable use name. A challenge is that companies processing waste (including end-of-service life articles), are not downstream users under REACH, i.e. none of the related information mechanisms under REACH apply[16].

2.4.2. Workers

The assessment of exposure and risk to workers has some aspects that are specific to metals and inorganics, like the simultaneous exposure to different inorganic substances and the fact that measured data are often used for the assessment via inhalation route. Analysis of existing CSRs resulted in a series of observations from which the following recommendations were discussed in the webinar:

- Where uptake of species differs on the inhalation route, is should be corrected in the DNEL derivation.
- For modelled estimates, the contributing scenarios (CS) should clearly reflect the input parameters used for the modelled estimate and ensure consistency between the conditions of use reflected and the input parameters of the modelling tools.
- Where measured data are used, they must fit the situation to be assessed and should represent a reasonable worst-case exposure level. If the CS prescripts respiratory protective equipment (RPE), it should be clear whether the estimated exposure takes into account the RPE.
- Additional information is to be supplied to enable understanding on the adequacy of the measured data for supporting the exposure estimate and the corresponding risk characterisation.

Regarding acceptability, in general, the number of measurements needs to be higher if there is a high variability in the exposure distribution, if the exposure value is close to the DNEL or a high number of sites /workers is to be covered.

The MISA workshops also discussed how to handle impurities: a 3-step-approach was designed to help the registrant to determine if a separate risk assessment is required for an impurity or whether the risk is covered by the assessment for the main constituent (= substance). The application of the approach requires some data to be available, namely: the concentration of the impurity during the life cycle of the registered substance (may change from one life cycle stage to another), hazard profile of the impurity, differences in exposure potential between main constituent and impurity. It is important to document how the decision has been taken (no separate assessment needed, separate assessment to be carried out)[17].

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[16] The learnings of the workshop are summarised in sort paper, available at: https://echa.europa.eu/documents/10162/17220/misa_4_exposure-webinar_1_lct_executive_summary_en.pdf/48fed307-1876-c545-822e-2c82d4622d92 and https://www.reach-metals.eu/uploads/pdf/MISA%204%3A%20Exposure/MISA%204%20Exposure%201%20-%20LCT-%20%20Executive%20Summary.pdf

[17] See: https://www.reach-metals.eu/uploads/pdf/MISA%204%3A%20Exposure/MISA%204%20Exposure%202%20Workplace-Main%20Learnings%2023112020.pdf and https://echa.europa.eu/documents/10162/17220/misa_4_exposure_webinar_2_workplace_learnings_en.pdf/ba6473f9-1513-7617-649f-f2e0056f3a95

2.4.3. Environment

A complete set of exposure information is required when risk characterization is based on measured exposure (as for modelled exposure): condition of use, resulting releases, resulting exposure. Reliable and representative monitoring data, often extensively available on metals, always prevail modelling. In case models like the European Union System for the Evaluation of Substances (EUSES) are used, adjustments for metal specificities should be made. Estimates for releases and exposure from widespread use could be obtained from municipal sewage treatment plants. Also, regional data from emission sources could be used, the emission from non-REACH sources can be substantial and needs to be indicated in the dossier. The combination of modelling and monitoring estimates allows for source allocation and proper exposure management[18]

2.4.4. Consumers

Exposure assessment for consumers is needed when hazards are identified for metals in articles, mixtures or in the matrix of other materials (like plastics). Models for direct exposure exist (ECETOC TRA, ConsExpo), but are not metal specific. Specific data on for instance use conditions, concentrations and migration rates are needed for estimates. For consumer uses that are borderline to professional/industrial use like soldering, sanding, spray painting, occupational exposure models offer an alternative.

An important discussion focused on the importance of sufficiently substantiating the 'no release' claim when waiving exposure estimates for some or all compartments.

The assessment of exposure for man via the environment is required for tonnages above 1000 tpa and above 100 tpa for metals classified as STOT RE1, carcinogenicity, mutagenicity or reprotoxicity 1. Existing tools however are not entirely suitable for metals. The use of measured data, for instance by concentrations in food, require explanation of the representativeness, contextual information and calculations of the ingestion. This could be facilitated by further updating EUSES.

It is important to distinguish a local and regional scenario. Diet or market basket studies are a good solution for the regional assessment. Usually, modification is needed when transforming to local situation, using specific modelled or measured data. When using models, like Chesar and EUSES, the default factors need to be substituted by metal specific evidence. Case studies, for instance on Pb and Ni show that this is feasible.

In general, it is better to work with monitoring data that includes all sources (including fertilisers, industry emissions). However, as REACH is substance based the use of monitoring data that includes all sources comparison may be difficult[19].

[18] Key points form the webinar are summarised here: https://www.reach-metals.eu/uploads/pdf/MISA%204%3A%20Exposure/MISA%204%20Exposure%203%20Environment%20-%20Main%20Learnings%202627012021.pdf and https://echa.europa.eu/documents/10162/17220/misa_4_exposure_webinar_3_environmental_exposure_en.pdf/9de84a36-5f10-262f-acf4-081fba82fbf2

[19] More details in: https://www.reach-metals.eu/uploads/2021%2005%2007%20MISA%204%20Consumer%20HvE%20Exposure_Main%20Learnings.pdf

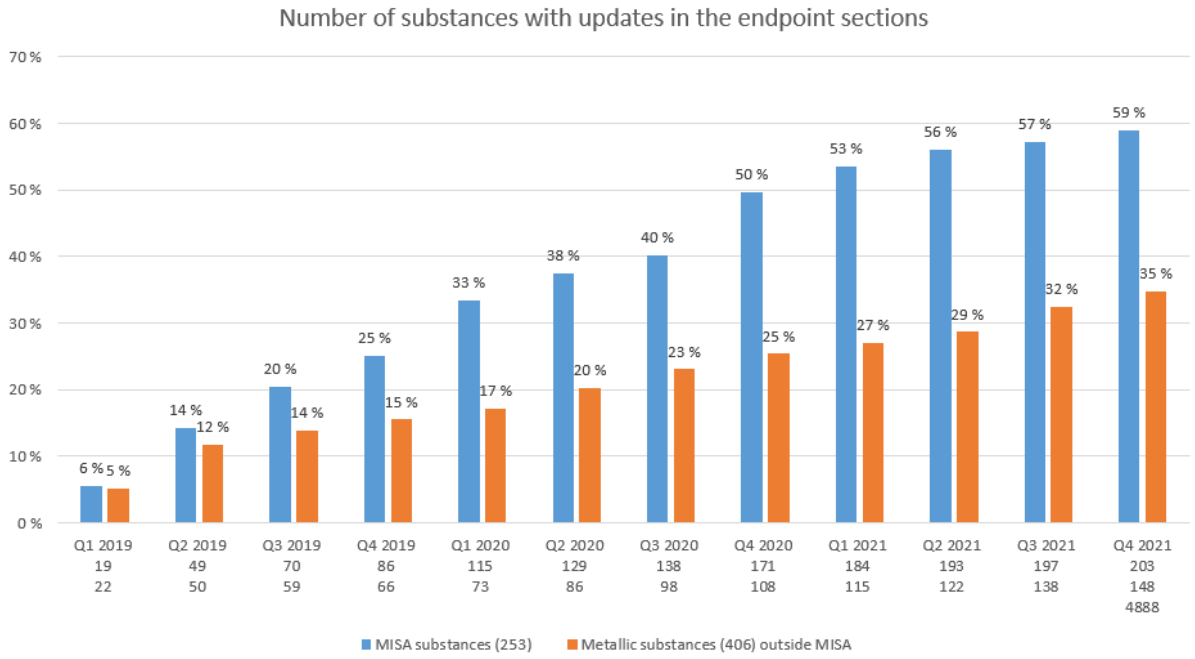
3. Registration dossiers

3.1. Dossier updates

During the programme, the envisaged timeframes for dossier updates have been extended by the consortia for most of the substances. In a dedicated workshop early 2020, several reasons were put forward by participating consortia with reasons such as limited resources and scarcity of external capacity (labs, consultants and later COVID-19) most often mentioned. Several updates on human health and environment endpoints are still expected in 2022.

Dossier update activity was monitored during the program quarterly, by detecting changes in endpoints relevant for the human health and environmental risk assessment. ECHA did not open dossiers to assess the quality of the updates. The graph below shows the percentage of substances with endpoint sections updated, of MISA substances (253) and of metallic substances (406) outside of MISA programme.

Figure 3.1 Development of the number of substances with updates in the human health and environment endpoint during the MISA programme.



During the MISA programme, update activity has been 30-80 % higher in all registration types, compared to 1) group of metallic substances (406) outside MISA programme and 2) all registered substances (11172). Substances with only intermediate registrations and UVCB-substances have been excluded from the numbers[20].

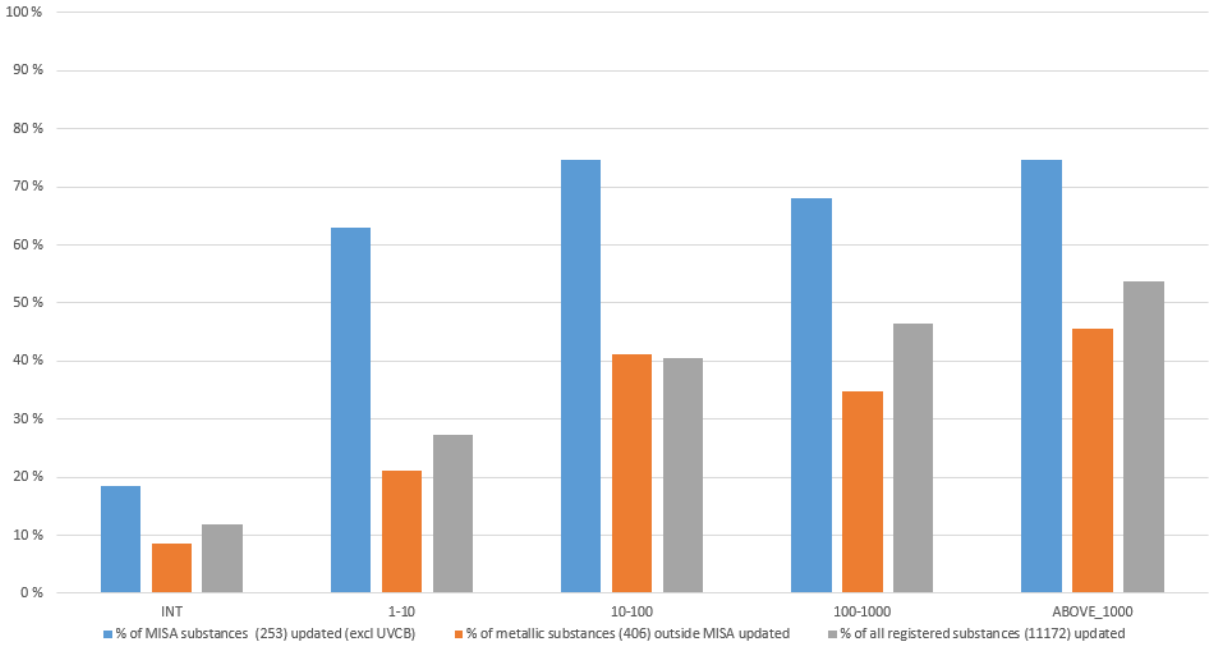
The technical and scientific work on UVCBs and Exposure were, mainly due to the COVID restrictions, only completed by mid-2021. As a result, the related dossier updates are delayed. According to the consortia's work plans updates are expected for about 100 substances on human health, and around 160 for environment. The updates include UVCBs, exposure and CSRs, further improvement of already updated submissions, and

[20] Reason is that the technical/scientific was not completed in time to allow for dossier updates within the timeframe of the programme.

substances that have not been updated yet. ECHA will follow if the committed updates will be realised.

It should be noted that in the context of the programme it has not been possible to assess the nature and quality of any updates made and whether the updates would result in a compliant dossier.

Figure 3.2 Comparison between the number of substances with updates (blue) and metal compounds outside MISA (orange) and all substances (grey).



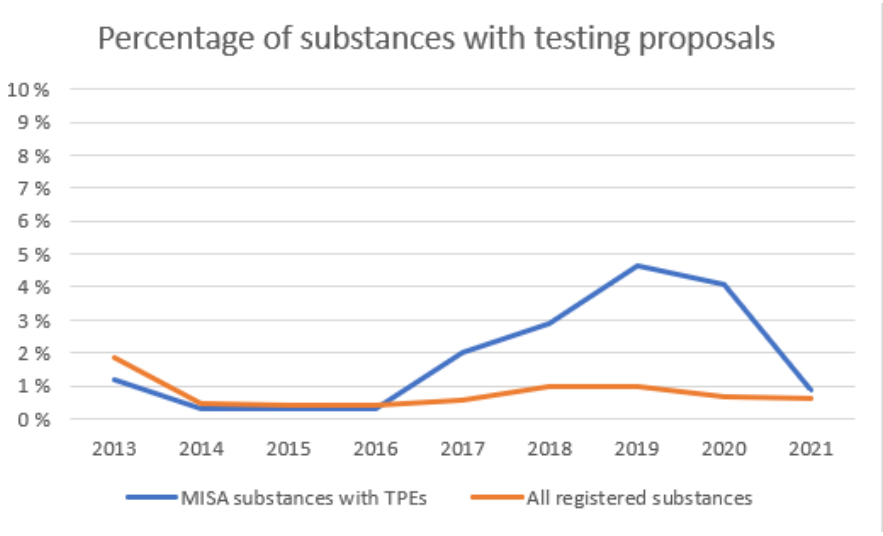
3.2. Data generation and testing proposals

Earlier estimates by ECHA on the data availability, indicated that for several metal compound groups the data density for the higher tier endpoints is rather low. However, as the indicative graph below shows, after 2016, the percentage of substances with testing proposals has been consistently higher for MISA substances than on average for all registered substances. This is despite MISA covering substances that are more data-rich than average. Multiple testing proposals in one dossier were counted as one in this analysis. Where the metal-ion is the driving moiety for the hazard, a single testing proposal may be relevant for several substances due to the read-across possibilities.

For data-rich substances the focus on strengthening the read-across approaches can be justified. Improving and strengthening the read-across argumentation for data-rich substances may in many cases be sufficient to render the dossiers more transparent and compliant. In the environmental assessment part the read-across approaches would most easily be strengthened by relating the toxicity to the bioavailable metal ion by using the T/Dp. Additional data generation for strengthening read-across (like generation of bridging studies) could not be analysed. Considering the more data-poor substances, the number of testing proposals to fill data gaps was expected to be higher, where it is recognised that for instance the availability of labs or delays in draft decisions on testing proposals may have impeded filling data gaps.

Figure 3.3 Development of percentage of substances with testing proposals over time for MISA

substances (blue) and all registered substances (orange).



4. Outcomes and conclusions

Apart for the deliverables of the technical and scientific work and workshops and the realised registration dossiers, the MISA programme had spin-offs for ECHA's regulatory strategy and follow up activities on management of hazardous metal compounds by industry.

4.1. Spin-offs

As positive additional outcomes, the following was noted:

- Increased knowledge on hazard and risk assessment for metals and inorganic substances, allowing prioritisation and improving assessments of possible regulatory needs.
- The insights obtained from the programme allowed ECHA to prioritise groups of metal and inorganic substances for the grouping approach and subsequent further action. Though the quality of updates is still uncertain, it can be expected that the updates make the assessment more efficient and effective.
- A higher level of consistency and harmonisation of methods and approaches is obtained, reducing the need for individual discussions.
- A better understanding by authorities of the main challenges in metals hazard and exposure assessments for REACH.
- A significantly updated assessment strategy for inorganic UVCBs resulted from the MISA programme which promotes a much more harmonised approach for those complex substances.
- Increased knowledge on the demonstration of proof for "reasonable use of the massive forms" to feed the Environmental classification assessment and more clarity on how to include and consider metal specificities in Registration dossiers and self-classifications (e.g., massive vs. powder forms)

- Development of a multi-metallic database by industry that aims to be the most up-to-date source of reference data necessary to conduct risk assessment and classification of metal and inorganic substances and mixtures. It promotes the consistent use of (eco-)toxicological data and consistency of approaches to assess and classify metal and inorganic materials under REACH, CLP or other scientific and regulatory frameworks. It will make the set of information used to develop the effects database easily accessible, and help to explain the effects assessment by virtue of the inclusion of other key effects assessment data (e.g. assessment factors). It aims also at facilitating the entry and updating of the relevant dataset in line with the IUCLID file structure and content.

- MEED: metals environmental exposure data collection programme 2022-2024. This programme designed by Eurometaux, in close cooperation with the consortia/commodities/associations/companies, aims at collecting exposure data to address the open action points on exposure in MISA (STP, update regional exposure) but also to anticipate the Mixture Assessment Factor (MAF) proposed under REACH by the Chemicals Strategy for Sustainability (CSS) and the Zero Pollution Action Plan.

4.2. Conclusions

Overall, it can be concluded that:

- The participation of industry in the programme was very good, 29 consortia/associations taking part and 35 substance groups with 347 individual substances, covering most of the volume of non-ferrous metals and some of the non-metal inorganics on the EU market. However, some important non-ferrous substances and substance groups are missing, most of them being outside the membership of Eurometaux.

- Progress on the activities announced in the rolling action plan was good, technical and scientific topics were handled in time until the COVID-19 pandemic. The restriction on physical meetings led to delays in activities planned in 2020 and in the end one planned activity is foreseen to continue outside the MISA context.

- While not all issues could be resolved, in most cases good quality deliverables or solutions were identified.

- The in-depth self-assessments proved to be a powerful tool to define common aspects for clarification and improvements of the registration dossiers

- Participation in workshops has been high, allowing generic agreements and discussion on consistent approaches on technical and scientific issues across substances.

- The written and undersigned commitment of consortia/associations, and the common program ran by Eurometaux, had a positive effect on the involvement. Most consortia/associations lived up to their commitment to do comprehensive self-assessments, to provide a work plan for updating their registration dossiers. A few consortia however did not fulfil their commitment, showing some limitations of a voluntary approach.

- Even though in many cases planned updates were delayed, by the end of 2021 a marked increase in the number of dossiers on human health and environment

endpoints is visible for substances in the MISA programme. Further updates are expected in 2022 and 2023.

- While new data is generated and testing proposals are submitted, it must be noted that, in particular for several more data poor substances, more proposals to fulfil the data gaps would be expected.

- In general MISA raised the attention, awareness and organisation of the sector for the assessment, prioritisation and delivery on REACH registration updates, a drive that seems still to be present in 2022. The interactions with the ECHA experts, the MISA blog and the stimulating role of Eurometaux were key success factors.

- A relatively strict management of the work programme, strong support from the industry association and regular and focussed feedback on the deliverables and dossier updates to the participants has mitigated the risk of shortfall to the expectations.

- On the whole the balance in resource efficiency at ECHA side is positive. A relatively limited investment resulted in a continued activity in the sector, also after the registration deadline and resulted in spin-off projects that will further improve the metals registration files. A relatively broad audience could be reached.

Annex. Feedback from participating consortia

What worked well:

- the SATs were an excellent trigger to review dossiers and identify 'weaknesses'. MISA participants could prepare a workplan to solve these gradually. The identification of multi-metallic weaknesses helped in the acceptance of the multiyear research program to further improve e.g. the environmental exposure sections.
- the MISA actions/recommendations were a clear trigger and valid justification to update dossiers e.g. from annex III exempted to regular Annex VII (via additional data generation or read-across), to remove waiving statement in metal dossiers and fill relevant endpoints with data (via additional data generation or read-across)
- there has been clear guidance agreed on how read-across needs to be performed, documented and reported.
- Good progress was made for some critical dossiers for the metals' industry, with the UVCBs being the best example. This progress includes the communication between regulators and industry, as well as the setup of a UVCB platform to ultimately have uniform UVCB dossiers being submitted.
- MISA has improved the dialogue between ECHA staff/regulators and MISA participants
- MISA was helpful in the context of data-sharing; MISA (and the resulting actions) was accepted by e.g. Letter of Access buyers as justification for additional work to be done and cost sharing. Example is the metal dossiers where additional work has been performed post-registration to remove waiving statements, upon recommendation from MISA.
- MISA has improved consistency in justifications and methodologies between the MISA-participants.
- MISA is a clear trigger to continue the updating work in the post-MISA years (>2021). Due to prioritisation of the work, there is still work pending that has been agreed within the association membership to be performed after 2021.
- if a second MISA would ever be considered…happy to sign again

- Participation in MISA framework added more value to the consortium update work and basically enabled resources to be made available to continue updating dossiers in the period rightly described as 'REACH fatigue after 2018'.

- MISA motivated better prioritisation and structuring of dossier update content.
- workshops and particularly the possibility for informal discussions with ECHA around the issues taken up at the workshops were a big asset
- positive and a learning experience in terms of building relationships with ECHA staff and the need to improve transparency
- the consortium included some additional documentation/justifications e.g. on read-across, hoping it has improved transparency, and these actions were not foreseen before/outside of MISA

What was in some cases a bottleneck and unintentional cause for delay:

- datagap filling: depending on the (experimental) work needed (e.g. acute test vs subchronic, 'easy' phys-chem test vs mammalian tox testing, single datagap vs numerous datagaps for a single substance, update of exposure/risk assessment),

there might be limitations in resources (budget & human) within a consortium/association. This often triggers an internal prioritisation of the work, with part of the work being delayed to spread the work / costs. This prioritisation is clearly communicated in the workplans

- testing is not always as straightforward as it seems, with some critical aspects causing delays:

  -test slot availability at Contract Research Organisations (CROs) is often a bottleneck to initiate testing. Even for relatively low tier tests like in vivo MN/Comet test, there is a delay of several months before a test can be initiated, provided all analytical methodologies are being set-up and validated. If not, a further delay can be expected.

  -some in vitro/in vivo testing is not straightforward and needs preliminary testing. If all goes well, the CRO can proceed directly to a main test afterwards. If not, additional in vitro/in vivo testing needs to be initiated to ensure a proper setup of the main test, resulting in further delays of data availability.

  -administrative processes within a consortium/association take time, e.g. a budget for testing needs to be approved and available, a test plan/protocol needs to be revised and approved by the membership, data need revision and approval by the membership. This time & effort needs to be added to the time for testing and might cause an extension of the timing to dossier resubmission.

- the resubmission of a dossier cannot be done on an endpoint specific basis, but the entire dossier needs submission. This also means that each update is associated with a possible incompliance due to revisions of the compliance check process. This drives industry to resubmit a dossier only once all work has been performed and finalised, and not after each individual step has been taken (obviously recognising timelines set by regulators), e.g. if an in vivo test triggers a change of the exposure/risk assessment, then the dossier will not be resubmitted after the hazard part has been finalised but only once the exposure/risk assessment has been updated (obviously recognising timelines set by regulators).
- some experimental work and dossier resubmissions are directly depending on approval by regulators. Examples are testing proposals that need to be approved or the UVCB dossiers where a final agreement on reporting is pending. Despite industry is willing to progress, it can not to avoid incompliance.
- in the UVCB dossiers, industry has the impression there is sometimes a disconnect between services/groups within ECHA, or between groups involved in MISA and others. This complicates the dialogue and avoids a smooth progress.
- MISA is unknown to non-MISA-participants, e.g. companies that are buying Letter of Access and not a member of a MISA-participating association/consortium. There might have been a missed opportunity to give MISA a wider recognition.
- Some fundamental/technological issues/guidance/agreement (e.g. reporting substance identity of UVCB substances after the new-format Substance Identity Profile was developed) required quite some time to completion (or close to completion). Has enough energy been injected in the track of methodological improvements?