IUCLID demo dossiers: project summary

NP/EFSA/TS/2022/03

Julia Cara
GAB Consulting GmbH

Project objectives and implementation

Project results and outcome

Conclusions and recommendations

Project objectives and implementation

- During 2022, EFSA launched a call for Tender (NP/EFSA/FDP/2022/03) to perform IUCLID-related tasks.
- This project was launched as follow up of the *proof-of-concept* dossiers prepared in 2019 with IUCLID 6.4.
- Goal: assess the fitness of the newer IUCLID versions (IUCLID v. 7.0.1 and higher), as well as available supporting materials, to meet the needs for plant protection EU procedures.

efsa
European Food Safety Authority

TENDER SPECIFICATIONS

Reference: NP/EFSA/TS/2022/03
Subject: IUCLID demo dossiers

Project objectives and implementation

Objective 1: create different IUCLID dossier types for demonstration purposes

- Basic substance
- Microorganism
- MRL dossiers (four types corresponding with different scenarios)
- Chemical dossiers of different complexity (approval, increasing sizes, confidential and light)

→ **Deliverable:** non-confidential IUCLID dossiers

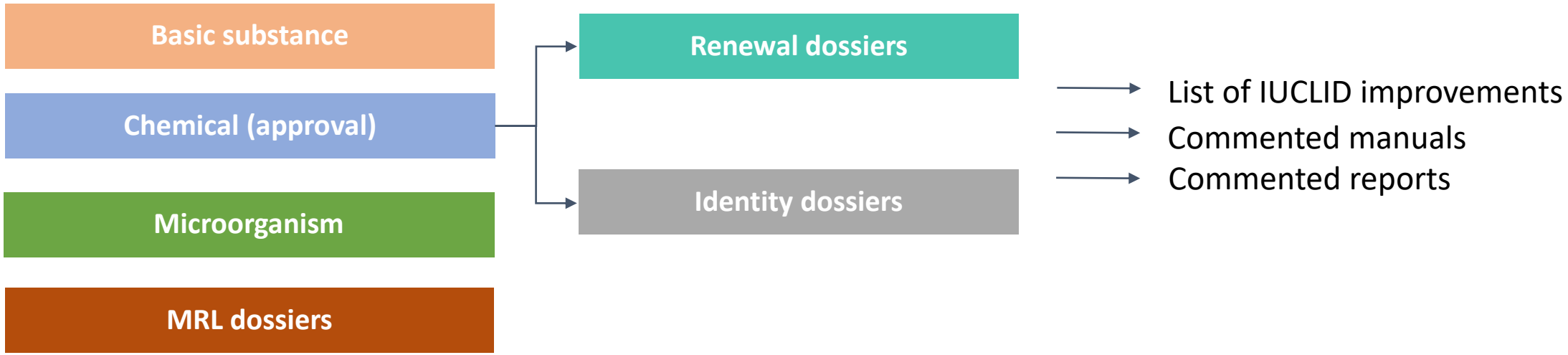
Objective 2: analyse IUCLID for improvements and fixes

- Critical review of IUCLID entries and systems, while completing dossier types above
- Revision of all EFSA IUCLID manuals (basic substance, MRL, chemical, microorganism)
- Check of relevant generated reports

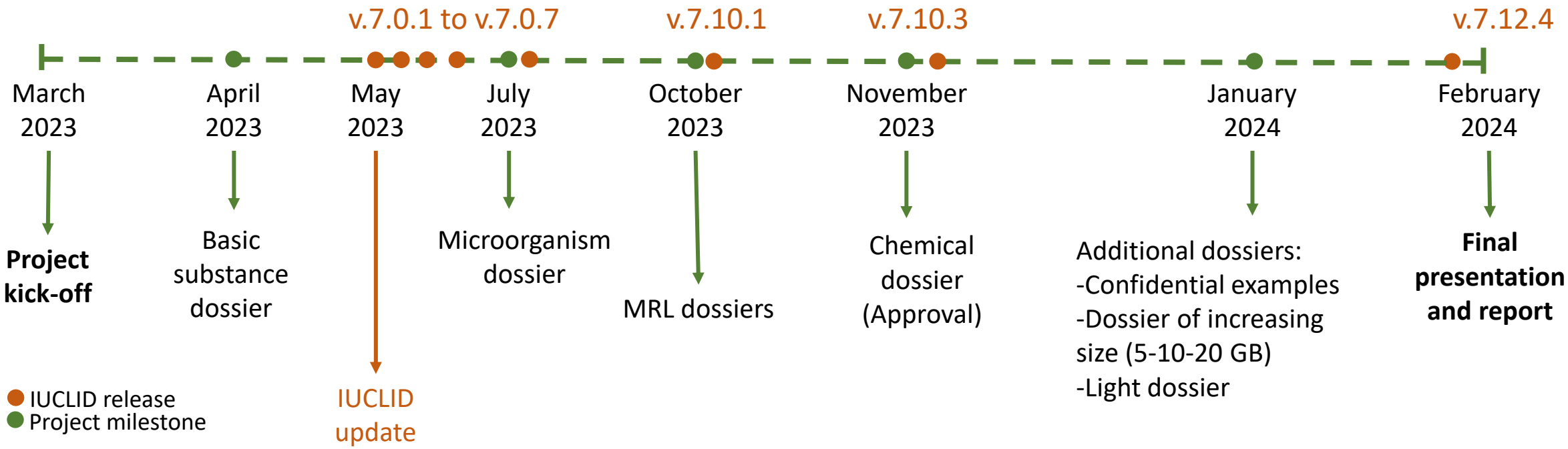
→ **Deliverable:** final project report and presentation

Project implementation

- Scientific and regulatory experts per section completed each part of the IUCLID dossiers according to the manual. Issues and improvements were centrally listed in an Excel file.
- All parts of the respective IUCLID manuals and generated reports were commented by the section expert.



Project implementation



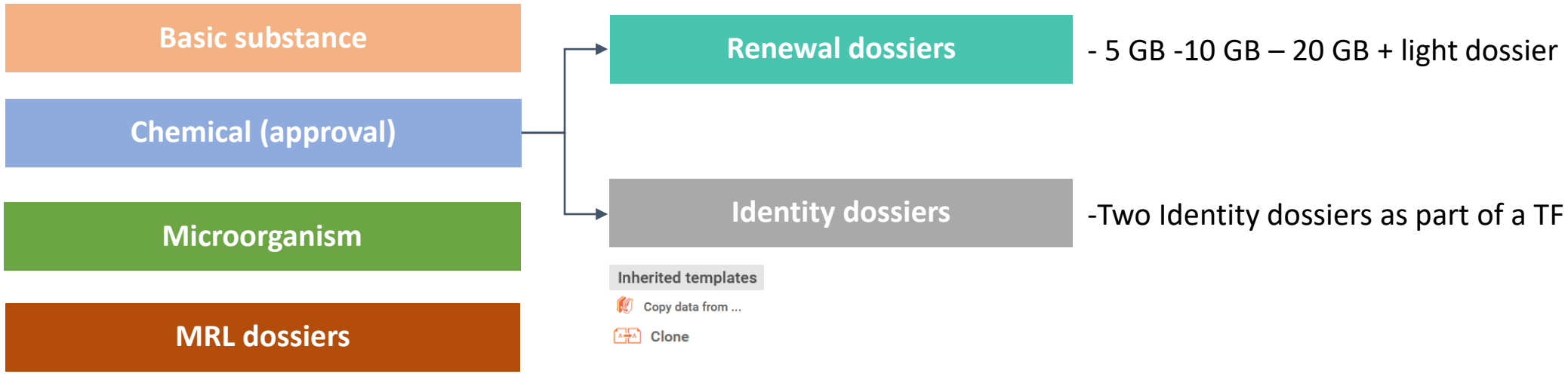
The IUCLID dossiers were prepared in alignment with the relevant IUCLID releases, e.g. microorganism requirements, IUCLID drive for large files.

Project results and outcome

Project results' overview

Thirteen IUCLID dossiers were completed containing dummy (no personal or confidential data), as part of Objective 1.

The dossiers were built by reusing information from previous steps as much as possible.



- 5 GB -10 GB – 20 GB + light dossier

-Two Identity dossiers as part of a TF

- MRL dossier submitted after the active;
- MRL dossier submitted for not approved a.s.;
- MRL dossier submitted as part of the a.s.;
- MRL dossier to delete MRLs

Project results' overview

For the 13 dossiers completed, objective 2 was fulfilled. All results are summarized in the final project report.

Considering the analysis of issues encountered - a quick glance for the presentation today…

Manual comments Over **1000** comments were made in the IUCLID manual files;

Report generator Ca. **400** comments were made in the generated reports, and

IUCLID comments More than **300** comments were made on IUCLID issues and fixes (Excel list of improvements).

Project results' overview

For the 13 dossiers completed, objective 2 was fulfilled. All results are summarized in the final project report.

Considering the analysis of issues encountered - a quick glance for the presentation today…

Manual comments Over **1000** comments were made in the IUCLID manual files;

Report generator Ca. **400** comments were made in the generated reports, and

IUCLID comments More than **300** comments were made on IUCLID issues and fixes (Excel list of improvements).

IUCLID manuals – general comments

All the IUCLID EFSA manuals available during 2023 were reviewed. The following main points were found:

- The structure for the manuals is long and difficult to follow (ca. 1000 pages for microorganism and 2200 for chemicals, status September 2023).
- High level information is mixed with specific details, e.g. introductory text and detailed tables where sometimes special instructions are listed.
- New data requirements (microorganism) as well as new IUCLID entries are not presented.
- Mentions are made to the microorganism specifics in the active substance (chemical) manual and vice versa.

User manuals:

- Active substance manual
- MRL manual
- Microorganisms manual
- Microorganisms IUCLID 6.7 mini-manual
- Basic substance manual

IUCLID manuals – recommendations

- Main comments: text clarifications, proposals for erasing/re-writing or updates to relevant guidelines, links and screenshots.
- Recommendation to simplify and shorten the document structure by presenting the most relevant information at the beginning.
- Modify the text to include only the relevant context, e.g. no microorganism dossier peculiarities in the active substance (chemical) manual.
- To use as much as possible links to other available documents.
- Some of the comments have already been applied to the updated versions of the manuals in Zenodo.

Project results' overview

For the 13 dossiers completed, objective 2 was fulfilled. All results are summarized in the final project report.

Considering the analysis of issues encountered - a quick glance for the presentation today…

Manual comments Over **1000** comments were made in the IUCLID manual files;

Report generator Ca. **400** comments were made in the generated reports, and

IUCLID comments More than **300** comments were made on IUCLID issues and fixes (Excel list of improvements).

IUCLID generated reports

- The relevant reports were generated for each IUCLID dossier type finalized (IUCLID versions v7.0.2 to IUCLID v7.10.1).
- All specific comments for the generated reports were compiled directly in the .rtf file for ease of understanding. No backlog list but complete reports commented.
- Some of the most found issues in the generated Document M were:
  - Formatting problems

Formatting problems: missing spaces

Observations and examinations performed and frequency

CAGE SIDE OBSERVATIONS: Not specified

DETAILED CLINICAL OBSERVATIONS: Yes
- Time schedule: twice daily on working days and once daily on weekends and holidays

BODY WEIGHT: Yes
- Time schedule for examinations: pre-test and weekly

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):
- Food consumption for each animal determined and mean daily diet consumption calculated
- Compound intake calculated as time-weighted averages from the consumption and body we

FOOD EFFICIENCY:
- Body weight gain in kg/food consumption in kg per unit time X 100 calculated as time-weigh

Examinations:

Observations and examinations performed and frequency:

CAGE SIDE OBSERVATIONS: Not specified DETAILED CLINICAL OBSERVATIONS: Yes - Time schedule: twice daily on working days and once daily on weekends and holidays BODY WEIGHT: Yes - Time schedule for examinations: pre-test and weekly FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study): - Food consumption for each animal determined and mean daily diet consumption calculated as g food/kg body weight/day: Yes - Compound intake calculated as time-weighted averages from the consumption and body weight gain data: Yes FOOD EFFICIENCY: - Body weight gain in kg/food consumption in kg per unit time X 100 calculated as time-weighted averages from the consumption and body weight gain data: Yes WATER CONSUMPTION AND COMPOUND INTAKE (if drinking water study): Yes - Time schedule for examinations: once daily OPHTHALMOSCOPIC EXAMINATION: Yes - Time schedule for examinations: pre-test and at the end of treatment - Dose groups that were examined: control and high dose HAEMATOLOGY: Yes - Time schedule for collection of blood: end of the treatment period - Anaesthetic used for blood collection: Yes (ether) - Animals fasted: Yes - How many animals: All surviving animals - Parameters checked in Table 1 were examined. CLINICAL CHEMISTRY: Yes - Time schedule for collection of blood: end of the treatment period - Animals fasted: Yes - How many animals: All surviving animals - Parameters checked in Table 2 were examined. PLASMA/SERUM HORMONES/LIPIDS: No URINALYSIS: No NEUROBEHAVIOURAL EXAMINATION: No

IUCLID generated reports - examples

Formatting problems:

- Empty tables, inconsistent/wrong formatting and alignment in IUCLID tables
- Lack of formatting in picklists/automatic texts

Storage stability - animals:

Table CA 6.2.

Category	Commodity	Substance(s)	Temp.	Tested period	Stability period	Remarks

Primary crops:

Table CA 6.5.

Studies	Crop groups	Commodity	Treatment type	Application rate	DAT	
	cereals/grass	0500090 -	foliar	0.2 kg a.s./ha	BBCH 89	

b) Results

Effect levels:

LD50: 1400 mg/kg bw (male) based on: (test mat.)

LD50: 1800 mg/kg bw (male/female) based on: (test mat.)

Table CA 5.18.

Endpoint	
Genetic toxicity in vitro	no adver
Genetic toxicity in vivo	no adver

Table CA 8.5.

Test type	Organism	Substance	Endpoint
acute tier 1	freshwater fish - Oncorhynchus mykiss	EFSA Tender: Active substance BC (parent)	RACtier1: 6µg/L (assessment factor: 100)
chronic tier 1	freshwater fish - Oncorhynchus mykiss	EFSA Tender: Active substance BC (parent)	RACtier1: 15µg/L (assessment factor: 10)
acute tier 1	marine aquatic invertebrates - Americamysis bahia	EFSA Tender: Active substance BC (parent)	RACtier1: 8.19µg/L (assessment factor: 100)

IUCLID generated reports - examples

IUCLID tables shown as unformatted text in report

Test results + New item Import file

#	Key result	Species / strain	Metabolic activation	Genotoxicity	Cytotoxicity / choic...	Vehicle controls va...	Untreated negative...	True negative contr...	Positive controls v...
1	☑	S. typhimurium TA 1535	with and without	negative	no cytotoxicity	valid	not examined	not examined	valid
2	☑	S. typhimurium TA 1537	with and without	negative	no cytotoxicity	valid	not examined	not examined	valid
3	☑	S. typhimurium TA 98	with and without	negative	no cytotoxicity	valid	not examined	not examined	valid
4	☑	S. typhimurium TA 100	with and without	negative	no cytotoxicity	valid	not examined	not examined	valid

b) Results

Test results:

For S. typhimurium TA 1535 [bacteria]: Genotoxicity: negative. Cytotoxicity: no cytotoxicity.
(with and without metabolic activation)
Controls: Vehicle: valid. Negative: not examined. True negative: not examined. Positive: valid.

For S. typhimurium TA 1537 [bacteria]: Genotoxicity: negative. Cytotoxicity: no cytotoxicity.
(with and without metabolic activation)
Controls: Vehicle: valid. Negative: not examined. True negative: not examined. Positive: valid.

For S. typhimurium TA 98 [bacteria]: Genotoxicity: negative. Cytotoxicity: no cytotoxicity.
(with and without metabolic activation)
Controls: Vehicle: valid. Negative: not examined. True negative: not examined. Positive: valid.

For S. typhimurium TA 100 [bacteria]: Genotoxicity: negative. Cytotoxicity: no cytotoxicity.
(with and without metabolic activation)
Controls: Vehicle: valid. Negative: not examined. True negative: not examined. Positive: valid.

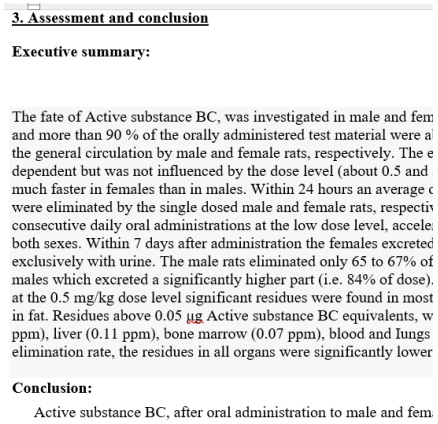
IUCLID generated reports

- The relevant reports were generated for each IUCLID dossier type finalized (IUCLID versions v7.0.2 to IUCLID v7.10.1).
- All specific comments for the generated reports were compiled directly in the .rtf file for ease of understanding.
- Some of the most found issues were:
  - Formatting problems: missing spaces, too many tabs, empty tables, inconsistent formatting and alignment in IUCLID tables, missing italics, subscripts…
  - Missing fields: materials and methods in all cases [fixed in last IUCLID version]
  - *“Field content is not in a valid XML format and thus ignored!”*.

IUCLID generated reports - examples

“Field content is not in a valid XML format and thus ignored!”.

Directly tested with the same IUCLID dataset and comparing reports generated with different IUCLID versions.



3. Assessment and conclusion

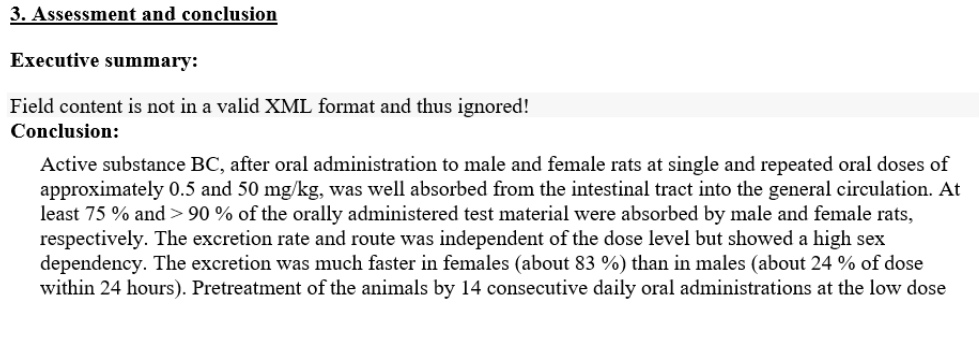
Executive summary:

The fate of Active substance BC, was investigated in male and fem
and more than 90 % of the orally administered test material were a
the general circulation by male and female rats, respectively. The e
dependent but was not influenced by the dose level (about 0.5 and
much faster in females than in males. Within 24 hours an average
were eliminated by the single dosed male and female rats, respecti
consecutive daily oral administrations at the low dose level, accele
both sexes. Within 7 days after administration the females excreted
exclusively with urine. The male rats eliminated only 65 to 67% of
males which excreted a significantly higher part (i.e. 84% of dose).
at the 0.5 mg/kg dose level significant residues were found in most
in fat. Residues above 0.05 µg Active substance BC equivalents, w
ppm), liver (0.11 ppm), bone marrow (0.07 ppm), blood and lungs
elimination rate, the residues in all organs were significantly lower

Conclusion:

Active substance BC, after oral administration to male and fem

v.7.0.2



3. Assessment and conclusion

Executive summary:

Field content is not in a valid XML format and thus ignored!

Conclusion:

Active substance BC, after oral administration to male and female rats at single and repeated oral doses of approximately 0.5 and 50 mg/kg, was well absorbed from the intestinal tract into the general circulation. At least 75 % and > 90 % of the orally administered test material were absorbed by male and female rats, respectively. The excretion rate and route was independent of the dose level but showed a high sex dependency. The excretion was much faster in females (about 83 %) than in males (about 24 % of dose within 24 hours). Pretreatment of the animals by 14 consecutive daily oral administrations at the low dose

v.7.10.3

For the example of same Document M, Section 5:

20 fields lost data from IUCLID v7.0.2 to v7.10.3.

Project results' overview

For the 13 dossiers completed, objective 2 was fulfilled. All results are summarized in the final project report.

Considering the analysis of issues encountered - a quick glance for the presentation today…

Manual comments Over **1000** comments were made in the IUCLID manual files;

Report generator Ca. **400** comments were made in the generated reports, and

IUCLID comments More than **300** comments were made on IUCLID issues and fixes (Excel list of improvements).

IUCLID comments

Due to the high amount and diverse nature of comments, a prioritisation was made among the issues listed.

General improvement	routine maintenance, harmonization and nice-to-have additional functionalities.	minor bug fixes, correction of absent units, inconsistencies, missing links, rewordings or clarifications
Important improvement	substantial enhancements that directly impact the software's usability and may influence the successful completion of the IUCLID dossier.	additional functionalities or fields that increase consistency or that would help the users, where there is currently an alternative or workaround
Critical improvement	essential for the accurate preparation of the IUCLID dossier and presently hinder its completion.	major bug fixes, issues reg. transparency and confidentiality, procedures too time consuming for users with no satisfactory workaround

*Technical feasibility was not considered as part of the prioritisation exercise.

IUCLID comments

Due to the high amount and diverse nature of comments, a prioritisation was made among the issues listed

General improvement	routine maintenance, harmonization and nice-to-have additional functionalities.	**267**
Important improvement	substantial enhancements that directly impact the software's usability and may influence the successful completion of the IUCLID dossier.	**46**
Critical improvement	essential for the accurate preparation of the IUCLID dossier and presently hinder its completion.	**23**

*Technical feasibility was not considered as part of the prioritisation exercise.

IUCLID comments

Due to the high amount and diverse nature of comments, a prioritisation was made among the issues listed

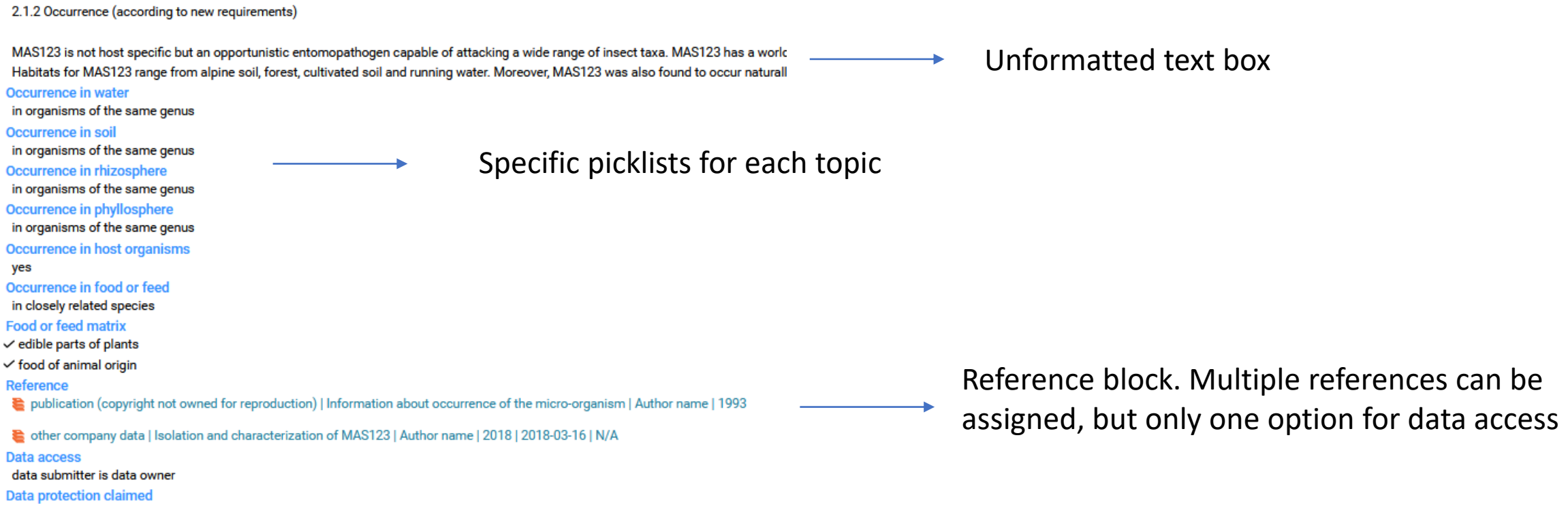
General improvement	routine maintenance, harmonization and nice-to-have additional functionalities.
Important improvement	substantial enhancements that directly impact the software's usability and may influence the successful completion of the IUCLID dossier.
Critical improvement	essential for the accurate preparation of the IUCLID dossier and presently hinder its completion.

Focus on a couple of examples

*Technical feasibility was not considered as part of the prioritisation exercise.

Biological properties – data organization

- This section allows for the creation of one type of flexible record covering for all data requirements (2.1-2.9).
- The flexible record contains a text box (no format), picklists and a reference/data access/data protection tab for each topic. The confidentiality justification applies to the whole entry.



Biological properties – data organization

Quick evaluation made to check the amount of data submitted to support the biological properties section.

2. Biological properties (Old data requirements*)		Bacterium example (2019)	Fungus example (2019)	Virus example (2021)
2.1	History of the micro-organism and its uses.	None	None	None
2.1.1	Historical background	None	2 (P)	6 (P)
2.1.2	Origin and natural occurrence	28 (P+S)	19 (P)	8 (P+S)
2.2	Information on target organism	None	17 (P)	None
2.2.1	Description of the target organism(s)	None	None	1 (P)
2.2.2	Mode of action	10 (P)	None	7 (P)
2.3	Host specificity range and effects on species other than the target harmful organism	None	3 (P)	7 (P)
2.4	Development stages/life cycle of the micro-organism	6 (P)	7 (P)	8 (P)
2.5	Infectiveness, dispersal and colonisation ability	2 (P+S)	21 (P)	11 (P)
2.6	Relationships to known plant or animal or human pathogens	1 (P)	1 (P)	1 (P)
2.7	Genetic stability and factors affecting it	3 (P+S)	1 (P)	16 (P+S)
2.8	Information on the production of metabolites (especially toxins)	3 (P)	11 (P)	None
2.9	Antibiotics and other anti-microbial agents	1 (SR)	1 (SR)	None

*The dossiers were submitted under the old data requirements, nonetheless the amount of data is expected to be similar or higher

P: publication; S: statement; SR: study report

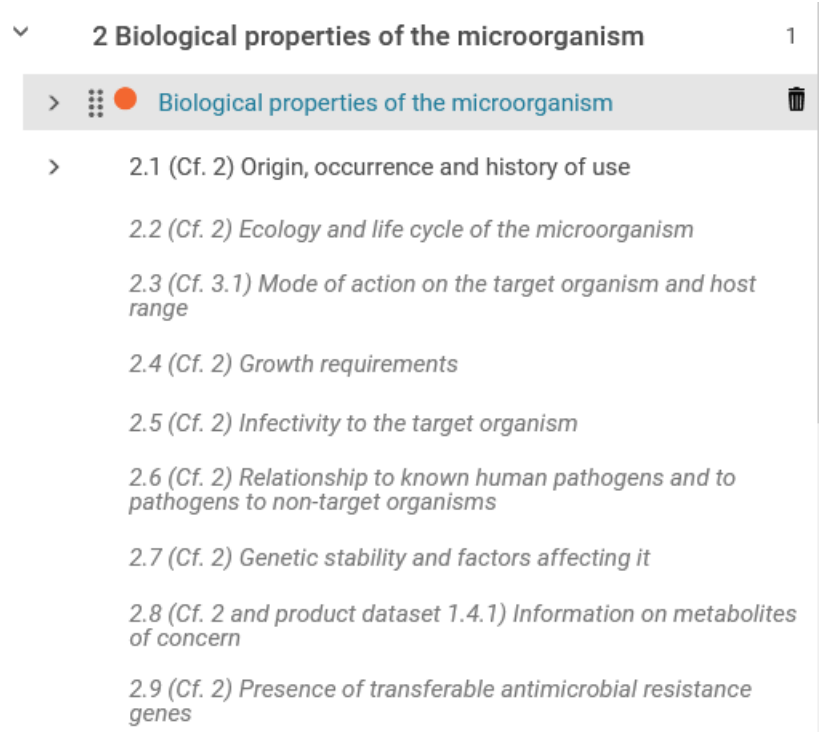
Approximately 50-80 references were provided in these real examples under Section 2 to meet the data requirements.

Biological properties – data organization

The current structure of the flexible record prevents the correct completion of section 2 for the following:

- The study summaries can only be stated as plain text in each text box
- The references need to be assigned all in the same point for each sub-data requirement. Data access/protection cannot be specifically completed for each reference.
- Any confidentiality claims needed, need to be added to the top of the point, no possibility for a closer claim
- Validation is limited by the flexible record structure (e.g. NoS ID not checked)

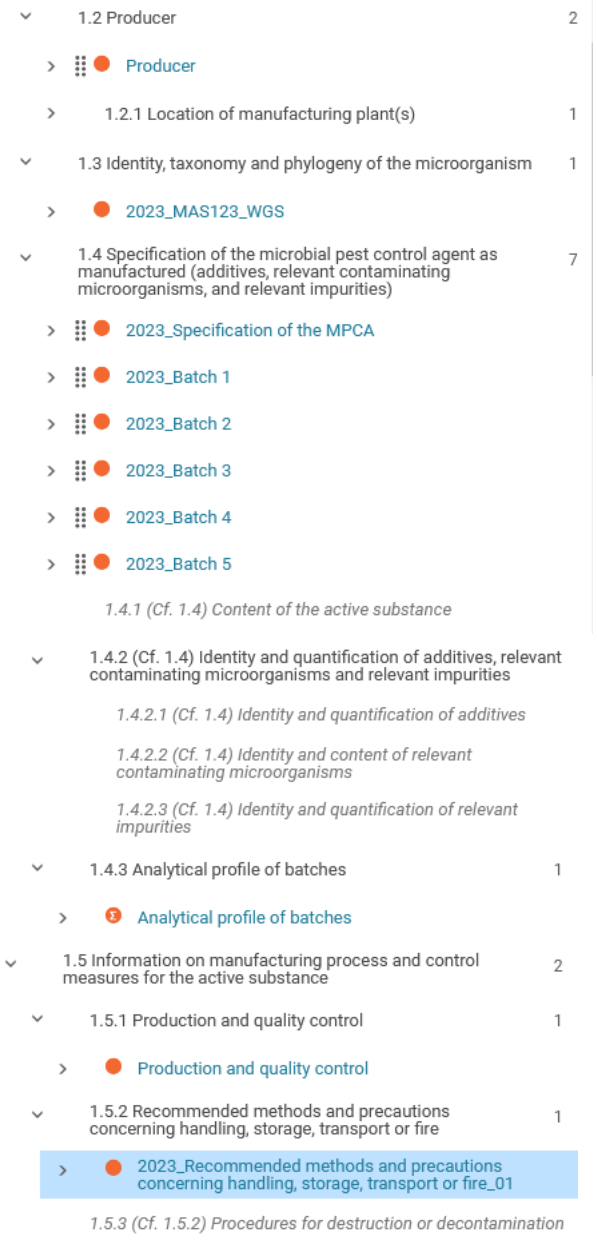
Proposal: To allow for the creation of endpoint study records under IUCLID point 2 (or within each currently blocked data requirement)



IUCLID comments

Identity - Document J / Vol. 4

- The completion of the identity sections (MA/CA) is complicated, the majority of points do not allow for the creation of standard entries or the attachment of files.
- Due to the planned phase out of the Document J, it is important to allow for the creation of study summaries (IUCLID study endpoint records), the assignment of references and the organized insertion of confidentiality claims.
- Other points that are usually collected in Doc J/Vol. 4 and not in IUCLID:
  - assessment of the equivalence of batches in the (eco)toxicological studies
  - assessment of the relevance of impurities



Identity - Document J / Vol. 4

Proposal:

- To allow the attachment of references/background documents in all relevant points.
- Allow for the creation of simple endpoint study records. These should be available at least to summarize the 5-batch analysis reports.
- To create a new flexible record type to be able to report assessment of relevance of impurities when necessary [will be addressed in April 2024].
- To add a solution for the assessment of the equivalence of batches.

Conclusions and recommendations

- All the project's objectives were successfully completed. Thirteen IUCLID dossiers have been generated and the relevant supporting materials have been reviewed.

- Currently, the generated reports are not fit to substitute the M documents/DAR/RAR volumes. A good balance between the use of the report generator and the user friendliness of the data insertion should be considered in each case.

- Major IUCLID changes are necessary in the biological properties section, and for the Identity section of both microorganism and chemicals. No critical issues were found for the other working context types. A list of all improvements is available.

- The final project report will be available in Zenodo, together with the list of all improvements.

Thank you for your attention!

Any questions?

Thanks to all the GAB colleagues and EFSA Team for the work and cooperation!

Julia Cara
Regulatory expert
Project and IUCLID manager

www.syntechresearch.com