Final Report of the Study on the Role of Robust Study Summaries in Hazard Assessment

Work package 3 final report delivered
under contract ECHA/2021/46[1]

16 December 2022, edited by ECHA for publication in April 2023

Executive Summary

According to the EU REACH Regulation[2], article 3(28), 'a Robust Study Summary (RSS) is a detailed summary of the objectives, methods, results, and conclusions of a full study report, providing sufficient information to make an independent assessment of the study, minimising the need to consult the full study report'.

The OECD has developed Harmonised Templates[3] (OHT) to report the relevant information in the context of the risk assessment of chemicals, including Robust Study Summaries for several regulatory endpoints. IUCLID 6[4], a software tool developed by the European Chemicals Agency[5] (ECHA), in collaboration with the OECD, serves as the reference implementation for the OHTs, and provides data entry screens for users to provide the relevant information in an agreed format, within a regulatory context.

As part of an OECD project, ECHA commissioned a study to Yordas Group, referred to as "the contractor" in this report, to evaluate the confidence in the RSS approach for hazard assessment and to identify potential improvements. Stakeholder engagement activities were conducted, including a survey and semi-structured interviews, to capture the comments and suggestions of RSS users in the first part of this project. The findings were published on the ECHA website in April 2022[6] in the report "*Study on the role of robust study summaries in hazard assessment*". During the second phase of this project (WP2) the contractor analysed the quality and the accuracy of a series of RSS and the findings were also published on the ECHA website in April 2023[6].

The first work packages of the project concluded that the RSS concept is a trustworthy tool that provides reliable key information to conclude on hazard assessment with a high level of consistency. RSSs describe the specific characteristics of the endpoints in such a way that they allow an independent assessment of the reliability and completeness of the studies.

Overall, there were relatively few shortcomings affecting the interpretation of the results and the hazard conclusion. While this study has proved the reliability of the RSS concept, it also proposes, in this final part of the project, some areas of improvement to enhance, even further, the quality, usefulness and accuracy of the RSSs.

The objective of Work Package 3 (WP3) was to identify ways to improve the usefulness of robust study summaries (RSSs) for the purpose of hazard assessment. During WP3 the information gathered from WP1 and WP2 was reviewed and further evaluated. The strengths and weaknesses of RSSs retrieved from stakeholders through a survey, interviews, and a literature review during WP1 were listed and categorised to establish approaches that could be used to improve the overall quality/accuracy of the RSSs and ultimately their usefulness for hazard assessment. Previously, in WP2, RSSs generated by registrants were analysed to assess both the quality of the registrants' RSSs and their ability to accurately summarise the full study reports for a hazard evaluation without access to the full study report.

Final report of the study on the role of RSS in Hazard Assessment (ECHA/2021/46)

The findings of WP2 were also analysed in WP3 to identify the strengths of RSSs and to categorise any identified deficiencies into potential areas of improvement. Subsequently, the areas for improvement proposed in WP1 were combined with those observed in WP2 to propose several approaches to strengthen the quality and usefulness of RSS for the purpose of hazard assessment. This work led to the identification of various areas of improvement that affect the usefulness and the quality of the RSS. These were classified into the following categories:

- Validation rules
- OHT update
- IUCLID user interface
- Study quality criteria
- Guidance
- RSS review process
- Author experience/expertise
- Training
- Human error

The areas of improvement were then further assessed based on endpoint as well as section/sub-section of the RSS in which they were identified with a view to determine the categories that would have the highest impact on the quality of RSS. The results of this analysis show that the tools in place (e.g., IUCLID validation tool, guidance documents, OHTs, etc.) already contribute to enhancing the quality of the RSS, by defining their structure which minimises bias and confusion and provide a detailed summary of the relevant aspects of a study report, for the purpose of hazard assessment. Amongst other, the following suggestions for improvements, if implemented, would further strengthen the usefulness and quality of the RSS for hazard assessment:

- Implementation of a RSS review process following a Standard Operating Procedure (SOP)
- Develop training specific to RSS authoring
- Continue developing validation assistant rules

Table of Contents

Glossary of Key Terms

Term	Definition
Author(s) / RSS author(s)	The terms author(s) and RSS author(s) in this report refers to the person(s) responsible for preparing the RSS from the contractor side. In this report, when this term is used in context of RSS authored from the SOP (see below), it refers to person(s) who prepared a new RSS for this project from the full study report provided by ECHA; whereas, when this term is used in context of registrant's RSSs, it refers to person(s) from industry who prepared the RSS for REACH registration dossiers submitted to ECHA.
Completeness Check	A check performed by ECHA on incoming REACH registration dossiers to ensure information as per Article 20 of the REACH Regulation has been provided. It also includes a manual verification by ECHA staff.
Full Study Report	A complete and comprehensive description of the activity performed to generate the information. This covers the complete scientific paper as published in the literature describing the study performed or the full report prepared by the test house describing the study performed Source: REACH Regulation: Retrieved: https://eur-lex.europa.eu/legal-content/en/TXT/HTML/?uri=CELEX:02006R1907-20210215
Lab report	A full study report prepared by a test house.
Peer reviewed scientific publication	A study report published in a scientific journal after peer review.
Robust Study Summary (RSS)	A detailed summary of the objectives, methods, results, and conclusions of a full study report providing sufficient information to make an independent assessment of the study minimising the need to consult the full study report Source: How to report robust study summaries: Practical Guide 3 - ECHA. Retrieved: https://echa.europa.eu/practical-guides
Standard Operating Procedure (SOP)	SOPs are detailed written instructions to achieve uniformity of the performance of a specific process, which is repetitive and can be standardised.
Validation Assistant	A tool within the IUCLID software to perform computer-based checks on IUCLID data including the RSSs therein.

Glossary of Acronyms

Acronym	Terms
BPR	Biocidal Products Regulation
CRED	Criteria for Reporting and Evaluating Ecotoxicity Data
ECHA	European Chemicals Agency
IUCLID	International Uniform Chemical Information Database
KL	Klimisch Score
OECD	Organisation for Economic Co-operation and Development
OHT	OECD Harmonised Templates
PPP	Plant Protection Products
PPORD	Product and Process Oriented Research and Development
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
Registrant's RSS	RSS included in a dossier submitted to ECHA for REACH or BPR purposes.
R4BP	The Register for Biocidal products
RSS	Robust Study Summary
SciRap	Science in Risk Assessment and Policy
SOP	Standard Operating Procedure
SOP-guided RSS	RSS created for this project by the contractor using the full study reports included in the registrant's RSS.
UVCB	Unknown or variable composition, complex reaction products or of biological materials
WoE	Weight of Evidence
WP	Work Package

1. Introduction

The REACH regulation requires companies to demonstrate to the European Chemicals Agency (ECHA) how the substances they manufacture, or import can be safely used along with the risk management measures to the users. IUCLID is a format and a tool that must be used to prepare the registration dossiers that are submitted to ECHA. Moreover, and following the EU Biocidal Products Regulation (BPR)[7], all biocidal products require an authorisation before they can be placed on the market, and the active substances contained in that biocidal product must be previously approved. IUCLID is also used for preparing these applications.

For each registration submitted to ECHA under REACH, and to ensure that the dossiers include all the information that is required, a completeness check[8] of the provided data is performed. Completeness checks are performed both on new registrations and updates of existing registrations. The completeness check can only be successful if all the information in the dossier is complete. The dossiers used for this study have passed this check and allow a reliable assessment of the quality of the data entered in the RSSs. Note that the information submitted in the registration dossier may or may not be compliant with the legal requirements. This compliance is part of an additional process called compliance check[9] which evaluates the substance identity and the safety information in the dossier. Therefore, the samples used for the purpose of this project may or may not be compliant, but the scope of this project is to fully understand how RSS are used and to suggest improvements in areas that will increase the trust and reliability of the RSS concept.

Hazard assessments form the foundation of regulatory decisions for industrial chemicals, pesticides, pharmaceuticals, biocidal products, and cosmetics. The goal of chemical hazard assessments is to have a full understanding of the intrinsic properties of a chemical substance and the nature, magnitude and probability of a potential adverse health or environmental effect. The hazardous properties of a substance are usually identified using testing protocols and comparing the test results with pre-set criteria for specific effects. However, full study reports can be very technical and lengthy documents, for example, within a REACH registration dossier, the amount of study reports that are needed is such that it can become overwhelming for the assessor to review all the documents in a timely manner. For this reason, study summaries, or more specifically Robust Study Summaries (RSSs), were adopted to help alleviate the review load on the assessors and allow for quicker turnaround of the evaluation of registration dossiers.

The Robust Study Summary (RSS) is intended to summarise, in a standardised format, key details from a lengthier full study report. When the data and results are entered in this format it allows assessors to review study outcomes and relevant remarks on the quality of the data much more efficiently in comparison to reviewing the full study report. By nature, RSSs are designed to capture a limited amount of data fields across a range of endpoints potentially leading to insufficient reporting for the purpose of the hazard assessment.

---

[7] BPR:https://echa.europa.eu/regulations/biocidal-products-regulation/understanding-bpr
[8] Technical completeness check: https://echa.europa.eu/technical-completeness-check
[9] Compliance check: https://echa.europa.eu/regulations/reach/evaluation/compliance-checks

Final report of the study on the role of RSS in Hazard Assessment (ECHA/2021/46)

To understand how RSSs are currently used by hazard assessors and what factors influence the assessor's confidence in the quality of RSSs, the contractor evaluated the confidence in the RSS approach in hazard assessment and identified potential improvements to the process. The work has been divided into three work packages (Table 1) allowing ECHA and the OECD Steering Committee to review the outcomes from one before progressing further.

Table 1: Work packages of the study

Work Package	Description
WP1	Examine the role of robust study summaries in hazard assessment
WP2	Analysis of the quality of robust study summaries
WP3	Improving the usefulness of and trust in robust study summaries

Before the work detailed in this report, a stakeholder engagement analysis, and a literature review were undertaken in Work Package 1[10] to understand stakeholders' views on the role of RSSs in hazard assessment. Stakeholders' comments and suggestions on the strengths and weaknesses of the RSS concept were collected and analysed to understand how RSSs are currently used by hazard assessors and the factors that influence their confidence in RSSs. The results indicated that both RSS authors and hazard assessors found RSS to be a reliable source of information for hazard assessment purposes, particularly when they are completed correctly. They reported (see page 51 of the WP1 report) that the following areas of the RSS give a good level of confidence which helped the RSS to achieve its role for the purpose of hazard assessment:

- Toxicology endpoints
    - Test material information
    - Repeated dose studies: frequency of dosing
    - Dose applied, vehicle information, maximum volume of dose
    - Inhalation endpoints: form of test material e.g., gas, vapour, aerosol, dust, mist etc and diameter
- Ecotoxicology endpoints
    - Exposure duration
    - Basis of effects
    - Nominal and measured concentrations
    - Test material information
- Environmental fate endpoints
    - Biodegradation endpoint
    - Complete results for the observations / examinations

It should be highlighted that these areas were gathered from questions specifically relating to toxicological, ecotoxicological and environmental fate endpoints and did not include physicochemical endpoints.

---

[10] Study on the role of Robust Study Summaries in hazard assessment: Survey and interviews report available at https://echa.europa.eu/technical-scientific-reports

Final report of the study on the role of RSS in Hazard Assessment (ECHA/2021/46)

The other key strengths of the RSS revealed in WP1 were consistency of format as well as the time and resource savings that result from using the summary data. The stakeholder engagement analysis also highlighted some weaknesses which could impact the reliability and stakeholder confidence in RSSs. It was interesting to note (see Table 3.4 of the WP1 report) some overlap between perceived areas of strength and weakness, with some stakeholders noting the usefulness (in relation to overall confidence in RSS) of certain areas (such as test material information and complete results from the observations/ examinations) but some also highlighting the difficulty in completing these sections.

The WP1 report also identified that, in the literature, concerns were raised regarding both intrinsic structural issues (e.g., missing data requirements, more support for non-standardised testing) and extrinsic factors (e.g., poorly completed RSS, missing information in reporting, test guidelines yet to be developed, laboratory reporting recommendations). In addition, the quality of RSSs was also regularly mentioned, with some authors suggesting that the use of Klimisch scores to indicate the quality of the underlying study did not account for other quality factors such as relevance. A brief investigation highlighted that other evaluation methods are available for assessing the quality of a study such as the Criteria for Reporting and Evaluating Ecotoxicity Data (CRED) and the reporting recommendations in Science in Risk Assessment and Policy (SciRAP) for toxicity and ecotoxicity studies.

Considering the findings from the literature results of WP1, the overall objective of WP2 was to assess the quality of registrant's RSS and whether each registrant's RSS can accurately summarise full study reports so that hazard can be properly assessed without access to the full report. A qualitative and quantitative comparison was performed between an RSS prepared by a registrant and an RSS prepared by the contractor, following a predefined standard operating procedure (hereafter referred to as 'SOP guided RSS'). The SOP was based on ECHA's Practical Guide 3[11] 'How to report robust study summaries', the OECD Harmonised Templates (OHTs) as well as strengths and weaknesses in RSS perceived from the Stakeholder Engagement analysis. The document was developed by the contractor's technical team, who are experienced with RSS generation, and was designed to be a best practice guide to authors of RSS from supplied full study reports/literature references.

Each RSSs pairs were based on the same full study report or literature reference across a range of regulatory endpoints. The following Table 2 contains a list of the endpoints considered in the WP2 and WP3 analysis.

---

[11] ECHA's Practical Guide How to report robust study summaries available at https://echa.europa.eu/practical-guides

Table 2: Endpoints included in the WP2 and WP3 analysis

S. No	Endpoint Group	Endpoints
1	Physicochemical	Vapour pressure
		Partition coefficient
		Water solubility
		Flammability (solid)
2	Environmental fate	Hydrolysis
		Bioaccumulation: aquatic/sediment studies
		Biodegradation in water: screening
		Biodegradation in water: simulation test
3	Ecotoxicology	Long term aquatic toxicity (three trophic levels)
		Short term aquatic toxicity (three trophic levels)
		Toxicity to aquatic microorganisms (sludge respiration)
		Toxicity to soil microorganisms and macroorganisms except arthropods
		Toxicity to terrestrial plants (added later based on a recommendation from the OECD steering committee)
4	Toxicology	Genetic toxicology in vitro and in vivo
		Repeated dose toxicity oral and inhalation
		Developmental toxicity
		Toxicity to reproduction
		Carcinogenicity
		Skin sensitization in vivo and in vitro
		Skin irritation in vitro

Each of the registrant's RSSs used in WP2 of this project, were extracted from dossiers originally submitted to ECHA under the EU Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) and Biocidal Products (BPR) regulations. The main criterion to select the RSSs and full study report pairs was the Klimisch (KL) score. The KL score has an impact on the way information is extracted from a full study report and written in an RSS as, under these EU regulations, a Robust Study Summary must be provided for key studies (KL 1 or 2) whereas only a study summary is sufficient for lower quality sources. Therefore, only KL1 and KL2 lab reports and peer reviewed scientific publications were selected because they are usually reported as 'Key studies' in the registration dossiers and are used to draw conclusions on the hazard classification and for possible use in risk assessment. Any endpoint in a registration dossier that only uses KL3 and KL4 studies needs to use a weight-of-evidence (WoE) approach and WoE was not within the remit of this project. Supporting studies were not considered for the purpose of this study. Three KL1 and three KL2 RSS were requested per endpoint to provide equal weighting to each type of report. Within each endpoint, different types of full studies were examined with at least two peer-reviewed scientific publications and four lab reports included out of a total of six full study reports.

A total of 103 RSS reports were provided for this analysis, 79 RSSs (and their corresponding full study reports) were originally submitted under the REACH regulation and 24 under BPR. The distribution of BPR and REACH RSSs across endpoint groups is provided in Figure 1. They covered a wide range of companies both large and medium with the majority being large companies and mainly manufacturers. Although the company size and role in the supply chain are not a factor in the results of this analysis, further details about RSS sources and collection are provided in Annex I for information. Additionally, amongst the 24 BPR dossiers used for this study, 19 were BPR active substance applications, and five were biocidal product authorisations dossiers.
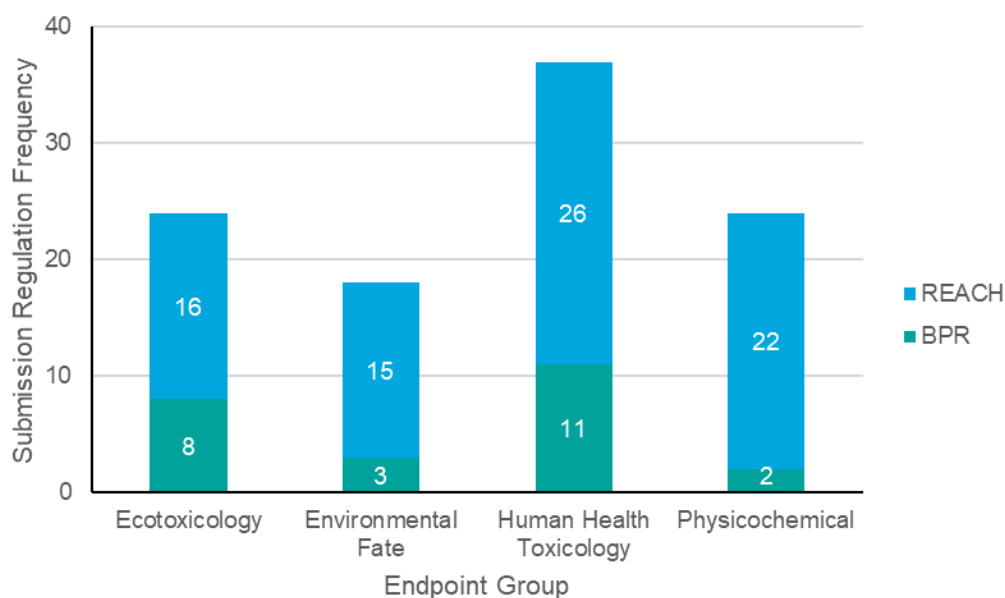

Figure 1: The distribution of BPR and REACH RSSs across endpoint groups included in this study. The bars represent the count of RSSs

The WP2 report revealed that SOP guided RSSs showed higher accuracy and completeness as well as a lower number of deficiencies that could affect the resulting interpretation/hazard conclusion (See section 5.3.1. Level 1 analysis: Endpoint groups of WP2 report). Within registrant RSSs human health toxicology and physicochemical RSSs showed better fidelity to the full study reports than ecotoxicology and environmental fate RSSs. Furthermore, WP2 showed that, statistically speaking, the quality of registrant RSSs did not depend on the individual endpoints and the following factors: type of full study report (laboratory report and publication), Klimisch score of the report and type of substance (See section 5.3.3. Additional analyses of WP2 report for further details). It was concluded that the lowest RSS scores and highest number of deficiencies could be due to poor use of available guidance, lack of author's experience, lack of a proper review process, or inadequacies in templates or guidance. It should be highlighted that, in WP1, stakeholders were largely divided on whether the nature of the substance impacted the RSS. In addition, respondents' perceptions were that RSS quality can vary based on several factors, including the author, endpoint complexity, substance, and study type (See section 4 conclusions of WP1 report). However, the WP2 analysis has provided no statistical evidence to support these claims.

For this WP3 final report, the findings from WP1 are used, together with the results of WP2, to assess the impact of the identified deficiencies on the overall quality of the RSS and finally suggest potential areas to improve the usefulness of RSS for the purpose of hazard assessment.

2. WP3 Methodology, Results and Discussion

WP1 examined the perceived strengths and weaknesses of the RSSs concept while WP2 focused on investigating the accuracy of registrants RSS by doing a critical comparison of pairs of RSSs submitted to ECHA with the same RSSs prepared by closely adhering to a predefined standard operating procedure. As a first step, the results of these work packages have been reviewed and summarised to categorise the identified strengths/weaknesses in WP1 and WP2 into areas for improvement.

2.1 Step 1: Findings of WP1 (literature search, survey, and stakeholder interviews)

2.1.1 Methodology

Chapter 3.5 'Areas of Improvement' from the WP1 final report was reviewed. All the RSS related issues and suggestions from WP1 provided by stakeholders during the survey and interviews, as well as those identified in the literature, were listed and divided into various categories drawing from the contractor's own experience and knowledge on hazard identification and characterisation. The purpose of categorisation was to summarise the perceived strengths and weaknesses of the RSS so that they can be compared with the findings of WP2.

2.1.2 Results and Discussion

The main strengths of the RSS that emerged from WP1 were related to the RSS format or template and their level of consistency in reporting study summaries.

As RSSs have a standardised format (cf. the OECD Harmonised Templates[12]), respondents to the survey and interviews appreciated the specific fields and free text areas in the templates as this facilitates the understanding of the type of information required. In addition, they considered the current RSSs' templates more consistent compared to the study summaries used previously. The defined structure and conciseness of the RSSs were particularly appreciated, as well as the ability to submit them in an electronic format which was considered a valuable way of saving time and resources.

The perceived weaknesses in RSS from stakeholders were classified into nine categories for areas of improvement:

1. Validation rules
2. RSS review process
3. Training
4. Author experience/expertise
5. IUCLID user interface
6. Guidance
7. Human error
8. OHT update
9. Study quality criteria

---

[12] https://www.oecd.org/ehs/templates/introduction.htm

These suggestions are summarised in Annex II along with the categorisation of improvement areas. It should be noted that the categorisation for the areas of improvement 'new OHT' and 'OHT upgrade' as indicated in previous reports have been combined into one more generic category 'OHT update'.

The weaknesses identified in the literature review report which were identified as areas for improvement in Table 3 were also summarised and categorised. No additional categories were identified. All the areas of RSS improvement listed in the Literature Review report could also be classified into one of the categories identified during the stakeholders' survey and interviews of WP1. These are described in more detail in Table 4.

Table 3: possible improvements identified from the literature search conducted in WP1

Improvements	Categories
Unclear and/or incomplete interpretation of the results	Author experience/expertise
Rationales for reliability provided by registrants were not always clear	Guidance Author experience/expertise
Full study reports should be provided to the regulators on request	Guidance
Unclear and/or incomplete reporting of results	Guidance Training Author experience/expertise
Omitted information that is important to understand the results	Guidance Training Author experience/expertise
Typing errors	Human error
More flexibility could be introduced to assess novel and/or independent research which does not utilise standardised testing methods	OHT update
Currently existing OHTs do not allow reporting observations at the molecular, cellular or tissue level, unless they are connected to a specific 'apical endpoint'	OHT update
Current framework focuses mainly on reporting and evaluating reliability, overlooking the aspect of relevance	Study quality criteria
Reliability evaluations follow the Klimisch method, which does not promote a systematic and transparent evaluation of data and is likely to favour studies conducted in compliance with GLP/standardised test guidelines	Study quality criteria
Poor reporting of a study was sometimes confused with poor quality when evaluating studies as not reliable	Study quality criteria
Ecotoxicity endpoints were found to be the main data-area of non-compliance. Reasons for non-compliance included test methods not suitable as a chronic test.	Guidance Study quality criteria

Improvements	Categories
The current technical completeness check under EU REACH covers some of the issues reported but it cannot cover when registrants do not adequately report information or provide sufficient and appropriate justification for any data waiving or deviations from test guidelines.	Study quality criteria

Although areas of improvements were identified during WP1, stakeholders recognised the RSS as an important source of information and confirmed the purpose of the RSS to summarise study reports for hazard and risk assessment purposes. In addition, most respondents indicated that RSSs are at least 'somewhat reliable' for conducting a hazard assessment.

2.2 Step 2: Defining the categories related to the RSS feedback identified in Step 1

2.2.1 Methodology

Before moving forward, it was considered necessary to provide a uniform description and scope for all the categories identified in step 1 so that these categories could be implemented consistently in the assessment of the areas of improvement identified in the registrants' RSS, as described in the following steps. These categories guided the drafting of suggestions for improving the sections and sub-sections of the registrants' RSSs for which deficiencies were identified in WP2. The strengths identified in WP2 were defined as the absence of deficiencies and specifically where no deficiencies were identified that would impact the hazard assessment process.

2.2.2 Results and Discussion

Step 2 consolidates all the feedback received in step 1 into defining a series of categories of improvement.

The same categories were used to develop potential reasons for the deficiencies identified in WP2 and elaborate suggestions for improvement.

A description for all categories identified in WP1 is provided in Table 4.

Table 4: Description for all the categories identified in WP1

Areas of improvement	Description
Author experience/expertise	This refers to the expertise and background of the author. Suggestions in this report that are related to 'Author experience/expertise' imply that: 1) the available guidance or OHT structure for the RSS field in question was deemed sufficient and the deficiency was clearly due to lack of experience/expertise in the endpoint or 2) the RSS author appeared to be responsible for the deficiency and a more experienced author or an author with higher expertise in the endpoint and/or RSS format could have avoided the deficiency in question.
Guidance	Guidance refers to the currently available guidance for writing RSS, such as ECHA Practical Guide on How to report robust study summaries[13], the help function denoted by [?] within the IUCLID fields as well as ECHA guidance R7.a, R7.b and R7.c specific to REACH[14] and BPR endpoint-specific guidance[15]. Any suggestions in this report that are related to 'Guidance' mean the potential changes in available guidance that will increase the quality of RSSs.
Human error	Simple human errors such as typing errors or lack of clarity in copy/pasted sections.
OHT update	The OECD Harmonised Templates (OHTs) are standard data formats for reporting information used for the risk assessment of chemicals. The templates can be implemented in a desirable user interface to report summary test results for any type of chemical. IUCLID is the reference tool implementing OHTs. For this exercise, the focus is on the implementation of OHTs in IUCLID to see if there is a need to update any OHT fields in any of the endpoints studied in this project. Any suggestions in this report that are related to "OHT update" indicate that a structural change in the OHT fields in question and their implementation in IUCLID would improve the way the information is presented in the future RSS, or that a new OHT could be proposed.
RSS review process	As the term itself indicates, this refers to any Quality Check/review process that could improve the quality of RSS. The general assumption is that the workers involved in the review process will be more experienced in the endpoint and the RSS/OHT compared to the author. Any suggestions in this report that are related to 'RSS review process' envisions the future RSS creation by registrants as a two-step process with drafting of the RSS as the first step and the review of the RSS with a more experienced person as the second step. Required experience for the reviewers are 1) Experience in RSS authoring 2) Experience in either the specific endpoint in question or the regulatory field to which the endpoint belongs i.e., human health toxicology, ecotoxicology, environmental fate, or chemistry (for physicochemical endpoints). The RSS review process appears to be an important category to consider in improving RSS because, as evident from WP2 findings, implementation of SOP and a review process led to a significant improvement in the RSS quality across all endpoint groups.

---

[13] https://echa.europa.eu/practical-guides
[14] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[15] https://echa.europa.eu/guidance-documents/guidance-on-biocides-legislation

Final report of the study on the role of RSS in Hazard Assessment (ECHA/2021/46)

Areas of improvement	Description
Study quality criteria	This category refers to studies for which the assessment of study quality using the Klimisch score does not seem sufficient to describe the relevance of the study.
Training	Any potential training requirements that could help RSS authors/reviewers to improve the quality of RSS.
User interface	This category is defined as any potential structural changes in IUCLID per se including interface and features. For example, changes in the way tables are inserted, including mandatory fields, free text from template or capacity to include image files etc.
Validation rules	For this exercise, validation rules refer to the rules implemented through the IUCLID validation assistant, which are also listed in the Annex II of the ECHA Guidance on How to prepare registration and PPORD dossiers[16]. It also refers to quality check warnings in the IUCLID validation assistant which usually warn you of common inconsistencies and shortcomings in the data Any suggestion in this report that is related to 'validation rules' implies that logical changes in the validation assistance performed during the RSS (and dossier) writing will improve the data completeness and will avoid similar problems in future assessment of RSSs.

2.3 Step 3: Findings of WP2 (RSS authoring and comparison to registrant's RSSs)

2.3.1 Methodology

The RSS authoring and comparison exercise in WP2 was reviewed to evaluate the deficiencies identified in the registrant's RSSs. During WP2, one of the tasks was to compare each of the SOP guided RSSs with the respective registrant's RSS, in which the responsible persons comparing the RSSs were asked to provide a detailed description of each deficiency identified in the RSS. In WP3, these descriptions were analysed by creating section-wise summaries for each endpoint and potential areas for improvement were assigned for each of the deficiencies. In addition, by examining the deficiencies, this analysis also served to identify and highlight the strengths of each section and subsection of the RSS.

2.3.2 Result and Discussion

During this activity, the descriptions of all the deficiencies identified in WP2 were analysed and classified into categories. During this step, no additional categories for improvement were identified outside those initially identified from the WP1 findings.

Examples of screenshots of this activity are provided in Figure 2. These examples show the descriptions of the deficiencies as well as their assigned potential areas of improvement.

---

[16] https://echa.europa.eu/documents/10162/22308542/manual_regis_and_ppord_en.pdf/891754cb-a6b6-4bb6-8538-52ccde74070e

Sections of RSS	Sub-sections	Endpoint	Study numb	Deficiencies in registrant's RSS	Classification of the deficiency	Potential area of improvement 1	Potential area of improvement 2
Results and Discussion	Any other information on results (tabular data or reference to tables attached)	Irritation-REG	47	Nothing mentioned	Missing information	RSS review process	
Results and Discussion	Any other information on results (tabular data or reference to tables attached)	Irritation-REG	48	Important tables should have been provided	Missing information	RSS review process	Training
Summary and Conclusions	Overall remarks and attachments	Genotoxicity in vivo-SOP	9	Paper has additional mechanistic information that could be relevant for understanding the genotoxicity of the substance. Those findings should have been discussed in the remarks section.	Missing information	Author experience/expertise	Training
Test Animals	Test animal details: food and water regimen (e.g. ad libitum), quality of food and water etc	Sensitisation-REG	42	No details were noted in the publication but this should be mentioned in the RSS	Missing information	Guidance	
Test Animals	Test animal details: Environmental conditions	Sensitisation-REG	42	No details were noted in the publication but this should be mentioned in the RSS	Missing information	Guidance	
Test Material	All test material related information available in report	Irritation-REG	47	Doesn't give expiry date or storage conditions	Partial/incomplete information	Completeness check rules	RSS review process

Figure 2: Example screenshots of the table detailing the results from Step 2, demonstrating identification of potential areas of improvement. These 'potential areas of improvement' are 'categories' identified in Step 1.

Then, the findings of WP2 were presented in summary tables for each endpoint against the sections and sub-sections of individual RSSs. Table 5 focus on the type of deficiencies noted in the registrant's RSSs by section and sub-section for each endpoint, including the categorisation for improvement identified in Step 1 and described in Step 2.

Table 5: A snapshot of the summary table presenting the nature of deficiencies in the RSS from the perspective of sections and subsections of the RSS for each endpoint.

Endpoint	Section	Subsection	Description of deficiencies identified in the registrant RSS	Categorisation for improvement
Vapour pressure	Administrative data	Adequacy (pick-list)	Summary from all six RSSs available for this endpoint: Wrong information was reported in one RSS	RSS review process; Training
Vapour pressure	Administrative data	Robust study summary (checkbox)	Summary from all six RSSs available for this endpoint: Wrong information reported in several RSSs. The registrants did not select the box where it should have been selected	Human error; RSS review process
Vapour pressure	Administrative data	Study Period	Summary from all six RSSs available for this endpoint: Partial/incomplete information reported in several RSSs. In some RSSs the year was provided or the subsection was left blank	Validation check rules
Vapour pressure	Administrative data	Reliability (pick-list)	Summary from all six RSSs available for this endpoint: Wrong information reported in several RSSs. Some RSSs had provided the wrong Klimisch score or had provided a Klimisch score which differed from the rationale selected	Training, RSS review process
Vapour pressure	Administrative data	Rationale for reliability incl. Deficiency	Summary from all six RSSs available for this endpoint: Wrong information reported in several RSSs. Some RSSs had provided a Klimisch score which differed from the rationale selected	Training, RSS review process
Vapour pressure	Materials and methods	Test guideline	Summary from all six RSSs available for this endpoint: Wrong information reported in one RSS Information such as version and deviation are missing in several RSS	Validation check rules; RSS review process, Author experience

The analysis in the WP2 report[17] revealed that within registrant RSSs human health toxicology and physicochemical RSSs showed better fidelity to the full study report than ecotoxicology and environmental fate RSSs. Fewer deficiencies that could affect the hazard conclusions or required access to the full study report were identified in these endpoint groups.

Further analyses in WP2 showed that the quality of registrants' RSS (i.e., the accuracy / completeness of the RSS together with the absence of need to access the full study and effect on hazard conclusions) did not depend on the individual endpoints within an endpoint group. This showed that the quality of RSS for high tier endpoints did not differ from that of low tier endpoints. In step 3 the same categories of improvements were identified for both high and low tier endpoints. In addition, the WP2 report revealed that there were no significant differences in the number of deficiencies affecting the hazard conclusions among RSSs created from different types of full study reports (lab report versus peer reviewed scientific publications), full study reports with different Klimisch scores (KL score 1, 2) and substance type (mono-constituent organic, inorganic, or multi-constituent/UVCB).

Thus, irrespective of the factors mentioned above, the type of deficiencies that could affect the interpretation of the results/hazard conclusion or required access to the full study were similar across the different endpoint groups. These types of deficiencies were:
- missing information
- partial/incomplete information
- incorrect information

The potential areas of improvement related to these gaps were often related to categories such as the RSS review process and author experience/expertise.

Overall, the results of WP2 were able to provide evidence in support of the perceived strengths of the RSS identified in WP1 in relation to its defined structure and level of consistency. The number and type of deficiencies identified in WP2 were considered independent of individual endpoint, type of study report, initial Klimisch score assigned by the author and type of substance. The findings suggest deficiencies identified in WP2 would appear to be more specific to the sections and sub-sections of the RSS's template.

2.4 Step 4: Comparison of proposed and identified areas of improvement

2.4.1 Methodology

The areas of improvement analysed in Step 3, were assigned one of the categories identified from WP1 (Step 1). This resulted in a comparative assessment of the proposed areas of improvement for RSSs in WP1 against the areas of improvement observed in WP2. In addition, Step 4 provided the opportunity to identify any new type of observed area of improvement not highlighted during WP1.

---

[17] ECHA published the WP2 report in March 2023 at https://echa.europa.eu/technical-scientific-reports

2.4.2 Results and Discussion

During this activity, the areas of improvement suggested in WP1 were compared with the deficiencies identified in WP2. As already discussed in Step 3, no new categories were considered needed beyond the 9 initially identified. This is because it was observed that the proposed areas of improvements identified in WP1 were similar to those identified in WP2.

This analysis also identified the categories that have the potential to resolve deficiencies in the RSS affecting hazard conclusions and requiring access to the full study report, as well as determining whether changes/improvements are needed in the documentation associated with these categories to enhance the usefulness of the RSS.

A qualitative comparison of the proposed areas of improvements in WP1 and the identified areas of improvement in WP2 was conducted; the findings are described in the following sections. For a detailed description of the categories please refer to Table 4.

RSS review process
In WP1, some participants proposed to make the authorities' comments and annotations visible on the RSS and more easily transferable and printable, while in WP2 the type of finding were not of the same type. In WP2, the type of deficiencies affecting the hazard conclusions associated with this category were often the following: missing information, partial/incomplete information, and wrong information. These findings clarified that the implementation of a review process in line with an SOP would significantly improve the RSS.

Validation rules
In WP1 several participants suggested that essential data should be mandatory so RSS cannot be submitted with empty fields. The same areas of improvement were observed in WP2. In addition, the analysis in WP2 identified which data could be considered essential (e.g., the test validity criteria, the test conditions, the results table, the conclusion, etc.). Further details are provided in Step 5.

IUCLID user interface
There were several suggestions in WP1 to improve the way essential data should be presented in IUCLID to improve the visibility of results and key information, e.g., by identifying mandatory fields with an asterisk and distinguishing between mandatory and non-mandatory fields. In WP2, similar areas of improvement were observed, for the sections "Other details on test conditions", which were often left blank, and "Results and discussion", where shortcomings were observed that did not allow proper visualisation of key results or provision of key information in the table due to lack of space.

Training
Participants in WP1 proposed to put into place RSS training for authors to address issues they experience with RSSs. The suggestion also included the possibility to obtain a certification of attendance to trainings. The potential added value of structured training was supported by the deficiencies observed in WP2, such as incomplete or missing information in the 'result and discussion' section of the RSS, which were not related to the quality of the study reports and could be easily addressed with training. The impact and added value of a certification scheme was not further assessed in the scope of this study.

Author experience/expertise

In WP1, the lack of clarity and/or incomplete interpretation of the results was often linked to the author's lack of experience. Therefore, several participants suggested that RSS authors should have a minimum level of experience and qualifications in writing RSSs. Some respondents also mentioned that a review of RSSs by more experienced authors should be sufficient to help improve the quality of RSSs. These suggestions for improvement were supported by the gaps identified in WP2, in the 'results and discussion' section and in the conclusion where incorrect or incomplete interpretations of the results/hazard conclusion were provided even though all information was provided in the report.

Guidance

In WP1 (see page 54), respondents suggested including more information in the template in the IUCLID fields through pop-up windows with explanations and examples of expected information in the fields. It was also suggested to provide more information in the guidelines for more complex studies and different types of substances. In WP2, the deficiencies observed, in the section "Test material", which was often left blank, or containing partial/incomplete information, were in line with the areas for improvement proposed in WP1. However, this potential area of improvement concerned only 8% of the deficiencies affecting the hazard conclusions identified in WP2. These deficiencies were found mainly in one section of the RSS, as mentioned above. This shows that currently available guidance documents are relatively complete and contribute to helping provide the correct information in the RSS to be able to conclude on the hazard.

Human error

A key finding of WP1 regarding hazard assessment was that RSS have been designed well, but in practice, human error can always happen when completing the templates. Evaluators are aware of this, so it equates to a trust issue that lowers confidence (see chapter 3.3.2 of the WP1 report). Some respondents in WP1 proposed the copy-paste of the discussion, conclusion, and summary sections from GLP reports to be mandatory, to avoid or reduce typing errors by authors. However, in WP2 only 4% of the deficiencies identified could be linked to this proposal. In the few cases identified, data on the concentration tested or dose descriptors were not reported correctly in the RSS.

OHT update

In WP1, it was often proposed to update the OHTs, either to extend the list of information available in picklists or to make it more flexible to assess non-standardised test methods. The areas of improvement proposed in WP1 were also identified in WP2, for the section "*Any other information on the method*" where essential information about the method used was missing, such as the validity criteria of the test. However, this potential area of improvement concerned only 2% of the deficiencies affecting the hazard conclusions in WP2. This shows the usefulness of the current OHTs in helping to provide the correct information in the RSS for the purpose of hazard assessment, although some OHT fields, such as "*Any other information on the method*" or "*Any other information on the result*", should be updated to clearly specify what is the key information expected in these fields, as observed in WP2.

In WP1 it was pointed out that the assessments of reliability follow the Klimisch method, which does not always support a systematic and transparent assessment of the data, overlooks the aspect of relevance and is likely to favour studies conducted according to GLP guidelines/standardised tests. It was also mentioned that poor reporting of a study is sometimes confused with poor quality when evaluating a study, e.g., an independent research study would be considered unreliable because it does not use standardised test methods, and therefore some RSS fields are left empty. It was therefore proposed to consider more criteria to assess the study report, rather than only assessing the reliability of the study design. In WP2, only two deficiencies supported the WP1 suggestion, in which the Klimisch score was considered higher than reported. The low number of deficiencies affecting the hazard conclusions observed in WP2 for this potential area for improvement can be explained by the fact that most of the studies selected for this project were key studies under the REACH or BPR regulations, which are often performed according to standardised methods. Furthermore, the findings in WP2 show that the Klimisch method is sufficient to evaluate GLP guidelines/standardised method.

Figure 3 summarises the distribution of potential areas for improvement for identified deficiencies in WP2 affecting the interpretation of the results and hazard conclusions across each section of the RSS.
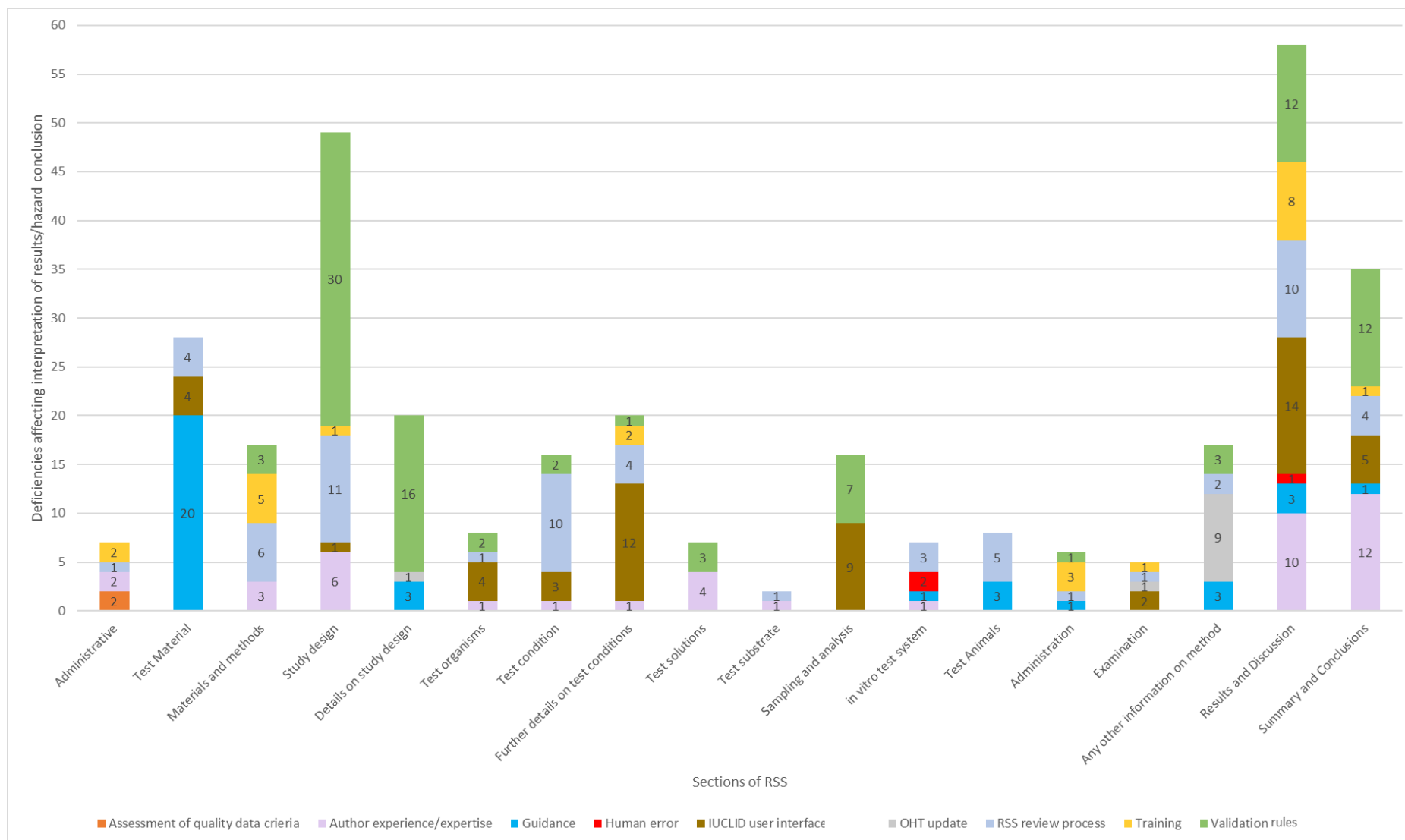
Figure 3: Distribution of potential areas for improvement related to deficiencies affecting the interpretation of the results and hazard conclusion identified in Step 3 for each section of the RSS. These "potential areas for improvement" are the categories identified in Step 1.

Overall, during this step, the potential areas of improvement identified in WP2 were of similar nature to the areas of improvement proposed in WP1. In addition, through this exercise it became clear that the guidance documents, OHTs and data quality assessments in place are relatively sufficient to help report the key information from the study report within the RSS. The guidance documents contribute to the usefulness of the RSS for the purpose of hazard assessment, although these documents should be updated to specify the information that should be provided as part of the 'Test material' section. This step also helped to identify the main categories of areas of improvements that have the potential to address the gaps in the RSS in WP2 to improve the usefulness of the RSS. These categories are:

- RSS review process
- Validation rules
- IUCLID format
- Training
- Author experience/expertise

2.5 Step 5: Identification of potential areas for improvement to enhance the quality and accuracy in the RSS for the purpose of hazard assessment

2.5.1 Methodology

As discussed in Steps 1 to 4, all areas of improvement were classified into different categories identified in WP1. Then, the potential reasons for the deficiencies in the registrant's RSS (WP2) and potential areas of improvement having an impact on hazard assessment and therefore the usefulness of the RSS for hazard assessment purposes were evaluated.

2.5.2 Results and discussion

A total of 9 categories of potential areas for improvement were consolidated after the work done in WP1, and no new categories had to be added after reviewing the deficiencies identified in WP2.

The suggestions for improvement were determined based on the deficiencies identified in the RSS sections and sub-sections of each endpoint group and their impact on the usefulness of the RSS for hazard assessment purposes.

Thus, during this step, for each of the deficiencies in the registrant's RSS a potential area of improvement and solution was proposed for each section and subsection of individual endpoints. Figure 4 shows an example of some of the potential areas for improvement and solutions to resolve those deficiencies.

Sections of RSS	Sub-sections	Endpoint	Study type	Deficiencies in registrant's RSS	Classification of the deficiency noted	Score	Potential areas of improvement and solutions
Administrative	Rationale for reliability	Invertebrate acute - REG	Lab report	comparable to guideline study with acceptable restrictions (restrictions not recorded here); Yordas RSS guideline study GLP study conducted according to TG	Missing information	0	Completeness check: When 'comparable to guideline study with acceptable restrictions' is selected, then it should be made mandatory to provide what deviations from the guidelines are in the report so that it can judged whether it is 'acceptable' or not.
Administrative	Rationale for reliability incl. Deficiencies	Algae - REG	Lab report	Insufficient, no details on deficiencies	Missing information	0	Training: Endpoint specific training for this endpoint is required to understand the guideline requirement. IUCLID format: create a more structured and guided field to make this section more intuitive to complete RSS Review Process: internal review would catch this deficiency
Further details on test conditions	Test system details (such as vessel, material, replicates, loading rate, aeration detail etc)	Invertebrate acute - REG	Lab report	Details on test vessel, volume, replicates, concentrations are missing	Missing information	0	RSS review process: internal review would catch the missing information IUCLID format: make these mandatory fields
Further details on test conditions	Test system details (such as vessel, material, replicates, loading rate, aeration detail etc)	Algae - REG	Lab report	(1) cell density: 104 instead of 10^4 (2) information on analytical methods	Wrong information	0	Human error: may have missed the "^" or did not input correctly when copy/pasting RSS review process: internal review would catch any important missing information IUCLID format: a more robust input fields would minimise missing information deficiencies
Materials and methods	Guideline followed	Fish acute - REG	Lab report	(1) states that OECD Guideline 203 (Fish, Acute Toxicity Test) was followed, (2) additionally states that other guideline was followed	Wrong information	0	RSS review process: internal review would catch the omission. IUCLID format: if guideline followed is selected, it should be mandatory to specify which.
Materials and methods	Guideline followed	Algae - REG	Lab report	Wrong statement ('according to guideline'), 'equivalent or similar to guideline' is more appropriate. Also, for Chloroacetic acid, the procedure was similar to DIN 38412 Part 9, but modified for substances with strong odor	Wrong information	0	Author experience/expertise: a more experienced author would better understand the nuances of according to vs equivalent/similar to in guidelines

Figure 4: Example screenshots of Step 5, demonstrating the identification of potential areas of improvement identified in step 1 along with some ways to solve those deficiencies.

A summary of proposed approaches for improvement for each section and subsection of the RSS is provided in the following chapters. The potential solutions described in the following chapters can also be applied to the areas of improvement perceived in WP1, as Step 4 made clear that the proposed and observed areas of improvement were similar in nature.

2.5.2.1 Sections and subsections common to all the endpoints

The summary of the objectives, methods, results, and conclusions of a full study report are detailed in the general sections and subsections of an RSS. The RSS also contains endpoint-specific sections and subsections, depending on the specifics of each endpoint.

The general information requirements for RSS for all endpoints are given in the sections and sub-sections presented in Table 6.

Table 6: General sections and subsections for all endpoints and detailed analysis of identified deficiencies affecting hazard conclusions

Section	Subsection	Number of deficiencies identified in WP2	Number of deficiencies in WP2 affecting interpretation results/hazard conclusion	Percentage of deficiencies affecting the interpretation results/hazard conclusion based on the total number of deficiencies identified in a section.
Administrative data	Endpoint (picklist)	5	1	1%
	Type of information (picklist)	0	0	0%
	Adequacy of study (picklist)	15	11	7%
	Robust study summary (checkbox)	17	0	0%
	Study period (free text)	47	0	0%
	Reliability (picklist)	38	5	3%
	Rationale for reliability (picklist/free text)	47	3	2%
	Total:	**169**	**20**	
Data source	Detailed reference	5	0	0%
	Data access and data protection claims (picklist)	11	0	0%
	Total:	**16**	**0**	
Materials and methods	Test guideline followed including fields 'deviation', 'version'	102	12	9%
	Principles of method if other than guideline (free text)	11	4	3%
	GLP compliance (picklist)	10	4	3%
	Total:	**123**	**20**	
Test materials	**Total**:	**59**	**40**	68%

Final report of the study on the role of RSS in Hazard Assessment (ECHA/2021/46)

Section	Subsection	Number of deficiencies identified in WP2	Number of deficiencies in WP2 affecting interpretation results/hazard conclusion	Percentage of deficiencies affecting the interpretation results/hazard conclusion based on the total number of deficiencies identified in a section.
Applicant's summary and conclusion	Conclusions (free text)	20	15	22%
	Executive summary (free text)	41	8	12%
	Total:	**61**	**23**	

The two key sections where the hazard conclusions were impacted by the deficiencies in WP2 are 'Test materials' and 'Applicant's summary and conclusion'.

Administrative data

The main aim of this section of the RSS is to identify the purpose of the RSS. In IUCLID 6 the Administrative data main heading is used to identify the purpose of the record (e.g., 'key study'), the type of result (e.g., 'experimental study'), data waiving indication (if any), reliability indication, and flags for specifying the regulatory purpose envisaged and/or any confidentiality restrictions. This kind of data characterises the relevance of a study summary and are therefore displayed at the top of each Endpoint study record.

While analysing the registrants' RSSs in WP2, most of the deficiencies affecting the hazard conclusions (20/169) identified in the "Administrative" data sub-sections concerned the assessment of the data quality following the Klimisch score method. For example, for some registrant's RSSs, a low Klimisch score was given instead of giving a higher score which led to an inappropriate rationale selection and then to an inappropriate study adequacy to fulfil the information required by the legislation. In some registrants' RSS subsection's 'reliability' and/or 'rationale for reliability' were also left blank. Assessment of data quality and reliability was also an area of improvement pointed out by the Stakeholders in WP1.

Proposed approaches for improvement

During step 3 of this project, for each deficiency listed in WP2 observed in the "Administrative" data subsection, three potential areas for improvement were identified, which were ranked from those that would bring the most improvement to the quality of RSS if implemented. Figure 5 shows the percentage value of the frequency with which an area of potential improvement is suggested to reduce the deficiencies identified in that subsection (i.e., adequacy, reliability, and rationale for reliability) influencing the hazard conclusions.
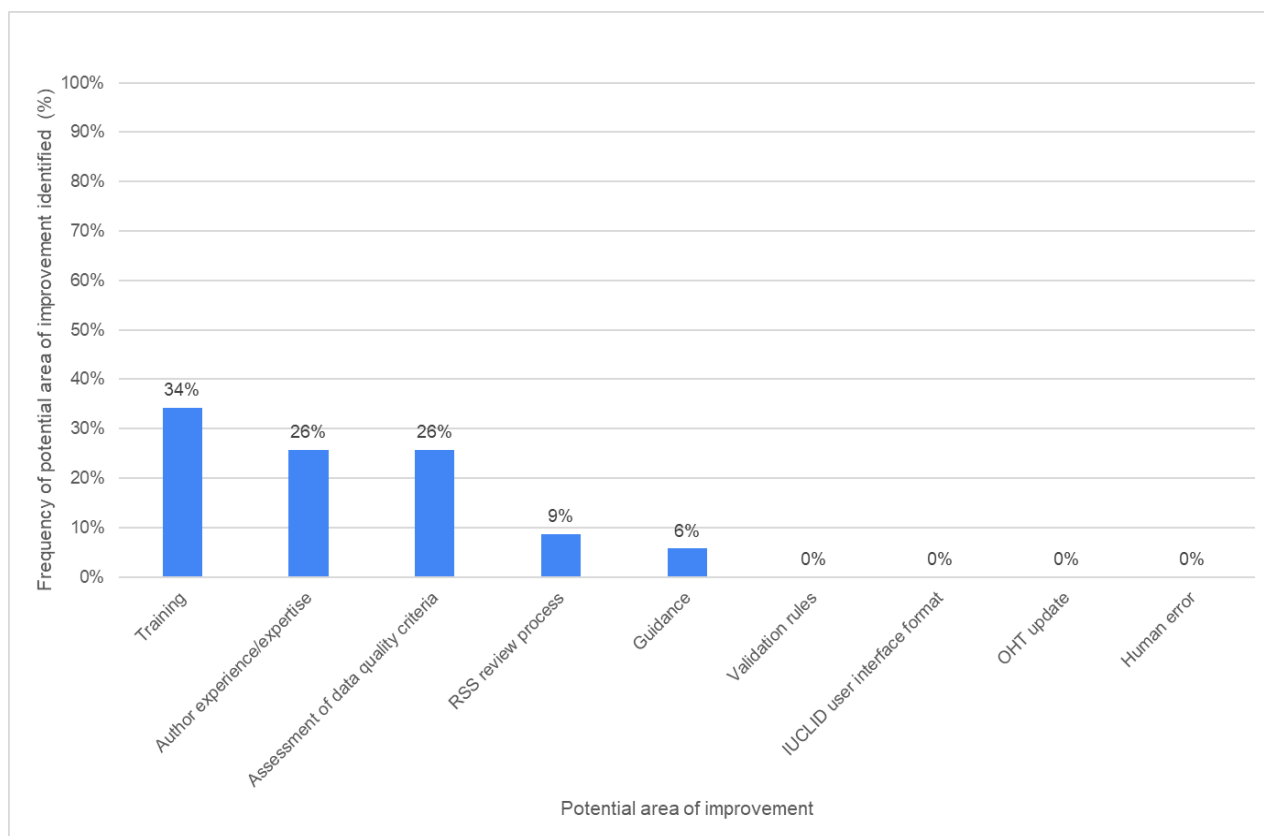
Figure 5: Frequency of potential areas of improvement observed in the "Administrative" data subsections that could prevent deficiencies that could affect the interpretation of the results/ hazard conclusions. These "potential areas for improvement" are the categories identified in Step 1.

Therefore, the following options for improving the section on administrative data in the RSS for the purpose of hazard assessment could be considered:

● Training of RSS authors so that they can properly assess the quality and adequacy of a study

● Updating the system used to assess the quality, relevance and adequacy of a study, perhaps taking into account available data reliability and relevance review system such as CRED (Criteria for Reporting and Evaluating Ecotoxicity Data) and SciRap (Science in Risk Assessment and Policy)[18], review schemes developed by international and national agencies such as WHO (World Health Organization and International Labour Organization), U.S NTP (National Toxicology Program) Office of Health Assessment and Translation.[19]

---

[18] Science in Risk Assessment and Policy. Accessed on Sep 3, 2022. Available at:
http://www.scirap.org/Page/Index/9ced3317-ab2b-4617-86f4-f2d3b86a419f/reporting-checklist
[19] NTP (National Toxicology Program). (2015a). Handbook for conducting a literature-based health assessment using OHAT approach for systematic review and evidence integration. U.S. Dept. of Health and Human Services, National Toxicology Program. https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf;
NTP (National Toxicology Program). (2015b). OHAT risk of bias rating tool for human and animal studies. U.S. Dept. of Health and Human Services, National Toxicology Program.
https://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool_508.pdf; NTP. (2019). Handbook for conducting a literature-based health assessment using OHAT approach for systematic review and evidence integration. Research Triangle, NC: National Institute of Environmental Health Sciences.
https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookmarch2019_508.pdf

- ● Experienced RSS authors, familiar with the OECD guidelines or the test methods used to provide the information required by the legislation, should be able to properly assess the quality of a study.

In addition, the assessment of the quality data criteria affecting the hazard conclusions was observed in relatively few registrants' RSS in WP2 (see Table 6), which might be explained by the fact the studies selected for this project were considered as key studies under the REACH or BPR regulations, for which OECD test guidelines or other standardised methods are often used to fulfil the required information. It shows that the Klimisch method is still a sufficient basis for assessing the quality of GLP guidelines/standardised methods.

The completeness check rules for the administrative data section are also currently included in the IUCLID validation assistant tool when a study record is marked as 'key study' or 'weight of evidence', and therefore the low number of shortcomings affecting the hazard conclusions for this section show that implementing completeness check rules in the IUCLID validation helped to report the essential data required for the hazard assessment.

Data source

The information on the data source is mainly related to the full reference of the study and data access. In addition, under the Data Source heading in IUCLID, fields are subsumed for identifying the source of the information summarised in the record and, in the case of company data, an indication of whether the data are protected or accessible. In addition, for cases where the same study is recorded in another IUCLID section, a cross-reference to that section can be given.

During analysis of registrants' RSSs, the deficiencies identified in this section did not influence the interpretation of the results/hazard conclusion. The type of deficiencies listed in WP2 was the reporting of incomplete information. The majority of these (11/16) concerned data access and data protection claims. The field data protection claim was left empty. However, these types of deficiencies are not information that can be extracted directly from study reports and are related to how registrants decide to share their data. Also, in some registrant's RSSs, all aspects of the reference, such as the title, were not reported or were incomplete.

Proposed approaches for improvement

The deficiencies identified in WP2 did not influence the hazard assessment, as such any improvement of this section would have a minor role in improving RSS for the purpose of hazard assessment.

The implementation of an RSS review process would help to improve this section.

In addition, as for the "Administrative data" section, completeness check rules are already included in the IUCLID validation assistant tool for the section "Data source". Thus, the results in Table 6 show that, among other factors, the implementation of completeness check rules in the IUCLID validation assistant tool helps the registrant to understand the information required in this section. The format used in IUCLID for this section, the guidance provided in the help function (indicated by "?") in the respective IUCLID fields and the OHT template also contribute to the understanding of the information required.

Materials and methods

The information on materials and methods is mainly related to the method or guideline followed.

Most of the deficiencies affecting the hazard conclusions (20/123) listed in the generic sub-sections of the Materials and Methods section in WP2 include information on the guideline or methodology used for testing such as a guideline or standardised method followed, its version and if there are any deviations from the method. For the majority of the registrant's RSSs, the version of the test guideline or standardised method used was not specified, the field 'deviation' was left blank, whereas 'no deviation' should have been reported if no deviation was observed. In a few registrants' RSS, incorrect information was selected in the 'GLP compliance' picklist.

Proposed approaches for improvement

It is necessary to ensure that the above-mentioned information on the guideline or the method used is correctly provided in the RSS for the purpose of the hazard assessment. This information is important to conclude on the compliance with the guideline, the relevance of the method used as well as the reliability of the results.

Figure 6 shows the most frequently suggested potential areas for improvement in Step 3 to improve the usefulness of this section of the RSS for hazard assessment.
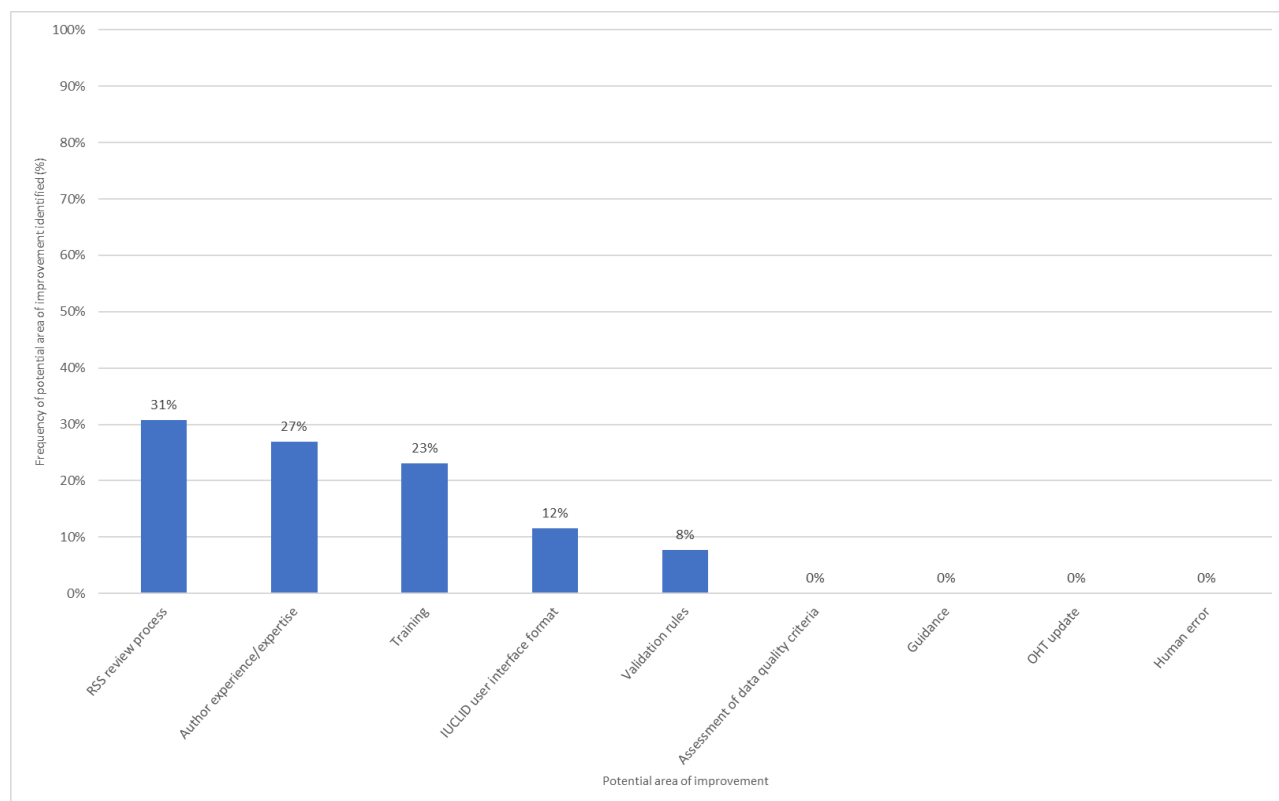

Figure 6: Frequency of potential areas of improvement observed in *Material and methods* generic subsections that could prevent deficiencies that could affect the interpretation of the results/hazard conclusions in percentage. These "potential areas for improvement" are the categories identified in Step 1.

Final report of the study on the role of RSS in Hazard Assessment (ECHA/2021/46)

Thus, based on this analysis the following options for improving the section on material and methods in the RSS for the purpose of hazard assessment could be considered:

- Implementation of an RSS review process to avoid providing incomplete and leaving empty fields in this section
- Experienced RSS authors who are familiar with the OECD guidelines and standard methods used to fulfil the endpoint requirements should be able to provide information on the guideline/standard method used, its version and if there are any deviations
- RSS author training to identify the information to be reported in this section

As with the sections 'Administrative data' and 'Data source', completeness check rules are included in the IUCLID validation assistant tool for this general part of the 'Material and methods' section. The limited instance of deficiencies affecting hazard conclusions identified in WP2 (see Table 6) shows that the implementation of completeness check rules in IUCLID validation assistant for this section facilitates the reporting of essential data for the purpose of hazard assessment in this section. Although the list of rules should be updated to include that for each endpoint study record marked as "key study" or "weight of evidence", or indicated as a testing proposal, the fields "deviation", "version" and "principle of the method followed" should not be left blank. If this information is not available or applicable, it should be stated as "not applicable " or " not specified ". This would increase the reliability of RSS.

Test material

The section on test material provides detailed information on the test substance.

Most of the deficiencies identified in this section affect the hazard conclusions (40/59). In this section, information is either missing or incomplete. For example, in some RSS only the identity (i.e., CAS Nr, EC Nr) of the test material was reported, while information on the test material such as purity, expiry date, storage condition etc were missing.

Proposed approaches for improvement

Information On test material used for a study such as its purity, source, information on stability and storage conditions of the test material as well as if applicable radiolabelling information needs to be provided to ensure the suitability of the test material to conclude on hazard assessment. Figure 7 below shows the most frequently suggested potential areas of improvement to address the deficiencies in WP2 in relation to the hazard conclusions.
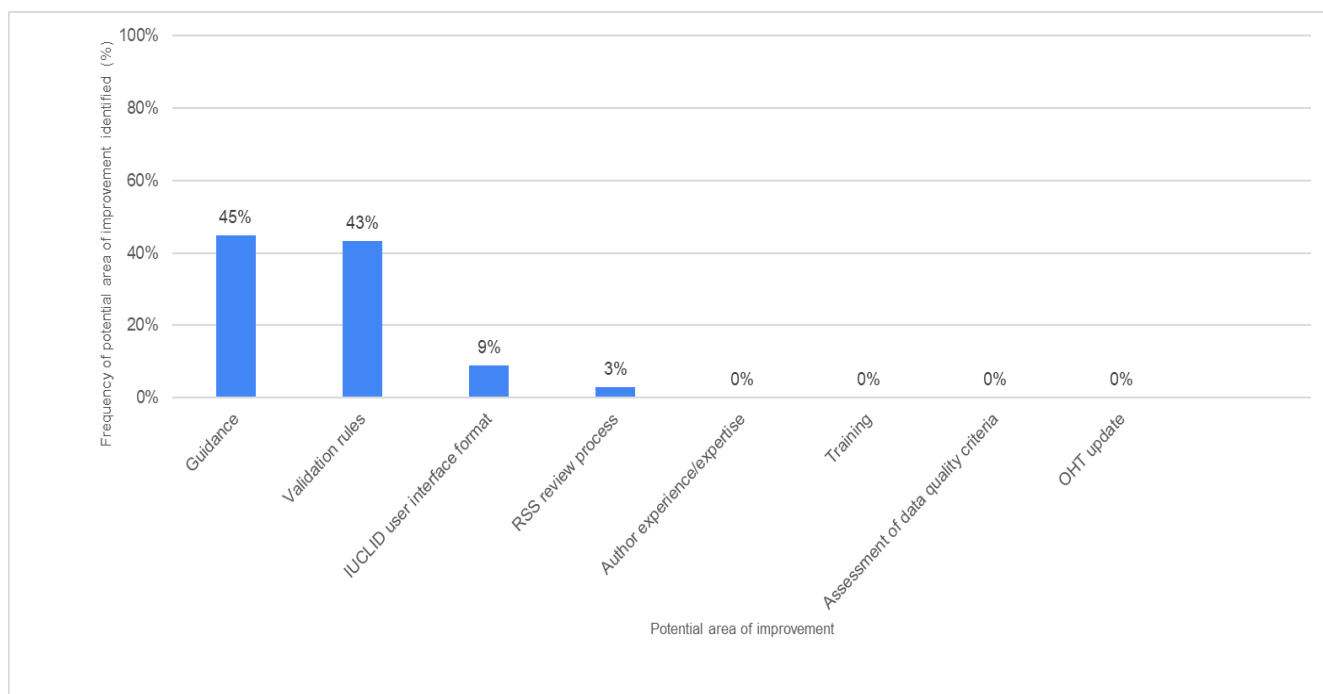
Final report of the study on the role of RSS in Hazard Assessment (ECHA/2021/46)

Figure 7: Frequency of potential areas of improvement observed in the Test material section that could prevent deficiencies that could affect the interpretation of the results/hazard conclusions in percentage. These "potential areas for improvement" are the categories identified in Step 1.

Therefore, the following options for improving the section on test material in the RSS for the purpose of hazard assessment could be considered:

- Validation rules are currently included in the IUCLID validation assistant tool for this section. However, these rules only refer to the identity of the test material (i.e., CAS Nr, EC Nr, IUPAC name, composition, type of substance). Updating the list of rules to include that for each endpoint study record marked as "key study" or "weight of evidence", or indicated as a testing proposal, fields on specific details on the test material used for the study such as its purity, source, information on stability and storage conditions of the test material and if applicable radiolabelling information should be completed. If the information is not available, "not specified" should be indicated in the corresponding IUCLID field. This could help to assess the suitability of the test material for hazard assessment and save time and resources for the assessor.

- Emphasising in ECHA's Practical Guide on *How to report robust study summaries* and the IUCLID help text that the above-mentioned specific information of the test material is required for hazard assessment.

Applicant's summary and conclusion

In this part of the RSS, conclusions are presented, including a brief summary of the relevant aspects (methodology, results) of the study and the conclusion reached (such as hazard classification).

Most of the deficiencies affecting the hazard conclusions identified in WP2 (23/61) concerned the summary of relevant aspects of the study, including the conclusions made. In some RSSs, the sub-sections 'conclusion' and/or 'executive summary' were left empty, or the summary of the study was incomplete, missing information such as the guideline used and data on the study design with only the results presented without any reference to the outcome of the study and hazard classification.

Furthermore, the subsection 'conclusion' was often left empty despite the fact that the subsection executive summary was filled in.

Proposed approaches for improvement

Summary of the relevant aspects of the study and conclusions made influence the hazard assessment. This information is essential for the robustness of the results and the hazard assessment. This also contributes to the main strength of an RSS, which is to provide sufficient information to allow a technically qualified person to independently assess a given study report without having to go back to the full report. In the WP1 report, one of the key reasons for poor quality RSS was adjudged to be lack of data, specifically, tabulated data (see chapter 3.4.5 of the WP1 report).

Figure 8 shows the most frequently suggested potential areas of improvement to address the deficiencies in WP2 in relation to the hazard conclusions.
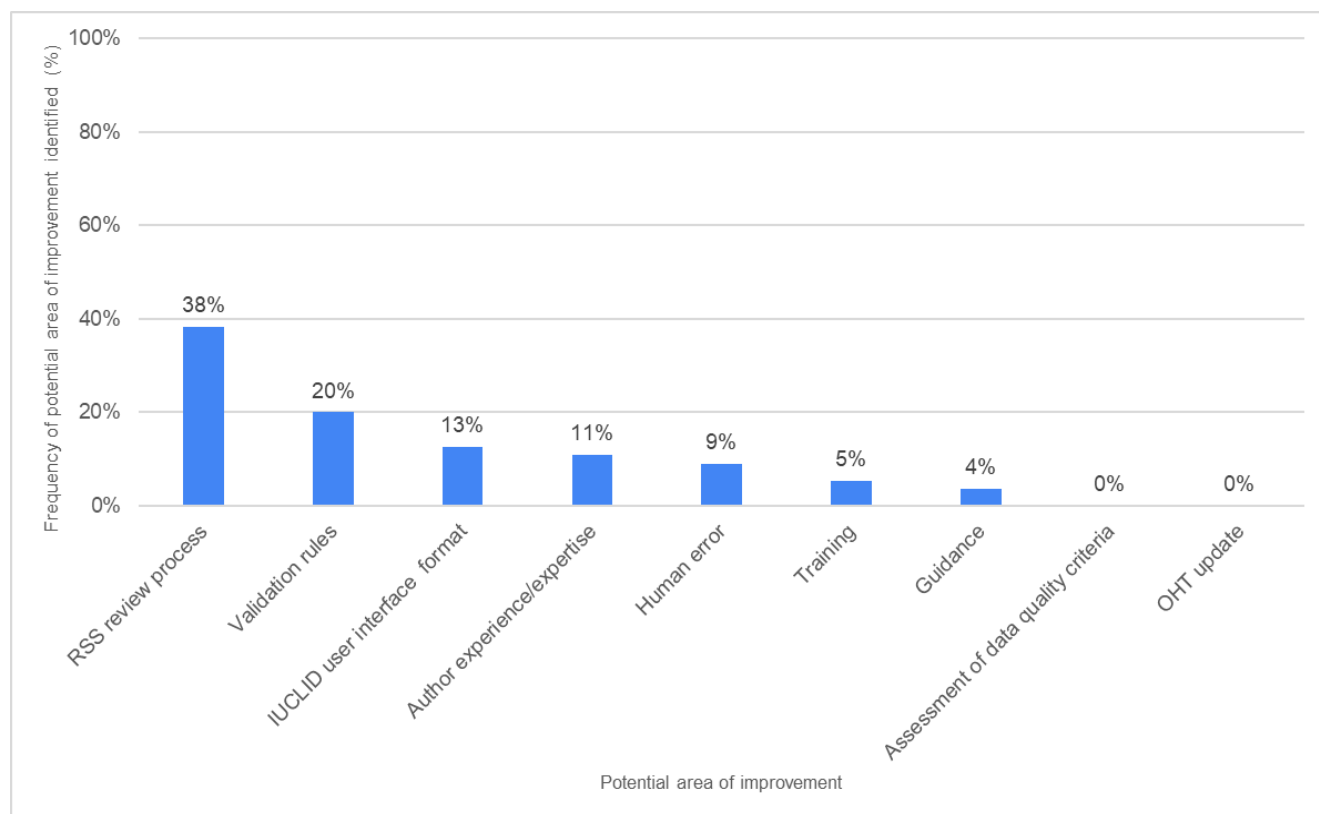

Figure 8: Frequency of potential areas of improvement observed in Applicant's summary and conclusion section that could prevent deficiencies that could affect the interpretation of the results/hazard conclusions in percentage. These "potential areas for improvement" are the categories identified in Step 1.

The analysis suggests considering the following options for improving the section on Applicant's summary and conclusion in the RSS for the purpose of hazard assessment:

- Implementation of an RSS review process
- Currently, there are no compliance check rules in place for this section in the IUCLID validation assistant tool, whereas this is the case for the generic sections mentioned above. The IUCLID validation assistant tool should be updated and include that for each endpoint study record marked as 'key study' or 'weight of evidence' the 'conclusion' field should contain the hazard conclusions made and 'executive study summary should contain a summary of the relevant aspects of the study (i.e., reference to the guideline or standardised method used, relevant aspect of the study design, results, and hazard classification conclusion)
- Updating the RSS format and making 'Executive summary' a mandatory field and automatic inclusion of key information from the results or conclusion sections where relevant.

2.5.2.2 Endpoint-specific IUCLID sections and subsections

As described in chapter 2.5.2.1, in IUCLID, the summary of the objectives, methods, results and conclusions of a full study report are detailed in the general sections and subsections of an RSS. The RSS also contains endpoint-specific sections and subsections, depending on the specifics of each endpoint. These sections and sub-sections correspond to the details (e.g., test conditions, apparatus, etc.) of the applied method corresponding to a test method (EU or OECD) used to fulfil the information requirement of a specific endpoint.

The results and conclusions sections are also related to this test method and detail whether the validity criteria of the test method have been met, as well as any specific results and conclusions that can be drawn from the underlying data.

The potential areas for improvement to reduce the number of deficiencies affecting the hazard assessment in the specific sections and subsections are presented below for each of the endpoint groups described in Table 2.

Physicochemical information

The specific information requirements for the RSS for the physicochemical endpoints considered in this project are given in the sections and subsections presented in Table 7.

Table 7: Endpoints-specific sections and subsections for physicochemical endpoints considered in this project and detailed analysis of listed deficiencies in WP2

Endpoints	Specific section	Specific sub-section	Number of deficiencies identified in WP2	Number of deficiencies in WP2 affecting interpretation results/hazard conclusion	Percentage of deficiencies affecting the interpretation results/hazard conclusion based on the total number of deficiencies identified in a section.
Vapour pressure; Partition coefficient; Water solubility	Materials and methods	Type of method (picklist)	0	0	0%
Partition coefficient; Water solubility Partition coefficient; Water solubility	Study design	Analytical method (picklist)	3	0	0%
		Details on method (template)	9	6	**50%**
		Total:	**12**	**6**	
Vapour pressure; Partition coefficient; Water solubility; Flammability (solids)	Any other information on methods incl. tables (block free text)		**8**	**3**	**38%**
Vapour pressure; Partition coefficient; Water solubility; Flammability (solids)	Results and discussion	Results table specific to each endpoint (repeatable table)	4	0	0%
Flammability (solids)	Summary and conclusion	Interpretation of results (picklist)	0	0	0%

The deficiencies identified in the RSS sections '*study design*' and '*Any other information on methods incl. Tables*' are deemed to have an impact on the conclusions on hazard assessment.

Material and methods

Under the Material and Methods heading of IUCLID for physicochemical endpoints, the endpoint-specific fields are subdivided to identify the type of method used according to the guideline or methodology used, followed by data of the study design, i.e., the analytical method, method validation and any relevant aspects of the study design to determine the relevance of the method and the test material for the purpose of hazard assessment.

Most deficiencies affecting the hazard conclusions for physicochemical endpoints (9/20) concerned the details provided on the method (purity of the test material, impurities, composition), including additional information on the test method such as the description of the apparatus or reference to the standard or test method applied, the test condition (temperature, concentration tested, etc.) applied.

The subsection "Details on the method" include information such as purity of the test material, impurities, composition, method of analysis and method validation data was left empty or incomplete in the RSSs of many registrants. The section "Any other method information" includes, for the flammability endpoint, information such as a description of the apparatus and dimensions or a reference to the standard or test method applied; test temperature; concentrations tested, and other information related to the corresponding endpoint was also left blank.

Proposed approaches for improvement

The RSS should provide sufficient detail on the test method, study design and test equipment used to allow an independent assessment of the suitability and adequacy of the test material and methods used, respectively.

Figure 9 shows the most frequently suggested potential areas of improvement to address the deficiencies in WP2 in relation to the hazard conclusion.
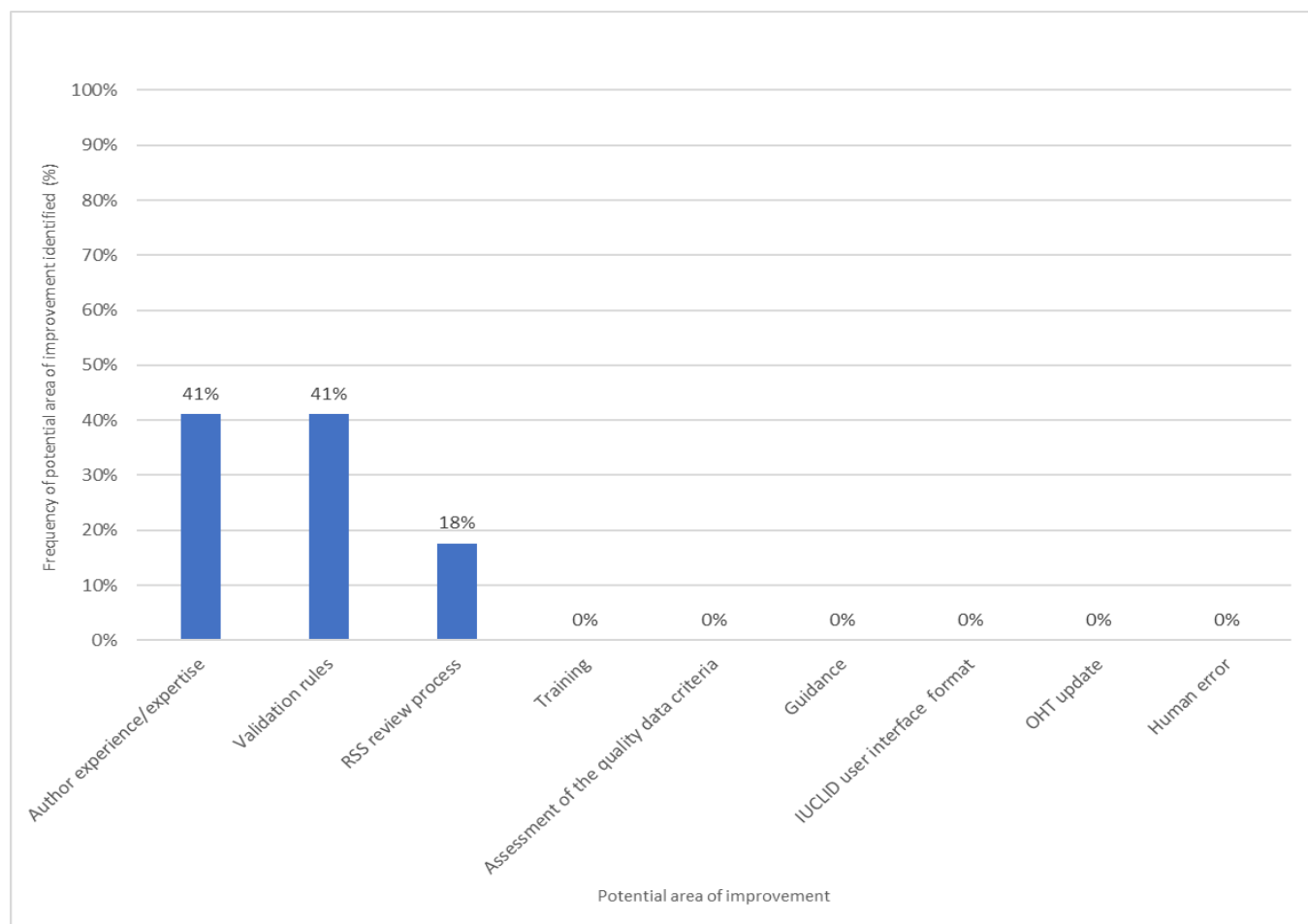
Figure 9: Frequency of potential areas of improvement observed in the Material and method endpoint-specific subsection that could prevent deficiencies that could affect the interpretation of the results/hazard conclusions in percentage. These "potential areas for improvement" are the categories identified in Step 1.

Therefore, the following options for improving the endpoint-specific section on material and methods in the RSS for the purpose of hazard assessment could be considered:

● Currently, there are no validation rules in place to provide information on the testing method in the IUCLID validation assistant tool, whereas this is the case for the section 'type of method'. The IUCLID validation assistant tool should be updated and include for each endpoint study record marked as 'key study' or 'weight of evidence' the 'details on method' field should contain enough information to assess the suitability of the test material and relevance of the method

● An experienced RSS author would know where to find the guidance to fill out this section. Furthermore, knowledge of the guidelines/standardised methods required to assess the physicochemical property of a substance under the respective legislation would help to improve this section for the purpose of hazard assessment.

Results and discussion

The deficiencies listed in this section of registrants' RSSs did not have an impact on the hazard assessment. They were deemed human errors, as the author may have forgotten to select the key result box.
Proposed approaches for improvement

The deficiencies in WP2 did not influence the hazard assessment. The implementation of an RSS review process would help to improve this section as highlighted by the lack of these deficiencies in the SOP guided RSS.

Validation rules are already included in the IUCLID validation assistant tool for the endpoint-specific section 'results and discussion' for the physicochemical endpoints considered in this project. The outcome of the analysis of this section shows that the implementation of completeness check rules in the IUCLID validation assistant tool helps the registrant to understand the information required in this section. However, the selection of the box key result is not checked by the IUCLID validation assistant tool while it could be considered important for the purpose of hazard assessment of a substance. This would help the hazard assessor to identify the main results of the study report and reinforce the strengths of RSS perceived in WP1 which is that a good quality RSS could save time and resources. Therefore, for a study record marked as a key study or as weight of evidence the box key result should be listed as an error when running the IUCLID validation assistant tool when the field is left empty without justification. This would help to strengthen the usefulness of the RSS.

Conclusions on specific information requirements for RSS (physicochemical endpoints)

Overall, in the physico-chemical endpoint group, only deficiencies listed in the material and method specific-subsections impacted the hazard conclusions. While low numbers of deficiencies were identified during WP2 in the result and discussion endpoint-specific subsections. It shows that the tools already in place to help report data in this section (e.g., IUCLID validation assistant tool) are useful. The specific characteristics of the physico-chemical endpoints are described in such a way that the RSS allows an independent assessment of the reliability and completeness of the endpoints.

Environmental and ecotoxicological endpoints

In IUCLID, RSSs for each environmental endpoint are composed of the common general parts described in chapter 2.5.2.1 and the endpoint specific parts, dependent on the applied methodology and characteristic for each endpoint. Some endpoint specific sections in an RSS are similar for environmental fate and ecotoxicological endpoints. Therefore, the endpoint-specific information required in the RSS for the environmental fate (e-fate) and ecotoxicological (ecotox) effects considered in this project are presented together in Table 8.

Table 8: Endpoints-specific sections and subsections for environmental and ecotoxicological endpoints considered in this project and detailed analysis of listed deficiencies in WP2 affecting hazard conclusions
n/a: not applicable. It is used when the section or sub-section is not available in the RSS for the environmental or ecotoxicological endpoints examined in this project

Endpoints	Specific section	Specific sub-section	Number of deficiencies identified in WP2	Number of deficiencies in WP2 affecting interpretation results/hazard conclusion	Percentage of deficiencies affecting the interpretation results/hazard conclusion based on the total number of deficiencies identified in a section.
Biodegradation in Soil	Materials and methods	Test type (picklist)	e-fate: 0 ecotox: n/a	e-fate: 0 ecotox: n/a	0%
Bioaccumulation and all ecotoxicological endpoints considered in this project	Sampling and analysis		e-fate:7 ecotox: 17	e-fate: 7 ecotox: 8	e-fate: 100% ecotox: 47%
Terrestrial ecotox. endpoints considered in this project	Test substrate		e-fate: n/a ecotox: 2	e-fate: n/a ecotox: 2	e-fate: n/a ecotox: 100%
All e-fate and ecotoxicological endpoints considered in this project	Test solutions		e-fate: 7 ecotox: 7	e-fate: 4 ecotox: 3	e-fate: 57% ecotox: 43%
Bioaccumulation and all ecotoxicological endpoints considered in this project	Test organisms		e-fate endpoint: 4 ecotox: 12	e-fate endpoint: 2 ecotox: 6	e-fate: 50% ecotox: 50%
All e-fate and ecotoxicological endpoints considered in this project	Study design		e-fate endpoint: 45 ecotox: 14	e-fate endpoint: 38 ecotox: 4	e-fate: 84% ecotox: 28%
Biodegradation;	Details on study design		e-fate endpoint: 23 ecotox: n/a	e-fate endpoint: 20 ecotox: n/a	e-fate endpoint: 87% ecotox: n/a
All e-fate and ecotoxicological endpoints considered in this project	Test condition		e-fate endpoint :3 ecotox: 25	e-fate endpoint: 3 ecotox: 13	e-fate endpoint:100% ecotox: 52%
Bioaccumulation and all	Further details on test		e-fate endpoint: 5	e-fate endpoint: 1	e-fate endpoint: 20%

Endpoints	Specific section	Specific sub-section	Number of deficiencies identified in WP2	Number of deficiencies in WP2 affecting interpretation results/hazard conclusion	Percentage of deficiencies affecting the interpretation results/hazard conclusion based on the total number of deficiencies identified in a section.
ecotoxicological endpoints considered in this project	condition (text template)		ecotox: 46	ecotox: 26	ecotox: 56%
Biodegradation in Soil	Details on experimental conditions (Text template)		e-fate endpoint: 0 ecotox: n/a	e-fate endpoint: 0 ecotox: n/a	e-fate endpoint: 0% ecotox: n/a
All e-fate and ecotoxicological endpoints considered in this project	Any other information on materials and methods incl. tables (e.g., validity criteria)		e-fate endpoint :13 ecotox: 4	e-fate endpoint: 11 ecotox: 3	e-fate endpoint: 84% ecotox: 75%
All e-fate and ecotoxicological endpoints considered in this project	Results and discussion	Results in table (repeatable table)	e-fate endpoint: 9 ecotox: 11	e-fate endpoint: 7 ecotox: 8	e-fate endpoint: 77% ecotox: 72%
		Details on results (Template, free text)	e-fate endpoint: 33 ecotox: 29	e-fate endpoint:17 ecotox: 11	e-fate endpoint: 51% ecotox: 38%
		Any other information on results (Box free text)	e-fate endpoint:13 ecotox: 8	e-fate endpoint:1 ecotox: 5	e-fate endpoint: 7% ecotox: 62%
Biodegradation and all ecotoxicological endpoints considered in this project	Summary and conclusion	Validity criteria fulfilled (picklist)	e-fate endpoint: 6 ecotox: 7	e-fate endpoint: 6 ecotox: 5	e-fate endpoint: 100% ecotox: 71%
Biodegradation		Interpretation of results (free text)	e-fate endpoint: 3 ecotox: n/a	e-fate endpoint: 3 ecotox: n/a	e-fate endpoint: 100% ecotox: n/a

Final report of the study on the role of RSS in Hazard Assessment (ECHA/2021/46)

As a general point in WP2, registrant RSSs for human health and physicochemical endpoints showed better fidelity to the full study reports than ecotoxicology and environmental fate RSSs. Furthermore, conclusions of the WP2 report revealed that only 8.3% of registrant ecotoxicology RSSs and 5% of registrant environmental fate RSS demonstrated an ideal status, compared to human health toxicology (48.7%) and physicochemical RSSs (25%).

Most of the deficiencies affecting the hazard conclusions in registrants' RSS for environmental and ecotoxicological endpoints concerned missing information (149/203), the reporting of incomplete (25/203) or incorrect (28/203) information, as well as misplaced information (1/203). This observation was consistent with the findings in the WP1 stakeholder engagement report (see page 53 of the WP1 report) where one of the key reasons specified for the poor reporting of RSS was that tabulated data was often missing. This point was particularly highlighted by evaluators who (for both toxicological and ecotoxicological endpoints) commented that tables with quantitative results and raw data could improve the usefulness of RSS.

These deficiencies are further summarised below for each endpoint-specific section and subsection for the environmental and ecotoxicological endpoints. The sections where deficiencies most affected the interpretation of the results/hazard conclusion were related to the information available on testing method, reporting of results and the 'summary and conclusion' section.

The next figure, Figure 10, shows the most frequently suggested potential areas of improvement to address the deficiencies in WP2 in relation to the hazard conclusions.
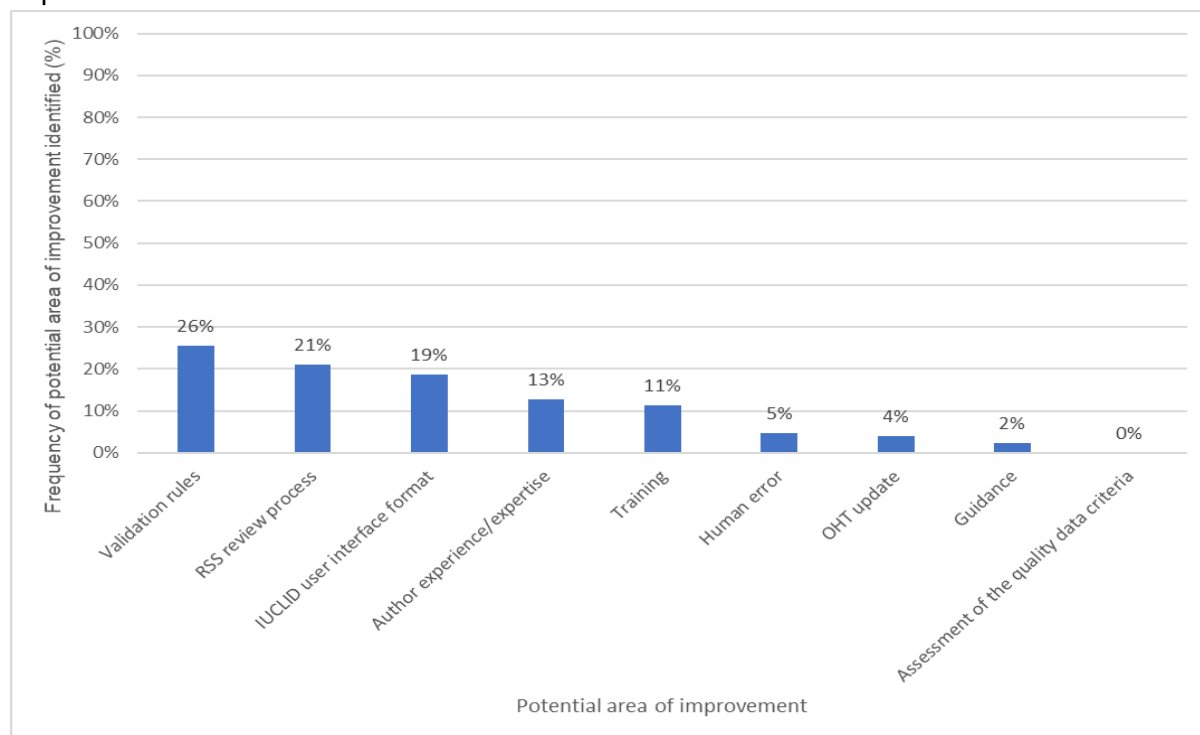

Figure 10: Frequency of potential areas of improvement observed in the endpoint-specific section and subsection of environmental and ecotoxicological endpoints that could prevent deficiencies that could affect the interpretation of the results/hazard conclusions in percentage. These "potential areas for improvement" are the categories identified in Step 1.

Materials and methods

Under IUCLID Materials and Methods for environmental and ecotoxicological endpoints, the endpoint specific sections are subdivided to identify whether and how the test material was monitored and analysed; the type of vehicle used, information on the test species, details of the study design and test conditions all help to determine the suitability of the method.

Sampling and analysis

In several registrant RSSs the information on analytical method (i.e., pre-treatment, identification, quantification data) and sampling (i.e., interval, frequency, storage, media/organism sampling) methods were either missing or incomplete which influenced the assessment of the reliability of the study and the hazard conclusions.

Proposed approaches for improvement

The following options for improving the section on sampling and analysis in the RSS for environmental and ecotoxicological endpoints could be considered.

Listing information on analytical and sampling methods as an error when running the IUCLID validation assistant when these fields are left empty would help to address the deficiencies described above. The missing information should be listed as a validation rule which will increase the transparency and usefulness of the RSS. Furthermore, an experienced author would be able to provide adequate information on analysis and sampling methods, as guidance is available in the OHT.

Test solution

In some registrant RSSs for environmental fate endpoints wrong information was reported in the field 'vehicle' (yes/no picklist). Also, in several registrants' RSS for environmental fate and ecotoxicology endpoints, the information on the preparation of the test solution (e.g., method, control, vehicle name and concentration) was either missing or incomplete although that information was available in the study report. The deficiencies identified for the section are important to assess the suitability of the test method used and so impact the hazard assessment if not correctly reported.

Proposed approaches for improvement

Like above, listing information on test solution preparation as an error when running the IUCLID validation assistant when these fields are left empty would help to address these deficiencies. The missing information should be listed as a minimum as per quality check rules since few deficiencies (see Table 8) affecting the hazard conclusions were listed in WP2 for this section. If not applicable because it is a publication, 'not applicable' or 'not specified' should be reported in the field. In addition, an expert/experienced author with knowledge of the test should be able to provide adequate information on the use of the vehicle and information on the preparation of test solutions.

Test organism

In some registrant RSSs the information on test organisms such as common name, strain, source, age, weight, length, lipid content, food type amount and frequency; acclimation details were either missing or incomplete although that information was available in the study report or publication.

Proposed approaches for improvement

Thus, like above, listing information on test organisms as an error when running the IUCLID validation assistant when these fields are left empty would help to address this deficiency. The missing information should be listed as a minimum as per quality check rules. If not applicable because it is a publication, 'not applicable' or 'not specified' should be reported in the field.

Study design

In several registrants RSSs the information regarding analytical monitoring, information on buffer, test conditions, duration of test, replicate, and controls were either missing because they were not mentioned in the study report (but this should be mentioned in the RSS as 'not specified') or information in the study report not reported in the RSSs or incorrectly reported in the respective fields. In addition, in the picklist fields such as route of exposure, test type, water sediment type of some RSSs, as well as in the field corresponding to the initial concentration of the test substance, incorrect information was provided.

Proposed approaches for improvement

This section is where deficiencies most affected the hazard conclusions. Therefore, to improve this section the IUCLID validation assistant rules should be updated such that the most relevant aspects of the study design are provided such as information on the controls, details on the type of study and those mentioned in the previous paragraph

In addition, the areas of improvement in relation to the hazard assessment for this section are more frequent in the e-fate endpoints (38/59) than in the ecotoxicological endpoints (4/59). Most of the fields in the "Study design" section of IUCLID are picklists for the ecotoxicological endpoints considered in this project. It appears that updating the RSS format of this section for e-fate endpoints, by replacing free text with a picklist where possible, will also improve this section for the purpose of the hazard assessment and strengthen the transparency and trustworthiness of the RSS in the hazard assessment. All required information which should be reported in this section is noted in OHTs of the environmental fate and ecotoxicological endpoints, therefore, an experienced author, aware that guidance is available and/or an expert in these tests, should be able to provide the information correctly.

Final report of the study on the role of RSS in Hazard Assessment (ECHA/2021/46)

Test condition

Information influencing hazard conclusion such as the data on test conditions (e.g., temperature, hardness, pH, dissolved oxygen (DO), salinity, conductivity) were missing or incorrectly reported in two out of six RSSs for bioaccumulation endpoint. In one RSS, nominal concentration was provided but not the measured concentrations.

The same information gaps were observed in the aquatic toxicity endpoints examined in this project.

Proposed approaches for improvement

As above, it is recommended that the validation rules are updated so that the most relevant aspects of the test conditions are provided to allow the information provided to be checked against the guideline and to interpret the results correctly. In addition, all required information which should be reported in this section as noted in the OHT for the bioaccumulation endpoint, therefore, an experienced author, aware that guidance is available and/or an expert in this test, should be able to provide the information correctly.

Any other information on the materials and methods incl. tables

In several RSSs, the information on the range finding study and validity criteria for the test was missing.

Proposed approaches for improvement

Thus, updating the current OHT would help to avoid this error. Under the 'any other information section' in the current OHTs, there is no mention of validity criteria and data on the range finding study. It states only that it is a free text box. The update should mention that validity criteria and data on the range finding study should be included in this section. If it is not relevant to provide information on the range finding study, it should be mentioned as 'not conducted' or 'not applicable' in the field.

Overall, the endpoint-specific information provided in IUCLID under the heading 'Materials and Methods' allows for the assessment of the suitability of a method used and has an impact on the hazard assessment. Thus, completeness check rules should be included for the endpoint specific fields in the Materials and Methods section, as is already the case for the physico-chemical endpoints. In addition, guidance, endpoint specific OHTs are already available, these documents are comprehensive enough to properly fill in this section and, together with the updated validation rules, this will enhance the usefulness of the RSS for hazard assessment.

Furthermore, during this analysis, it was observed that the same section or sub-sections can be used for several endpoints, which confirms the strengths of the RSS as a defined structure and also prevents additional work for the RSS author and the hazard assessor.

Final report of the study on the role of RSS in Hazard Assessment (ECHA/2021/46)

Results and discussion

It is under this section of the RSS for environmental and ecotoxicological endpoints that the greatest number of deficiencies affecting the hazard assessment have been identified in WP2 (see Table 8).

In some RSS, the endpoint-specific sub-sections were left empty (results tables available in the report and not reported in the RSS), or partial/incomplete or incorrect information was reported in these same sub-sections.

The recommendations to improve the subsection which affects the hazard conclusions are presented below.

Proposed approaches for improvement

Any other information results

Under 'any other information section' in the current OHTs for environmental and ecotoxicological endpoints, there is no mention of result tables from the study report or publication. It is only stated in the OHT that it is a free text box. The OHT update should mention that the results table available in the report or publication should be included in this section. In addition, ECHA's Practical Guide on *How to report robust study summaries* update should provide more information on what should be provided in this section.

Tables filled with results (e.g., effect concentration table for ecotoxicological endpoints)

Deficiencies are likely to be avoided when the RSS is written by an experienced author who knows what information is useful and should be included in the subsection. Training is also likely to reduce errors, as trained authors should have expertise with the endpoints and be able to identify and communicate them, and thus complete the result table correctly.

Reported statistics

This section was left blank in some RSS. If the field is marked as mandatory in the IUCLID interface, this may also help to avoid errors.

Summary and conclusion

Validity criteria fulfilled

In several RSSs for environmental and ecotoxicological endpoints, either incorrect information was selected in the picklist or information on whether the validity criteria were met were missing when the field was a free text field.

For these endpoints, it is important to know whether the validation criteria are met or not to successfully evaluate the hazard of a substance. Thus, making the validity criteria a mandatory field for all environmental fate and ecotoxicological endpoints and updating the validation rules with information on validation criteria fulfilled would help to avoid these errors. In the current IUCLID validation assistant tool, missing information in this field does not result in a validation error.

Conclusions on specific information requirements for RSS (environmental and ecotoxicological endpoints)

Overall, in the environmental and ecotoxicological endpoints group, more deficiencies in the material- and method-specific subsections than in the results- and conclusion-specific subsections affected the hazard conclusions, this could be because the tests used to address these endpoints are more complex and require more detail. In addition, unlike for the physico-chemical endpoints, the validation rules are not included in IUCLID validation assistant for the material and method endpoint-specific section. On the other hand, this analysis shows that the same section or subsections can be used for several endpoints, which confirms the strength of the RSS as a defined structure and also avoids additional work for the RSS author and the hazard assessor. Furthermore, the tools already in place to help report data in the RSS (e.g., IUCLID validation tool, guidance, OHTs) are useful but need to be updated to provide more clarity on what information should be included and how it impacts the hazard conclusions.

Toxicology

The specific information requirements for the RSS for the toxicological endpoints considered in this project are given in the sections and subsections presented in Table 9.

Table 9: Endpoints-specific sections and subsections for toxicological endpoints considered in this project and detailed analysis of listed deficiencies in WP2 affecting hazard conclusions

Endpoints	Specific section	Specific sub section	Number of deficiencies identified in WP2	Number of deficiencies in WP2 affecting interpretation results/hazard conclusion	Percentage of deficiencies affecting the interpretation results/hazard conclusion based on the total number of deficiencies identified in a section.
Repeated dose toxicity oral and inhalation; Developmental toxicity; Toxicity to reproduction	Materials and methods	Limit test (picklist)	6	0	0%
Genetic toxicology in-vivo; Repeated dose toxicity oral and inhalation; Developmental toxicity; Toxicity to reproduction; Carcinogenicity; Skin sensitization in vivo	Test animal		16	9	56%
Carcinogenicity; Repeated dose toxicity oral and inhalation; Developmental toxicity; Toxicity to reproduction	Administration/exposure		34	6	18%
Carcinogenicity; Repeated dose toxicity oral and inhalation; Developmental toxicity; Toxicity to reproduction	Examination		9	5	56%
Skin sensitization in vitro; Skin irritation in vitro	In vitro system		12	7	58%
Genetic toxicology in vitro	Methods and study design		18	2	11%
Skin sensitization in vivo	Study design		4	3	75%
All toxicological endpoint considered in this project	Any other information on method		7	5	71%
All toxicological endpoint considered in this project	Result and discussion		44	13	29%

The sections where deficiencies most affected the conclusions on hazards were related to data on test animal, administration routes and details on examinations performed as well as reporting related to the in vitro system and the results.

Figure 11 shows the most frequently suggested potential areas of improvement to address the deficiencies in WP2 in relation to the hazard conclusions.
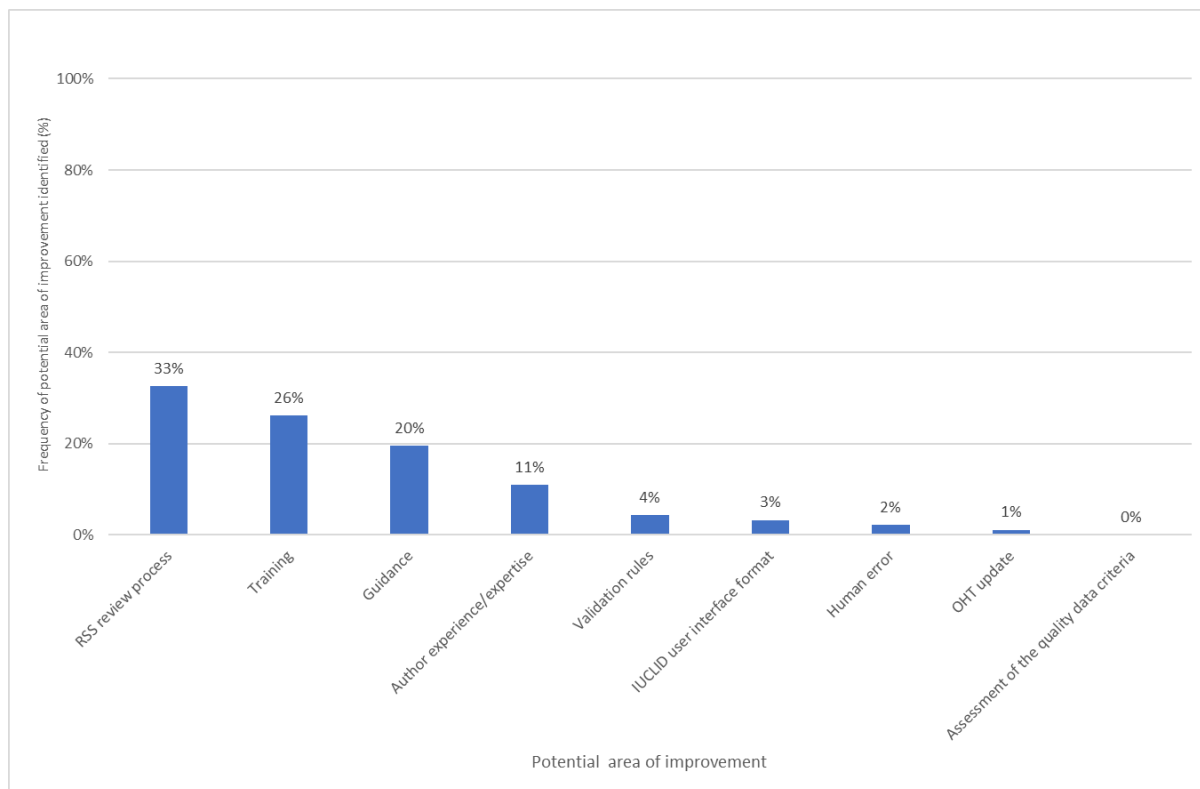

Figure 11: Frequency of potential areas of improvement observed in the endpoint-specific section and subsection of toxicological endpoints that could prevent deficiencies that could affect the interpretation of the results/hazard conclusions in percentage. These "potential areas for improvement" are the categories identified in Step 1.

The recommendations to improve the section and subsections which affect the hazard conclusions are presented below.

Materials and methods

Test animals

This section is specific to all in vivo toxicological endpoints. Deficiencies could influence hazard conclusions were mainly identified in RSSs for in vivo skin sensitisation, and reproductive toxicity endpoint.

These deficiencies only concerned the subsection 'Details on test animals or test system and environmental conditions. In several RSSs, the information on test animals such as environmental conditions, food and water regimen, source, age, and acclimation data were either not provided in full/original report or incomplete.

Proposed approaches for improvement

ECHA's Practical Guide on *How to report robust study summaries* update and the IUCLID help text should include information on how to report missing information in the study report or publication in the RSS; this would help to improve this section. Furthermore, a trained RSS author would know how to report the information required on test animals. These proposed approaches of improvement combined with the implementation of an RSS review will provide the key data on test animals necessary for the hazard assessment.

In vitro system

This section is specific to skin sensitization in vitro and skin irritation in vitro endpoints.

Proposed approaches for improvement

Some deficiencies were simple typing errors. Therefore, with the implementation of an RSS review process, errors related to the reporting of incorrect information are likely to be avoided. The others (the majority) were incorrect. Thus, training for RSS authors would improve their understanding of the type of information required in this section leading to better quality RSS. Furthermore, authors with knowledge and experience in NAMs can complete this section with greater accuracy and contribute to its improvement for hazard assessment purposes.

Study design

This section is specific to in vivo skin sensitisation. The deficiencies affecting the hazard conclusions were related to the reporting of the controls. In some RSSs information such as positive control and challenge controls were missing. Information reported in the induction and challenge tables was incomplete as well as the details on study design.

Proposed approaches for improvement

Training is likely to reduce errors related to the reporting of missing or incomplete information in the RSS, as trained authors should know how to report relevant information in this field. Training together with the implementation of an RSS review process would help to improve this section.

Methods and study design

This section is specific to *in vitro* genotoxicity endpoints. Only two deficiencies affecting the conclusions on hazards were listed in WP2, they were related to information on the test system, experimental condition, and reporting of statistical methods. This information was missing. The low number of instances shows that the tools already in place allow for avoiding errors relative to hazard assessment.

Proposed approaches for improvement

Like above, author training is likely to reduce errors related to the reporting of missing or incomplete information in the RSS, as trained authors should know how to report relevant information from the report in this area.

It should also be emphasised in the guidance that the information of the field on test system and experimental condition and statistics should not be left blank and that they are important to assess the relevance and reliability of the method.

Administration/exposure

This section is specific to all in vivo endpoints. In several RSSs information required in this field was either incomplete, missing, incorrect or misplaced.

The deficiencies affecting the hazard conclusions were mainly listed in the subsection related to the field named *'Analytical verification. If yes, details'* (4/6 deficiencies related to hazard), one deficiency affecting the hazard conclusions was listed in the subsection 'Animals/sex/dose' and another one in the subsections related to 'Duration and frequency'. These sections allow us to assess the relevance and reliability of the testing and therefore the reliability of the results.

Proposed approaches for improvement

Our recommendations to improve each subsection of this section affecting the hazard conclusion are presented below:

Analytical verification and details

The update of the validation rules with data on analytical verification would help to address the identified deficiencies. In the current IUCLID validation assistant tool, missing information in this field does not result in a validation error. Thus, the missing information should be listed as minimum as a quality check. In addition, current guidance specifies that achieved concentrations should be discussed, so formal training should include the meaning of analytical verification and its importance from a toxicological perspective. A more detailed introduction of the basic principles of analytical methods should be provided in the guidelines to reduce errors in this field.

Animal/sex/dose

The update of the validation rules with information on animal number per sex and dose would help to avoid identified deficiencies as well as the update of the guidance documents to emphasise the importance of this field for the purpose of hazard assessment. In addition, specific to the carcinogenicity endpoint, to avoid errors due to incomplete reporting, the OHT for carcinogenicity should be updated. The current field should be replaced by two new subfields to indicate the number of animals in the main dose group and the recovery/satellite group.

Duration of treatment/exposure and frequency of treatment

The update of ECHA's Practical Guide on *How to report robust study summaries* and IUCLID help tab emphasising that these fields are important to assess the relevance of the testing method and the reliability of the data and results for the purpose of hazard assessment and should not be left empty. It would help to increase the RSS quality and reliability for the purpose of hazard assessment.

Examination

This section is specific to in vivo endpoints. In several RSSs, the information required in this field was either incomplete or missing. The deficiencies affecting the hazard conclusions were mainly listed in the subsection related to the field statistics' (3/6 deficiency related to hazard).

Proposed approaches for improvement

The deficiencies identified in this field are likely to be avoided if an update of the OHT is made following an update of the guidance documents. Free text fields should be converted to mandatory fields with an option for "not examined/no data/not available in the report" in each field. Then, after the OHT update, the IUCLID validation assistant should check each of these fields and no field should be left blank. Authors will have to select "not examined" if the data is not available in the report.

Any other information on method

This section is specific to all toxicological endpoints. Deficiencies were observed mainly in RSSs for the skin sensitisation endpoint. The field was left blank while it should report criteria for considering studies as positive or negative and give details on historical positive control (if available).

Proposed approaches for improvement

These deficiencies can be avoided if providing this information is explicitly mentioned in the guidance document. Training in a specific endpoint is also likely to reduce errors related to the reporting of missing or incomplete information in this field, as trained authors should know which relevant information on study design should be reported in this field.

Results and discussion

In some RSS, the endpoint-specific sections and subsections were left empty (results tables available in the report and not reported in the RSS), or partial/incomplete or incorrect information was reported in these same subsections.

The deficiencies affecting the hazard conclusions were related to the following subsections: results of examination (for high tier in vivo endpoints), effect levels, target system/organ toxicity, any other information on results and information on positive control.

The recommendations to improve the section and subsections which affect the hazard conclusion are presented below.

Proposed approaches for improvement

Effect level table

This subsection is specific to chronic in vivo toxicity endpoints.
The reporting of incorrect information is likely to be avoided when the RSS is written by an experienced author who knows the relevant information that should be included in the subsection. Training is also likely to reduce errors, as trained authors should be familiar with effect parameters and be able to identify and report them, and thus complete the results table correctly. These actions would help address some of the weaknesses observed when evaluating effect level calculations (see chapter 3.3.3 of the WP1 report).

Positive control data

This subsection is specific to the skin sensitisation endpoint.
This subsection was left blank in some RSSs mainly because the information was not included in the report. However, this should have been specified. Therefore, training is likely to reduce these errors, as trained authors should know to report missing information from the report in this field. In addition, if the field is marked as mandatory in the IUCLID interface, this may also help to avoid errors.

Results of examination

This subsection is specific to in vivo chronic toxicity endpoints.
Training is likely to reduce errors related to incomplete or incorrect reports, as trained authors should be able to report relevant information from the report in this field. Similarly, an RSS review process would help to avoid the reporting of incorrect information.

Target system/organ toxicity

This sub-section is specific to chronic in vivo toxicity endpoints.
This subsection has been left blank or incorrect information has been reported in some RSS. As above, training is likely to reduce these errors, as trained authors should know the basic meaning of the target organ and how to report information in this field. In addition, ECHA's Practical Guide on *How to report robust study summaries* should specifically highlight this field. Finally, if the field is marked as mandatory in the IUCLID interface, this may also help to avoid errors.

Conclusions on specific information requirements for RSS (toxicological endpoints)

Overall, there were not many shortcomings in the toxicological endpoints that affected the interpretation of the results and the hazard conclusion. These gaps could be avoided by training, a suggestion supported by the participants of the WP1 stakeholder engagement report (see chapter 3.4.3 of the WP1 report) where training and practice were strategies proposed to gain experience in RSS authoring.

In addition, updating the already available guidance documents to clarify the information that needs to be included to have a complete RSS and its impact on the hazard assessment. Furthermore, the findings of the WP2 report revealed that 48.7% of the RSSs had no deficiencies affecting the hazard conclusions and this number increased when implementing a review process with an SOP. The SOP-guided RSSs showed 3 times fewer deficiencies than the registrants' RSSs. Therefore, the current RSSs for toxicological endpoints are considered reliable for hazard assessment. This would appear to be in contradiction to the perceptions of evaluators, 48% of whom had the least confidence in drawing conclusions using RSS for systemic human health endpoints (see chapter 3.3.5 of the WP1 report). The development of an SOP to be used in a review process could strengthen stakeholder confidence in these RSS.

3. Suggestions for improvements

In this project, the accuracy and quality of RSSs and how they are currently used by hazard assessors were evaluated to understand the reliability of RSS for the purpose of hazard assessment. The analyses performed in each work package were used to develop suggestions for improvements based on the categories defined in WP3 (as shown in Table 4). An assessment was conducted to identify the areas of improvement that would have the greatest impact on the quality and the usefulness of the RSS and in improving the confidence of the hazard assessors.

The results of this assessment are presented in Figure 12, which illustrates the top main areas of improvement that should be prioritised, according to the percentage value of the frequency for which each area of improvement was suggested to potentially reduce the deficiencies identified in each section/subsection, as derived from the analyses in WP2 and WP3.
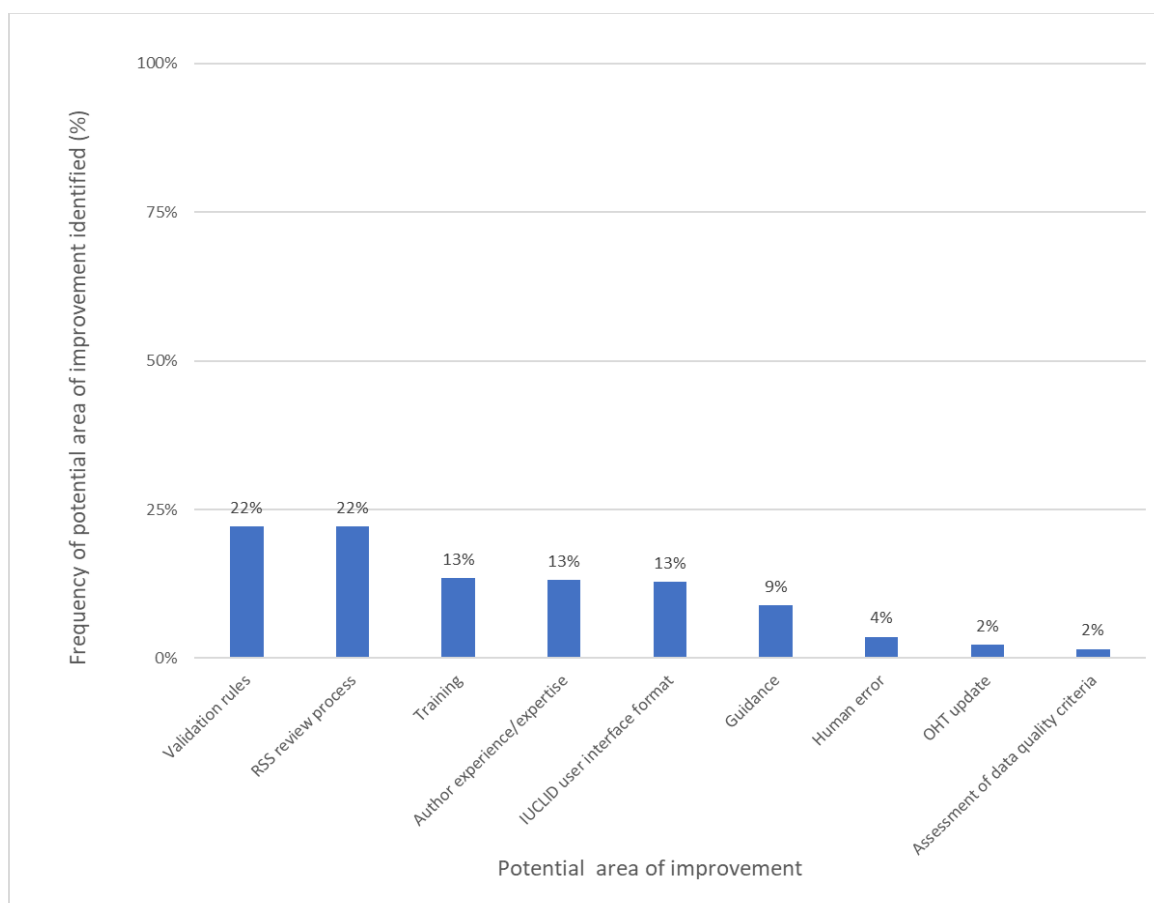

Figure 12: IUCLID RSS Improvement Overview. The figure illustrates the prevalence of potential areas for improvement identified across all common and endpoint-specific sections and subsections of IUCLID RSS that could prevent deficiencies that could affect the interpretation of the results/hazard conclusions.

The top two individual areas of improvement identified were 'validation rules' and 'RSS review process' at 22% frequency followed by 'training', 'author experience/ expertise' and 'IUCLID user interface' with equal frequency at 13%. The least frequent areas of improvement were 'OHT update' and 'Study quality criteria' at 2% frequency.

The suggestions for improving the IUCLID user interface were focused on enhancing the visibility of the results and key fields in the RSS, such as identifying mandatory and non-mandatory fields. However, it was concluded that the implementation of an RSS review process, the update of the validation rules and making more training available could be prioritised before, for example, considering the update of the IUCLID user interface. It is believed that the overall quality of the information in the RSS will be enhanced by implementing these three areas of improvements, while the update of the user interface may not necessarily improve the content and quality of the RSS, but only improve the user experience.

Implementing the suggestions for improvement in the areas highlighted in Table 4 of this report has the potential to improve hazard assessment in all chemical regulatory frameworks. In this chapter we proceed to elaborate on each of the categories.

RSS review process

This refers to any QC/review process that can improve the quality of the RSS, with the assumption that the persons involved in the review process will be more experienced with the endpoint and the RSS/OHT than the author.

In WP2, the results of the comparison between the SOP-guided RSS and the RSS of the respective registrants showed that SOP guided RSSs resulted in higher accuracy and completeness as well as a lower number of deficiencies that could affect the resulting interpretation/hazard conclusion. The conclusions of WP2 and analysis in WP3 also highlighted the fact that the quality of an RSS does not depend on the endpoints, type of study or Klimisch score which shows that RSS are a defined structure. Furthermore, the RSS review process was an area of improvement often identified as a solution in WP3.

Implementation of an RSS review process in line with an SOP
● Implementation of a two-step process with the drafting of the RSS as the first step and the review of the RSS with a more experienced person as the second step.
● An SOP was developed in WP2 by the contractor's technical team to ensure that the RSSs were written to the highest quality and then tested in a 2-week pilot study. This pilot study involved the use of RSS authors from different backgrounds to ensure that it was equally accessible to every author involved in the study.
● A Q&A session to answer any questions on the RSS and SOP could be organised following the implementation of the SOP during the pilot study to ensure the same level of quality when writing the RSS.

Final report of the study on the role of RSS in Hazard Assessment (ECHA/2021/46)

In the WP1 stakeholder engagement report, only one reference to an RSS review process was identified but, despite this, during the authoring of the RSS in WP2, it was evident that the SOP-guided RSSs had significantly fewer deficiencies.

A key finding of WP1 regarding hazard assessment was that RSSs have been designed well, but in practice, it is down to human error in completing the templates. WP2 provided evidence that the implementation of a review process with experience reviewers significantly reduces deficiencies (this includes those due to human error) and if implemented could improve overall trust in the RSS.

Overall, the improvement of the IUCLID validation assistant for the key sections of the hazard assessment, i.e., "Applicant's summary", subsection "Specific details of the test material used in the study" and "Material and method", will have a significant impact on the reliability of the RSS. The implementation of a review process will further improve the reliability, quality and confidence in the RSS for hazard assessment. The following suggestions for improvement are secondary in comparison.

Training and Guidance for authors

This includes any potential training and guidance recommendations that could help RSS authors/reviewers to improve the quality of RSS.

Throughout WP1 and WP2 it has been clear that the available guidance documents and OHTs provide sufficient information to be able to develop a reliable RSS for the purpose of the hazard assessment. In WP1 (see page 53 of the WP1 report) authors considered that there was a lack of sufficient guidance or little details on pesticides, nanomaterials, inorganic substances such as metals and how to report physico-chemical properties of UVCB and multi-constituent substances. However, WP2 demonstrated that this is not the case for the guidance on physico-chemical properties on UVCBs and multi-constituent substances, while there were not sufficient examples and evidence to draw conclusions on nanomaterials, inorganic substances and pesticides. In WP3 step 5, the categories guidance and the OHT update were only displayed in 9% and 2% of the cases respectively, as areas of improvement to address the deficiencies in WP2 with regard to the hazard conclusions. In addition, in WP1 (see Annex II in this report), several participants in the survey and interviews mentioned that they were ignoring the available guidance documents because they were too long and difficult to navigate.

Therefore, the implementation of formal training, on RSS writing for authors (for which up to 70% of the respondents of the survey (see WP1 final report p.67) were in favour of) would help to improve the quality and confidence of RSS for the purpose of hazard assessment, as each author would receive consistent and topic-specific training.

Final report of the study on the role of RSS in Hazard Assessment (ECHA/2021/46)

Implementation of training on RSS authoring
●   Training could be offered not mandatory

●   The training provided by the hazard assessors of the institution or agency responsible for the relevant legislation could be improved. The training could be available online in the form of video training and/or webinars, as also suggested in the survey and interviews in WP1 (see page 67 of the WP1 report), so that it can be reviewed if necessary. It should include:
    -   Technical requirements of an RSS
    -   How to prepare a compliant RSS
    -   Context of regulatory review of hazard assessment (to help authors understand how the information is used by regulators, and why certain data is requested)
    -   Understand how risk assessors make conclusions
    -   How to evaluate reliability of a study
    -   Endpoint specific training
    -   Review content of OECD guidance documents

●   Evidence of training or some form of accreditation of RSS authors could be adopted and added on a voluntary basis to dossiers submitted to the authorities to enhance the quality and trustworthiness of the RSSs.

Author experience and expertise

This refers to the expertise and background of the author in the endpoint and/or RSS. The following recommendations are derived from the analyses in WP2 and WP3. Many times, the shortcomings in WP2 were due to a lack of expertise from the author. In many cases, guidance, and endpoint specific OHTs provided a sufficient level of guidance to explain how to report the data in the RSS and the shortcomings were clearly due to the author's lack of experience/expertise in the endpoint and/or RSS concept. An experienced/expert author should therefore write the RSS, which would improve the quality and trustworthiness of the RSS for the purposes of hazard assessment.

RSS authoring by an experienced author and/or with expertise in the endpoint
●   Implementation of a minimum threshold of years of experience as RSS author, having used IUCLID or a minimum threshold of qualifications.
●   Setting up a clause when submitting a lead registration dossier indicating that the RSSs have been written and/or peer reviewed by an author with experience as an RSS author

Validation rules

ECHA performs a completeness check on each REACH registration to ensure that the required information is provided as per Article 20 of the REACH Regulation. This completeness check includes a technical completeness check relying on validation rules and a manual verification by ECHA staff. Within the technical completeness check, the validation rules refer to the rules implemented by the IUCLID validation assistant. The IUCLID Validation Assistant has been developed to check the completeness of the registration dossier before it is submitted to ECHA. The IUCLID Validation Assistant reports a series of rules (technical completeness check and business rules failures) under the heading Submission Checks, and quality warnings under the heading Quality Checks.

Thus, all failures reported under the Submission Checks heading must be corrected for the submission to be successful. If these deficiencies are not corrected before submitting a dossier, the submission will not be accepted by ECHA.

Differently from REACH, the submission of a BPR application is not automatically checked by the IUCLID Validation Assistant and does not undergo an automated completeness check. This system will allow submission of IUCLID dossiers that have not gone through any validation check using the IUCLID validation assistant although the submission system for BPR dossiers is performing some level of submissions verification (so called business rules). However, it is important to highlight that each BPR application will be screened and evaluated either by ECHA or by the evaluating Competent Authorities before an approval or an authorisation is granted. This is not the case for REACH where a registration is granted if the technical completeness check is successful while a compliance check is done by ECHA afterwards.

It was not possible to accurately evaluate the effect of using validation rules in REACH RSSs versus none in BPR RSSs, as the sample size assessed was not large enough to draw a conclusion. However, as indicated in Figure 1 of this report, relatively more BPR RSSs were available for toxicological and ecotoxicological endpoints compared to the other two categories of endpoints. As such, Table 10 below illustrates the level of completeness for BPR and REACH RSSs for the Toxicology and Ecotoxicology endpoint groups for the purpose of hazard assessment.

Table 10: Percentage of deficiencies per RSS affecting the interpretation of results/hazard conclusion for REACH and BPR registrant RSSs for Toxicology and Ecotoxicology

Endpoint group	Percentage of deficiencies affecting interpretation results/hazard conclusion REACH	Percentage of deficiencies affecting interpretation results/hazard conclusion BPR
Toxicology	23% (26 RSS)	0.4% (11 RSS)
Ecotoxicology	26% (16 RSS)	16% (8 RSS)

Although the objective of the project was not to compare the quality of study summaries provided under REACH and BPR, the results observed above, particularly for Toxicology studies can be surprising considering that no validation rules were applied to the BPR RSSs. The results from the project indicate that the deficiencies observed for RSSs submitted under REACH are potentially more impactful for the hazard assessment than the deficiencies identified for RSSs submitted under the BPR framework. Assumptions for this observation are proposed hereafter:

- Authors of the RSSs under BPR are more trained, have more experience or are following robust procedures and review processes
- The selected RSSs were not representatives of the BPR dossiers

Final report of the study on the role of RSS in Hazard Assessment (ECHA/2021/46)

- The fact that authorities are reviewing the summaries systematically for BPR dossiers could play a role. This could mean that relying on robust automated validation rules is even more important for REACH dossiers which are checked for compliance after the registration is granted

The following recommendations are derived from the observations made in step 5 of WP3: There are fewer failures affecting the hazard conclusions in sections and sub-sections for which validation rules are included in the IUCLID validation assistant. This shows that the validation rules increase the overall quality of the RSS, by helping the RSS author to understand the required information.

Update IUCLID Validation assistant
● Currently validation rules are included in the validation assistant for all sections common to all the endpoints except the section "Applicant's summary". Therefore, to improve RSS quality for the purpose of hazard assessment IUCLID Validation assistant should be updated to include validation rules for the field's conclusion and executive summary of the section Applicant summary when the study record is marked as a key study or weight of evidence. These sections are key elements in the hazard assessment.
● The existing validation rules refer to the identity of the test material, but they should also refer to the information provided in the field "Specific details of the test material used for the study", which helps to assess the suitability of the test material. Therefore, the IUCLID Validation Assistant should be updated to specify information on the test material such as purity, source, information on stability and storage conditions of the test material and, if applicable, radiolabelling should be provided.
● For endpoint specific sections, validation rules should be implemented for 'material and methods' sections. Thus, updating the validation rules would help the registrant to understand which information they should provide so that the assessor can assess the relevance of the test used without going back to the study report. This will greatly improve the usefulness and trustworthiness of the RSS.

IUCLID User Interface

IUCLID is a user interface that reflects the format of the OHTs in a web interface. Therefore, the changes made to the OHT are implemented in IUCLID following their structure and any suggestion to improve the way data is visualised and presented to the user. Following up the feedback received by stakeholders in WP1, IUCLID can facilitate the work of the authors and evaluators by working on how data is presented.

Implementation of changes in the IUCLID User interface
● Allowing more flexible data handling displayed (i.e., formatting options such as entering data together with images, graphs, etc.)
● Improve tabular data options

OECD Harmonised Templates (OHT)

The standard data format used for reporting information (OHT) has the lowest frequency, together with the study quality criteria, to be considered as an area for improvement of the RSS. Nevertheless, updating slightly the OHTs would help avoid a series of deficiencies in certain sections where there is no mention of validity criteria, for instance.

Implementation of new/update OHT
● Include an RSS form for systematic review results
● Include additional fields to cover individual test data, i.e., where adverse effects are observed
● Enhance the channels to provide feedback

4. Conclusion and outlook

The findings of WP3 showed that there were relatively few shortcomings affecting the interpretation of the results and the hazard conclusion. Most of the limitations observed in the RSS for the endpoints considered in this project were minor for the hazard assessment, as they did not affect the hazard conclusions. Overall, this study has proven that RSSs can be considered reliable because they describe the specific characteristics of the endpoints in such a way that they allow an independent assessment of the reliability and completeness of the endpoints. Whilst some areas of improvement have been identified to enhance the quality, usefulness and accuracy of the RSS, this work has demonstrated that the RSS can currently provide reliable key information to conclude on hazard assessment with a high level of consistency.

To keep the usefulness and the quality of the RSS concept at its best, the results of this analysis show that the RSS concept would benefit from improvements in the following areas:

- RSS review process,
- Training and guidance
- Author's experience and expertise
- Validation rules
- IUCLID user interface
- OHT updates

To assess the impact of the implementation of the proposed improvements to the quality of the RSS, future analysis work could be conducted in at least 5-7 years from their implementation. This is to allow enough time to capture meaningful and significant changes. Specifically, the steps that could be taken include:

1. Updating the literature review with additional studies dealing with the quality and use of RSS for hazard assessment that have been published after 2021, and specifically looking at changes and any new recommendations.

2. Conducting a new survey to gather stakeholder opinions on the changes made and whether trust in the RSS has increased since the implementation of updates such as the IUCLID Validation Assistant for key RSS sections and subsections for hazard assessment (e.g., 'Applicant Summary', 'Test material and 'Material and Method') and RSS authoring training. The stakeholder should also be asked if they are aware of the changes that have been made to the guidance and supporting documents because of the implementation of the above suggestions.

3. Selecting a sample of registrant RSSs that have been submitted after the implementation of recommendations described in Chapter 3. Then, these RSSs would be reviewed against the criteria developed in the SOP. The sample of registrant RSSs should be similar to the one assessed in this project and a similar number of RSSs should be assessed for each type of regulation (i.e., REACH, BPR, PPP etc). RSS should be made available for the same endpoints assessed in this project. Additionally, the sample should include RSSs from a wide range of different size companies and a similar number of RSSs per chemical regulatory framework and per endpoint group.

This would allow to determine whether the quality of the RSS for hazard assessment has improved after the implementation of the suggested improvements outlined in Chapter 3; the expectation will be that the implemented areas of improvements will enhance the quality of the RSS that no further action will be necessary. However, it may be possible that new areas of improvements are identified or that areas of improvements already identified during this project may need to be prioritised. This future work will aim to test whether the implemented areas of improvements have enhanced and refined the quality of the RSS for hazard assessment.

5. Annexes

Annex I: RSS source and collection

A total of 103 RSS reports were provided for the analysis in WP2 79 RSSs (and their corresponding full study reports) were originally submitted under the REACH regulation and 24 under BPR.

Among REACH RSSs, the majority were submitted by large and medium sized companies along with two RSSs each for human health toxicology and physicochemical endpoints from small companies and one human health toxicology RSS from a micro-size company (Figure I). Company size was assigned in accordance with Commission Recommendation 2003/361/EC. Information on the company size was not available for the RSSs submitted under BPR.
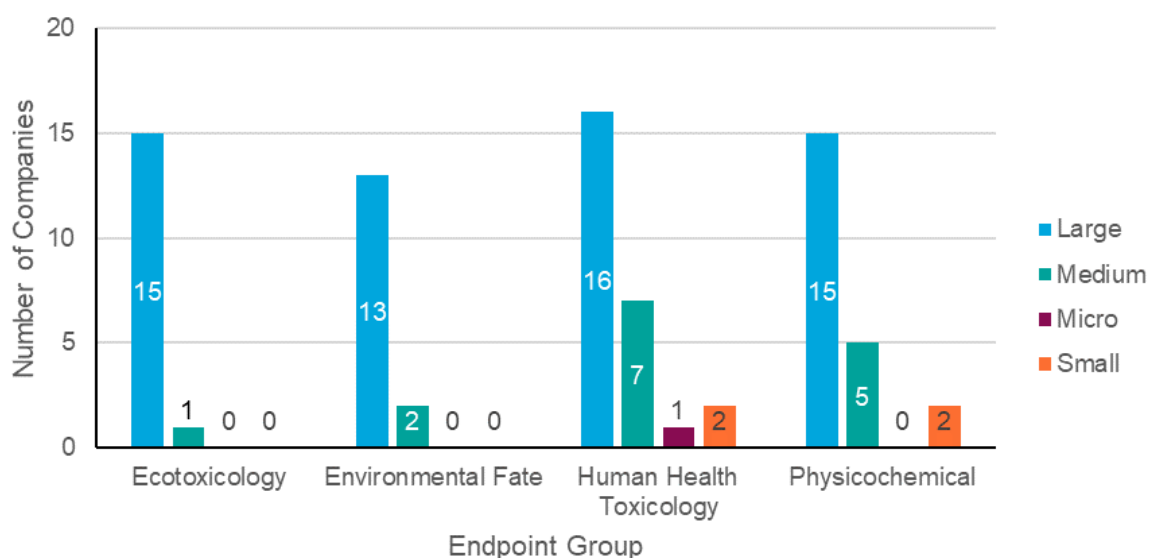

Figure I: Information on the company size for the RSSs submitted by registrants used in this study. The bars represent the count of RSSs. The information is only for RSSs submitted under the REACH program.

In both the REACH and BPR RSSs, the highest number of RSS submitters were identified as manufacturers and importers. In addition, some RSSs under REACH were submitted by only representatives i.e., European-based companies which act on the behalf of companies based outside the European Economic Area (EEA) and take over the tasks and responsibilities of importers for complying with REACH. A few BPR RSSs were submitted by downstream users. For some BPR RSSs, the information on company type was not available (Figure II).
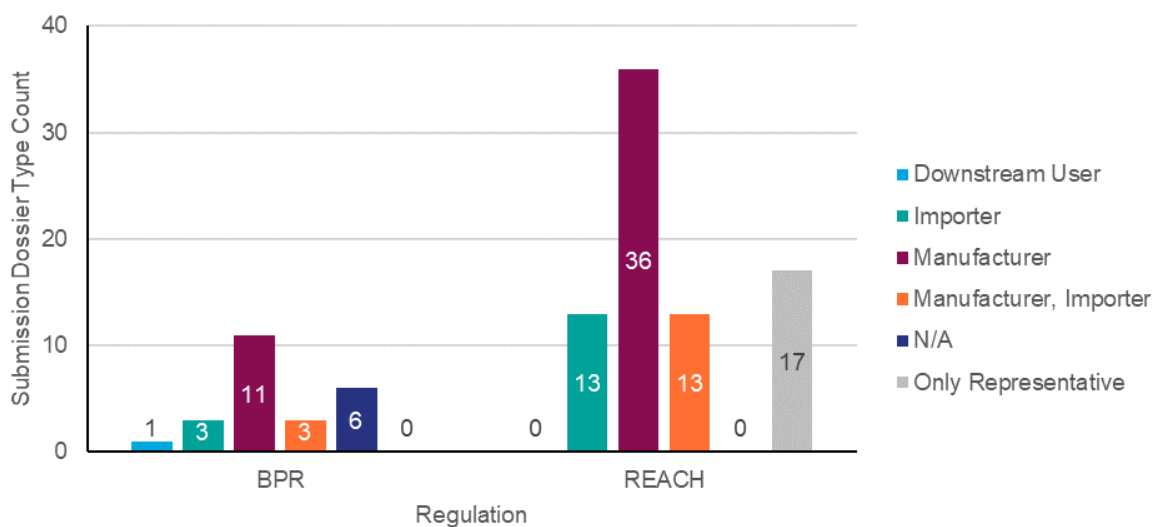
Figure II: Information on the company type for the RSSs submitted by registrants used in this study. The bars represent the count of RSSs.

Furthermore, as set out in Article 20(2) of the REACH Regulation, all dossiers submitted to ECHA undergo initial administrative and technical checks to ensure that the dossiers include all the information that is required. Such checks are called Business Rule (BR) and Technical Completeness Check (TCC), respectively. IUCLID Validation assistant has been developed to allow registrants to check their dossier before submitting them to ECHA. IUCLID validation assistant reports technical completeness check and business rule failures under the Submission checks heading, and quality warnings under the Quality checks heading. So, any failures that are reported under the Submission checks must be corrected for a successful submission. If these failures are not corrected before submitting a dossier, the submission will not be accepted by ECHA.

Thus, it has also been confirmed that among REACH RSSs provided for this project, validation rules were applied using the IUCLID validation assistant tool for all RSSs during the original submission except for the RSSs for the carcinogenicity endpoint as described in the manual on 'How to prepare registration and PPORD dossiers'[20]. On the other hand, the submission system for BPR, is different from that of REACH, and specific validation rules have not been applied to BPR dossiers. However, for BPR submissions, all dossiers are subject to a full review by Competent Authorities (CAs) during evaluation and updates can be requested if needed. For clarity during this project ECHA provided the contractor with 103 RSS of which 76 had been checked by ECHA using the IUCLID validation assistant tool, and 27 had not. Of those 27, 24 were submitted as part of BPR submissions.

---

[20] European Chemicals Agency. (2022, October). How to prepare registration and PPORD dossiers. Retrieved from https://echa.europa.eu/documents/10162/1804633/manual_regis_and_ppord_en.pdf/891754cb-a6b6-4bb6-8538-52ccde74070e?t=1635319761435

Annex II: Areas of improvement for the RSSs as gathered to address the suggestions suggested by the participants in the survey and interviews conducted in WP1

Areas of improvement identified by the participants in the survey conducted in WP1	Categorisation for the area of improvement
Testing laboratories could complete the RSS as they conduct the studies	Author experience/expertise
It would be useful for RSS authors to meet a minimum threshold or qualifications. The following criteria were suggested: Educational background; Years of experience in a technical field; Years of experience as an RSS author; Years of experience using IUCLID	Author experience/expertise
Some respondents mentioned that peer review of RSS by more experienced authors is an efficient process	Author experience/expertise
More details should be included in the template through pop-up windows with explanations and examples of information expected in the fields	Guidance
The most frequent recommendation is to include a practical guide and worked examples of completed RSS for various endpoints and study types, including non-standard studies (e.g., old literature reviews). More details could be provided for more complex studies and different types of substances.	Guidance
Some suggestions for developing guidance: Guidance by type of endpoint; Provide clear guidance as to what is meant in each data field; improve the layout of the guidance so it is more user friendly; Clearly indicate minimal data requirements for each endpoint; potentially in a summary table; Clearly indicate which parameters are mandatory;	Guidance
The Help function in IUCLID could also be enhanced with more guidance to avoid people having to search for responses outside of IUCLID	Guidance
Several respondents suggested linking the guidance directly to IUCLID, so it is accessible from the tool. For example, some suggested including context dependent help directly in the relevant IUCLID fields, including minimum data requirements and mandatory fields directly in the tool to avoid having to refer to separate guidance.	Guidance IUCLID user interface
Those who said they ignore the guidance, the main reason stated is because it is too long, complex, poorly formatted and difficult to navigate.	Guidance
Make copying/pasting discussions, conclusions and summaries from GLP reports mandatory to reduce author bias and	Human error

Areas of improvement identified by the participants in the survey conducted in WP1	Categorisation for the area of improvement
censorship	
Identify mandatory fields (e.g., with an asterisk), as well as those that are not mandatory	IUCLID user interface
Improvements are needed in the way to present tabular data, especially to reduce human error	IUCLID user interface
The current process to recreate tables in the IUCLID fields can lead to errors. The template should be more flexible to fit data in multiple formats	IUCLID user interface
One respondent suggested reorganising IUCLID section 7 under the BPR working context (Intended uses and exposure)	IUCLID user interface
Include more options to provide alternative units of measurements, specifically in the context of EU BPR	IUCLID user interface
Some participants suggested attaching the full study report to the RSS, however, other respondents do not agree	IUCLID user interface
Free text cells that align better with the formatting in MS Word	IUCLID user interface
Opportunity to include images and screenshots of the results table that can be combined with explanatory text in free text fields	IUCLID user interface
Improve formatting options for text and tables	IUCLID user interface
A data uploader for tables and graphs in various formats	IUCLID user interface
Interface between IUCLID and SAP to map data	IUCLID user interface
Improve the visualisation of results to highlight the key results in a more distinct manner.	IUCLID user interface
Include an RSS form for systematic review results	OHT update
It would be useful to have a set of specific templates for different study types, to increase or decrease the mandatory fields to fill in and reduce errors.	OHT update
Include additional fields to cover individual test data, i.e., where adverse effects are observed	OHT update
Expand pre-selection options in the picklists, e.g., to choose characteristics of the substance (inorganic vs UVCB), to describe toxicological effects, avoid the use of "other" in picklists	OHT update
Redundant fields, such as "additional information" and potentially the executive summary, should be removed from the RSS template	OHT update
Update the format to follow OECD test guidelines more closely	OHT update

Areas of improvement identified by the participants in the survey conducted in WP1	Categorisation for the area of improvement
Several survey respondents indicated that it would be helpful to provide more feedback on the OECD Harmonised Templates. Some respondents suggested that an effective way to provide feedback is when asked directly for their opinion, such as in a survey. For example, several of the OHTs are not adapted for certain regulations (e.g., PPP), so it is difficult to provide all relevant information. This feedback could then be provided to ECHA or OECD so that improvements can be made.	OHT update
Respondents were clear that RSS is very EU-centric, and that it is important to move to a global scale soon	OHT update
Several participants suggested considering using different criteria or additional criteria to evaluate the reporting of the study, as opposed to only evaluating the reliability of the study design. They considered that it would help identify whether there are issues with the study design, or the study report, or both and help understand how the authors concluded whether this is a supporting or key study	Guidance
Comments and annotations by authorities should be visible on the RSS and easily transferable and printable	RSS review process
Proof of training or a certain RSS authoring accreditation could even be adopted to allow RSS submission to the authorities.	Training
RSS author training would address this issue better, as every author would receive consistent training that is specific to the topic.	Training
The key training recommendation was that ECHA evaluators should deliver the training, if possible. The training should be offered but should not be mandatory and should be free of cost. Contents of training are also suggested in the survey (reported in WP1 report)	Training
Some respondents highlighted that author training and author experience should be prioritised over changes in guidance, as most authors ignore the guidance.	Training Guidance
Several participants suggested that essential data (e.g., result data table) and required fields should be mandatory so RSS cannot be submitted with empty mandatory fields. The IUCLID validation assistant should also check that all hazard assessment fields are filled in to indicate any data gaps to the author	Validation rules
To assess that all the data is included in the RSS, implement the OECD test validity criteria checklist into the RSS	Validation rules

Areas of improvement identified by the participants in the survey conducted in WP1	Categorisation for the area of improvement
Automated module that would assess the fitness of the information included in the RSS based on the requirements of the OECD test guidelines. The results could be a score that indicates how the information matches the guidelines, and how much overlap there is with the provided information. The example given was that "the provided data has an 85 percent match with test guidelines 421 and 422 reproductive developmental toxicity screening test, 45 percent overlap with an extended one generation reprotoxicity study". The respondent mentioned that this score would allow evaluators to see how well certain elements of the test guidelines are reported and covered.	Validation rules

Disclaimer

Reasonable efforts have been made throughout the review process to reach the conclusions and recommendations provided. The conclusions and recommendations given in this report are based upon and therefore limited to the information available and provided by the client at the time of writing. As such, Yordas Group accepts no liability if any regulating or enforcement bodies do not reach the same conclusions or recommendations.