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Analysis of the informational flow of pesticide related metabolism studies

Part Comparison of OHT58 „Basic toxicokinetics“ and DER Composer

1 Background

According to the specific agreement SA1 under the framework partnership agreement No GP/EFSA/AMU/2020/02, a comparison of OHT58 „Basic toxicokinetics“ and the DER Composer should be delivered under topic D 4.1.1.

The comparison based on the following two XML Schema definitions:

- ENDPOINT_STUDY_RECORD-BasicToxicokinetics-6.0.xsd
- DER13.xsd

Because of splitting IUCLID into different generic templates the following additional schema were used:

- REFERENCE_SUBSTANCE-6.0.xsd
- LITERATURE-6.0.xsd

For the semantic interpretation, the following additional documents were used:

- Word template OHT58 Basic toxicokinetics (Version [8.4]-[October 2020])
- 5x study summaries created according to DER version 5.2.
 - in the XML view and
 - in addition in the user view of the RatComposer_v5r2

2 Summary

Both XML Schema definitions are semantically equivalent for study summaries of metabolism studies in terms of the content submitted.

The DER composer concept has more advantages compared to the OHT58 in IUCLID in terms of the implemented formats and supporting tools.

3 Comparison

3.1 Semantic aspects

3.1.1 Method

The xpath of elements of the following schema templates were extracted into an Excel table.

- IUCLID ENDPOINT_STUDY_RECORD-BasicToxicokinetics-6.0.xsd
- REFERENCE_SUBSTANCE-6.0.xsd
- LITERATURE-6.0.xsd
- DER13.xsd

In principle, one could have added the generic schemes for SUBSTANCE and TEST-MATERIAL on the IUCLID side also. However, this was not done because this differentiated data model was not used in DER schema.

The following rules were used:

- Element nodes with child nodes were excluded from the comparison.
- In case of element nodes of the IUCLID-Templates, which are coded via pick lists only the direct parent node for the element "value" was included into the comparison.
- In case of XML table definitions of the DER schema only the direct parent node was included into the comparison.
- The line numbers of the word versions of the used IUCLID-Templates were added.

These elements were grouped into the following groups according the **information content**:

- **"Equivalent"** on the semantic layer means: The referenced information could be transported in both XML schema. The user is able to read the stored information. The used format of the elements were not analysed in this step.
- **"Additional OHT58 element"** on the semantic layer means: There is not equivalent information in the DER schema.
- **"Additional DER element"** on the semantic layer means: There is not equivalent information in the OHT58 schema.

These elements were grouped into the following two categories according the **information type**:

- **"Study"** if the information depends on the study itself.
- **"Legal act"** – this information has its origin in legal act or in the workflow organisation of the evaluation / publication of the study.

3.1.2 Findings

Please note that the semantic comparison did not include the IUCLID schemes for SUBSTANCE and TEST MATETRIAL, even though the OHT 58 references a TEST MATETRIAL. This three-step substance referencing mechanism was not used.

Please compare the detail result data in the attached Excel file.

- 179 elements were included into the comparison (=100%).
- 121 (=68%) of these elements are **"Equivalent"** on a semantic layer.
- 34 (of 58 =59%) of the additional elements could be assigned to the information type **"Legal act"**.
- Only 24 (of 58 =41%) of the additional elements are related to the information type **"Study"**.
- The OHT58 offers much more additional study elements compared to the DER scheme.

However, it should be noted that the determined degree of overlap and the subsequent determination of the categories are not "measured values". The semantic comparison presented is based on the expert opinion regarding the interpretation of the element contents. Furthermore, the lack of textual documentation of the contents in the individual DER scheme elements made the comparison difficult.

3.2 Aspects of format and supporting tools

It seems that both templates are equivalent in the semantic content layer according to chapter 0. Nevertheless, the format aspects and the implemented supporting tools are influencing the usability of such data interfaces.

3.2.1 Method

The DER composer was used as the comparative model. Only aspects were summarized in chapter 4.2 where the format usage or the implemented supporting tools were reasons for a different quality of user functions.

The result table contain a semi-quantitative rating of the aspects. The following scale was used:

Icon	Textual interpretation	Score
-	A deficit in the functionality	-1
+	A benefit in the functionality	1
++	A significant advantage in the functionality	2
+++	A important advantage in the functionality	3

3.2.2 Findings

DER Chapter	Aspect	Comment	OHT58	DER
I. General Info	Test Material Purity	The DER composer has no validation of the numeric value implemented		+
II. Material and Methods/ A Materials	Test Compound	IUCLID uses a high sophisticated substance model with the levels: Test material → substance → Reference substance Metabolism studies were carried out with substances not with products. Only a simple substance model is needed.	-	+
II. Material and Methods / A Materials Test Compound/ Radiolabelled test material	Radio – labelled purity Specific activity and unit	The DER composer has no validation of the numeric value implemented. No picklist for the units is implemented		-
II. Material and Methods / A Materials Test Compound/ Radiolabelled test material	Structure	It should be possible to create a structure for each different radiolabelled position. IUCLID has only one reference to one test material. The OHT 58 has no repeatable block with a reference to a radiolabelled “Reference substance” characterized by his smiles notation code. IUCLID could store regarding “Radiolabelled” only „Yes, No, other“. This element is not helpful. The structure characterisation of the radio-labelled test material and the 2D structure editor are the most important advantages of the DER composer.	-	+++
II. Material and Methods / A Materials Test Compound/	Physicochemical Properties	IUCLID would be able to refer specific sections for the phys-chem properties. The DER data model could produce inconsistent data values for one compound via data input of different studies.		-

		It is not clear if evaluators need this information for the interpretation of metabolism studies.		
II. Material and Methods / B Study design and methods	Table 1a – Group arrangement	<p>The detailed summary of the treatment groups is essential for all interpretations.</p> <p>IUCLID is very open for a textual description of the treatment groups.</p> <p>The DER uses an input template, which is suitable to describe the dose groups and the study design regarding other parameters. The dose route should be converted into a picklist value</p>		++
II. Material and Methods / B Study design and methods	Table 2a – Sample collection	<p>The detailed summary of the sample collection is essential for all interpretations.</p> <p>IUCLID is very open for a textual description of the sample collection.</p> <p>The DER uses an input template, which is suitable to describe the sample collection for each defined matrix. The metadata for the sample collection are free text.</p> <p>There are dependencies between "Appendix 1a" and "Table 1a - Group Classification" that prevent a sample collection of a specific matrix as a time series.</p>		-
III. Results / A Pharmacokinetic studies	Absorption	<p>The Total Radioactive Residues (TRRs) are basic values, which could be used in toxic kinetic models.</p> <p>IUCLID uses a predefined table in a rich text field, which could be modified flexibly.</p> <p>The DER offers to create flexible tables. The structure description is similar to HTML and would thus be very transparently usable for potential interfaces to models.</p>		+
III. Results / A Pharmacokinetic studies	Excretion	<p>Statements on the elimination balance are essential.</p> <p>IUCLID uses a predefined table in a rich text field, which could be modified flexibly.</p> <p>The DER offers to create flexible tables. The structure description is similar to HTML and would thus be very transparently usable for potential interfaces to models.</p>		+
III. Results / B Metabolite characterization studies	Distribution of parent and metabolites in matrices	<p>These values are in addition to the absorption TRRs.</p> <p>IUCLID uses a predefined table in a rich text field, which could be modified flexibly.</p> <p>The DER offers to create flexible tables. The structure description is similar to HTML and would thus be very transparently usable for potential interfaces to models.</p>		+

V. Appendix	Appendix 1a	<p>The description of the “Dose groups” is needed for all calculations and reports. It is good that the DER composer defines such an important table.</p> <p>There exists an algorithm to subsumes test-numbers and create corresponding rows for table II. Material and Methods / B study design and methods.</p>		+
V. Appendix	Appendix 2	<p>The list of metabolites detected, their structure if applicable, and the presumed relationships to the applied labelled substances should be the highlight of a metabolism study summary.</p> <p>IUCLID has only a text field for this list implemented.</p> <p>The DER composer provides the 2D structure editor for the parent and for the metabolites.</p>	-	+++
Data Container	Metabolism study export file	<p>IUCLID exports the study as a i6z container with XML files and attachment files for all object types.</p> <p>The DER XML file contains all information in one file. This file is “self-contained”.</p> <p>An external editor could modify this XML file.</p>		++

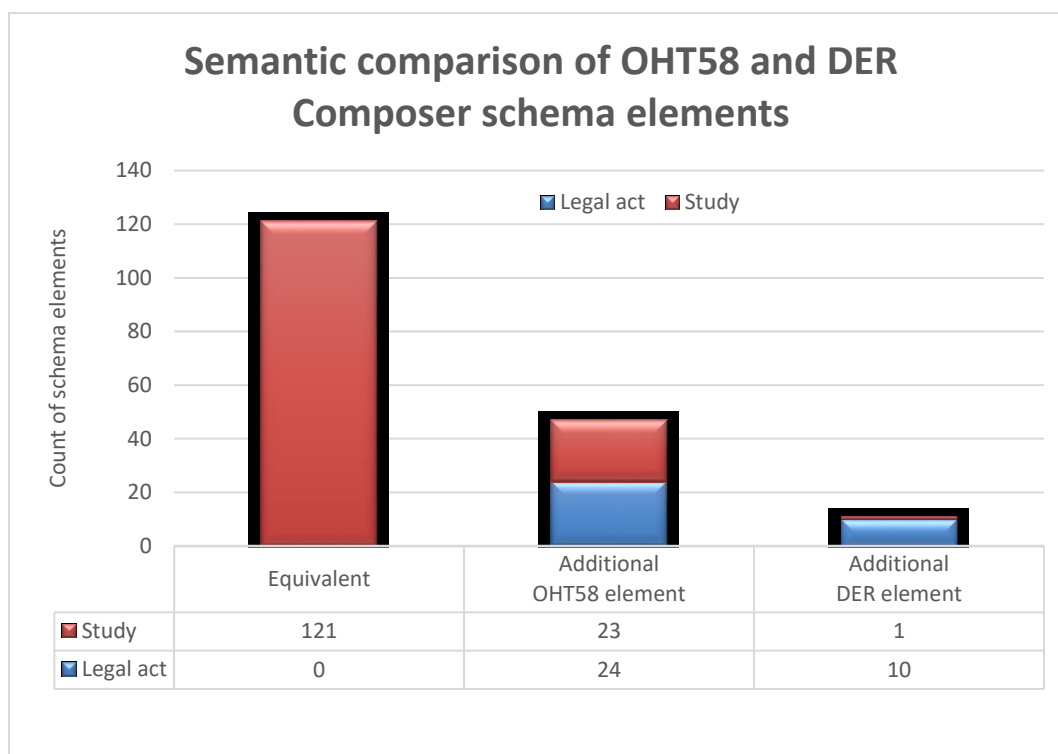
4 Conclusions

There is a large overlap regarding the possibility to transport study summary information of metabolism studies via the DER composer schema and via the OHT58, created by IUCLID.

Most of the additional elements are from type “**Legal act**”. From these elements, there is no threat of loss of information regarding the transmission of the study summaries.

The reason for these differences lies in the historical development of both templates. The template for DER-composer should be comparable to the OECD template OHT58 in terms of content, but at the same time should correspond to the specifics of US EPA and PMRA.

However, if you analyse the significance of the additional schema elements of the OHT58, there are also useless fields of the generic approach of the chemical legislation.



On the basis of this analysis, it can be concluded that both templates can be considered as semantic equivalent for study summaries for metabolism studies in terms of the content submitted.

However, the results table in chapter 3.2 shows that the DER composer concept has considerably more advantages than disadvantages compared to the OHT58 in IUCLID in terms of implemented formats and supporting tools.

5 Attachment

[Comparison OHT58 and DER Rat Composer.xlsx](#)