MSS COMPOSERS ADVISORY NOTICE

This notice was reviewed in 2022 by Pesticide Residues and Food Safety Unit (DEPR- ANSES) in the framework of the project GP/EFSA/PREV/2021/01 - SA01-2021-ANSES and refers to the versions v.1.12 of the MSS Plants, Livestock and Crops Composers.

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Chapter 1: Presentation of the MSS Composers

MSS (Metabolism Study Summary) composers are satellite programs built to facilitate the creation and editing of metabolism study summaries.

Three different MSS Composers are available. Depending on the type of metabolism study to be encoded, it is necessary to chose between the following ones:

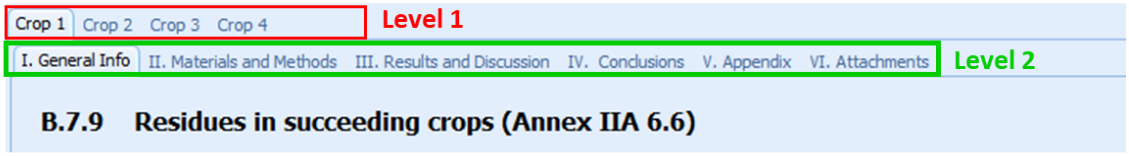
- MSS Composer (**Plants**) for metabolism studies carried out on **primary crops**;
- MSS Composer (**Crops**) for metabolism studies carried out on **rotational crops**;
- MSS Composer (**Livestock**) for metabolism studies carried out on **animals**.

All MSS Composers are organised in a consistent manner:

- a first level of tabs (**Level 1**) allows you to precise the type of plant or animal group used in the study. The MSS Composer automatically opens on the first tab (Crop 1 or Poultry);
- a second level of tabs (**Level 2**) to encode data from the study such as the references, information about the protocol, results and conclusions.

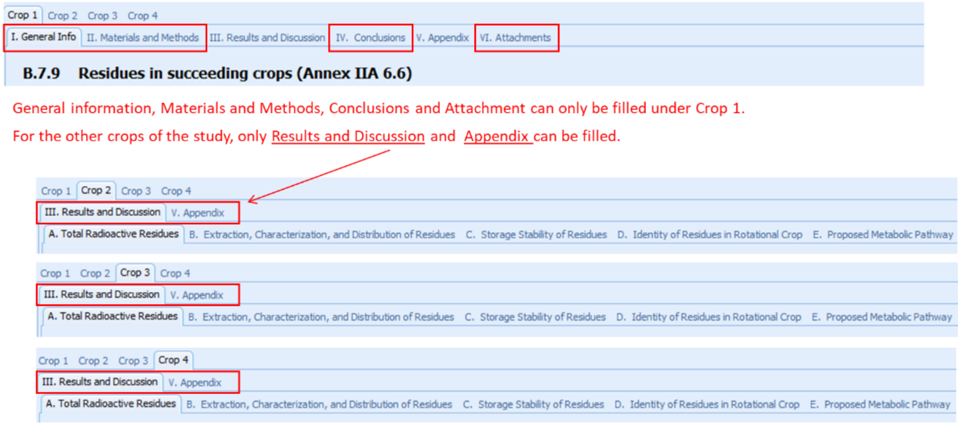
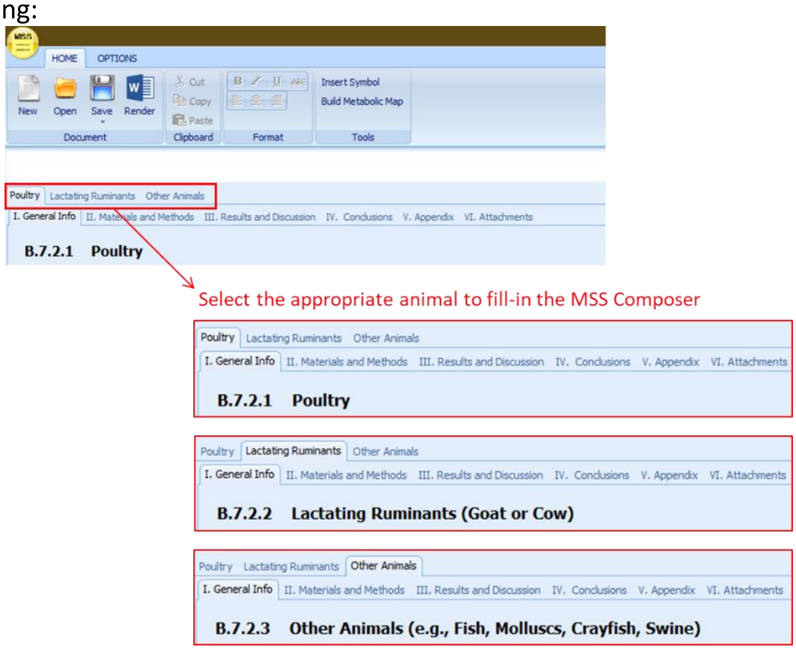
MSS Composer (Plants):

MSS Composer (Crops):



MSS Composer (Livestock):

Level 1:

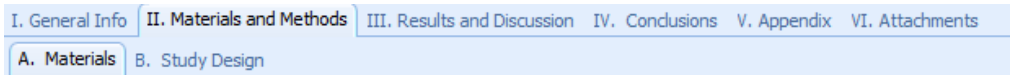
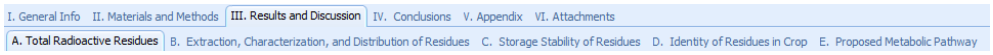
<table>
<tr><td>Plants
(primary crops)</td><td>In case metabolism is investigated for more than one plant in a single study, it is possible to add information for a second crop. All tabs from level 2 will have to be filled for the crops. If the study covers more than two crops, it might be necessary to create a second MSS file.</td></tr>
<tr><td>Crops
(rotational crops)</td><td>Metabolism in rotational crops should be investigated in representative crops from the following crop groups: root and tuber, small grain and leafy vegetables (OECD n°502).
As the protocol is usually the same for all three crops, the tabs I. General info, II. Materials and Methods, IV. Conclusions and VI. Attachments can only be filled for Crop 1.
 
</td></tr>
<tr><td>Animals</td><td>As metabolism study can be carried out on poultry, lactating ruminants or other animals, it is important to select the appropriate tab before beginning the encoding:
 
</td></tr>
</table>

To be noted that the tabs in level 1 cannot be renamed in the current version (v.1.12).

Level 2

As previously explained, all three MSS Composers are organised in a consistent manner. Data from a metabolism study are therefore populated in a similar logic.

Briefly, the following information can be found in each section:

I. General Info	References of the study, guidelines used, if the study is GLP, abstract…
II. Materials and Methods	Chemical information on the active substance, radiolabel and physicochemical properties Information on the crops/animal used, the soil properties (for plant/rotational studies)… Information on the study design 
III. Results and Discussion	Total Radioactive Residues measured in each matrix as well as in the different fractions during the extraction procedure Residues identified and proportion measured in each matrix 
IV. Conclusions	Conclusions of the study
V. Appendix	Residues identified in tested matrices and metabolic scheme
VI. Attachments	Files in the following format can be attached in this section: *.txt*, *.docx, .xlsx, .pdf, .xml, .pptx*, *.JPG*

Rules to fill-in the 6 sections are given Chapter 3.

Chapter 2: Preliminary information and writing rules

- **Select the appropriate MSS Composer**

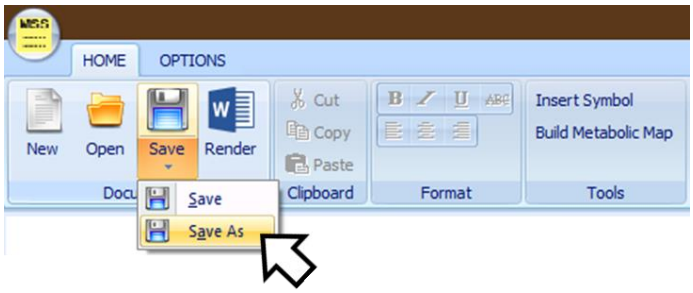
Please refer to the explanation in Chapter 1, Level 1.

For livestock metabolism studies encode the study in the correct tab *i.e.* poultry, lactating ruminants or other animals.

- **Save your work**

Xml files are not automatically saved when closing the MSS Composers:

- Click on "SAVE AS" to save your work as a *.xml* file.
- Regularly save your work by clicking on the floppy disk icon.

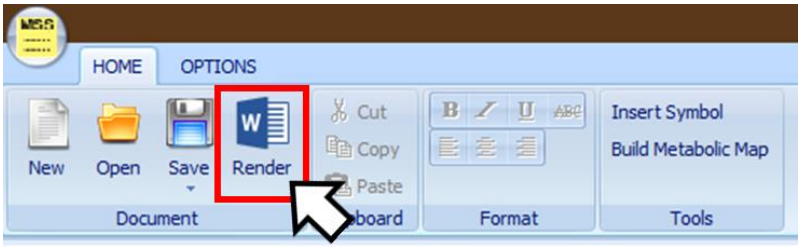


- **How to name *.xml* files**

Please respect the following nomenclature when naming the *.xml* files:

- **Plant** metabolism studies: **StudyReference_activesubstance_p_crop_vX.xml**
  (e.g.: SREF123_1,3-dichloropropene_p_tomato_v1.xml
  SREF987_amisdosulfuron_p_linseed_v2.xml)
- **Rotational crop** metabolism studies:
  StudyReference_activesubstance_c_crop1_crop2_crop3_vX.xml
  (e.g.: SREF321_difenoconazole_c_wheat_mustard_turnip_v1.xml)
- **Livestock** metabolism studies: **StudyReference_activesubstance_l_species_vX.xml**
  (e.g.: SREF456_amisulbrom_l_goat_v1.xml; SREF345_tolpyralate_l_hen_v2.xml)

- **Render function**



The Render function generates a Word file with all the encoded inputs. It can be a useful tool to copy/paste information directly into a report or in case you have to re-code a study into a new MSS Composer.

Please note that if you encounter an anomaly while coding on the MSS Composer, the anomaly will be passed on to other MSS *xml* files if these are opened at the same time. In such a case, the RENDER function can also be interesting not to lose the information already encoded.

When *.xml* files and Word files are opened at the same time, there is no problem of anomaly's transmission.

- **Mandatory fields**

In the EFSA document "*Reporting structured results of metabolism studies on rats, plants and livestock - Description of process steps of the information flow in EU*"[1], fields identified as mandatory are listed. Those fields have been highlighted in light green in the following section (Chapter 3: How to fill in the sections of the MSS composers?).

- **Writing rules**

The following writing rules are defined to insure the absence of encoding errors in the MSS Composers and a correct import of the *.xml* files into MetaPath.

In addition, it is important to respect the defined nomenclature to allow a proper use of MetaPath various functions in the database (especially search queries, which are highly sensitive to the spelling).

→ For the sake of harmonisation, please respect the described rules.

- **Do not use slash " / "**

- **Use of N/A (na), N/D (nd)**

N/A stands for "Not Applicable". It is used to say that a criterion is not relevant. In the tab "Results and Discussion" B. and D., it describes that the information in a line (e.g. MeOH extraction) does not apply, i.e. a sample has not been extracted in this way, not been partitioned etc. NA could also be used for Not Available, synonym as not reported.

N/D stands for "Not detected". It applies only to the tables of "Results and Discussion" when a compound has been searched for but not found. In case the report states the value of the LoQ or LoD, this value should be preferred (e.g. LoD 0.001). In case a metabolite cannot be found in a sample due to the label position, this compound should be deleted from the list. " - " should be used preferably over ND, as it increases readability in MetaPath.

- **Dash " – "**

A single dash "-" may stand for all of the above-mentioned acronyms. Its use must be accompanied by an explanation in the free-text field located above the different tables.

- **Writing of names with a capital letter**

Always begin with a capital letter to write chemical names, crops, crop groups, animals, species/breed/variety…

- **Writing of decimal numbers**

To enter decimal numbers, **use the point "."** and not the comma ","

In case a unit is required, always begin with the number (dose rate, treatment level, growth stage…).

[1] https://zenodo.org/record/4785179#.Yy2Me3ZBwdW

Chapter 3: How to fill in the sections of the MSS composers?

I. General Info

The section "General info" is completely common to the three MSS composers (plant, crops and livestock). This section provides general information on the study report such as references, identifiers, used guidelines...

References:

Click on "**ADD**" to fill in the field "References" – Right-click on *Citation#1* to rename the reference with the number of the study report (*E.g., Report No 1261W-1*).

You may have different reports for the same study (field report, analytical report, addendum…). For each report, you must add a reference because some parameters change from one study report to another (author, title for instance) – Each reference (*Citation#*) has to be renamed according to the corresponding report.

→ You must fill in I. General information for all references.

→ The others sections (II. Materials and Methods, III. Results and Discussion, IV. Conclusion, V. Appendix and VI. Attachments) are common to all references.

For each reference, fill-in the following information:

	Character limits + nomenclature → information on how to fill in the field	**Example**
Author(s):	Text, 1000 characters → Same format as for a scientific paper	*Anonymous, X. and Author, N.*
Date:	Drop-down menu → Select month, day and year from the drop-down lists	*September 7 2001*
Pages:	Text, 20 characters	*112*
Study Title:	Text, 1 000 characters	*Distribution and metabolism of ^{14}C-Bifenazate in grapes*
Reference Type:	Text, no limit → Fill in with the most available information as possible	*Company Report No.: XX-000-NN; Study No.: ST0001*
Testing Laboratory:	Text, 255 characters	*Research Center XN, Postal Code, Street, State, Country*
Company Study Number:	Text, 250 characters	*2022-0311*
Identifiers	Use "Manage Ids" (Tool bar > Options) to create new Identifiers and EDIT to add them **The procedure is described in Annex 1** → An Identifiers referring to the Company and/or the study can be added here	

	Character limits + nomenclature → information on how to fill in the field	**Example**
Test Material:	Text, 2 000 characters → Common name of the active substance used in the study (same as in II Materials and Methods A. Material) **+ if available:** company experimental code in brackets	*bifenazate (D2341)*
Identifiers:	Use "Manage Ids" (Tool bar > Options) to create new Identifiers and EDIT to add them **The procedure is described in Annex 1** → Add the **PARAM Code specific to the active substance** (see more details in Appendix 1) → A US EPA code (filled in by US EPA) can also be added	*PARAM Code:* *RF-0044-001-PPP*

Guidelines:	Text, 5 000 characters → Free field for additional information regarding guidelines	*OPPTS (OCSPP) 860.1300* *EU 7028/VI/95* *JMAFF 12Nohsan No.8147* *PMRA Chemistry Guidelines DIR98-02 Nature of the Residue*

GLP:	Drop-down menu → select yes or no	*yes*
	Text, 5 000 characters → Free field for additional information on GLP standards	*This study was conducted in accordance with EPA Good Laboratory Practice Standards, 40 CFR 160, effective October 16, 1989 with the following exceptions…*

Acceptability:	Drop-down menu → select yes or no	*yes*
	Text, 2 000 characters → Free field for additional information regarding the study acceptability	

Evaluators:

Evaluator Name	Text, 100 characters → Applicants should fill-in "Applicant" and Regulatory Authority should fill-in "Regulatory Authority"	*Applicant* *or* *Regulatory Authority Name*
Evaluator Affiliation	Text, 250 characters → Organisation supporting the application	*Applicant* *or* *Regulatory Authority*

BACKGROUND INFORMATION	Text, 5 000 characters → Free field for pertinent information on the active ingredient, its target mode of action, and the purpose of the end-use product	

The two following fields do not exist in the Livestock MSS Composer:

Product Type:	Text, 250 characters → Pesticide function	*acaricide*
Product Use:	Text, 250 characters → Intended crops	*grape, fruiting vegetables*

In all MSS Composers:

EXECUTIVE SUMMARY	Text, 20 000 characters → Study summary or abstract	*Executive summary (abstract) of the study report*

II. Materials and Methods

Information to report in this section, especially for subsection B. Study Design, depends on whether the study is carried out on plants or animals.

A. MATERIALS

1. Test Material

This first section is common to all three MSS Composers. The following information should be reported:

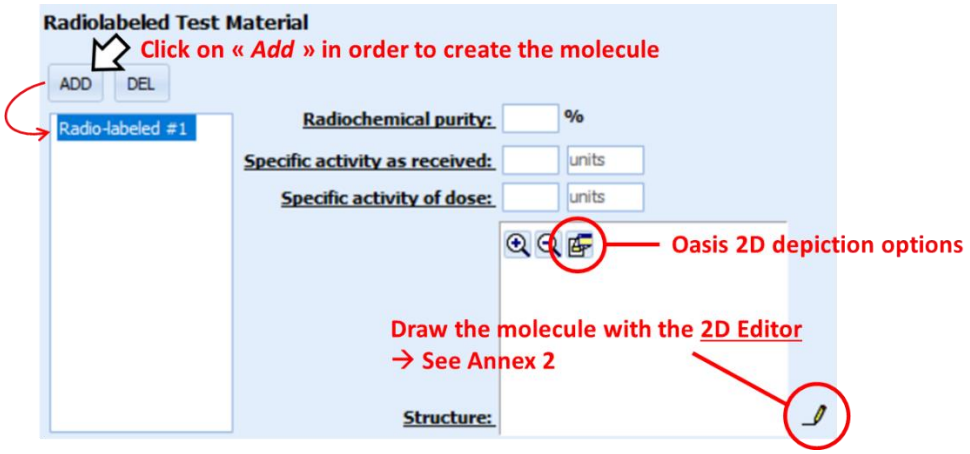
	Character limits + nomenclature → information on how to fill in the field	**Example**
Common name	Text, 192 characters → Common name of the active substance (same common name reported in *I. General Info*) → **Begin the name with a CAPITAL letter**	*Penthiopyrad*
IUPAC name	Text, 2 000 characters → Enter IUPAC Name – usually, it can be found in the List of EndPoints available in the Conclusion on the peer review of the pesticide risk assessment of the active substance (a.k.a. EFSA Conclusion)	*1-methyl-N-[2-(4-methylpentan-2-yl)thiophen-3-yl]-3-(trifluoromethyl)pyrazole-4-carboxamide*
CAS Chemical Name	Text, 500 characters → Enter CAS Chemical Name - usually, it can be found in the List of EndPoints available in the Conclusion on the peer review of the pesticide risk assessment of the active substance (a.k.a. EFSA Conclusion)	*N-[2-(1,3-dimethylbutyl)-3-thienyl]-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide*
CAS no.	Valid CAS number	*183675-82-3*
Company experimental name	Text, 250 characters → Same experimental name as the one reported in brackets in *I. General Info > Test Material*	*MFT-753*
Other synonyms (if applicable)	Text, 5 000 characters → Any other name(s) used in the study	*If no information: NA*
Molecular Formula	Text, 250 characters	*C16H20F3N3OS*
Analytical Purity	Text, 250 characters	*98.5 %*
Impurities	Text, 250 characters → Enter the identity of the radiolabelled impurities present at significant levels (i.e., > 5%)	
Physical State	Text, 250 characters	*Liquid*
Stability Under Test Conditions	Text, 250 characters → Storage stability of the substance tested in the study	*1 year at < -20°C*

Expiration Date	Text, 20 characters → Enter the date in the following format: "YYYY/MM/DD", "YYYY/MM" or "YYYY"	*March 2008*

Radiolabeled Test Material

The structure of the tested substance and the position(s) of the radiolabeled test material must be defined here.

Click on "ADD" to create/add a radiolabelled test material.



→ **One radiolabelled test material has to be designed for each type of radiolabelled position** (examples: ^{14}C-Phenyl, ^{14}C-Pyrazole, Cyclohexyl-UL-^{14}C).

→ If a **mixture of two radiolabelled test materials** is applied on the same crop, **every radiolabelled test material should be created separately** (because information on specific activity and purity is specific for each radiolabelled molecule) - in addition to these two molecules, **a third radiolabelled test material with the two radiolabelling site should also be created.**

→ **When creating the radiolabelled test items, you have to know how many matrices will be analysed in the study.** Indeed, as only 10 columns are available in the results sections B and D, the radiolabelled material(s) has/have to be duplicated in order to add new columns and enter all the results. However, please keep in mind that the number of radiolabelled test items should be minimised. An additional radiolabelled material should be created only if necessary. As it is exactly the same as the first one, it should be named **"[radiolabelled group]-common name#2"** or "**[radiolabelled group]-common name_2**".

Example: *for animals, a low and a high dose can be tested. This requires duplicating the radiolabel material in order to differentiate the results according to the dose. In addition, total radioactive residues can be measured and further characterised in more than 10 matrices: urine, excreta, eggs/milk, blood, GI tract, fat (renal, omental, subcutaneous), muscles (breast/loin and flank), skin, kidney and liver. As a column cannot be added, the radiolabel must be duplicated*.

/! It is impossible to insert a radiolabelled test item between the ones that have already been drawn, so try to foresee the number of matrices.

→ **For each radiolabelled material,** right-click on "*Radio-labeled #1*" to rename the radiolabelled molecule following this nomenclature: **[radiolabelled group]-common name.**

The following information should then be filled-in for each radiolabelled test material created:

	Character limits + nomenclature → information on how to fill in the field	**Example**
Radiochemical purity:	Value in percentage, without unit → Report the exact number or a numeric range → Less-than (<) and more-than (>) signs authorised	*98.7*
Specific activity as received:	First cell: range of values or value → Report the exact number or a numeric range Second cell: Unit (Text, 50 characters)	*4.11 MBq/mg*
Specific activity of dose:	First cell: range of values or value → Report the exact number or a numeric range Second cell: Unit (Text, 50 characters)	*1.85 MBq/mg*
Structure	→ To draw the radiolabelled molecule with 2D Editor, click on the pen button "  " → Once you have drawn the first radiolabelled molecule, you can save time by copy and pasting the SMILES code of the first molecule to draw the second one. **/!\ If you do so, don't forget to change the radiolabelling site** (tip: to erase the radiolabelling, remove "{LBLXX}" from the SMILES code) → For mixtures of isomers, the SMILES code of the different isomers should be separated by an underscore. Also, when available, please indicate the isomeric ratio of the applied substance using function "Ratio"  (last one) of 2D Editor. The ratio will be automatically included in the SMILES code. *See below for illustration and some explanations on how to encode stereochemistry of molecules using SMILES code.* **Further information on the 2D Editor is provided in Annex 2**	*[14C-pyrazole]-penthiopyrad* *[14C-thienyl]-penthiopyrad* *Mixture of py and th*

Table PhysChem Physicochemical Properties.

	Character limits + nomenclature → information on how to fill in the field	**Example**
Melting point/range	Text, 250 characters → Fill-in at least columns "values" and "reference" → Add units when necessary → Column "Notes" can be filled in to specify the conditions (when available)	
pH		
Density		
Water solubility (_°C)		
Solvent solubility (mg/L at _°C)		
Vapour pressure at _°C		
Dissociation constant (pKa)		
Octanol/water partition coefficient Log(Kow)		*Notes: at 20°C, pH 5, 99.8%* *Value: 3.9* *Units:* *Reference: EFSA Journal 2013;11(2):3111*

→ The next subsections are different depending on the type of MSS Composers for plants and rotational crops or MSS Composer for livestock:

- **For plants and rotational crops**, the following subsections are intended to describe the test crops and the soil type of the study;
- **For livestock**, they are intended to describe the general information on animals.

For plants and rotational crops

2. Test Crops

Table B.7.1.1-1 (plants) **/ B.7.9-1.** (rotation) **Crop Information.**

	Character limits + nomenclature → information on how to fill in the field	**Example**
Crop/Crop Group ***Primary crops***	Text, 250 characters → Please respect the following nomenclature: **Crop / Crop Group** → Crop / Crop Group has to **begin with a capital letter** and **be written in the singular** → The Crop Group refers to one of these 5 crops groups: root vegetables, leafy crops, fruits, pulses and oilseeds, and cereals (OECD n°501) → **Repeat this step for every tested crop (one row per crop)**	*Cabbage / Leafy crops*
Rotational crops	Text, 250 characters → Please respect the following nomenclature: **Crop / Crop Group** → Crop / Crop Group has to **begin with a capital letter** and **be written in the singular** → The Crop Group refers to one of these 3 rotational crop groups: root and tuber, small grain and leafy vegetable (OECD n°502) → Specify rotational crop in brackets (rotation) - this will allow easily distinguishing between maps of primary and rotational crops once the MSS xml files are imported into MetaPath → **Repeat this step for every tested crop (one row per crop)**	*Tomato **(rotation)** / Fruits and fruiting*
Variety	Text, 250 characters → Crop variety to be specified	*Dutch Round Cabbage*
Growth Stage at Application	Text, 250 characters → Expressed in BBCH stage → Begin with the number followed by BBCH → If no BBCH is reported in the study, for the sake of harmonisation please enter **0 : N/A** or **0 : description of the stage** (**do not forget the space between the zero and the colon** → When a description of the growth stage(s) is available in the study report, it is also possible to translate it directly into BBCH stages using the BBCH scale (https://www.reterurale.it/downloads/BBCH_engl_2001.pdf)	*19 BBCH* *10 - 19 BBCH* *0 : N/A*
Growth stage at Harvest		*49 BBCH* *0 : maturity*
Harvest Commodities	Text, 250 characters → Parts of the plants harvested for residue analysis	*Outer leaves, heads, roots of cabbage*
Harvesting Procedure	Text, 250 characters	*Manual*

Test Site Type	Drop-down menu → Select the right item from the drop-down list. If nothing corresponds, → Choose "other" and fill in the free-text field (max. 250 characters) → If another option than "other" is selected, you cannot write in the next box.	*greenhouse*

3. Soil Type

Table B.7.1.1-2 (plants) **/ B.7.9-2** (rotation) **Soil Physicochemical Properties.**

	Character limits + nomenclature → information on how to fill in the field	**Example**
Soil Type *mandatory for primary crop and rotational crops*	Text, 250 characters → Specify the type of method in brackets	*sandy loam (USDA system)*
pH *mandatory for **rotational** crops only*	Text, 250 characters → **pH in water should be given**. If another method was used, right-click on the column heading and specify the method in brackets → Possible to indicate a single value or a range of values	*5.8-6.1*
OM % *mandatory for **rotational** crops only*	Text, 250 characters → Possible to indicate a single value or a range of values → Do not indicate the units: they are automatically reported once the MSS xml file imported into MetaPath	*5.8*
Sand % *mandatory for **rotational** crops only*		*67.6*
Silt % *mandatory for **rotational** crops only*		*15*
Clay % *mandatory for **rotational** crops only*		*17.4*
Moisture Holding Capacity (at 1/3bar) *mandatory for **rotational** crops only*		*52.6*
CEC meq/100g *mandatory for **rotational** crops only*		*17.5*

Environmental Conditions

	Character limits + nomenclature → information on how to fill in the field	Example
Temperature	Text, 250 characters → Available data on the field phase should be added here	*15.2-21°C and 7.0-14.7°C*
Rainfall		*at least 8mm in 5 days*
Lighting		*sunshine 0-12.8h/day*
Potential for Photodegradation of Substance		

For Livestock

2. Animals

Table B.7.2.1-1. General Test Animal Information

	Character limits + nomenclature → information on how to fill in the field	Example
Species	Text, 250 characters → Use only the common name, not the Latin name → The name has to **begin with a capital letter** and **be written in the singular**	*Hen* *Goat* *Cow* *Fish* *Swine*
Breed	Text, 250 characters → The name has to **begin with a capital letter** and **be written in the singular**	*White Leghorn*
Age	Text, 250 characters → Begin with the number followed by the time unit (days/months/years) → Possible to indicate a single value or a range of values	*66 weeks at study initiation* *1-5 years*
Weight at Study Initiation (kg)	Text, 250 characters → **The study initiation corresponds to the day 0 of the dosing period**; acclimatation period should be excluded → Possible to indicate a single value or a range of values → Do not use the slash "/" because *.xml* file won't be imported into MetaPath	*1.317-1.877*
Health Status	Text, 250 characters → Indication of the health status of animals during the study	*Healthy - no clinically abnormal signs observed*
Description of Housing/Holding Area	Text, 250 characters → Indication of the type of animal housing, light/dark cycle, % of humidity…	*individual laying cages within gas collection chambers, 14h light/10h dark cycle, ca. 20°C, ca. 35% humidity*

B. STUDY DESIGN

This section totally depends on the type of MSS Composers for plants and rotational crops or MSS Composer for livestock.

For plants and rotational crops

Experimental conditions

Free-text field: briefly describe the experimental conditions (5000 characters).

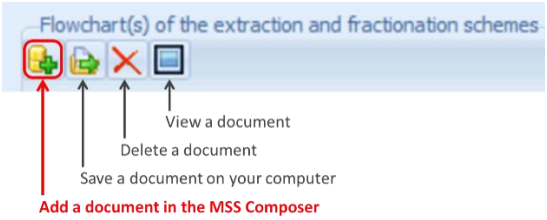
Table B.7.1.1-3 (plants) / B.7.9-3. (rotation) Use Pattern Information

	Character limits + nomenclature → information on how to fill in the field	**Example**
Chemical name	Text, 250 characters → Name of the applied molecule(s): **report the same name as the common name indicated in A. Material/1. Test Material** → specify when it is a mixture	*Prothioconazole* *mixture of [14C-pyrazole]-penthiopyrad and [14C-thienyl]-penthiopyrad*
Application method	Text, 250 characters	*Foliar spraying (hand-operated sprayer)* *soil treatment (spraying)*
Application rate	Text, 250 characters → Specify the nominal dose rate with units → Use a.s. as an abbreviation for "active substance" when stating the unit → Additional row could be added for experimental dose rate	*200 g a.s./ha* *1000 g a.s./ha*
Number of applications	Text, 250 characters	*2*
Timing of applications	Text, 250 characters → **Expressed in BBCH stage** → Begin with the number followed by the time unit (days/months/years) → If no BBCH is reported in the study, please enter **0 : N/A or 0 : description of the stage** (do not forget the space between the 0 and the colon ":") → When a description of the growth stage is available in the study report, it is also possible to translate it directly into BBCH stage using the BBCH scale (see the BBCH Monograph)	*65 BBCH*
PHI (Pre-Harvest Interval) for plants or PBI (Plant Back interval) for rotational crops	Text, 250 characters	*21 DA1A, 3 DALA*

Sampling

Free-text field, 5000 characters → Briefly describe how samples were taken, parts sampled, how samples were handled after harvesting (shipment, storage, etc.), and any preparation that was done prior to extraction	

Extraction and Analysis

Free-text field, 5000 characters → Briefly describe extraction and analysis procedures (measure of total radioactive residues by combustion, different extraction procedures leading to several fractions, analytical method methods used to analyse the extracts)	
flowchart(s) of the extraction and fraction schemes	
→ Click on "  " to add the flowchart of the extraction procedures of each matrix → In "Description", name the files according to the following nomenclature: "Extraction_matrix-name" → Accepted format: .PDF, .PNG, .JPEG 	

Identification and characterization

Free-text field, 5000 characters → Briefly describe here the procedures used to quantify, fractionate and purify the metabolites	

For Livestock

Dose Regime

	Character limits + nomenclature → information on how to fill in the field	**Example**
Number of Animals per Dose Group	Text, 20 characters	*6*
Rationale for Selection of Dose Group	Text, 2 000 characters	*The laying hen was chosen as a typical poultry species used for egg production*
Analysis of Feed and Water	Text, 5 000 characters	*Food consumption was measured and recorded daily during acclimatisation and study periods - Periodic analysis of the mains water supply was undertaken.*

Table B.7.2.1-2. Test Animal Dietary Regime.

	Character limits + nomenclature → information on how to fill in the field	**Example**
Composition of Diet	Text, 250 characters	*Standard commercially available non-medicated concentrate: Heritage Farmyard Layers Pellets*
Feed consumption (kg/day)	Text, 250 characters	*0.3 kg/day (once daily)*

Water	Text, 250 characters	*Drinking water was available ad libitum throughout the study*
Acclimation period	→ Indicate the duration of the acclimatation period number + days → Begin with the number followed by the time unit (usually days) → If a range of values is indicated, **hyphens have to be bounded by space characters**	*14 days* *6 – 8 days*
Predosing	Text, 250 characters → Indicate "Yes" or "No"	*No*

Table B.7.2.1-3. Test Animal Dosing Regime.

	Character limits + nomenclature → information on how to fill in the field	**Example**
Treatment Type	Text, 250 characters → Pre-filled by the software with "Oral": please change if different → In case different radiolable positions are tested, **create a line per position**. Respect the following nomenclature: **abbreviation of the radiolabelled test material_oral** This will allow distinguishing lines when filling the field "Dose Regime" of Appendix 1 → If another parameter than the radiolabel differs, use this parameter to distinguish the treatment types	*py_oral* *ph_oral*
Treatment Level (mg/kg)	Text, 250 characters → **Theoretical dose administered** to animals → Specify the unit for the sake of completeness: mg/kg DM or mg/kg bw/day → If different treatment levels are tested in the study, **create a line for each treatment level**	*50 mg/kg DM*
Vehicle	Text, 250 characters → Pre-filled by the software ("capsule, feed, bolus, etc."): select or write down the correct information	*Gelatine capsule*
Parameters	Text, 250 characters → Pre-filled by the software ("Test material in vehicle"): please change if different	*Test material in vehicle*
Dosage Rate	Text, 250 characters → **Experimental dose** (nominal dose) administered to animals → Specify the unit for the sake of completeness: mg/kg DM or mg/kg bw/day (use the same unit as in field "Treatment type" so that the rates can be more easily compared) → If the **administered dose is not the same between the radiolabelled test materials, create a line for each radiolabel**	*66.6 mg/kg DM*
Timing/Duration	Text, 250 characters	*once daily / 14 days*
Timing from final dose to sacrifice	Text, 250 characters	*10 hours*

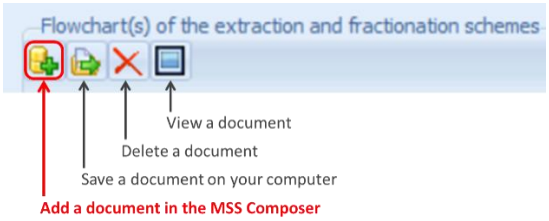
Sampling

Table B.7.2.1/2-4. Sample Collection Information

	Character limits + nomenclature → information on how to fill in the field	**Example**
Eggs / Milk Collected	Text, 250 characters → Indicate the frequency of daily collection	*Twice daily*
Number of Eggs / Amount of milk / Amount of … produced during normal production	Text, 250 characters → Indicate the daily production for one animal	*0.8 egg/day*
Excreta / Urine, Feces and Cage Wash Collected	Text, 250 characters → Indicate the frequency of daily collection	*Excreta: once daily / Cage wash: at sacrifice*
Interval From Last Dose to Sacrifice	Text, 250 characters → Begin with the number followed by the time unit (usually hours)	*10 hours*
Tissues Harvested and Analyzed	Text, 250 characters → Specify **all fluids and tissues collected**	*Liver, kidneys, peritoneal fat, subcutaneous fat with skin attached, combined leg and thigh muscle, breast muscle, GI tract and contents, blood, carcass, bile, partially formed eggs*

Free-text field, 5000 characters → Briefly describe how samples were taken, parts sampled, how samples were handled after harvesting (shipment, storage, etc.), and any preparation that was done prior to extraction	

Extraction and Analysis

Free-text field, 5000 characters → Briefly describe extraction and analysis procedures (measure of total radioactive residues by combustion, different extraction procedures leading to several fractions, analytical method methods used to analyse the extracts)	
flowchart(s) of the extraction and fraction schemes	
→ Click on "  " to add the flowchart of the extraction procedures of each matrix → In "Description", name the files according to the following nomenclature: "Extraction_matrix-name" → Accepted format: .PDF, .PNG, .JPEG 	

Identification and characterization

Free-text field, 5000 characters → Briefly describe here the procedures used to quantify, fractionate and purify the metabolites	

III. Results and Discussion

A. Total Radioactive Residues

The fisrt part is common to the three MSS Composers and the second table depends on the type of MSS Composers for plants and rotational crops or MSS Composer for livestock.

Extraction efficiency of radioactive residues from plant/livestock metabolism study using residue enforcement method

	Character limits + nomenclature → information on how to fill in the field	**Example**
Enforcement method		
Recovered equivalents (mg/kg)	Text, 250 characters → Possible to indicate a single value or a range of values → Fill-in information regarding the method(s) used in the study and available in the report	
Overall extraction efficiency (%)	Text, 250 characters	100%
Defined residue (mg/kg)	Text, 250 characters	
Defined residue extraction efficiency (%)	Text, 250 characters	100%
Extraction method used in the study		
Recovered equivalents (mg/kg)	Text, 250 characters → Possible to indicate a single value or a range of values → Fill-in information regarding the method(s) used in the study and available in the report	
Overall extraction efficiency (%)	Text, 250 characters	100%
Defined residue (mg/kg)	Text, 250 characters	
Defined residue extraction efficiency (%)	Text, 250 characters	100%

Quantitation

Free-text field, 5 000 characters → Briefly describe here the methods used for determining TRR values	

For plants and rotational crops

Table B.7.1.1-4 (plants) **/ B.7.9-4.** (rotation) **TRRs in Matrices.**

Column heading and column number are automatically adjusted according to the Radiolabeled Test Material(s) defined in section II. Materials and Methods / A. Materials.

	Character limits + nomenclature → information on how to fill in the field	**Example**
Matrix	Text, 250 characters → Insert as many lines as evaluated matrices → Matrices should be named briefly but unambiguously: specify in the name of the matrix every parameter that is different from one matrix to the other (dose, part of studied vegetable, days after application...)	*outer leaves _200g* *heads_200g* *whole cabbage_200g* *outer leaves_1000g* *heads_1000g* *whole cabbage_1000g*
Timing and Application	Text, 250 characters → Respect the following nomenclature: "application stage in BBCH, number of application(s) x dose rate in g a.s./ha" → Separate the two information with a comma → Start with a number and give the dose rate in g a.s./ha	*65 BBCH, 2 x 200 g a.s./ha* *65 BBCH, 2 x 1000 g a.s./ha*
Preharvest Interval (days)	Text, 250 characters → Begin with the number followed by the time unit (usually days)	*21 days*
PBI (days) ***→ for succeeding crops only***	Text, 250 characters → Begin with the number followed by the time unit (usually DAT for days after treatment)	*30 DAT* *120 DAT* *365 DAT*
TRR%	Text, 250 characters → Results obtained for each Radiolabeled Test Material should be filled in the corresponding column	*100.0*
ppm		*0.475*

→ For rotational crops, data on soil should be added if available.

Livestock

Table B.7.2.1/2/3.-5. TRRs in Eggs/Milk, Tissue, and Excreta

Column heading and column number are automatically adjusted according to the Radiolabeled Test Material(s) defined in section II. Materials and Methods / A. Materials.

	Character limits + nomenclature → information on how to fill in the field	**Example**
Matrix	Text, 250 characters → The table is pre-filled with Excreta / Urine, feces, Muscle, Fat, kidney, Liver, Milk/Eggs, GI tract, Other → Use the right click to insert additional lines if necessary → Insert as many lines as evaluated matrices → Matrices should be named briefly but unambiguously: **specify in the name of the matrix every parameter that is different from one matrix to the other.**	*Muscle* *Fat* *Liver* *Kidney* *Excreta* *Cage wash*
[radiolabeled test material] → column header automatically filled in from II. Materials and Methods > A. Materials > Radiolabeled Test Material	Text, 250 characters → Results obtained for each Radiolabeled Test Material should be filled in the corresponding column	*[phenyl-U-14C]-SYN545974* *[pyrazole-5-14C]-SYN545974*
% TRR	Text, 250 characters → Results obtained for each Radiolabeled Test Material should be filled in the corresponding column	*87.73*
ppm		*0.238*

TRRs

TRRs in eggs TRRs in milk TRRs	Drop-down menu → Select did or did not → **Do not use the drop-down list if you do not know whether or not a plateau has been reached**	*appear to have reached a plateau at the end of dosing (see Table 2.2.1-6)*

Table B.7.2.1/3/3.-6. TRRs in Eggs / TRRs in Milk / TRRs as Function of Time.

Column heading and column number are automatically adjusted according to the Radiolabeled Test Material(s) defined in section II. Materials and Methods / A. Materials.

	Character limits + nomenclature → information on how to fill in the field	**Example**
Interval	Text, 250 characters → Insert as many lines as there are interval times and rename them appropriately → **If available, also report data for faeces (poultry) and/or urine, excreta for lactating ruminants** → If data for several matrices are reported (urine, faeces, egg/milk), specify the matrix in the first line before adding the time interval	*Whole Egg* *Day 1* *Day 2* *Day 3* *Egg yolk* *Day 1* *Day 2* *Day 3*

[radiolabeled test material] → **column header automatically filled in from** II. Materials and Methods > A. Materials > Radiolabeled Test Material	Text, 250 characters → Results obtained for each Radiolabeled Test Material should be filled in the corresponding column	*[phenyl-U-14C]-SYN545974* *[pyrazole-5-14C]-SYN545974*
ppm	Text, 250 characters → Results obtained for each Radiolabeled Test Material should be filled in the corresponding column	*45*
% of dose		*0.014*

Image attachment

Image in .PDF, .JPEG or .PNG format can be attached here.

General Health of Animals

Free-text field: describe general health of the animals during the study

Free-text field, 5 000 characters → Briefly describe the general health of the animals during the study	

B. Extraction, Characterization, and Distribution of Residues

This section is mandatory for all 3 MSS Composers.

Table B.7.1.1-5. Distribution of the Parent and the Metabolites in Plant Matrices when dosed with 14C-Labelled. (Plants)

Table B.7.9-5. Distribution of the Parent and the Metabolites in Rotational Crop Matrices when dosed with 14C-Labelled. (Rotation)

Table B.7.2.1/2/3-7. Distribution of the Parent and the Metabolites in Poultry / Ruminant Matrices when dosed with 14C-Labelled. (Livestock)

The table is the same for the 3 MSS Composers and the same filling rules apply:

→ The section begins with a free-text field:

Free-text field, 5 000 characters → Report table notes, explain abbreviations, etc… → Footnotes in tables and free-text field are marked as (a), (b), etc. → **All abbreviations should be explained**, e.g.: DALA: Days After Last Application PES: Post-Extraction Solid RRR: Residual Radioactive Residue –: not detected (if reported in Assessment Report, copy LODs) LOQ: Limit of quantification LOD: Limit of detection N/D: not detected N/A: not available

→ If residues were measured with several methods (HPLC and TLC for example), results for both methods should be reported and the corresponding method specified.

/! Pay attention to the **number of columns required to report all the data available in the study** (one column per matrix). If more than 10 columns are required, a second radiolabelled test item to get the extra columns has to be added (please refer to section II. Materials and Methods / A. Materials).

/! If you need an additional table, try to **order matrices rationally**.

→ Column heading is filled in by default with automatic entries. Rename the headings "Matrix" appropriately: **right-click on "Matrix X"**, rename the column and click on "OK".
Matrices should be named briefly but unambiguously: specify in the name of the matrix every parameter that is different from one matrix to the other (part of studied vegetable, dose, days after application, ...).

/! If a **mixture of molecules** has been **applied**, **only fill in the subtab "Mixture of … and …".**

→ To clear, delete or add rows:

- To **delete all rows of the table**: right-click on the table and select "**Clear table**",
- To **delete a specific row**: right-click on a cell of this row and select "**Delete row**",
- To **clear a specific row**: right-click on a cell of this row and select "**Clear row**",
- To **add a row above/below the selected one**: right-click on a cell of the row located below/above and select "**Insert row above/below**".

→ The following signs can be used: more-than (>) and less-than (<).

/! If used, abbreviations or the sign "-" must be described in the free-text field.

/! Do not use "/".

C. Storage Stability of Residues

Free-text field, 5 000 characters → Briefly describe storage conditions, discuss whether or not residues are stable during storage	

Table B.7.2.1/2/3-8 Summary of Storage Conditions.

	Character limits + nomenclature → information on how to fill in the field	**Example**
Matrix (RAC or Extract)	Text, 250 characters → Report the available data from the study report	*Seed*
PBI (days) ***→for rotational crops only***		*30 DAT* *120 DAT* *365 DAT*
Storage Temperature °C		*-20°C*
Actual Storage Duration (Days or Months)		*2 months*
Interval of Demonstrated Storage Stability [specify crop/matrix if different] (days/months) ***→for plants and livestock***		
Limit of Demonstrated Storage Stability		

→ *for rotational crops only*	

D. Identity of Residues in Crop / Rotational Crop / Poultry / Ruminant / Other Animals

This section is mandatory for all 3 MSS Composers.

Table B.7.1.1-5. Summary of Characterisation and Identification of Radioactive Residues in Plant Matrices Following Application of Radio-Labeled #1. (Plants)

Table B.7.9-7. Summary of Characterisation and Identification of Radioactive Residues in Rotational Crops Matrices Following Application of Radio-Labeled #1. (Rotation)

Table B.7.2.1/2/3-9. Summary of Characterisation and Identification of Radioactive Residues in Poultry / Ruminant Matrices Following Application of Radio-Labeled #1. (Livestock)

The table is the same for the 3 MSS Composers and the same rules described in III.B Extraction, Characterization, and Distribution of Residues apply :

→ The section begins with a free-text field:

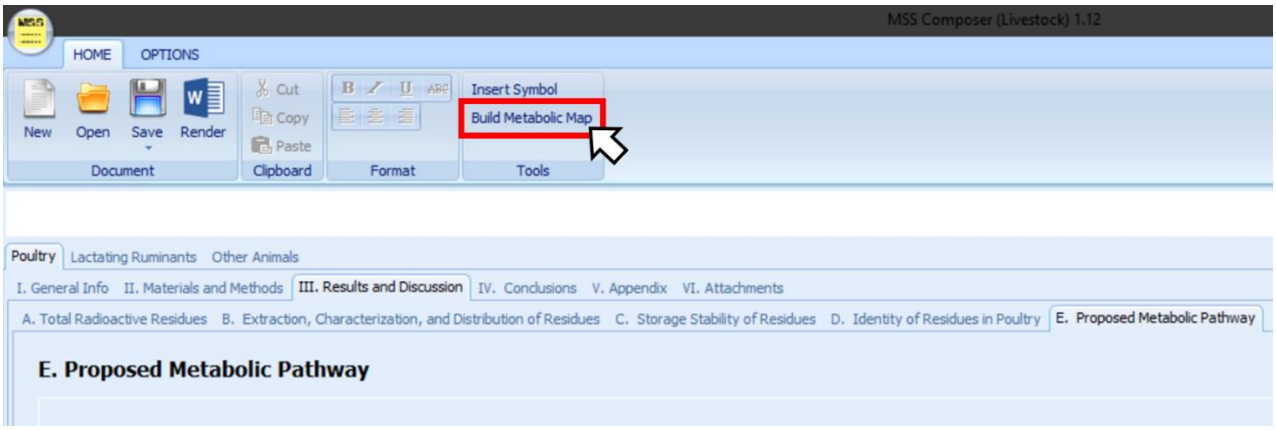
Free-text field, 5 000 characters
→ Report table notes, explain abbreviations, etc…
→ Footnotes in tables and free-text field are marked as (a), (b), etc.
→ **All abbreviations should be explained**, e.g.:
DALA: Days After Last Application
PES: Post-Extraction Solid
RRR: Residual Radioactive Residue
–: not detected (if reported in Assessment Report, copy LODs)
LOQ: Limit of quantification
LOD: Limit of detection
N/D: not detected
N/A: not available

E. Proposed Metabolic Pathway

Metabolic Map

In this section, a metabolic map can be built once section V. Appendix 2 has been filled in.

→ To build the metabolic map, go to **HOME** > **Tools** and click on "**Build Metabolic Map**". The Map is automatically generated.



Free-text field

In the free-text field below the map, briefly describe the metabolic pathway and reactions (oxidation, hydrolysis, etc.).

Free-text field, 5 000 characters
→ briefly describe the metabolic pathway and reactions (oxidation, hydrolysis, etc.)

Table B.7.2.1-10. Identification of Compounds from Metabolism Study (both proposed and found)

This table is automatically filled in from section V. Appendix > Appendix 2.

IV. Conclusions

CONCLUSIONS

Free-text field: briefly present the conclusions of the study

Free-text field
→ Briefly present the conclusions of the study. You can copy here the conclusions of the study report.

REFERENCES

Free-text field
→ Indicate here references to other metabolism studies (if applicable).

V. Appendix

The filling of appendices 1 and 2 is mandatory. It is required so that the xml file can be imported into MetaPath.

Appendix 3 is automatically filled in using information available in Appendix 1 and Appendix 2.

The following information can be found in each Appendix:

Appendix 1	**All matrices analysed and treatment conditions of the experiment** →Matrices reported must be compliant with section III. Results and Discussion, B. Extraction, Characterization, and Distribution of Residues and D. Identity of residues in Crop
Appendix 2	**Identified compounds** → Identified compounds reported are compliant with section III. Results and Discussion, D. Identity of Residues. Identified compounds and matrices in which they are detected should be linked.
Appendix 3	**Links between matrices reported in Appendix 1 and identified compounds described in Appendix 2** → Automatically completed following the filling of Appendices 1 and 2

Appendix 1

Completing Appendix 1 is mandatory.

→ Report all matrices for which attempts are made to characterise and/or identify residues (parents and metabolites). **Matrices reported should be compliant with section III. Results and Discussion, B. Extraction, Characterization, and Distribution of Residues and D. Identity of residues in Crop**.

→ **Report all matrices for each radiolabelled test material.** Bear in mind that there can be differences from one radiolabelled test item to the other.

→ **In case no residues are identified in any matrices** (for example because TRR were too low), Appendix 1 must be completed. **Add at least 1 matrix**.

How to procede:

Click on		to **add a new matrix (row).**
Click on		to **insert a matrix (row) between two existing ones** - the new row is inserted below the selected one.
The icon		to remove a matrix.
Click on		to **modify a row.** It can also be achieved by double-clicking on a cell of the row.

For plants and rotational crops

	Character limits + nomenclature → information on how to fill in the field	**Example**
Test#	Text, 100 characters → Matrices should be named briefly but unambiguously so that they can be easily distinguished 1. first letters of the labelling (mandatory) 2. portion analysed (mandatory) 3. dose applied (optional) 4. PHI/PBI (optional) … → Every information should be separated from the next with an underscore "_"	*ph+py_forage_200g_30DAA* *ph+py_forage_200g_120DAA* *ph+py_hay_100g_30DAA* *ph+py_hay_100g_120DAA*
Number	Number → Number of plants by radiolabelled test material	*9*
Application Method	Text, 50 characters	*soil spraying*
Application Rate	Dose and unit → Specify the dose rate and the unit → Make sure the same unit is used in all sections (for the sake of homogeneity) → Separated the value from the unit by a space → Use a.s. as an abbreviation for "active substance" when stating the unit	*408.6 g a.s./ha*
Number of Applications	Value	*1*
Timing of Applications	Number → Start with a figure followed by a space. If no information is available regarding timing of applications, the field should be filled in with **0 : NA or 0 : description of the stage** (do not forget the space between the zero and the colon)	*00 BBCH - bare soil*
***Plants:* PHI** ***Rotational Crops:* PBI**	Text, 250 characters → Separated the value from the unit by a space	*30 days*
Matrix	Text, 192 characters	*Wheat hay*
Experimental Descriptor	Text, 192 characters	
Remarks	Text, 32 760 characters → Free-text field. It can be used to explain terms and abbreviations which are used for naming "Test#" or give some additional information about the study	*DAA = Days After ApplicationActive substance applied as a mixture of two radiolabelled test items*
Citation	Drop-down menu → select corresponding citation	
Radiolabeled Test Material	Drop-down menu → select corresponding radiolabelled test material	*Mixture of ph and py*
Test Crop (from Table 1)	Drop-down menu → select the corresponding test crop	*Tomato (rotation) / Fruiting vegetables*
Soil type (from Table 2)	Drop-down menu → select the corresponding soil type	*Sandy loam*

For Livestock

	Nomenclature	Example
Test#	Text, 100 characters → Matrices should be named briefly but unambiguously so that they can be easily distinguished 1. first letters of the labelling (mandatory) 2. animal species (mandatory) 3. tissue analysed (mandatory) 4. dose applied (optional) … → Every information should be separated from the next with an underscore "_"	*ph_hen_liver* *ph_hen_egg yolk* *ph_hen_egg white* *ph_hen_muscle* *ph_hen_fat* *py_hen_liver* *py_hen_egg yolk* …
Gender	Multiple choice → Select "**Male**", "**Female**" or "**Not Reported**"	*Female*
Number	Number → Number of animals dosed with a given radiolabelled test material	*6*
Dose Route	Text, 192 characters → Route of administration, path by which the radiolabelled test item is taken into the animal body (= treatment type)	*Oral*
Dose Nominal	Exact number → **Theoretical dose** administered to animals → **Unit** can be modified - for the sake of completeness, please specify "**mg/kg DM**" or "**mg/kg bw/day**" → To avoid the use of "/" between two values . The tange of values should be presented as 22.4 - 23.2 instead of 22.4/23.2 mg/kg DM	*50 mg/kg DM*
Dose Measured	Number → **Experimental dose** administered to animals → **Unit** can be modified - for the sake of completeness, please specify "**mg/kg DM**" or "**mg/kg bw/day**" → To avoid the use of "/" between two values . The range of values should be presented as 22.4-23.2 instead of 22.4/23.2 mg/kg DM	*66.6 mg/kg DM*
Matrix	Text, 192 characters → Analysed tissues	*Liver*
Test Duration	Number → Duration of the study → **Units** can be modified - for the sake of completeness, please specify "**days**"	*14 days*
Experimental Descriptor	Text, 192 characters	
Dose Type	Multiple choice → Select "Single" or "Multiple" → clarify if available "on every …… for….."	*Multiple* *On every 24 hours for 14 days*
Remarks	Text, 32 760 characters → This free-text field can be used to explain terms and abbreviations which are used for naming "Test#" or give some additional information about the study	

Citation	Drop-down menu → Select the corresponding citation (according to the radiolabelled test material or the administered dose)	
Radiolabeled Test Material (RLTM)	Drop-down menu → Select the corresponding radiolabelled test material	
Animal Information (from Table 1)	Drop-down menu → Select corresponding to animal information	
Dietary Regime (from Table 2)	Drop-down menu → Select the corresponding animal's dietary regime during the study	
Dosing Regime (from Table 3)	Drop-down menu → Select the corresponding dosing regime	
Sampling Information (from Table 4)	Drop-down menu → Select the corresponding sampling regime	

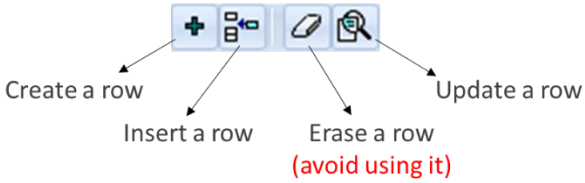
Appendix 2

Completing Appendix 2 is mandatory.

→ **Report <u>all metabolites</u> identified in section III. Results and Discussion, D. Identity of Residues**.

→ **In case <u>no residues</u> are identified in any matrices** (for example, because TRRs were too low), **<u>report at least the parent</u>**.

The same functions as in Appendix 1 are available and the same rules apply.



→ **<u>ALWAYS begin with the parent compound</u> and carry on with metabolites**.

Time-saving tips:

- Molecules can be drawn by copying and pasting the SMILES code of a close one that has already been encoded and then modifying it using the drawing tools.
- Build Appendix 2 following parent compound's degradation. This will help not losing the thread.

	Character limits + nomenclature → information on how to fill in the field	**Example**
Common Name/Code	→ common name / company experimental name → The same common name of the active substance and company experimental code should be reported as in *I. General Info > Test Material* and in *II. Materials and Methods > A. Materials*	*Pydiflumetofen / SYN545974*

	Character limits + nomenclature → information on how to fill in the field	**Example**
	→ Separate common name and experimental code with "space / space"	
Chemical Name	→ **Common name used in the study report** with the **company experimental name in brackets** **/!\ Do not write down the full chemical name** of the molecules (using common names of the molecules helps reading the results of MetaPath functions such as "Search chemical" and '"Search similarity")	*Pydiflumetofen (SYN545974)*
Chemical Structure	→ To draw a molecule, clik on  to open the **2D Editor** and draw the molecule or copy and paste the smile code. → Please refer to **Annex 2 for the complete procedure**.	
Parents	→ Describe the **relationship(s) between compounds** by ticking the box(es) that correspond(s) to **the compound(s) from which the metabolite can be generated.** → Relationships should be specified for all metabolites, except for the parent compound. The metabolic pathway is built based on the information encoded in this field.	
Treatment Groups	→ Tick the box(es) that correspond(s) to the matrix(ces) in which the compound has been identified. **This section must be compliant with the results reported in *III. Results and Discussion* > *D. Identity of Residue in Crops.***	
Expertise	→ If there is **no issue** drawing the compound, select "**None**" → If **uncertainties** were identified for the compound while drawing it, select "**Expertly specified**" and specify in "**Decision**" which assumptions were made when drawing the compound (e.g.: unknown site of conjugation). In **Expert**, specify Applicant or Regulatory Authority. → If **issues** were identified for the compound, select "**Expertly specified**"and specify **o Assumed by author(s)** for a compound that was not identified in the study but assumed as an intermediate **o Residue of Concern** for an active ingredient and its degradates for which risk is assessed, based on known or assumed toxicological and exposure concerns. A general rule used for present metabolites greater than 10%, but consideration is given to all metabolites exhibiting toxicity greater than parent.	

	Character limits + nomenclature → information on how to fill in the field	Example
	o **Tolerance** when a maximum residue level of a pesticide (usually measured in parts per million, ppm) that can legally be present in food or feed is defined as the result of a pesticide application	

Additional indications:

- **If the position of the conjugate is not determined or if a mixture of compounds is identified**

→ Draw the most logical arrangement and write in field Expertly specified > Decision: "**Unknown position of the [type of conjugation] conjugation**" (because the position of glucuronide is hypothetical and must be notified) or "**Mixture of compounds: various conjugates of [name of the conjugated compound]**".

- **If, according to the study report, only one peak (HPLC) was assigned to two different compounds**

E.g.: "one further peak was assigned to the metabolites M700F008 and M700F006 (0.111 mg/kg or 4.0 % TRR)"

→ Draw every compound individually and connect them both with their parent compound.

- **How to link isomer structures and their parent compounds**

→ When a molecule (A_1) and its isomer (A_2: molecule A with a hydroxylation undetermined on the alkyl chain) have been identified, you have to draw the two structures. However, if the exact position of the hydroxylation has not been determined, complete as follow the **Expertise** section of the **Appendix2 Editor**:

→ If another molecule (B) coming from molecule A_1 is identified (B corresponds to molecule A, A having an undetermined hydroxylation on the alkyl chain so that there are two A isomers), we would recommend linking B to the two isomers because, as the two hydroxylations are not determined, B could come from both molecules.

Appendix 3

This table is filled in automatically using the information available in Appendices 1 and 2.

You can link and unlink matrices and compounds by right-clicking the cells. This can also be done by scrolling **/!** but **it is very sensitive**.

Consequently, we strongly recommend updating this table using the "Treatment group" fields of Appendix 2.

Additional indications on the linking of compounds and matrices:

Example of a study on the metabolism of fluxapyroxad in soybean

"*It is proposed that BAS 700 F is metabolised in soybean by the following transformation reactions: N-demethylation of the pyrazole moiety and hydroxylation of the biphenyl moiety. Both reactions, combinations there of, and subsequent O- and N-conjugation reactions (glucose and/or, malonic acid) result in a range of related compounds*"

- **When it is not clear in which matrices the different compounds were identified but they appear in the metabolic pathway and are quoted in the conclusion of the study**

→ Only draw conjugates in Appendix 2 and do not specify in which matrices they could have been identified (the rows corresponding to these metabolites are left empty in Appendix 3).

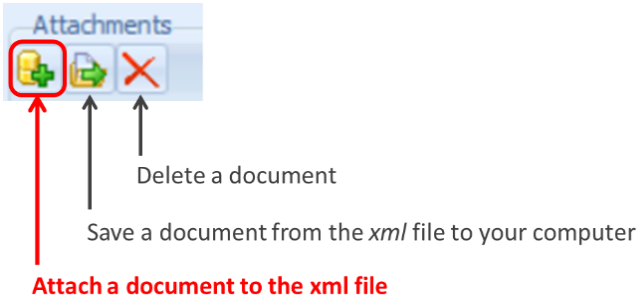
Conjugated compounds will appear in the metabolic map without being highlighted by function (see button  in the MetaPath software).

VI. Attachments

Attachments

Any file type (e.g. chromatograms, flow charts, study reports, addendum…) can be added to the MSS composer. The attachment will also be available when the xml file will be imported to the MetaPath database.

→ Use the following buttons: to attach a file:



→ In "**Description**", rename the file according to its nature (study report XXX, addendum number X, metabolism pathway for the active substance XXX, flow chart of XXX…).

→ Files in the following **format** can be attached in this section: **.txt, .docx, .xlsx, .pdf, .xml, .pptx, .JPG.**

ANNEXES

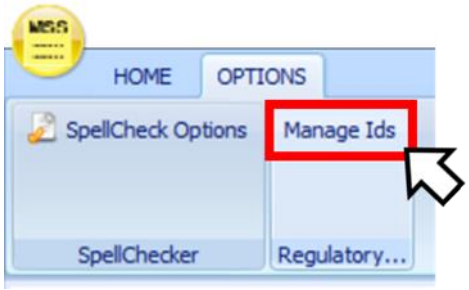
Annex 1 – Regulatory IDs in the MSS Composers

1. The Regulatory ID library

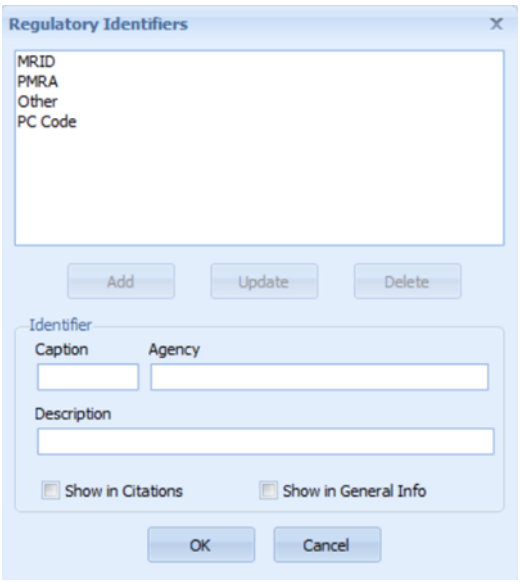
The three MSS Composers share a common library of Regulatory IDs. It comes prepopulated with the following IDs:

ID	Agency	Description
MRID	US EPA	Master Record Identification Number
PMRA	Health Canada	Pest Management Regulatory Agency
PC Code	US EPA	Pesticide Chemical Code
Other		Placeholder ID, kept for backward compatibility

The library can be viewed and edited in the Regulatory ID manager, accessible from the Manage IDs button on the Options tab of the Composer ribbon:



This brings up the following editor:



The top list contains all of the available identifiers. Clicking on an identifier displays its properties in the panel below. Each ID has a caption, agency and description. The Show in Citations and Show in General info checkboxes determine whether a particular ID would appear in the corresponding section of the Composer.

● **To edit an identifier**, the user needs to select it from the list, then make the changes to the properties and finally click on the Update button.

● **To delete an identifier** from the library, the user needs to select it and to click on the Delete button.

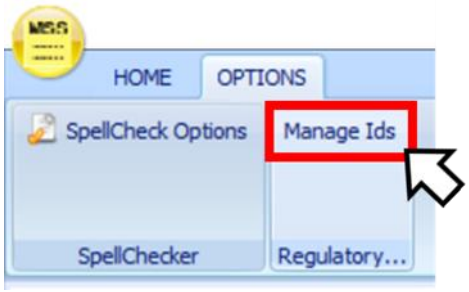
● **Adding a new identifier** is done by first filling in the properties and then clicking on the Add button. There cannot be two IDs with the same Caption and Agency.

Clicking on the OK button saves the made changes to the library and all of the current codes become available in all of the Composers.

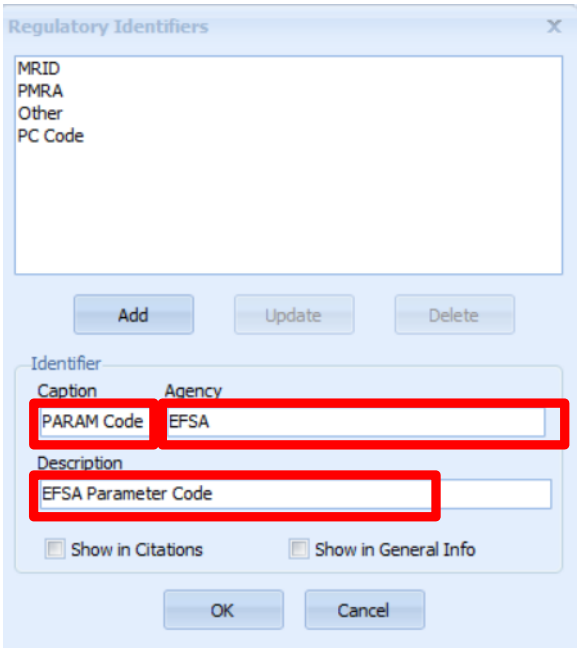
This editor only manages the properties of the identifiers and does not change the values that the users enter in each section of the composer. Entering of values is described in the next section.

→ To create the PARAM Code:

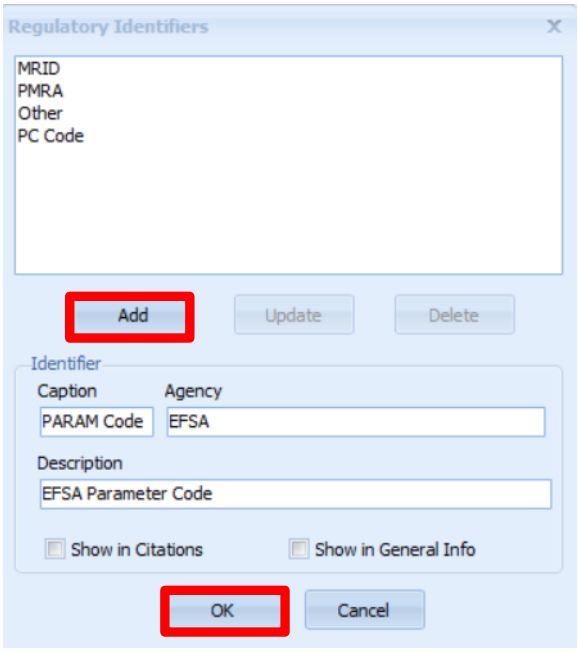
- Go in "OPTIONS" > Manage Ids



- Enter the following information for the PARAM Code:



- Press the button Add and the OK to save the created PARAM Code in the MSS Composer



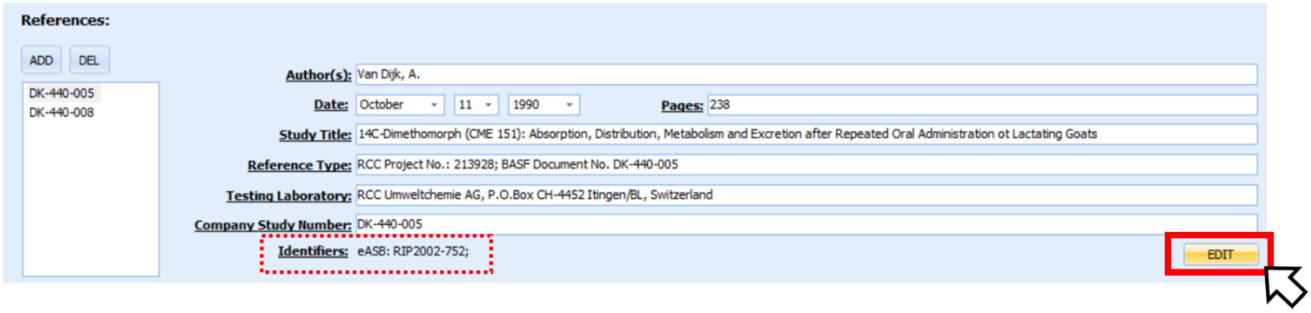
- PARAM Code has to be created in all three MSS Composers.

→ **The PARAM Code can be found and downloaded from the EFSA catalogue browser available on Zenodo**: European Food Safety Authority. (2020). Harmonized terminology for scientific research: https://zenodo.org/record/3243215#.YJU5LbUzbD4

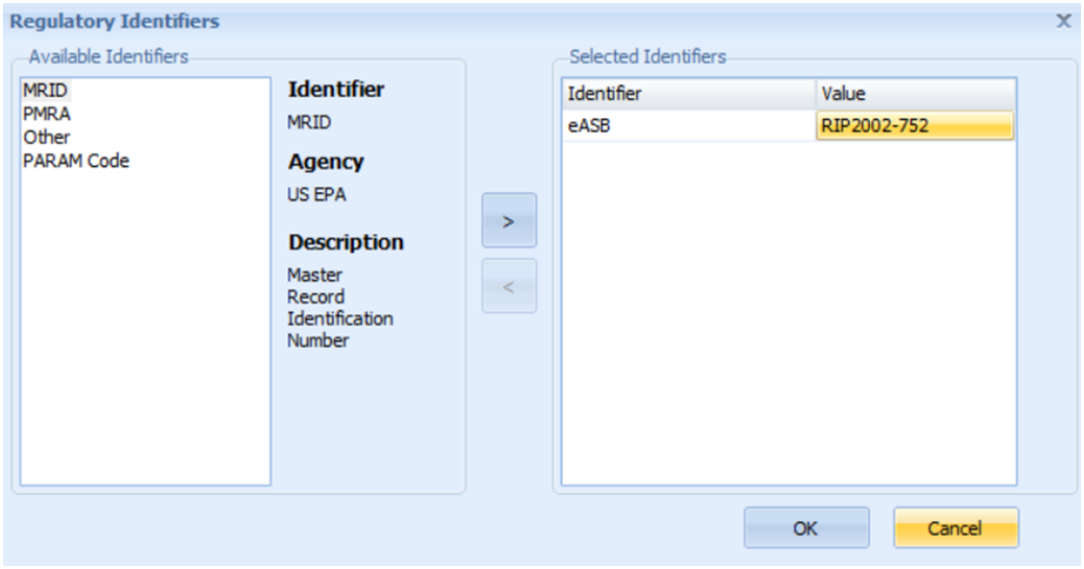
2. Regulatory IDs in References (citations)

In the references section of the Composers (I. General Info), each entry may have a different set of identifier-value pairs. The entered IDs are displayed in the identifiers panel.

To add an identifier or modify an existing value, click on the EDIT button:



This brings up the Regulatory ID editor:



The left section of the editor shows all the identifiers currently available in the ID library. Managing this library was explained in the previous section.

Clicking on an identifier in the list on the left selects it. Its properties (Caption, Agency, Description) are then displayed to the right.

The grid on the right side of the window displays identifier-value pairs that have already been entered in this section. Existing values can be edited directly in the text box.

To add a new identifier entry in the current section, the user needs to select it from the list on the left side and then click on the arrow pointing right (>). This makes a new entry in the grid on the left, with the value field empty. The user can fill in the value field directly in the text box.

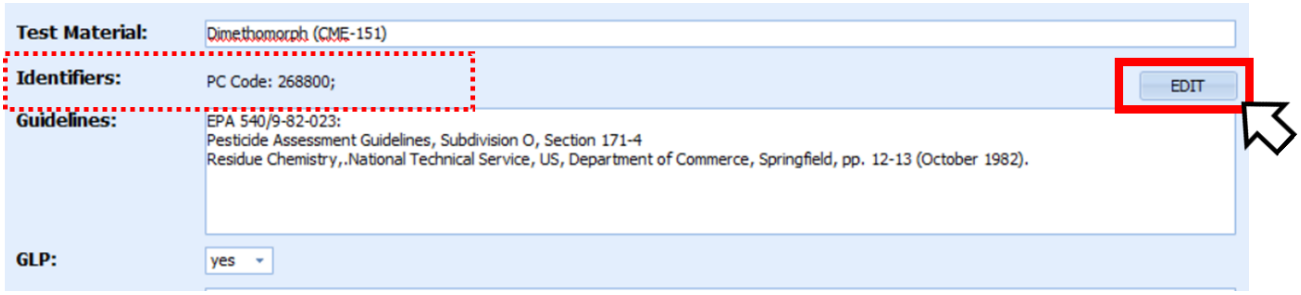
To delete an id-value pair, first select it by clicking on the Identifier entry in the grid on the left. The left arrow (<) button then removes the entry.

Clicking on the OK button updates the entries in the Identifier panel.

3. Regulatory IDs in General Info (related to the chemical compound)

Similar to the references section, identifier codes can be added and edited in the General Info section.

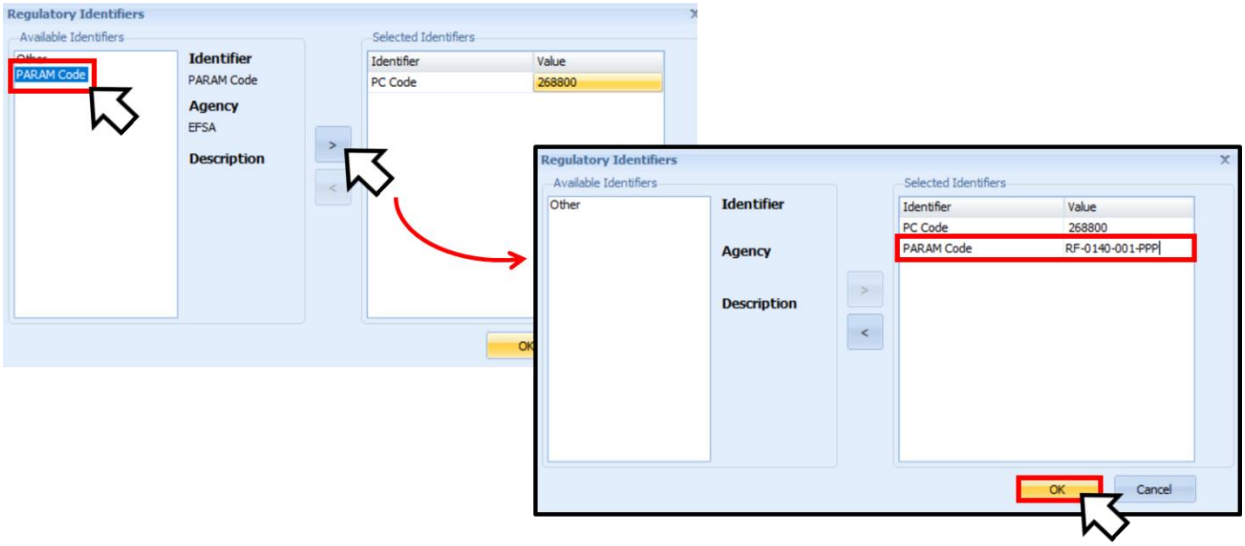
Clicking on the EDIT button brings up the editor explained in the previous section.



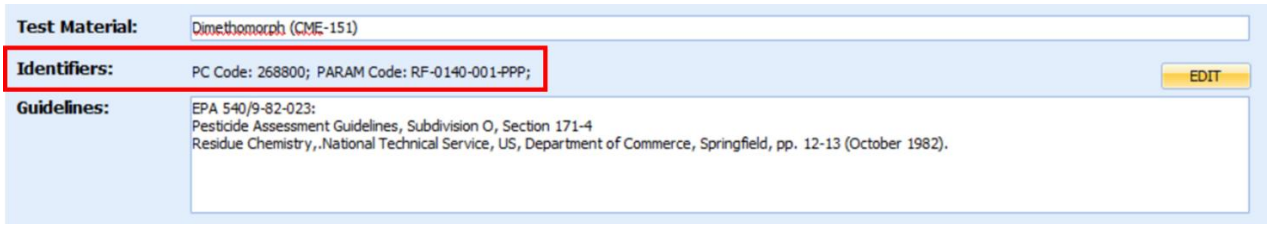
→ To add the PARAM Code:

- Click on the PARAM Code in the list of the Available Identifiers;

- Click then on the arrow icone (>) in the middle of the window (the Identifier will swich from the left screen to the right screen);
- Tip in the appropriate PARAM Code in the right screen;
- Press OK to save the changes.

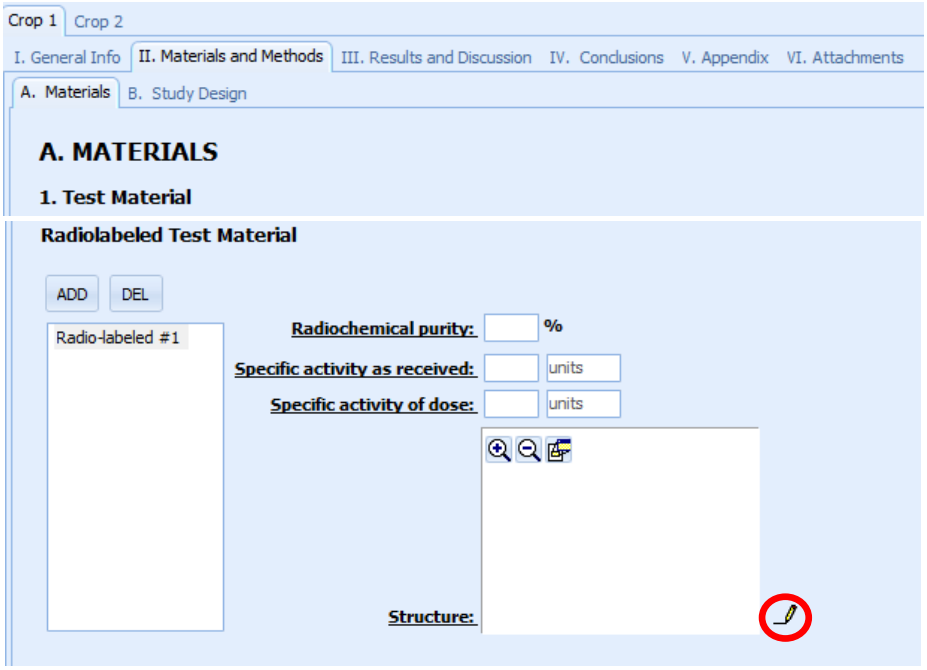


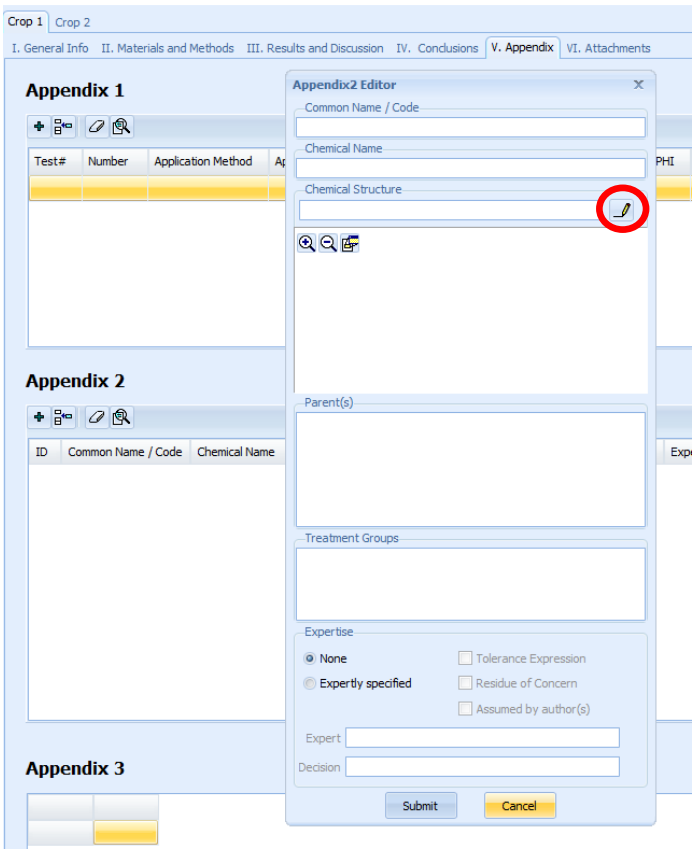
The PARAM Code is now visible in the MSS Composer:



Annex 2 – Drawing compounds with the 2D Editor

The 2D Editor is a tool allowing you to draw compounds. It can be opened by clicking on the "pen button"  in section II. Materials and Methods > A. Material (Radiolabeled Test Material) and section V. Appendix > Appendix 2.



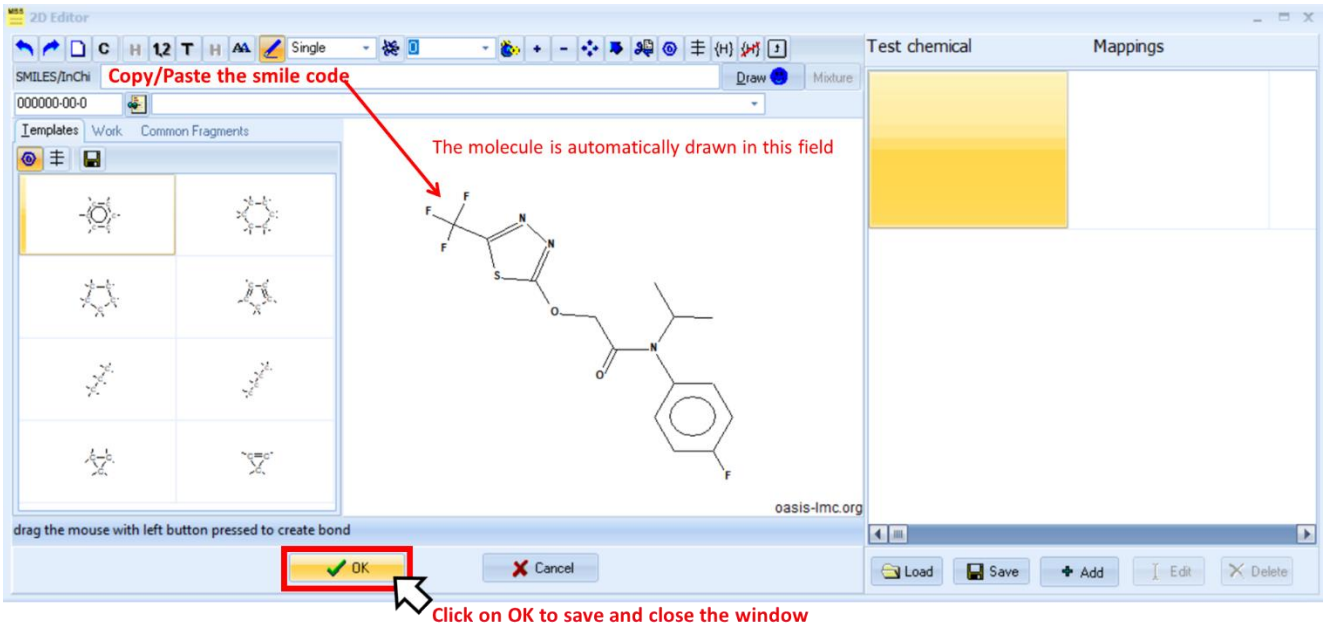


This brings up the Regulatory 2D Editor:

To draw a molecule

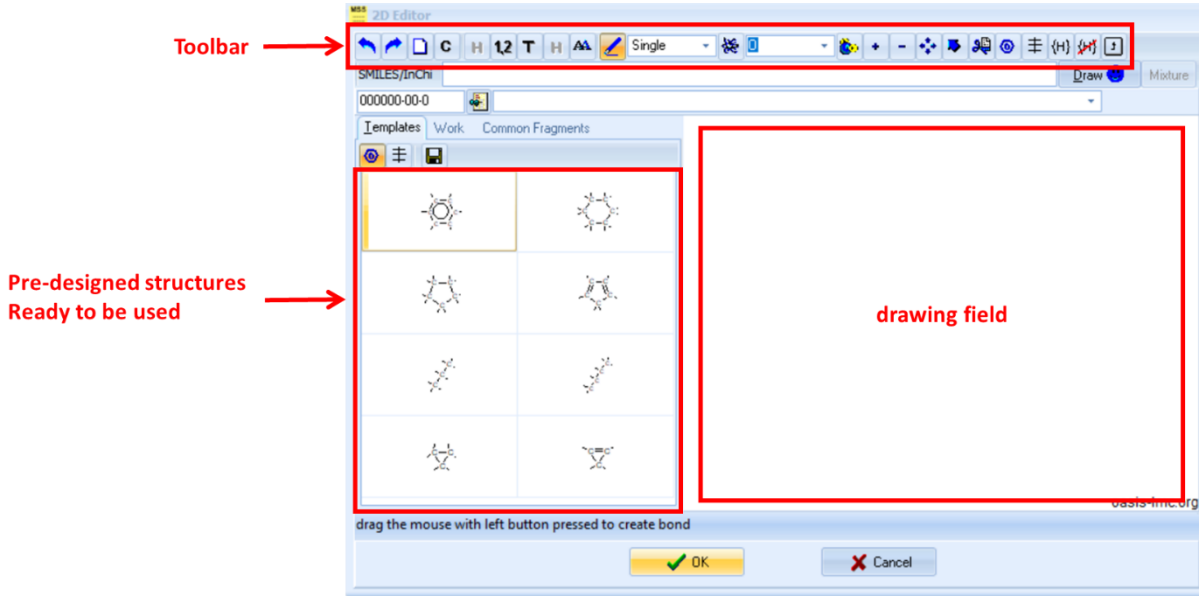
Option 1: Smile code available:

- Open the 2D Editor using the “pen button”,
- Copy/paste the smile code in the appropriate field,
- Check that the structure of the compound is correct,
- Click on OK to save the molecule structure and close the window.

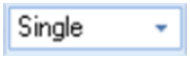


Option 2: Smile code not available:

The compound has to be drawn using the 2D Editor:

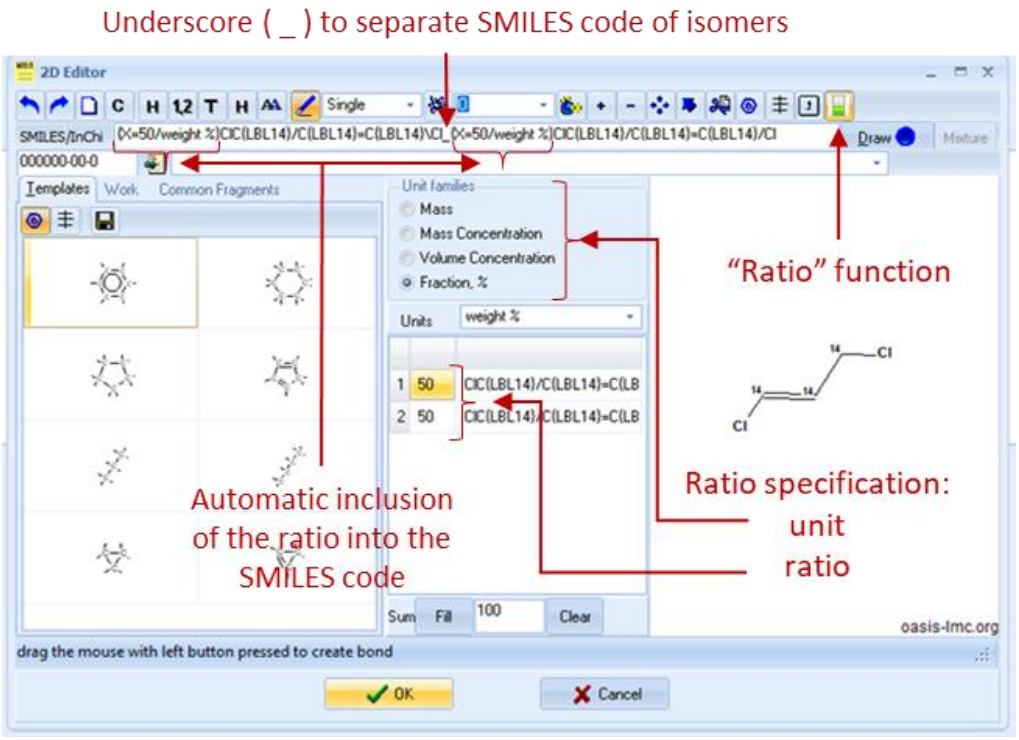


→ What you can find in the toolbar:

	UnDo/ ReDo
	Clear the canvas
	Hide / show heavy atoms
	Hide / show hydrogen atoms
	Show atom number
	Flip the structure
	Change the texte format in the drawing field
	Drag the mouse to create a bound
	Select the type of bound
	Select the icon and then click on the white field to draw the atom
	Select the kind of atom
	Select atom from the periodic table
	Set a positive or negative charge
	Move the drawn molecule in the white field
	Select / Move / Rotate / Zoom
	Cut a bounds and/or remove atoms (clearing function)
	Insert a benzen ring
	Add an explicit hydrogen
	Remove an already defined explicit hydrogen
	Indicate the isomeric ratio of the applied substance

How to deal with a mixture of isomers?

For a mixture of isomers, the SMILES code of the different isomers should be separated by an underscore. Also, when available, please indicate the isomeric ratio of the applied substance using the function “Ratio”  (last one) of 2D Editor. The ratio will be automatically included in the SMILES code. See below for illustration and some explanations on how to encode stereochemistry of molecules using SMILES code.

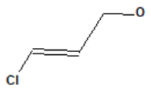
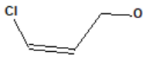
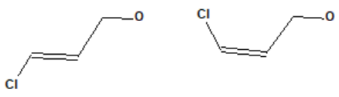


Encoding stereochemistry of molecules in 2D Editor

(Main source: https://www.daylight.com/meetings/summerschool98/course/dave/smiles-intro.html)

Specifying double-bond configuration

Configuration around double bonds is specified in SMILES by the characters `/' and `\' that are "directional bonds" and can be thought of as kinds of single bonds. These symbols indicate relative directionality between the connected atoms and have meaning only when they occur on both atoms that are double bonded.

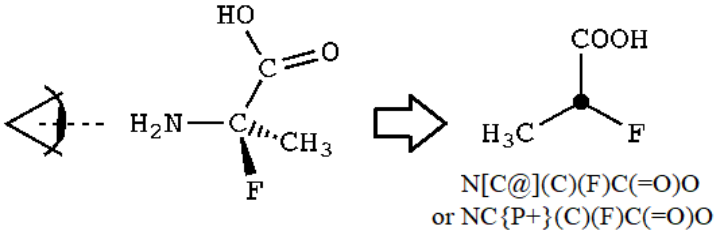
SMILES code	Picture of the molecule	Remarks
OC/C=C/Cl or OC\C=C\Cl		Cl and CH_2OH are on "opposite sides" of the double bond.
OC/C=C\Cl or OC\C=C/Cl		Cl and CH_2OH are on the "same side" of the double bond.
OC/C=C/Cl_OC/C=C\Cl		Mixture – SMILES code of the two molecules linked by an underscore (_)

Specifying tetrahedral chirality

SMILES uses a very general type of chirality specification based on local chirality and symmetry point groups. Instead of using a rule-based numbering scheme to order neighbouring atoms of a chiral centre, orientations are based on the order in which atoms occur in the SMILES string.

In SMILES, tetrahedral centres may be indicated by a simplified chiral specification (@ or @@ / {P+} or {P-}) written as an atomic property following the atomic symbol of the chiral atom. If a chiral specification is not present for a chiral atom, the chirality of that atom is implicitly not specified.

Looking at the chiral centre from the direction of the "from" atom (as per atom order in SMILES), @ or {P+} means "the other three atoms are listed anti-clockwise; @@ or {P-} means clockwise. If all atoms are explicitly specified in SMILES, e.g., N**[C@]**(C)(F)C(=O)O/ N**C{P+}**(C)(F)C(=O)O, the order of the atoms should be clear, i.e., N is the "from" atom, and the other atoms are anticlockwise in SMILES order (methyl, fluoro, carboxyl):

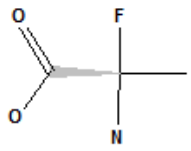
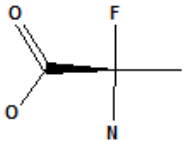
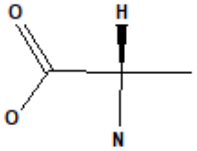
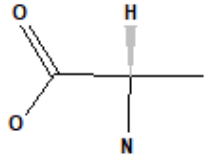


N[C@](C)(F)C(=O)O
or NC{P+}(C)(F)C(=O)O

If the chiral atom is the very first atom in the SMILES, e.g., [C@](F)(N)(C)CC, the first-appearing neighbour is taken to be the "from" atom.

If the chiral atom has a non-explicit hydrogen, (it can have at most one and still be chiral) it will be listed inside the chiral atom's brackets when using @/@@, e.g., F[C@H](N)C, but it can be omitted when using {P+}/{P-}, e.g., FC{P+}(N)C. The order of the non-explicit hydrogen is exactly as written in SMILES, i.e., in this case, the first of the three following atoms (H,N,C). Similarly, if a chiral atom has a ring closure, e.g., N1CCCO[C@H]1CC / N1CCCOC{P+}1CC, the O is the from atom, and three following atoms are in the order they are connected to the chiral centre as written in SMILES, i.e., H (immediately following the symbol), then N (the ring closure is next), then the ethyl carbon.

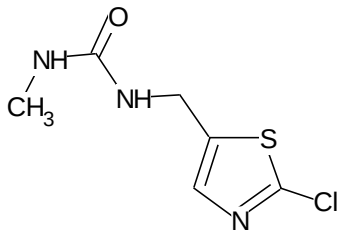
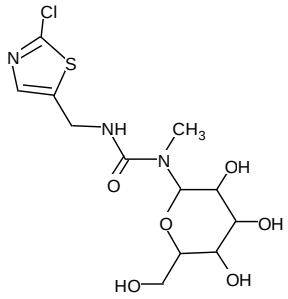
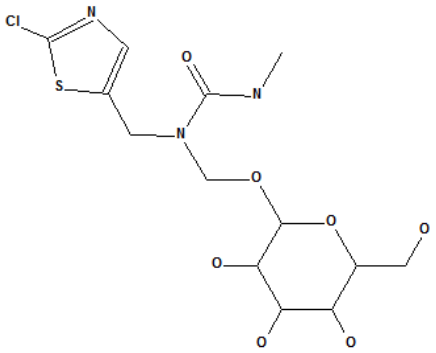
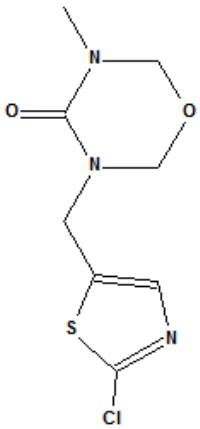
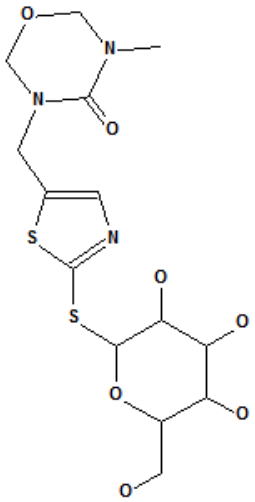
To reiterate, **the implied chiral order is always exactly as written in SMILES**.

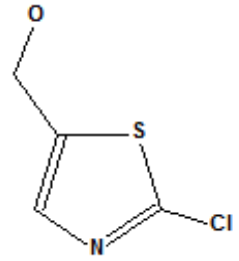
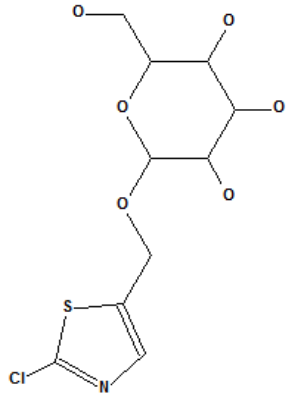
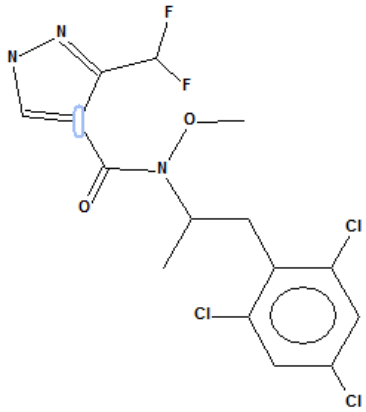
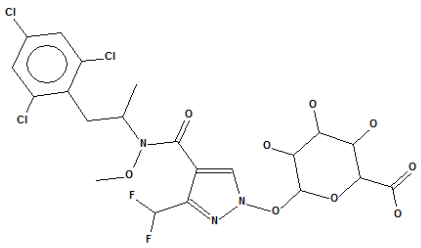
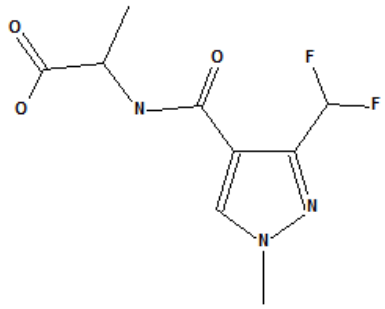
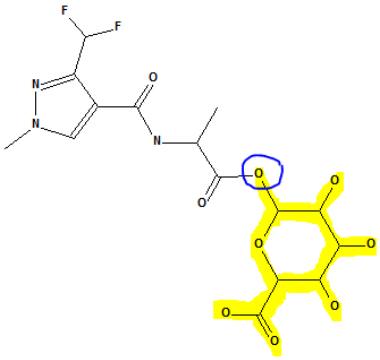
SMILES code	Picture of the molecule	Remarks
N**[C@]**(C)(F)C(=O)O or N**C{P+}**(C)(F)C(=O)O		From N: (methyl, F, carboxyl) appear anti-clockwise.
N**[C@@]**(C)(F)C(=O)O or N**C{P-}**(C)(F)C(=O)O		From N: (methyl, F, carboxyl) appear clockwise.
N[C@@H](C)C(=O)O or NC{P-}(C)C(=O)O		From N: (H, methyl, carboxyl) appear clockwise.
N[C@H](C)C(=O)O or NC{P+}(C)C(=O)O		From N: (H, methyl, carboxyl) appear anti-clockwise.

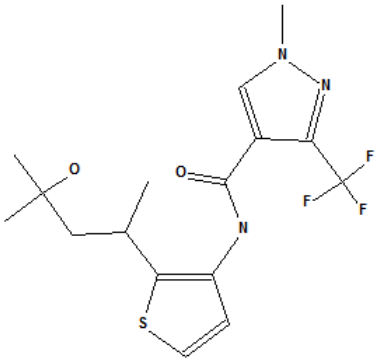
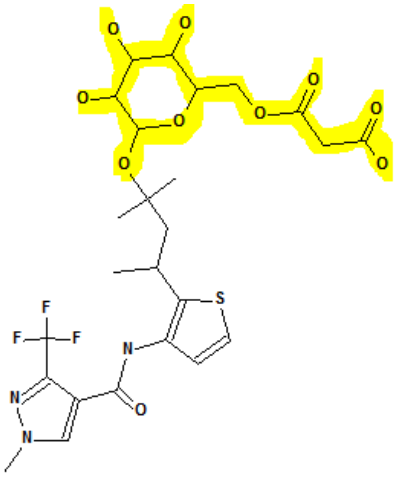
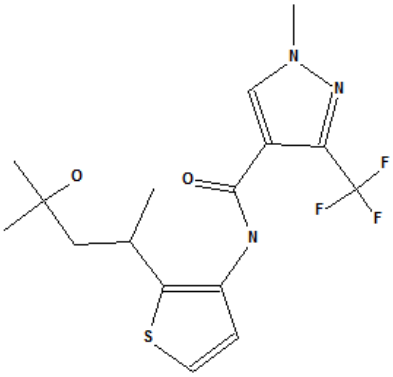
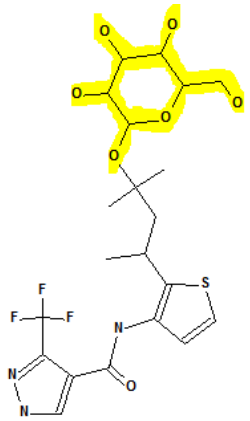
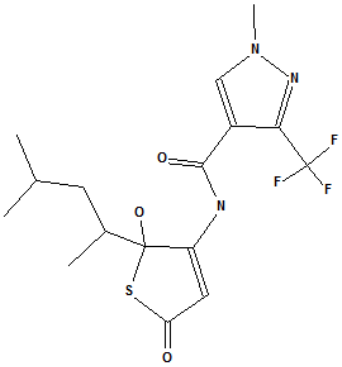
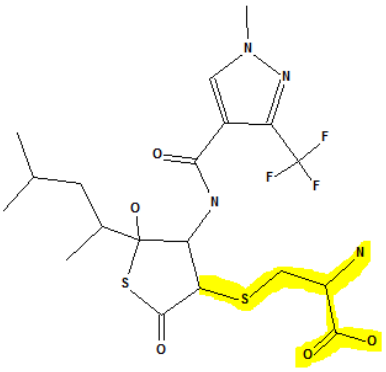
Further information on how to draw molecules can be found in:

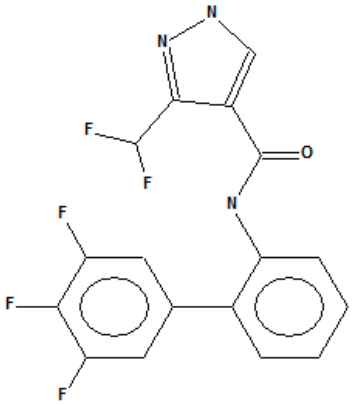
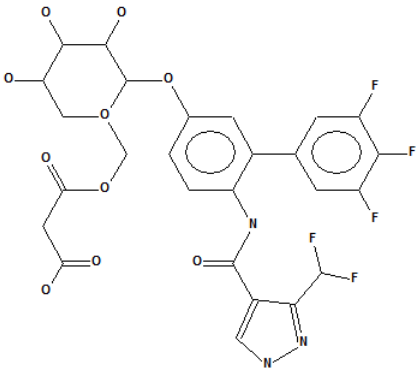
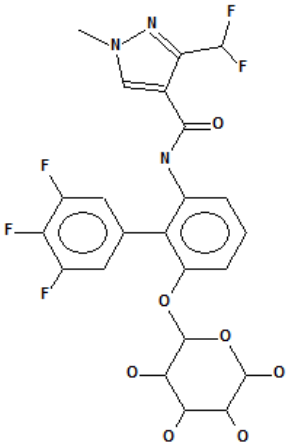
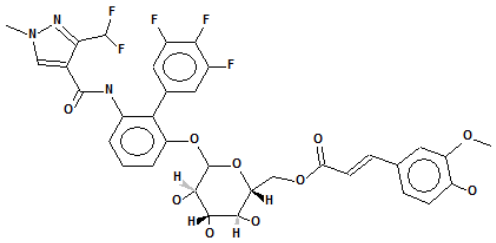
https://www.efsa.europa.eu/fr/applications/pesticides/tools

Annex 3 – Examples of conjugated forms

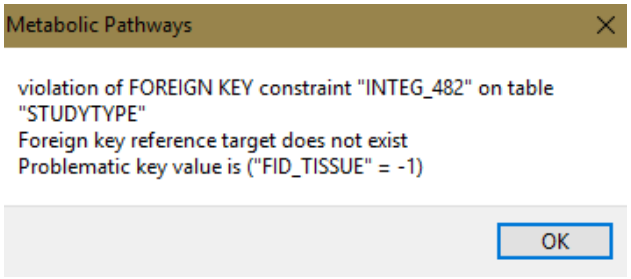
Unconjugated	Conjugated	Source
CGA353968 	CGA 353968-N-Sugar conjugate 	Thiamethoxam (tobacco, lettuce)
	CGA 353968-O-Glucose conjugate 	
CGA 355190 	CGA 355190-S-Glucose conjugate 	

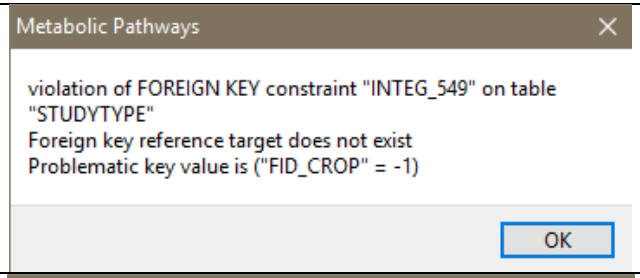
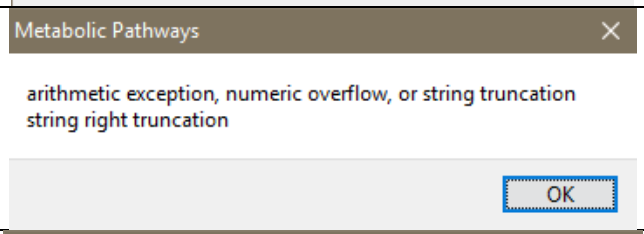
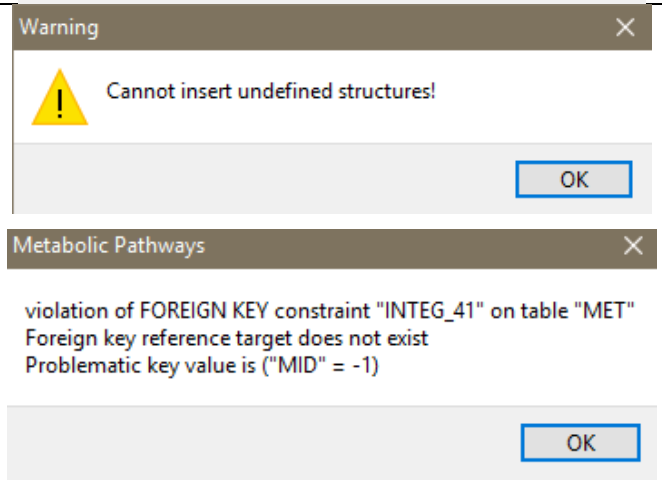
CGA 349208 	CGA 349208-O-Glucose conjugate 	
SYN547891 	SYN547891-N-Glucuronide conjugate 	Pydiflumetofen (poultry)
SYN548264 	SYN548264-O-Glucuronide conjugate **(O-GlcA)** 	Pydiflumetofen (goat)

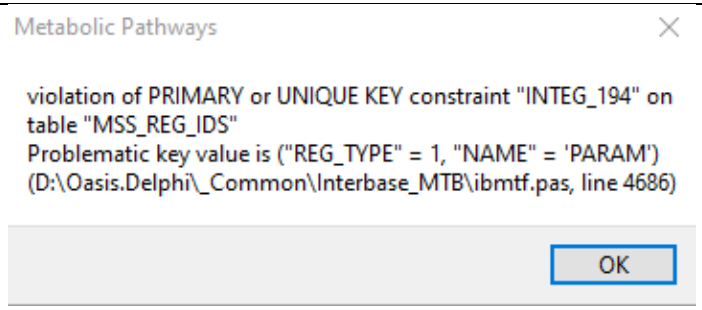
753-A-OH 	753-A-OH O-malonyl glucose conjugate 	Penthiopyrad (cabbage)
DM-753-A-OH 	DM-753-A-OH O-glucose conjugate **(O-Glc)** 	Penthiopyrad (canola)
753-T-DO 	Cys-T-DO 	Penthiopyrad (hen, study 2)

M700F008 	M700F052 (O-glucose and acid malonic conjugation) 	Fluxapyroxad (soybean)
M700F074 	M700F131 (O-glucose and feruloyl conjugation) 	Fluxapyroxad (wheat)

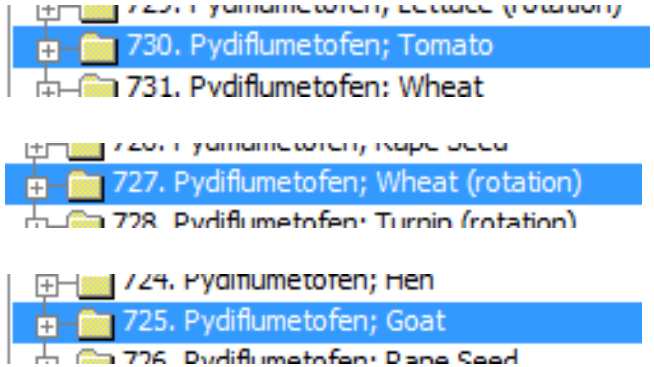
Annex 4 – Common error messages when importing MSS *xml* files into MetaPath

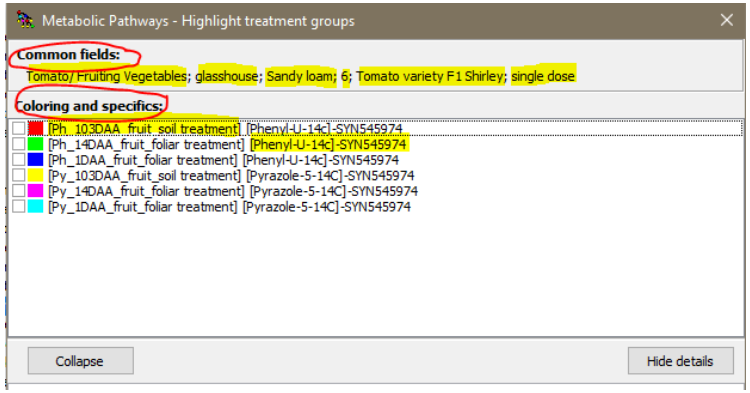
Error message	Solution
X no screenshot	**Appendix 1**: **make sure that all the following fields are filled in**: *MSS Plants and Crops Composers* ○ Test # ○ Application Method ○ Application rate ○ Number of Applications ○ Timing of Applications ○ PHI (Plants) /PBI (Crops) ○ Matrix ○ Citation ○ RLTM ○ Test Crop ○ Soil type *MSS Livestock Composer* ○ Test # ○ Gender ○ Dose route ○ Dose Measured ○ Matrix ○ Test duration ○ Citation ○ RLTM ○ Animal information ○ Dietary Regime ○ Dosing Regime ○ Sampling Information
	**MSS Composer (Livestock)** **Appendix 1**: information reported in the last fields is too long. → Review **II. Materials and Methods > B. Study Design > Sampling** > Table B.7.2.1-4. **Sampling Collection information** → Comply with the character limit and come down to 250 characters in column "Tissues Harvested and Analyzed"

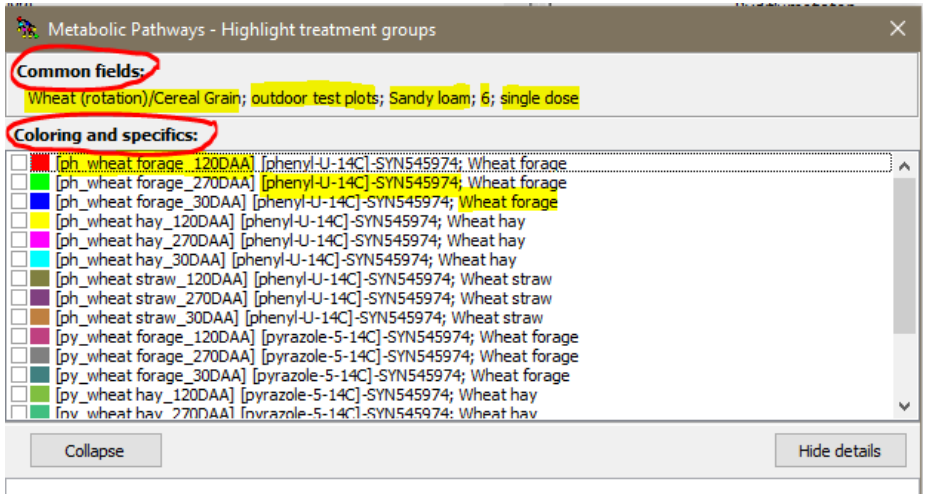
Error message	Solution
	**MSS Composer (Plants, Rotational Crops)** **Appendix 1**: information reported in the last fields is too long → Review **II. Materials and Methods** > **A. Materials** > **2. Test Crops >** Table B.7.9.1. **Crop Information** → Comply with the character limit and come down to 250 characters in column **"Crop/ Crop group"**
	Too many characters in one field – the following error message will specify in which section it occurs.
	**Appendix 2**: missing structure (SMILES code)

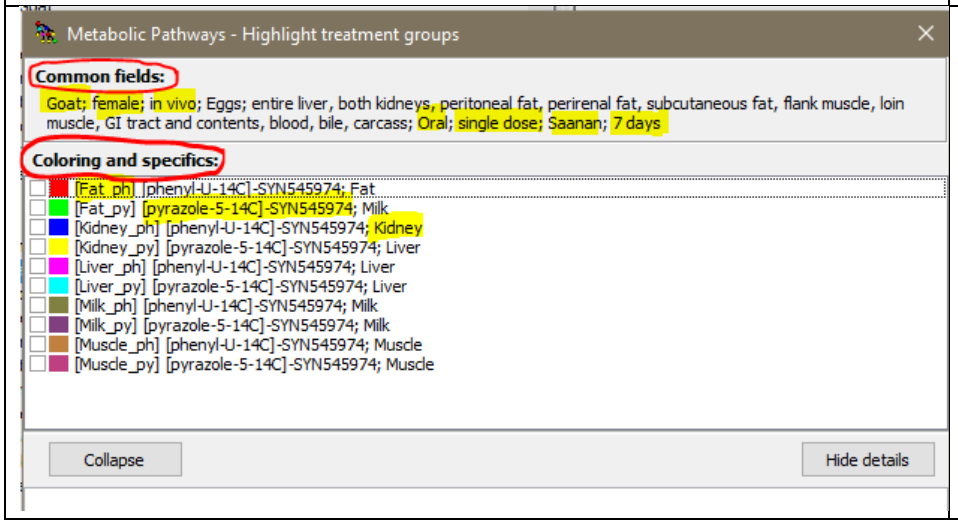
Error message	Solution
	**Wrong ParamCode** Check the information in section I. General Info, in particular if the Managers IDs information is correctly reported? Follow the procedure described in Annex I to add and/or modify the PARAM Code.

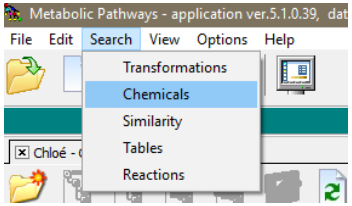
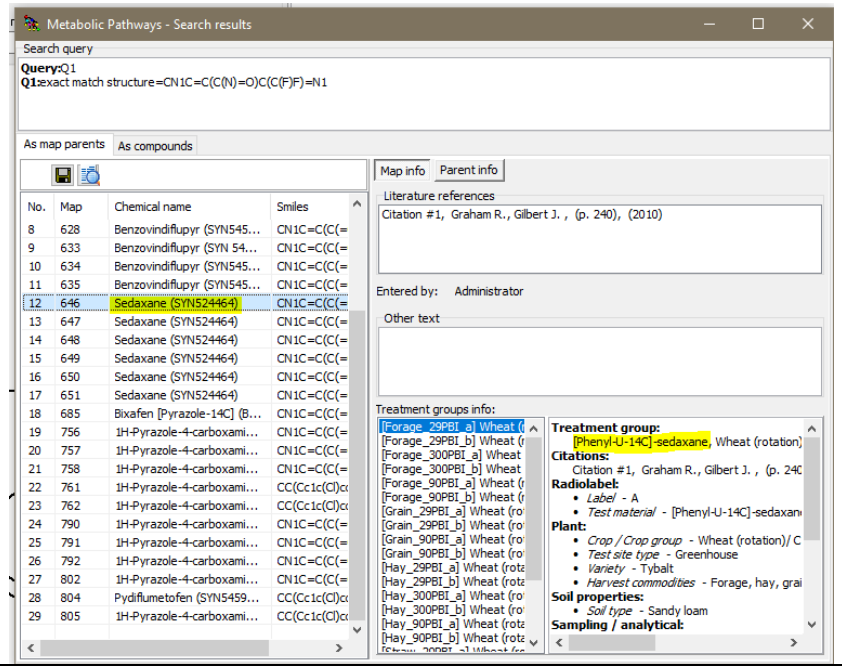
Annex 5 – From MSS Composers to MetaPath

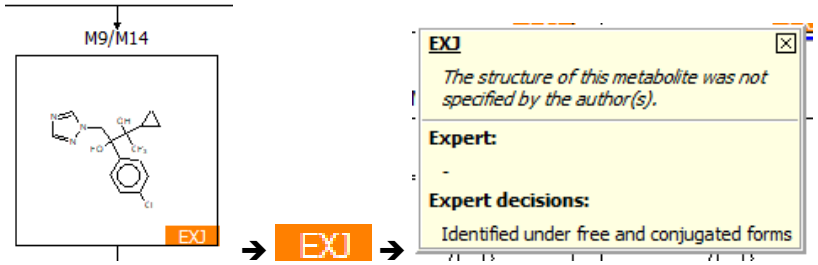
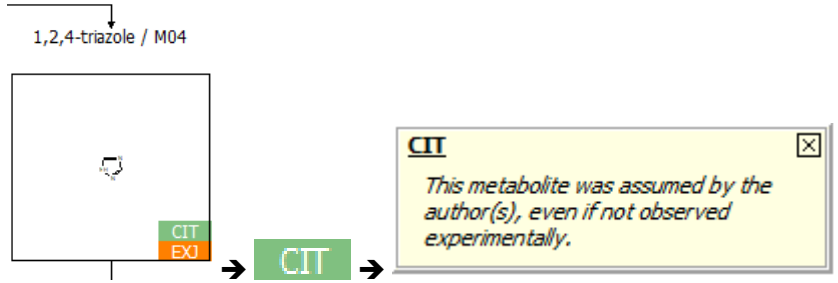
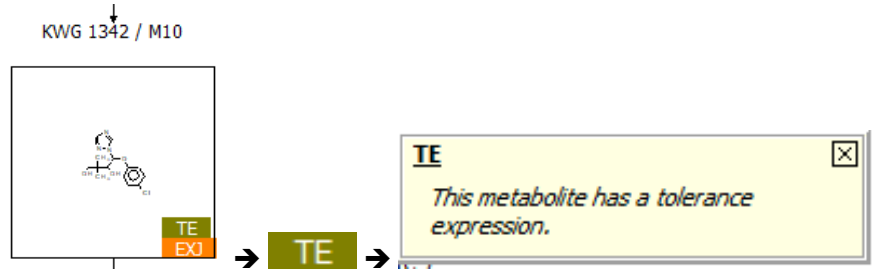
MetaPath	MSS Plants (P) /Crops (C) /Livestock (L) Composer	
	Type (P, C, L, All)	**Origin of the information displayed in MetaPath**
	All	Words which appear after the common name of the active substance come from fields : - "**Crop/Crop group**" of **Table B.7.1.1-1.** and **Table B.7.9-1** (**II. Materials and Methods, A. Materials, 2. Test Crops**) of MSS Plants and Crops Composer, respectively - "**Species**" of **Table B.7.2.1-1.** (**II. Materials and Methods, A. Materials, 2. Animals**) of the MSS Livestock Composer **To ease the search in MetaPath** and immediately see the name of the studied species, it is important to fill in the MSS Composer as follows: - for plants: **Crop/ Crop Group** (ex: Wheat/ Cereals) - for rotational crops: **Crop (rotation)/ Crop Group** (ex: Wheat (rotation)/ Cereals) - for livestock: **Species** (ex: Goat) Please note that what comes after the slash does not appear in the MetaPath's map directory

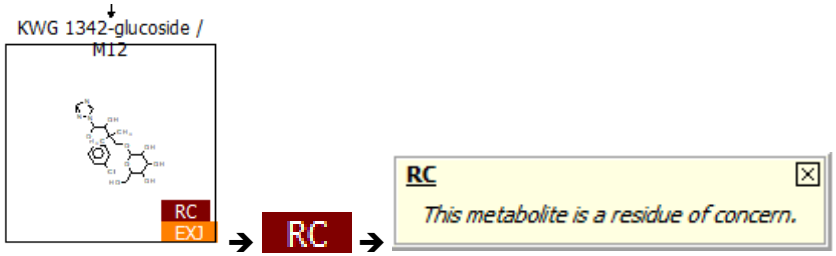
MetaPath	MSS Plants (P) /Crops (C) /Livestock (L) Composer	
	Type (P, C, L, All)	**Origin of the information displayed in MetaPath**
Function "**Highlight Treatment groups**"  	P	**Common fields :** "Tomato/ Fruiting Vegetables" ➔ II. Materials and Methods > A. Materials > 2. Test Crops > Table B.7.1.1-1 Crop Information > **Crop/ Crop Group** "glasshouse" ➔ II. Materials and Methods > A. Materials > 2. Test Crops > **Test Site Type** "Sandy loam" ➔ II. Materials and Methods > A. Materials > 3. Soil Type > Table B.7.1.1-2 Soil Physicochemical Properties > **Soil Type** "6" ➔ II. Materials and Methods > A. Materials > 3. Soil Type > Table B.7.1.1-2 Soil Physicochemical Properties > **pH** "Tomato variety F1 Shirley" ➔ II. Materials and Methods > A. Materials > 2. Test Crops > Table B.7.1.1-1 Crop Information > **Variety** "single dose" ➔ TBD **Coloring and specifics :** "[ph_wheat forage_120DAA]" ➔ V. Appendix > Appendix 1 > **Test#** "[phenyl-U-14C]-SYN545974" ➔ V. Appendix > Appendix 1 > **RTLM** "Wheat forage" ➔ V. Appendix > Appendix 1 > **Matrix**

MetaPath	MSS Plants (P) /Crops (C) /Livestock (L) Composer	
	Type (P, C, L, All)	**Origin of the information displayed in MetaPath**
Function "**Highlight Treatment groups**" 	C	**Common fields :** "Wheat (rotation)/ Cereals grain" ➔ II. Materials > A. Materials > 2. Test Crops > Table B.7.9-1 Crop Information > **Crop/ Crop Group** "outdoor test plots" ➔ II. Materials > A. Materials > 2. Test Crops > **Test Site Type** "Sandy loam" ➔ II. Materials > A. Materials > 3. Soil Type > Table B.7.9-2 Soil Physicochemical Properties > **Soil type** "6" ➔ II. Materials > A. Materials > 3. Soil Type > Table B.7.9-2 Soil Physicochemical Properties > **pH** "single dose" ➔ TBD **Coloring and specifics:** "[ph_wheat forage_120DAA]" ➔ V. Appendix > Appendix 1 > **Test#** "[phenyl-U-14C]-SYN545974" ➔ V. Appendix > Appendix 1 > **RTLM** "Wheat forage" ➔ V. Appendix > Appendix 1 > **Matrix**
Function "**Highlight Treatment groups**"	L	**Common fields :** "Goat" ➔ II. Materials and Methods > A. Materials > 2. Animals > Table B.7.2.2-1 General Test Animal Information > **Species** "female" ➔ V. Appendix > Appendix 1 > **Gender** "in vivo" ➔ TBD "Eggs" ➔ TBD "entire liver […] carcass" ➔ II. Materials and Methods > B. Study Design > Sampling > Table B.7.2.2-4 Sample Collection Information > **Tissues Harvested and Analysed** "Oral"➔ V. Appendix > Appendix 1 > **Dose route** "single dose" ➔ TBD

MetaPath	MSS Plants (P) /Crops (C) /Livestock (L) Composer	
	Type (P, C, L, All)	**Origin of the information displayed in MetaPath**
		"Saanan" ➔ II. Materials and Methods > A. Materials > 2. Animals > Table B.7.2.2-1 General Test Animal Information > **Breed** "7 days" ➔ V. Appendix > Appendix 1 > **Test Duration** **Coloring and specifics :** "[Fat-ph]" ➔ V. Appendix > Appendix 1 > **Test#** "[phenyl-U-14C]-SYN545974" ➔ V. Appendix > Appendix 1 > **RTLM** "Fat" ➔ V. Appendix > Appendix 1 > **Matrix**

MetaPath	MSS Plants (P) /Crops (C) /Livestock (L) Composer	
	Type (P, C, L, All)	**Origin of the information displayed in MetaPath**
Function "**Search Chemicals**"   	All	Sedaxane (SYN524464): information comes from V. Appendix > Appendix 2 > **Chemical Name** ➔ **Please respect the following nomenclature** so that the information appears clearly in MetaPath: **common name (company experimental name)** [Phenyl-U-14C]-sedaxane: information comes from II. Materials and Methods > A. Materials > Radiolabeled Test Material > name of radiolabelled test material "**Radio-labeled #1**" ➔ **Please respect the following nomenclature** so that the information appears clearly in MetaPath: **[radiolabelled group]-common name**

MetaPath	MSS Plants (P) /Crops (C) /Livestock (L) Composer	
	Type (P, C, L, All)	**Origin of the information displayed in MetaPath**
	All	**<u>In the metabolic tree:</u>** The orange icon "EXJ" means that expertise on this metabolite is available. Click on the orange icon "EXJ" to have access to the information reported in the "Decision" field (**V. Appendix > Appendix 2 > Expertise > Expertly specified > <u>Decision</u>**)
	All	**<u>In the metabolic tree:</u>** The green icon "CIT" means that the metabolite was assumed by author(s). It appears when "Assumed by author(s)" is ticked in **V. Appendix > Appendix 2 > Expertise > Expertly specified.** You can click on the icon to have access to its meaning.
	All	**<u>In the metabolic tree:</u>** The olive green icon "TE" means that the metabolite has a tolerance expression. It appears when "Tolerance Expression" is ticked in **V. Appendix > Appendix 2 > Expertise > Expertly specified**. You can click on the icon to have access to its meaning.

MetaPath	MSS Plants (P) /Crops (C) /Livestock (L) Composer	
	Type (P, C, L, All)	**Origin of the information displayed in MetaPath**
	All	**In the metabolic tree:** The burgundy icon "RC" means that the metabolite is a residue of concern. It appears when "Residue of Concern" is ticked in **V. Appendix > Appendix 2 > Expertise > Expertly specified**. You can click on the icon to have access to its meaning.