IUCLID – CLE Perspective

10th Pesticide Steering Network meeting
11-12h June 2024, Parma (IT) and online

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(on behalf of Crop Life Europe Electronic Submission Expert Group: CLE eSEG)

Topics for discussion

- **Future development of OHTs**
  - OHT 85-5 and 85-9
  - OHT 87
- **Lifecycle management of IUCLID**
- **Notification of studies: Workshop?**
- **Public Dissemination**

Future development of OHTs

OHT 85-5 and OHT 85-9: Residue studies

- Background
  - OHTs 85-5 and OHT 85-9 contain multiple repeatable, “nested” blocks which makes manual data entries impossible (mandatory: automated data input)
  - Established work around: Upload of Excel spreadsheets as attachments (as advised during the Hypercare meetings and currently practiced)
- Improvements – September / October 2023: Focus – Reduce nesting levels
  - Proposal of German BfR: Split of studies into trials / plots, reduce information e.g. on methods
  - Proposal of CLE: Development of a flowchart and an Excel spreadsheet: Revised structure
- Situation – May 2024
  - Both proposals were not considered in the April release (version 6.8)
  - ECHA publication of the “new draft versions” includes BfR proposal but no CLE input

CLE has provided extensive comments to EFSA / OECD which are so far are not further discussed / considered
High interest in a follow up

Future development of OHTs

OHT 85-5: Residue studies

- The new proposal (ECHA webpage), which splits studies into trials / plots especially for rotational crop studies, will lead to a substantial increase of OHTs. Early analysis shows that special attention must be paid
  - To the Plot ID Picklist and Sampling ID Picklist
  - To the picklist for sampled material (referring to the Annex 1 to the MRL Regulation)
- E.g. EU Renewal for Approval Section 6.3 Magnitude of residues in plants

Example	OHT 85-5 current	Proposed OHT 85-5*
Major crop (8 NEU/8 SEU)	2 - 4 Studies	16 Trials
Rotational Crops (Tier 2+3 accord. to new GD)	Min. 2 Studies	120 Trials with 3 Plots each = 360 Plots
	Min. 4 Studies	376 Trials/Plots

* Without control plots

Significant increase of number of OHT 85-5 (especially for rotational crops); impact on OHT 87 not yet included

Future development of OHTs

OHT 87: Analytical methods

- History / background
  - Analytical method section not subdivided as foreseen in the EU guidelines (Reg. 283/2013, Appendix)
  - 2021: Entry of analytical method data in a table (rich text field); structure recommended in HyperCare
  - 2023: Creation of database fields for entering method validation data; announcement of dynamic content rules
- Improvements – 2023
  - PSN (June): Proposal of CLE / ECCA: Improved structure of IUCLID section 4, split of OHT 87 into product chemistry and residue analytical methods, increased use of tabular data entry / upload
  - OECD (Oct): CLE Comments provided to OECD
- Situation – May 2024
  - No follow up on proposal to facilitate at least data entry / upload: Multiple validation errors
  - For Member States: No possibility to extract data from IUCLID (Feedback MS)

CLE would be interested to learn how to proceed with the discussion on OHT 87 and subsequent steps
Important: Any further CLE action is limited to the use of OHT 87 in crop protection submissions

Life Cycle Management

Life Cycle Management and Reporting

- Background
  - In February PSN MS raised concerns about correct reporting based on OHT 87
  - Some key values on recovery, LOQ/LOD etc. did not appear in the report

Results and discussion

Results using analytical (primary) method

Recovery + New item | Import file

Analyte	Matrix	MRM/ m/z	Fortification level	Number replicates	Range recovery (%)	Mean recovery (%)	RSD (%)	Remarks	Actions

Additional details on recovery results

The results show that the analytical method is suitable to determine residues of M720H002 (CL 312622) in soil. Field soil samples of trials L200535 and trial 20-00487-02 were fortified at LOQ (1.0 µg/kg) and 10xLOQ (10 µg/kg). The mean recoveries ranged between 87.2 % and 99.0 % for all fortification levels and mass transitions. Relative standard deviations (RSD, %) were below ≤ 10.4 %. Therefore, the obtained recovery values fulfill the legal requirement for recovery values according to the considered guidelines The detailed results are given in the tables below.

Repeatability + New item | Import file

Analyte	Matrix	Number replicates	Mean content	RSD^R (%)	RSD^r (%)	Horrat value	Remarks	Actions

LOQ/LOD + New item | Import file

Analyte	Matrix	Limit of quantification	Limit of detection	Remarks	Actions

Calibration + New item | Import file

Analyte	Standards	Matrix	MRM/ m/z	Calibration range	Calibration equation	Correlation coefficient (r)	Correlation coefficient (r2)	Number replicates	Remarks	Actions

Matrix effects (%)

Matrix effects remarks

Additional details on analytical (primary) method

Linearity Good linearity (r ≥ 0.9993) for the validation experiments was observed in the range of 0.05 ng/mL to 4.0 ng/mL for the mass transitions of M720H002 (CL 312622) using six calibration levels. Matrix-matched standards were used for quantification.

b) Results

Results using analytical (primary) method

Details:

The results show that the analytical method is suitable to determine residues of M720H002 (CL 312622) in soil. Field soil samples of trials L200535 and trial 20-00487-02 were fortified at LOQ (1.0 µg/kg) and 10xLOQ (10 µg/kg). The mean recoveries ranged between 87.2 % and 99.0 % for all fortification levels and mass transitions. Relative standard deviations (RSD, %) were below ≤ 10.4 %. Therefore, the obtained recovery values fulfill the legal requirement for recovery values according to the considered guidelines The detailed results are given in the tables below.

Additional details on analytical (primary) method

Linearity Good linearity (r ≥ 0.9993) for the validation experiments was observed in the range of 0.05 ng/mL to 4.0 ng/mL for the mass transitions of M720H002 (CL 312622) using six calibration levels. Matrix-matched standards were used for quantification. Specificity The method allows the specific determination of M750H002 (CL 312622) in plasma using HPLC-MS/MS. Detection is accomplished using two mass transitions. Since detection by MS/MS with two characteristic mass transitions is regarded to be highly specific, no further confirmatory method is required. Interference Significant interferences (> 30 % of LOQ) were not observed at the retention time and mass transitions of the analyte. Matrix effects As matrix-matched standards are used, potential matrix effects are negated. Limit of Quantification The method has a limit of quantification (LOQ) of 1.0 µg/kg corresponding to the lowest fortification level successfully tested. Limit of Detection The limit of detection (LOD) is 0.30 µg/kg in wet soil, corresponding to a concentration of 0.075 ng/mL in measurement solutions. Repeatability The relative standard deviation (RSD, %) across both soils, fortification levels and mass transitions was ≤ 10.4 %. Standard Stability Stability in calibration solutions at concentrations of 1.00 ng/mL and 2.50 ng/mL was confirmed for 28 days for M720H002 (CL 312622), when stored refrigerated at 2 - 8 °C in the dark. Final Extract Stability The stability tests confirmed that M720H002 (CL 312622) was stable in final volumes for 7 days in soils from trial L200535 and trial 20-00487-02, when stored under refrigerated conditions in the dark. Reproducibility Reproducibility of the method was not determined within this storage stability study.

Other information

No issue of report definitions or applicant – corresponding fields simply did not exist at the time of Dossier submission
Potential issue with any major release at any point, where data structures had been amended = incorrect reporting
Do we need to link reporting also to a certain version of IUCLID to make it fully functionable?

Life Cycle Management

Further points

- OECD activity 3: Re-using data sets for multiple submissions
  - Need for a Versioning/Life Cycle Management discussed beyond PPP
  - PPP minimum requirement to keep Dossiers stable under the IUCLID version at the time of initial submission
  - Need for such element not seen for other sectors
  - PPP Domain to discuss further with ECHA and feed back to OECD group as there are general implications for all users
- Just to repeat: CLE view
  - Elements of Life Cycle management are crucial for sufficient handling of PPP Dossiers with long evaluation timelines involving several steps and stakeholders
  - A “must-have” prior to even considering any further expansion of IUCLID within the PPP Domain

CLE would like to know how EFSA/ECHA are intending to proceed with this key topic

Notification of Studies

Linking to Pre-APP IDs

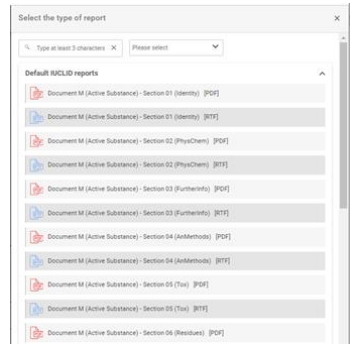
- Background
  - MS raised concerns on the ability to evaluate the non-submission of studies, which are conducted with the same substance, but not linked to the PAID of the current Dossier
  - Applicants raised concerns about not being able to judge upfront, when and in which regulated process some studies might become relevant for an EU process (most prominent example: Non-EU residue data)
- Improvement Ideas
  - Allow for unlinking of studies from a PAID – this would enable applicants to correct PAIDs
  - Treat residue data differently within the NoS DB, so the majority of unclear cases can be filtered upfront
- Way forward:
  - Conduct the proposed workshop to make study notification and the NoS DB more usable for all stakeholders covering all case scenarios
  - Important: Expansion to other sectors as currently discussed should only be considered after making the DB robust for more complex cases

CLE would fully support and actively participate in a workshop on Study Notifications and the Database
CLE considers EFSA as the right organization to host such a workshop as the DB and PAs are owned by EFSA

Public IUCLID and Dissemination

Public IUCLID is untransparent as a dissemination medium:

- Background
  - It take a large number of mouse clicks to navigate through a dossier
  - A very limited number of actions/functions are available to a public user;
    - No generation of reports for ease of analysis
    - Information where available must be downloaded individually



- Public participation in commenting – to date we are unsure if any public comment has been received on a “validated application”
- The removal of OECD summaries from applicant dossiers moving forward will make this situation worse
  - Lack of compare functionality in public IUCLID would mean that a commenter would need to completely review the dossier in entirety each time to comment (‘validation application’ vs dRAR background document)

CLE would request for User Acceptance Testing to be performed and a number of features to be implemented to Public IUCLID specifically to address these concerns