

Training Manual on MetaPath Data Evaluation Record (DER) Composer

European Food Safety Authority (EFSA),

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1. Introduction

The Transparency Regulation, which amends the General Food Law (GFL), means that EFSA has new requirements for capturing, managing, handling and distributing data on plant protection products (PPP).

These changes require the specification of data formats for regulated product dossiers and allow documents to be submitted, searched, copied and printed, while ensuring compliance with legal requirements. It has been decided to use IUCLID formats and the IUCLID tool (managed by the European Chemicals Agency – ECHA) for data preparation, electronic submission and management of pesticide dossiers, by means of the ECHA Cloud platform. Furthermore, applicants should provide data on metabolism in the areas of residues and mammalian toxicology as attachments generated with the MetaPath software package called composers.

This Manual is focus on the MetaPath Data Evaluation Record (DER) composer. For MetaPath Metabolism Study Summary (MSS) Composer the applicant is referred to ANSES, 2020.

The training manual describes the different steps for data entry of mammalian (rat) metabolism studies submitted under the pesticide peer review process by using the MetaPath Data Evaluation Record (DER) composer.

The MetaPath DER composer is freely available in the software developer webpage together with MetaPath software and the MSS composer software: <https://oasis-lmc.org/products/software/metapath.aspx>

This Manual has been written in collaboration with US EPA.

Nomenclature and drawing instruction as described in the MetaPath MSS Composer Training Manual (ANSES, 2020) is also applicable to the DER composer. The applicant is advised first to read MetaPath MSS Composer Training Manual before this manual.

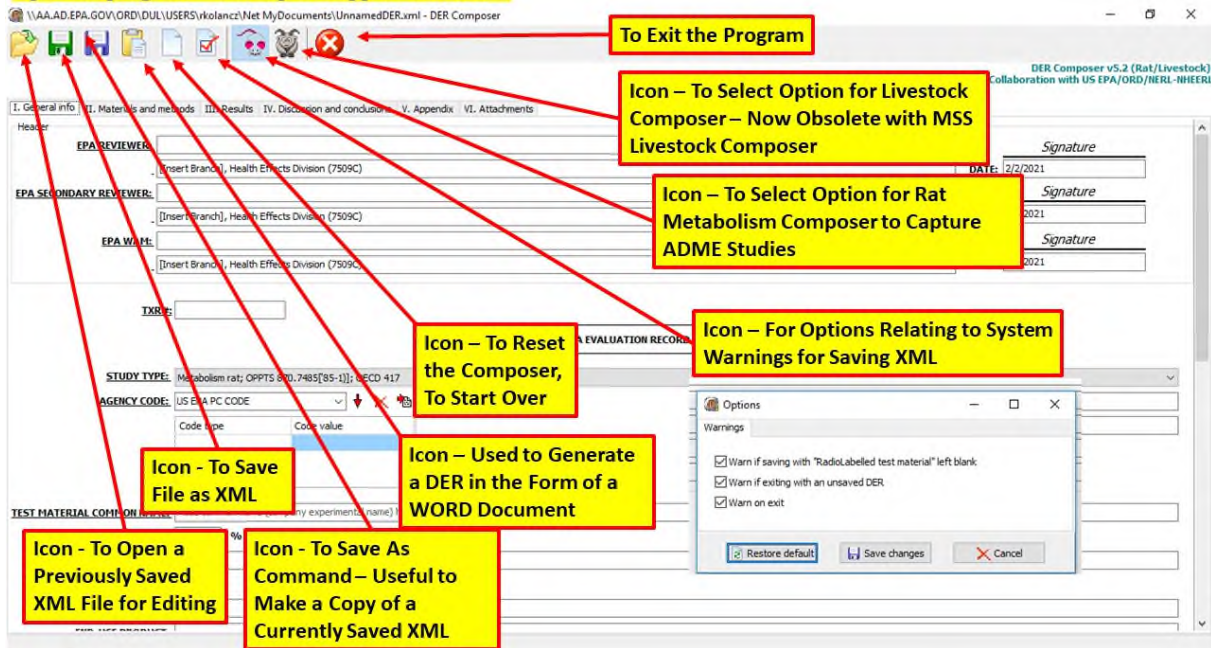
The xml file generated from the DER composer should be included as an attachment in IUCLID, under toxicokinetic study records as described in the EFSA MRL IUCLID Manual (EFSA, 2021).

2. Guideline for the use of DER/XML Composer – Rat Metabolism v.5.2

This guideline was prepared for use with DER Composer V5.2, a product resulting from the joint cooperation between the U.S. Environmental Protection Agency (USEPA) and the Laboratory of Mathematical Chemistry (LMC-Burgas, Bulgaria).

2.1. Opening DER Composer

Open the program – start up will appear as follows:



The screenshot shows the DER Composer v5.2 interface. The title bar reads "DER Composer v5.2 (Rat/Livestock) Collaboration with US EPA/ORD/NERL-NHEERL". The main window contains several sections: "EPA REVIEWER", "EPA SECONDARY REVIEWER", "EPA WORK", "TEST MATERIAL COMPOSITION", and "EVALUATION RECORD". A "Warnings" dialog box is open in the bottom right corner, showing options for warnings during saving and exiting.

Annotations with yellow callout boxes:

- To Exit the Program**: Points to the red 'X' icon in the top toolbar.
- Icon – To Select Option for Livestock Composer – Now Obsolete with MSS Livestock Composer**: Points to the icon of a cow in the top toolbar.
- Icon – To Select Option for Rat Metabolism Composer to Capture ADME Studies**: Points to the icon of a rat in the top toolbar.
- Icon – For Options Relating to System Warnings for Saving XML**: Points to the 'Options' dialog box.
- Icon – To Reset the Composer, To Start Over**: Points to the circular arrow icon in the top toolbar.
- Icon – Used to Generate a DER in the Form of a WORD Document**: Points to the document icon in the top toolbar.
- Icon - To Save File as XML**: Points to the floppy disk icon in the top toolbar.
- Icon - To Open a Previously Saved XML File for Editing**: Points to the folder icon in the top toolbar.
- Icon - To Save As Command – Useful to Make a Copy of a Currently Saved XML**: Points to the floppy disk icon with a plus sign in the top toolbar.

2.2. General information

Start with the tab **I. General info**. Begin by filling in pertinent information by mouse-clicking within the boxed areas designated for those parameters and typing information or by copying / pasting information from an electronic source down to the area to fill in citations.

Start with the tab I. General info. Begin by filling in pertinent information by mouse-clicking within the boxed areas designated for those parameters and typing information or by copying / pasting information from an electronic source down to the area to fill in citations.

Skip Reviewer Section and USEPA Specific Fields for TXR#, DP Barcode & Submission No. Begin with Agency Code. Select from Drop-down Menu (CAS, EFSA, PC Code, etc...) or New Additional Code then Add with Red Arrow. Then Fill Appropriate Value.

Then Continue Filling Test Material Common Name, Test Material Purity, IUPAC Name, Synonyms, and End Use Products.

A **CITATION EDITOR** box pops up. Fill in reference, MRID number and click generate tables, followed by clicking on submit. If there are additional references repeat the process - click the + to add each, populate, and click submit.

Click on "+" to Open Citation Editor

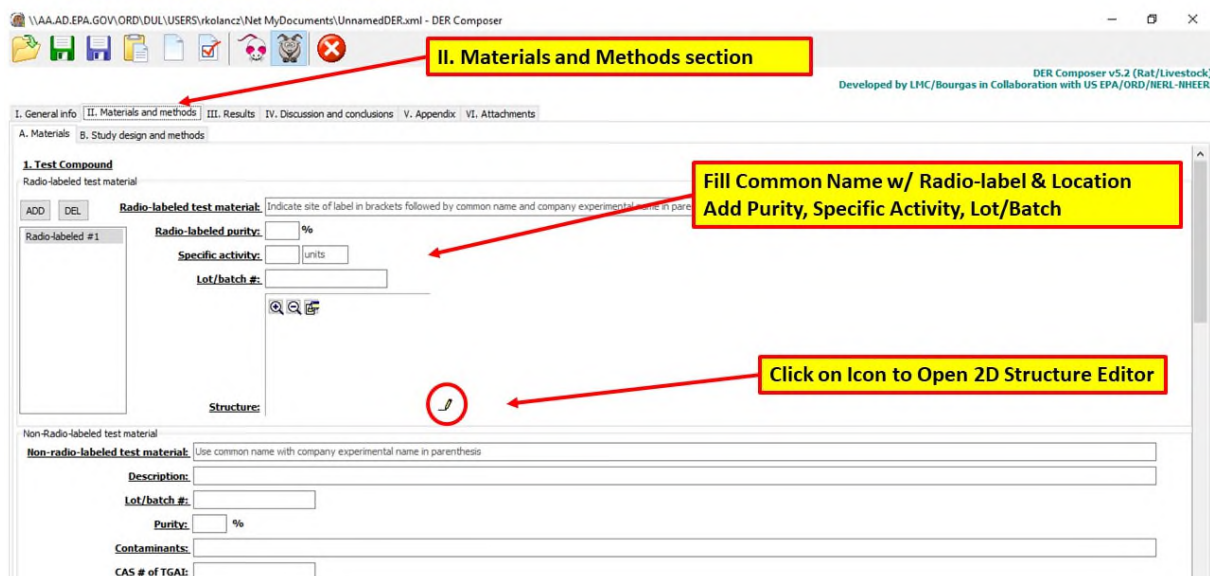
Fill-in Citation, MRID if associated with USEPA, and make sure Generate Table for Reference Box is Checked.

The citation is entered and tables are created and are ready for population. Additional references (MRID's) may be entered by repeat of the afore mentioned process

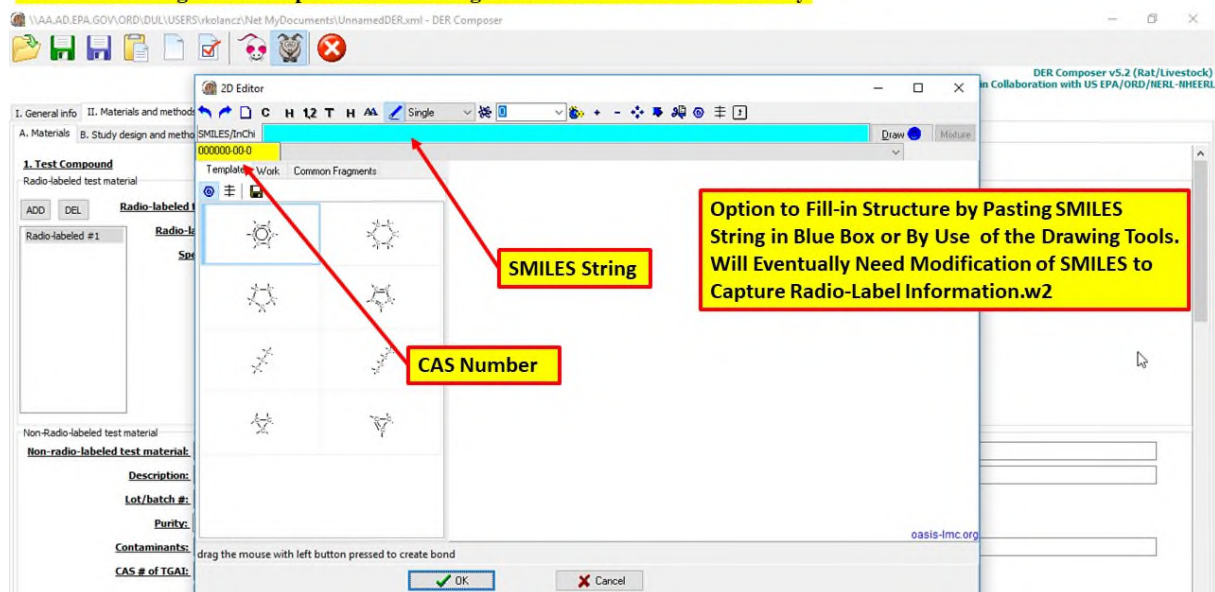
Fill-in Executive Summary & Compliance Text Boxes.

2.3. Material and methods

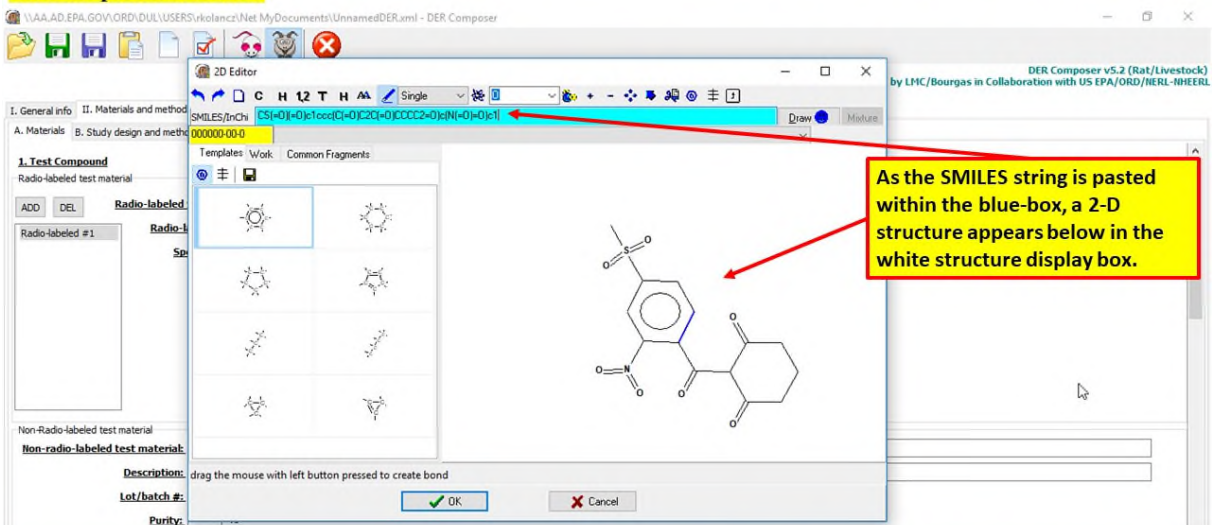
Next the tab **II. Materials and methods** and sub-tab **A. Materials** may be populated. Data is filled in via directly typing or copy/paste from electronic documents until reaching the structure entry. To enter the **Radio-labeled Test Material** and **Non-radio-labeled Test Material** structures:



Below is a graphic of the **STRUCTURE DRAWING** editor pop-up box. The large white area is the drawing workspace, the **light-blue box** is where a **SMILES** string may be entered or displayed, and the **yellow box** is where a **CAS** number can be entered. Scrolling over the top of the icons will give some indication of their utility.



Perform a right-hand click of the mouse in the light-blue box of the STRUCTURE DRAWING package and select paste to enter the parent structure.



DER Composer v5.2 (Rat/Livestock)
by LMC/Bourgas in Collaboration with US EPA/ORD/NERL-NHEERL

SMILES/InChI CS(=O)(=O)c1ccc(C(=O)C2C(=O)C(CCC2=O)N(=O)=O)c1

000000-00-0

Templates Work Common Fragments

As the SMILES string is pasted within the blue-box, a 2-D structure appears below in the white structure display box.

Description: drag the mouse with left button pressed to create bond

Lot/batch #:

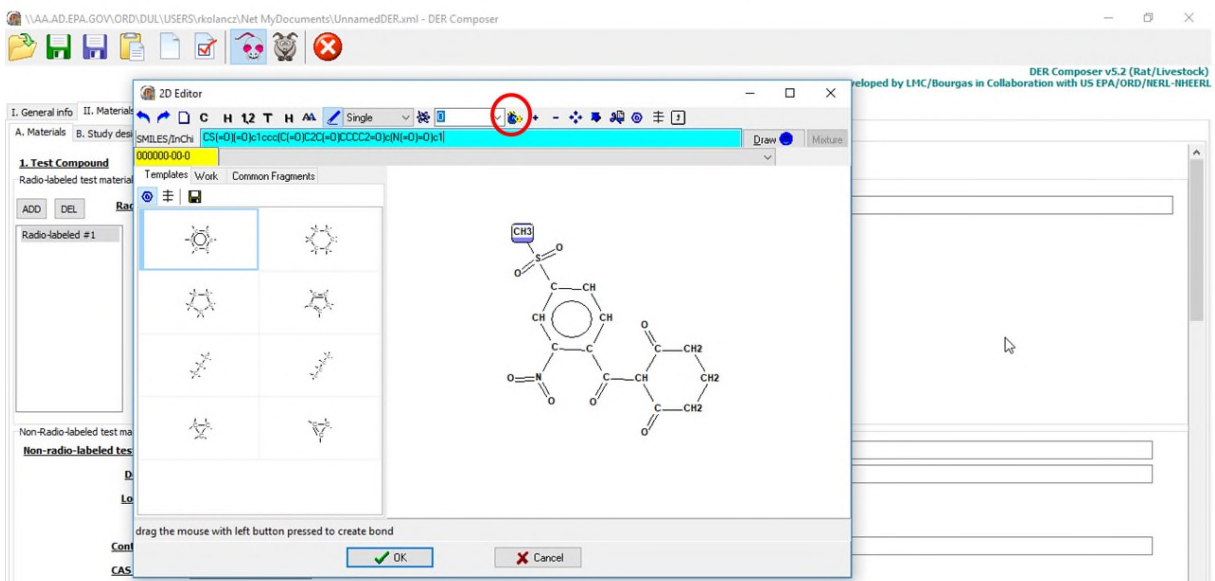
Purity:

OK Cancel

The parent structure (now present in the STRUCTURE DRAWING editor) may be modified utilizing tools within the editor. Specifically a label may be introduced in the structure of the radio-labeled parent.

Radio labeling of atoms

Within the STRUCTURE DRAWING window, open the periodic table by selecting the icon as circled in the figure below.



DER Composer v5.2 (Rat/Livestock)
Developed by LMC/Bourgas in Collaboration with US EPA/ORD/NERL-NHEERL

SMILES/InChI CS(=O)(=O)c1ccc(C(=O)C2C(=O)C(CCC2=O)N(=O)=O)c1

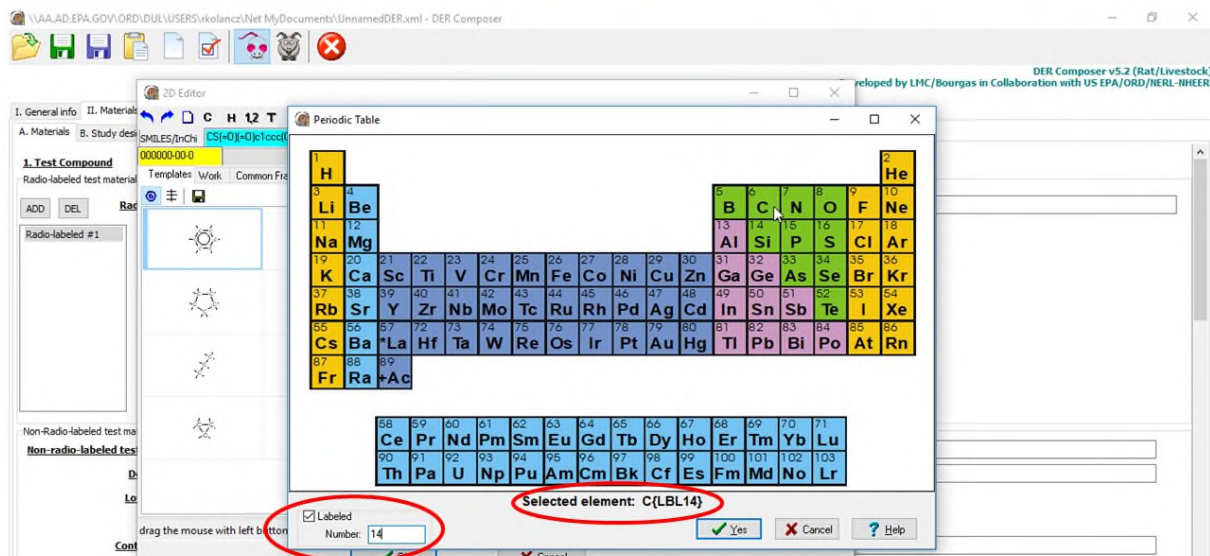
000000-00-0

Templates Work Common Fragments

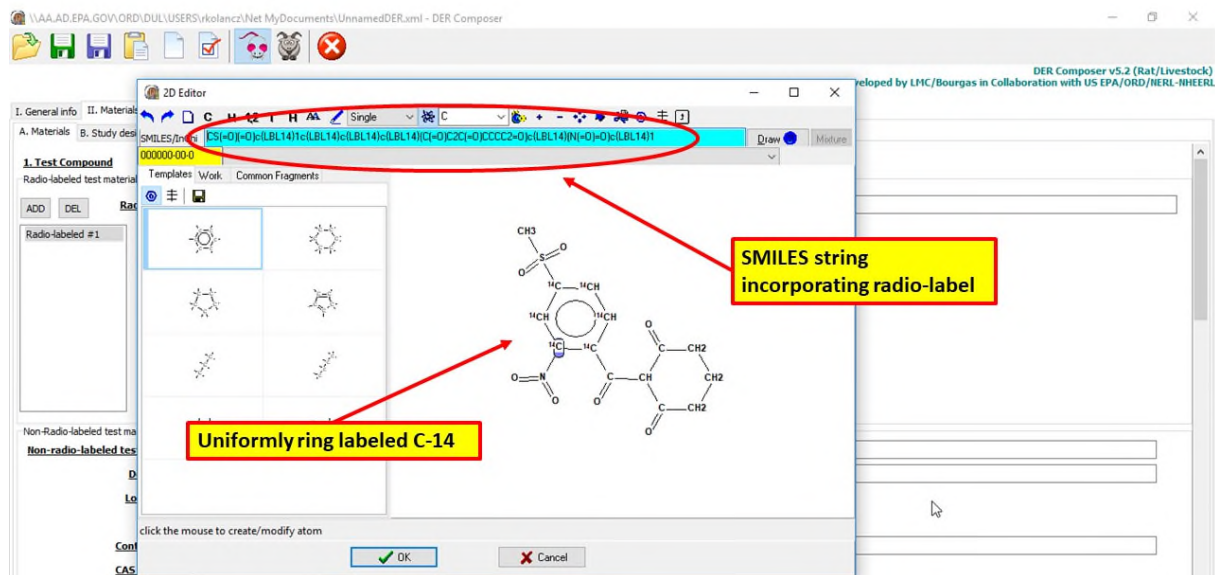
drag the mouse with left button pressed to create bond

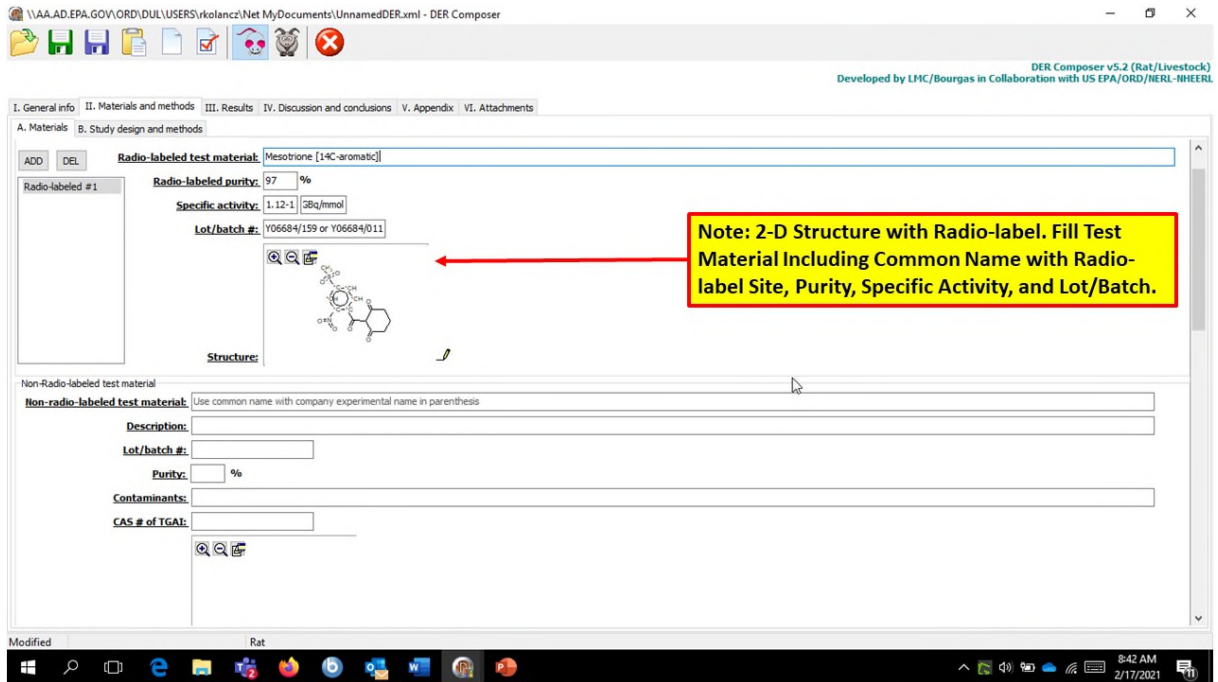
OK Cancel

A periodic table screen comes up where you should check labeled, in this example add 14 in the number box and click on C for carbon. Then hit YES.



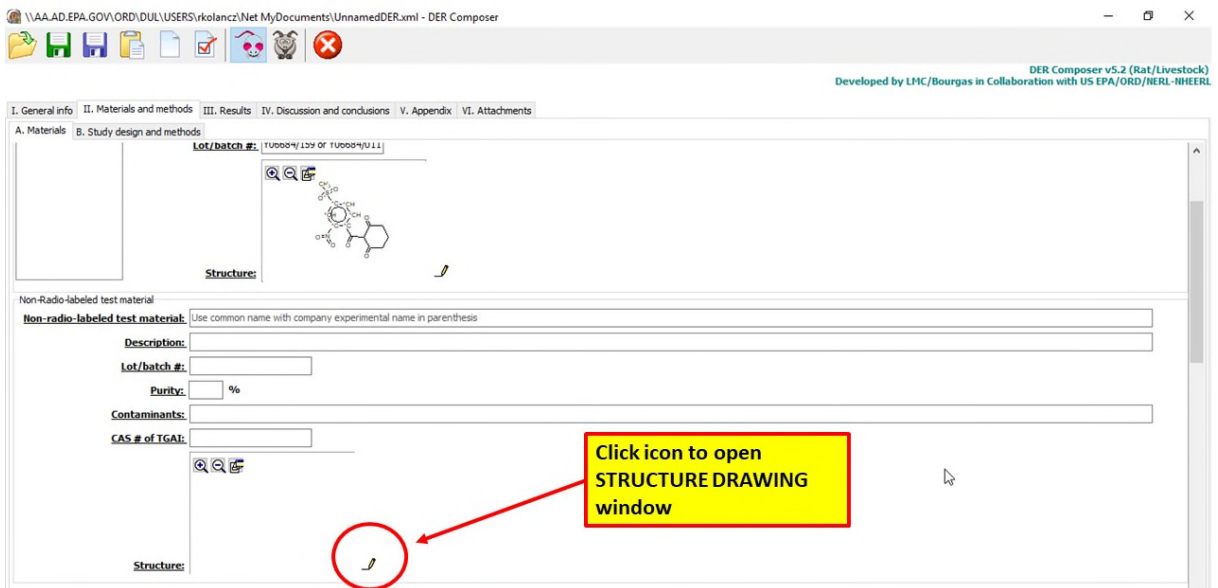
After clicking Yes on the previous screen, the periodic table closes, then you can add the C-14 label to each carbon in the example. The example below happens to be a uniformly labeled phenyl ring. Note that the information for the labeling is now contained in the SMILES.





Note: 2-D Structure with Radio-label. Fill Test Material Including Common Name with Radio-label Site, Purity, Specific Activity, and Lot/Batch.

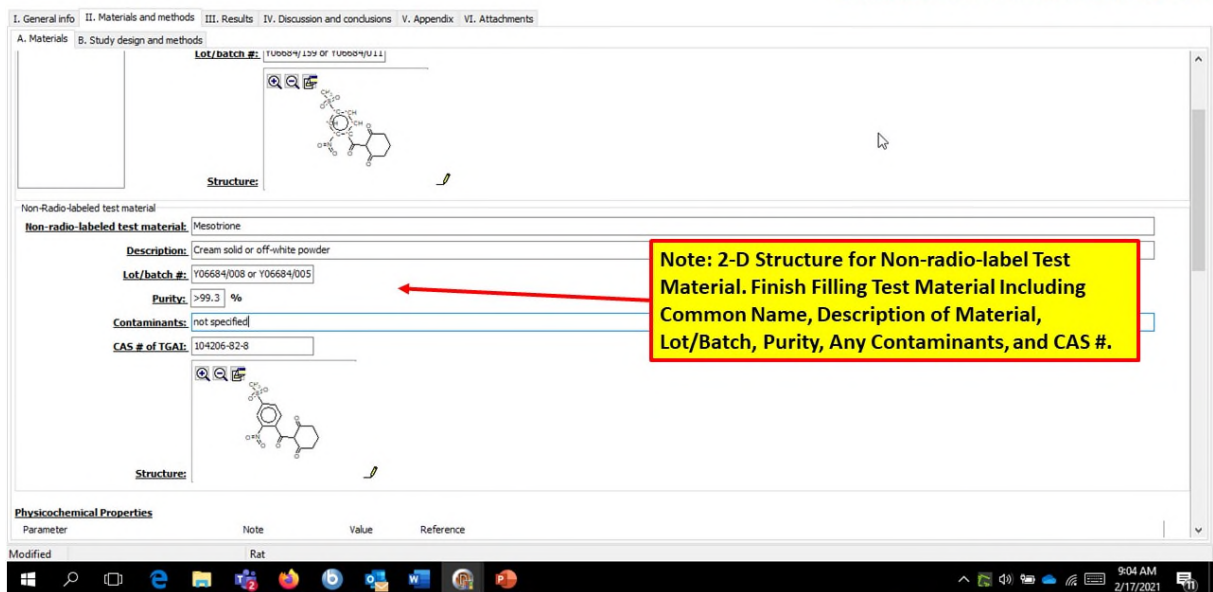
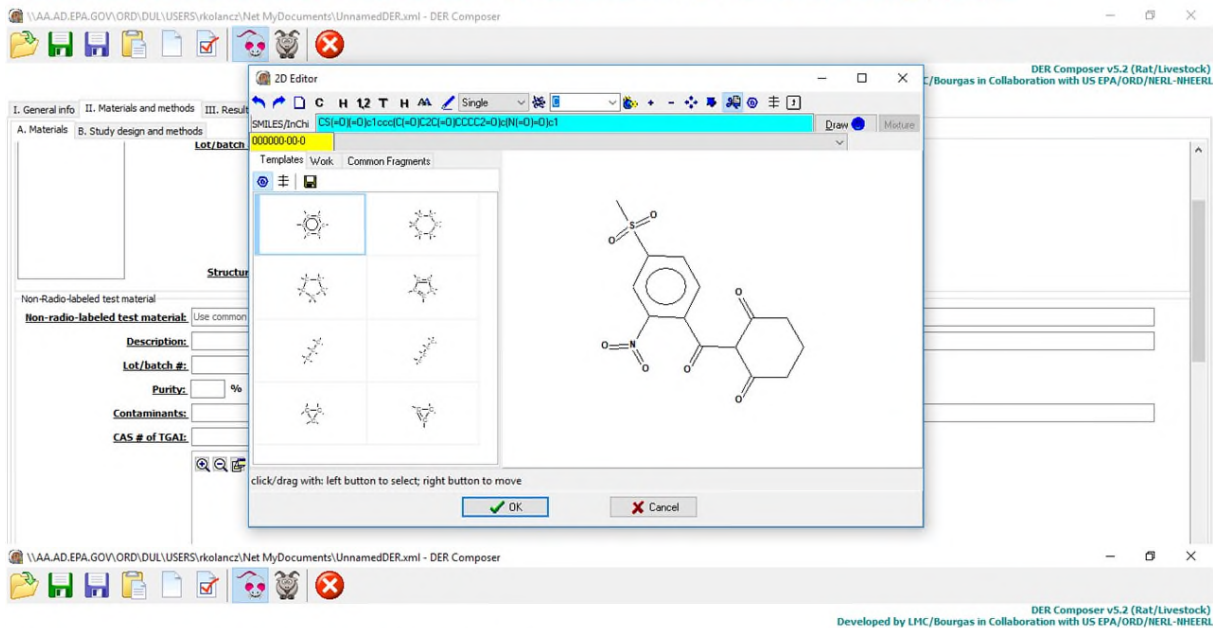
The Non-radiolabeled Test Material may be entered in the same fashion by opening the STRUCTURE DRAWING PACKAGE.



Click icon to open STRUCTURE DRAWING window

The SMILES string (from the excel list of parent structures) is entered in the light-blue box of the editor and the 2-D structure is immediately shown.

NOTE: The use of COPY/PASTE SMILES strings to generate the 2-D structures of parent chemicals serves to save time drawing structures, however the structures can be produced utilizing the tools of the drawing package.



Continue filling out the rest of II. Material and methods A. Materials

C:\Users\rkolancz\0_Working Files\MetaPath Users Group\EFSA Contract\Mesotrione.xml - DER Composer

DER Composer v5.2 (Rat/Livestock)
Developed by LMC/Bourgas in Collaboration with US EPA/ORD/NERL-NHEERL

I. General info II. Materials and methods III. Results IV. Discussion and conclusions V. Appendix VI. Attachments

A. Materials B. Study design and methods

3. Test animals

Species: Rat

Strain: Wistar-Kyoto

Age at study initiation: 7-9 weeks

Weight at study initiation: 175-300 g

Source: Biological Services Section or Barrieted Animal Breeding Unit, Zeneca Pharmaceuticals, Alderley Park

Housing: During initial acclimation, rats were housed in groups of the same sex in solid rat cages. During the in-life p

Diet: Pelleted PCD rat diet (Special Diet Services, Ltd, Stepfield, Witham, Essex, UK), ad libitum, except for 10-

Water: Tap water, ad libitum

Environmental conditions

Temperature: 21 ± 4 °C

Humidity: 30-70%

Air changes: At least 12/hour

Photoperiod: 12-hr photoperiod

Acclimation period: 4 days

4. Preparation of dosing solutions

For the low-dose groups, undiluted [¹⁴C-aromatic] mesotrione was dissolved in sodium bicarbonate solution. The composition of the final dosing solution was 0.25 mg mesotrione/g and 1.04 MBq/g of dosing solution. For the high-dose groups, [¹⁴C-aromatic]mesotrione was dissolved in sodium bicarbonate solution and isotopically diluted by mixing with non-labeled mesotrione. The final specific activity of the dosing solution was 4.19 MBq/mg for the low-dose groups and 65.31 kBq/mg for the high-dose groups. Following dosing, the radiochemical purity of the test substance was determined by HPLC analysis; for the binary study, the purity was determined using TLC and silica gel column chromatography. No results of these analyses were provided.

Fill-in Test Animal Fields

Fill-in Preparation of Dosing Solution

2.4. Appendix 1

Next go to tab V. Appendix – It is within this section that the various treatment groups are defined and listed as a TEST in the appendix 1 table below. A treatment group may be defined by gender, age, dose amount, dose route, sample matrix or other experimental descriptor (parameters that when varied may give rise to a different metabolic map for a particular chemical).

DER Composer v5.2 (Rat/Livestock)
Developed by LMC/Bourgas in Collaboration with US EPA/ORD/NERL-NHEERL

Appendix1a

| Test# | Sex | Number | Dose Route | Dose (nominal) | Dose (measured) | Dose Type | Test Duration | Matrix | Experimental Descriptor | Remarks |
|-------|-----|--------|------------|----------------|-----------------|-----------|---------------|--------|-------------------------|---------|
| | | | | | | | | | | |

Appendix1 Editor

Test#
1A

Gender
 Male
 Female
 Not Reported

Number: 5 Dose Route: Oral

Dose Nominal: 100 mg/kg Dose Measured: 100.11 mg/kg

Matrix: Urine Test Duration: 72 hrs

Dose Type
 Single
 Multiple
 on every: for:

Remarks
sed for metabolite identification and characterization

Submit Cancel

Click on submit to accept test – continue to add new tests via the same process until completed. Screen should appear as below:

DER Composer v5.2 (Rat/Livestock)
Developed by LMC/Bourgais in Collaboration with US EPA/ORD/NERL-III/ERL

| Test# | Sex | Number | Dose Route | Dose (nominal) | Dose (measured) | Dose Type | Test Duration | Matrix | Experimental Descriptor | Remarks |
|-------|--------|--------|------------|----------------|-----------------|-----------|---------------|--------|-------------------------|-----------------------------------------|
| 10A | Female | 2 | Oral | 50.0 mg/kg | 48.5 mg/kg | single | 48 hrs | Urine | | pooled samples of feces, urine, and bil |
| 10B | Female | 2 | Oral | 50.0 mg/kg | 48.5 mg/kg | single | 48 hrs | Feces | | pooled samples of feces, urine, and bil |
| 10C | Female | 2 | Oral | 50.0 mg/kg | 48.5 mg/kg | single | 48 hrs | Bile | | pooled samples of feces, urine, and bil |
| 11A | Male | 2 | Oral | 100.0 mg/kg | 104.8 mg/kg | single | 48 hrs | Urine | | used solely as a source of fecal and ur |
| 11B | Male | 2 | Oral | 100.0 mg/kg | 104.8 mg/kg | single | 48 hrs | Feces | | used solely as a source of fecal and ur |
| 12A | Female | 2 | Oral | 100.0 mg/kg | 110.7 mg/kg | single | 48 hrs | Urine | | used solely as a source of fecal and ur |
| 12B | Female | 2 | Oral | 100.0 mg/kg | 110.7 mg/kg | single | 48 hrs | Feces | | used solely as a source of fecal and ur |

Appendix 2

| ID | Common Name / Code | Chemical Name | SMILES | Parent(s) | Expertise |
|----|--------------------|---------------|--------|-----------|-----------|
| | | | | | |

The completed Appendix 1 will automatically populate the group arrangements Table 1 of section/tab II. Materials and methods sub-tab B. Study design and methods. This may be observed by clicking on the appropriate tabs.

DER Composer v5.2 (Rat/Livestock)
Developed by LMC/Bourgais in Collaboration with US EPA/ORD/NERL-III/ERL

1. Group arrangements
Animals were assigned to the test groups noted in Table 1

Table 1a

| Treatment Group | Sex | Number | Dose Route | Dose (nominal) | Dose (measured) | Dose Type | Remarks |
|-----------------|-----|--------|------------|----------------|-----------------|-----------|-------------|
| 1 | Mal | 5 | Oral | 100mg/kg | 100.11mg/kg | single | Feces,Tissu |
| 2 | Fer | 5 | Oral | 100mg/kg | 98.79mg/kg | single | Feces,Tissu |
| 3 | Mal | 5 | Oral | 1.0mg/kg | 1.0mg/kg | single | Feces,Tissu |
| 4 | Fer | 5 | Oral | 1.0mg/kg | 1.0mg/kg | single | Feces,Tissu |
| 5 | Mal | 5 | Oral | 1.0mg/kg | 0.99mg/kg | multiple | Feces,Tissu |
| 6 | Fer | 5 | Oral | 1.0mg/kg | 1.02mg/kg | multiple | Feces,Tissu |
| 7 | Mal | 5 | I.V. | 1.0mg/kg | 0.99mg/kg | single | Feces,Tissu |

2. Dosing and sample collection
Briefly describe dosing methods and sample collection

Table 2a

| Treatment Group | Matrix | Sample Time | Major Method | Conjugate Analysis | Analytical Separation | Analytical Detection | Remarks |
|-----------------|--------|-------------|--------------|--------------------|-----------------------|----------------------|---------|
| | | | | | | | |

In addition, an automatic partial entry of the dosing and sample collection Table 2 of section/tab II. Materials and methods sub-tab B. Study design and methods takes place. We will return to complete this table after completion of Appendix 2.

C:\Users\kolancz\0_Working Files\MetaPath Users Group\EFSA Contract\Mesotrione.xml - DER Composer

DER Composer v5.2 (Rat/Livestock)
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I. General info II. Materials and methods III. Results IV. Discussion and conclusions V. Appendix VI. Attachments

A. Materials B. Study design and methods

Table 2a

| Treatment Group | Matrix | Sample Time | Major Method | Conjugate Analysis | Analytical Separation | Analytical Detection | Remarks |
|------------------------|--------|-------------|--------------|--------------------|-----------------------|----------------------|---------|
| 10A, 11A, 12A, 1A, 2A | Urine | | | | | | |
| 10B, 11B, 12B, 1B, 2B | Feces | | | | | | |
| 1C, 2C, 3C, 4C, 5C, 6C | Tissue | | | | | | |
| 10C, 9C | Bile | | | | | | |

a. Pharmacokinetic studies
[Briefly describe how samples were handled after harvesting (shipment, storage, etc.) and any preparation that was done prior to extraction.]
[If warranted, include a graphic (i.e., flowchart) of the extraction and fractionation schemes and omit following textual description.]
[Briefly describe the extraction, fractionation and hydrolysis strategies for each tissue. The description should include solvents used (ratios), the order of their use, the extraction procedures employed (i.e., blending, maceration, Soxhlet, etc.) and procedures used to release bound and conjugated residues (i.e., acid, base, or enzyme hydrolysis, exhaustive extraction, etc.). Has the petitioner justified the use of severe conditions (e.g., strong acid hydrolysis in the presence of heat, etc.)]

b. Metabolite characterization studies
[Briefly describe the principle of the methods used for identification/characterization of the residues. Specify instrumentation (LC, TLC, GLC, HPLC, etc.) and detection method used (UV, ECD, FID, MS/MS, etc.). State the LOD and LOQ. If applicable, very briefly describe difficulties with methods that fail to elucidate the nature of the residues or bound residues as in protein or lipid fractions.]

3. Statistics
[List parameters that were analyzed and the statistical methods used; include a statement that the Reviewer considers the analyses used to be appropriate. If inappropriate, provide alternative/rationale]

2.5. Appendix 2

Next a Metabolite Inventory table should be completed as Appendix 2 of tab V. Appendix.

The screenshot shows the DER Composer v5.2 interface. Appendix 1a contains a table with the following data:

| Test# | Sex | Number | Dose Route | Dose (nominal) | Dose (measured) | Dose Type | Test Duration | Matrix | Experimental Descriptor | Remarks |
|-------|--------|--------|------------|----------------|-----------------|-----------|---------------|--------|-------------------------|-----------------------------------------|
| 10A | Female | 2 | Oral | 50.0 mg/kg | 48.5 mg/kg | single | 48 hrs | Urine | | pooled samples of feces, urine, and bl |
| 10B | Female | 2 | Oral | 50.0 mg/kg | 48.5 mg/kg | single | 48 hrs | Feces | | pooled samples of feces, urine, and bl |
| 10C | Female | 2 | Oral | 50.0 mg/kg | 48.5 mg/kg | single | 48 hrs | Bile | | pooled samples of feces, urine, and bl |
| 11A | Male | 2 | Oral | 100.0 mg/kg | 104.8 mg/kg | single | 48 hrs | Urine | | used solely as a source of fecal and ur |
| 11B | Male | 2 | Oral | 100.0 mg/kg | 104.8 mg/kg | single | 48 hrs | Feces | | used solely as a source of fecal and ur |
| 12A | Female | 2 | Oral | 100.0 mg/kg | 110.7 mg/kg | single | 48 hrs | Urine | | used solely as a source of fecal and ur |
| 12B | Female | 2 | Oral | 100.0 mg/kg | 110.7 mg/kg | single | 48 hrs | Feces | | used solely as a source of fecal and ur |

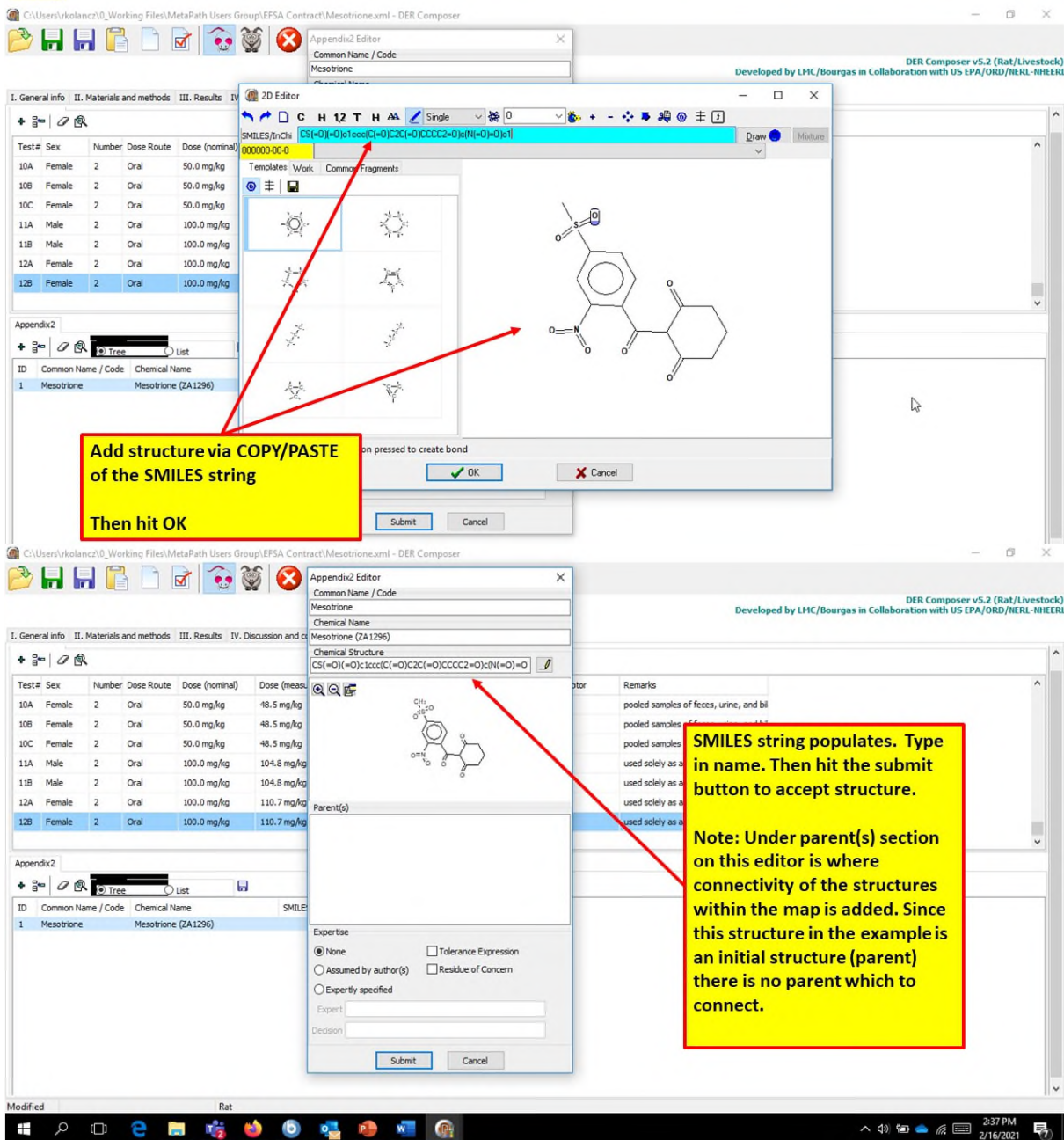
Appendix 2 Editor window details:

- Common Name / Code:** [Empty]
- Chemical Name:** [Empty]
- Chemical Structure:** [Empty]
- Parent(s):** [Empty]
- Expertise:**
 - None
 - Assumed by author(s)
 - Expertly specified
 - Tolerance Expression
 - Residue of Concern
- Expert:** [Empty]
- Decision:** [Empty]

Callout boxes provide the following instructions:

- Click on the + icon to add parent or metabolite structure** (points to the plus icon in the Appendix 2 toolbar).
- Click on this icon to bring up the STRUCTURE DRAWING EDITOR – follow directions from previous section in this guidance referring to structural drawing package.** (points to the drawing editor icon in the Appendix 2 Editor window).
- An Appendix 2 Editor window pops up, a chemical name is entered.** (points to the Chemical Name field in the Appendix 2 Editor window).
- Expertise may be added to a given structure. "Assumed by Author" is reserved for a structure presented by the Author in a submitted map but for which there is no proof via detection experimentally. "Expertly specified" is used to provide a likely structure whereby the Author did not definitively draw the exact location of ring-hydroxylation or conjugation for example. The Expert may then specify such a structure with some knowledge listed to base that decision.** (points to the Expertise radio buttons).

We will start by adding the parent structure – as was done in the materials & methods using COPY/PASTE of the SMILES string.



Add structure via COPY/PASTE of the SMILES string

Then hit OK

SMILES string populates. Type in name. Then hit the submit button to accept structure.

Note: Under parent(s) section on this editor is where connectivity of the structures within the map is added. Since this structure in the example is an initial structure (parent) there is no parent which to connect.

| Test# | Sex | Number | Dose Route | Dose (nominal) | Dose (mean) |
|-------|--------|--------|------------|----------------|-------------|
| 10A | Female | 2 | Oral | 50.0 mg/kg | 48.5 mg/kg |
| 10B | Female | 2 | Oral | 50.0 mg/kg | 48.5 mg/kg |
| 10C | Female | 2 | Oral | 50.0 mg/kg | 48.5 mg/kg |
| 11A | Male | 2 | Oral | 100.0 mg/kg | 104.8 mg/kg |
| 11B | Male | 2 | Oral | 100.0 mg/kg | 104.8 mg/kg |
| 12A | Female | 2 | Oral | 100.0 mg/kg | 110.7 mg/kg |
| 12B | Female | 2 | Oral | 100.0 mg/kg | 110.7 mg/kg |

Appendix2

| ID | Common Name / Code | Chemical Name | SMILES |
|----|--------------------|---------------------|---------------------------------------------------|
| 1 | Mesotrione | Mesotrione (ZA1296) | CS(=O)(=O)c1cccc(C(=O)C2C(=O)CCCC2=O)c(N(=O)=O)c1 |

C:\Users\kolancz\0_Working Files\MetaPath Users Group\EFSA Contract\Mesotrione.xml - DER Composer

DER Composer v5.2 (Rat/Livestock)
Developed by LMC/Bourgas in Collaboration with US EPA/ORD/NERL-NHEERL

I. General info II. Materials and methods III. Results IV. Discussion and conclusions V. Appendix VI. Attachments

| Test# | Sex | Number | Dose Route | Dose (nominal) | Dose (measured) | Dose Type | Test Duration | Matrix | Experimental Descriptor | Remarks |
|-------|--------|--------|------------|----------------|-----------------|-----------|---------------|--------|-------------------------|-----------------------------------------|
| 10A | Female | 2 | Oral | 50.0 mg/kg | 48.5 mg/kg | single | 48 hrs | Urine | | pooled samples of feces, urine, and bil |
| 10B | Female | 2 | Oral | 50.0 mg/kg | 48.5 mg/kg | single | 48 hrs | Feces | | pooled samples of feces, urine, and bil |
| 10C | Female | 2 | Oral | 50.0 mg/kg | 48.5 mg/kg | single | 48 hrs | Bile | | pooled samples of feces, urine, and bil |
| 11A | Male | 2 | Oral | 100.0 mg/kg | 104.8 mg/kg | single | 48 hrs | Urine | | used solely as a source of fecal and ur |
| 11B | Male | 2 | Oral | 100.0 mg/kg | 104.8 mg/kg | single | 48 hrs | Feces | | used solely as a source of fecal and ur |
| 12A | Female | 2 | Oral | 100.0 mg/kg | 110.7 mg/kg | single | 48 hrs | Urine | | used solely as a source of fecal and ur |
| 12B | Female | 2 | Oral | 100.0 mg/kg | 110.7 mg/kg | single | 48 hrs | Feces | | used solely as a source of fecal and ur |

Appendix2

| ID | Common Name / Code | Chemical Name | SMILES | Parent(s) | Expertise |
|----|--------------------|---------------------|--------------------------------|-----------|-----------|
| 1 | Mesotrione | Mesotrione (ZA1296) | CS(=O)(=O)c1ccc(C(=O)C2C(=O... | | |

Continue with the next structure (daughter to the parent) by clicking on the + icon once again.

Click on structure drawing editor icon

The parent SMILES string may be imported via COPY/PASTE to produce the parent 2-D structure and then modified to reflect the metabolite structure. With the new metabolite, usually there are only slight modifications to the parent structure. This can be a time saver rather than drawing each metabolite from scratch.

2D Editor

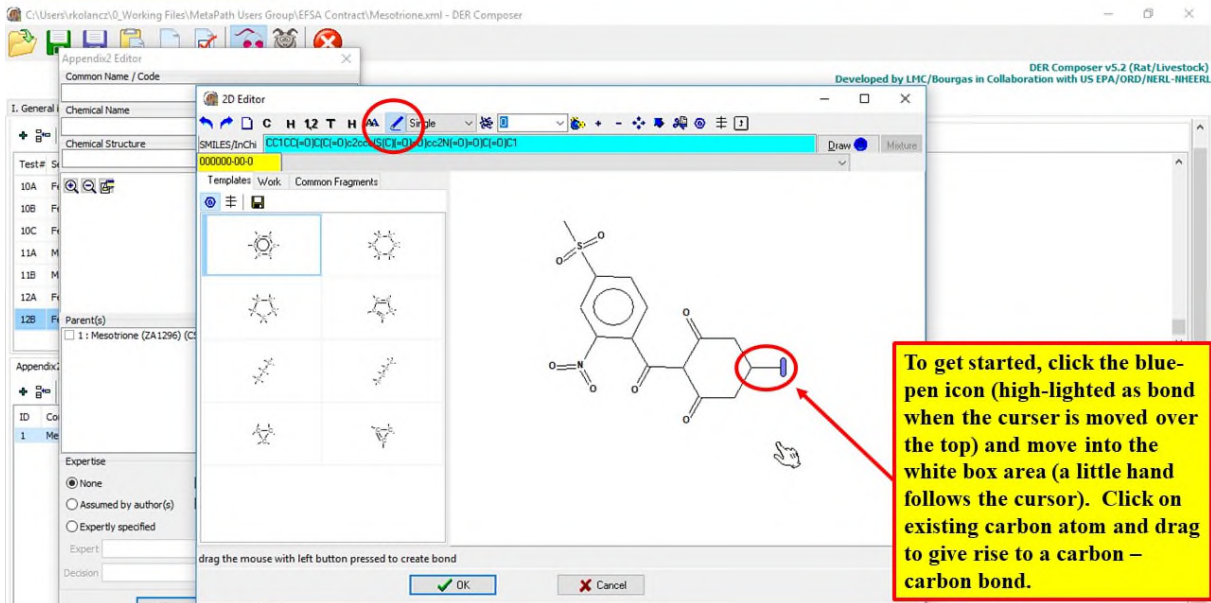
SMILES/InChI: CS(=O)(=O)c1ccc(C(=O)C2C(=O)C(C)C(=O)N(C)C(=O)C2)cc1

Templates / Work Common Fragments

click/drag with: left button to select; right button to move

9:47 AM 2/17/2021

In this example the metabolite is 5-hydroxy-mesotrione. The following steps will introduce a hydroxy group in the 5-position of the dione ring.



DER Composer v5.2 (Rat/Livestock)

Chemical Name: [Empty]

Chemical Structure: SMILES/InChI: CC1(C)C(=O)C(C)=O)c2cc(S(=O)(=O)C(=O)N)cc2N(=O)C1=O

Test# St: 000000-00-0

Parent(s): 1: Mesotrione (ZA1296) (C)

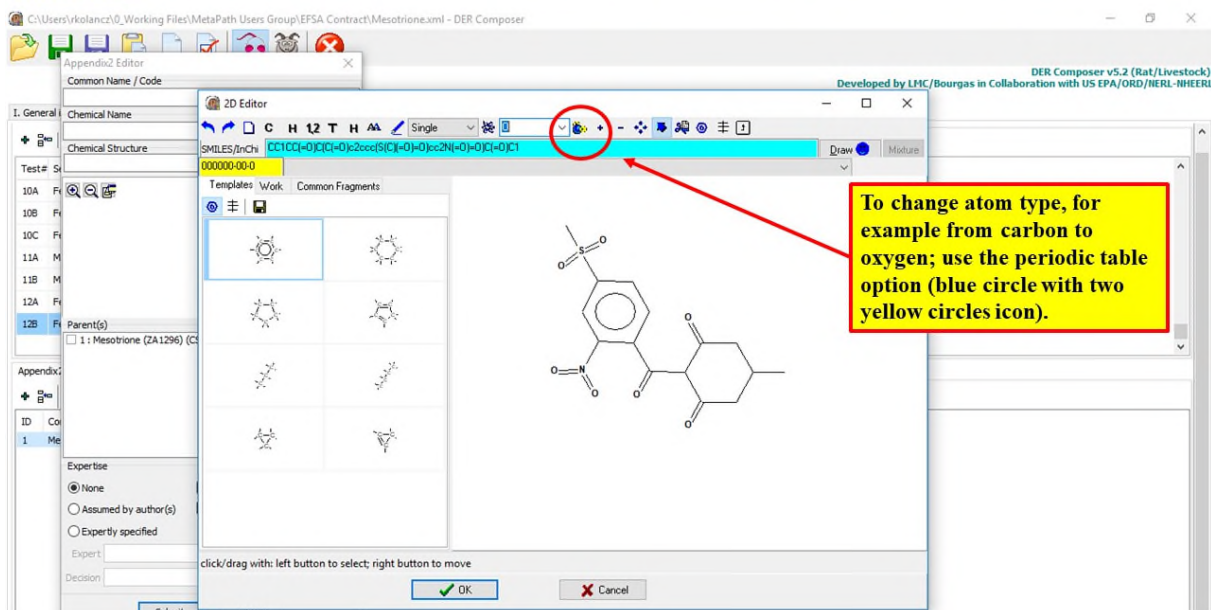
Expertise: None

Decision: OK Cancel

drag the mouse with left button pressed to create bond

To get started, click the blue-pen icon (high-lighted as bond when the cursor is moved over the top) and move into the white box area (a little hand follows the cursor). Click on existing carbon atom and drag to give rise to a carbon – carbon bond.

To change atom type, for example from carbon to oxygen; use the periodic table option (blue circle with two yellow circles icon).



DER Composer v5.2 (Rat/Livestock)

Chemical Name: [Empty]

Chemical Structure: SMILES/InChI: CC1(C)C(=O)C(C)=O)c2cc(S(=O)(=O)C(=O)N)cc2N(=O)C1=O

Test# St: 000000-00-0

Parent(s): 1: Mesotrione (ZA1296) (C)

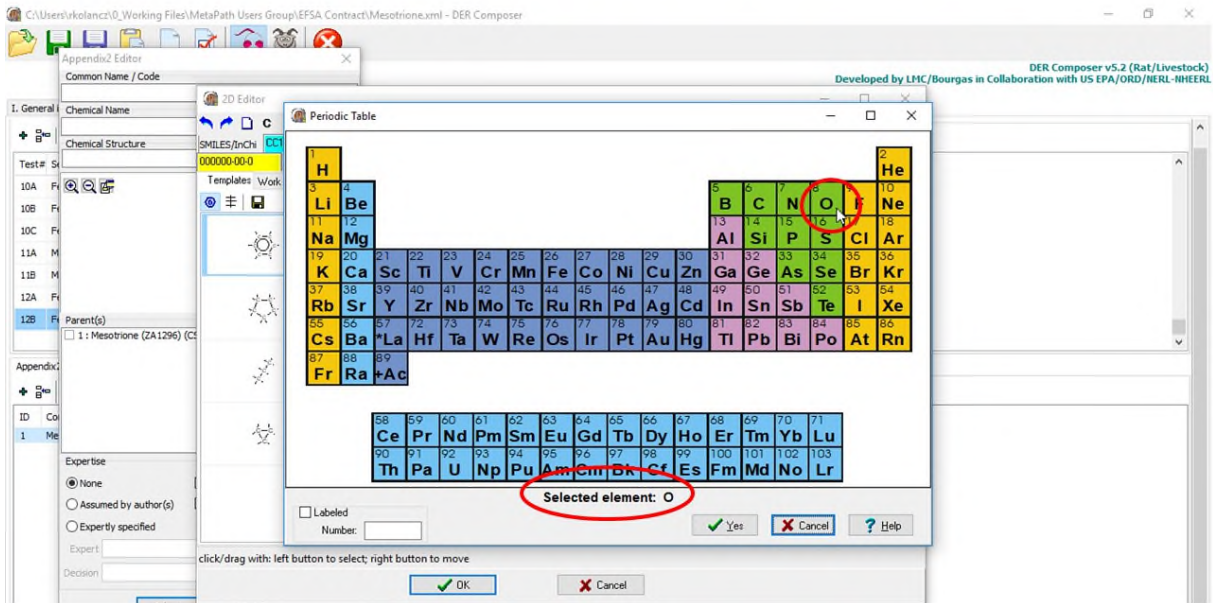
Expertise: None

Decision: OK Cancel

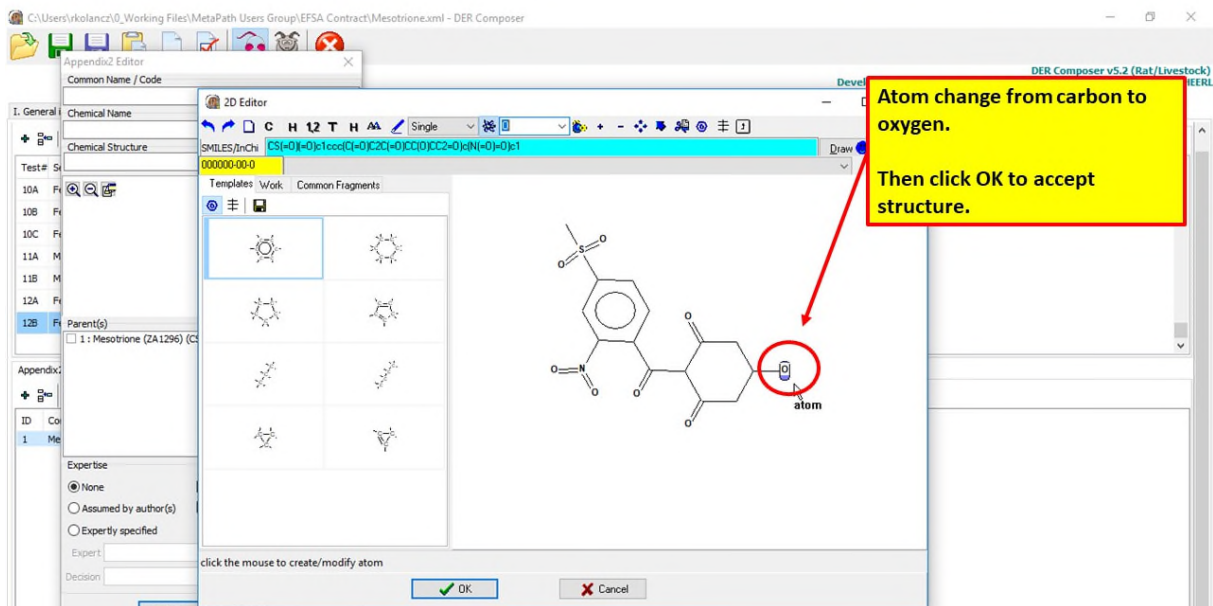
click/drag with: left button to select; right button to move

To change atom type, for example from carbon to oxygen; use the periodic table option (blue circle with two yellow circles icon).

The periodic table opens, click on atom choice, click Yes to accept choice and the table goes away.



Simply click on the atom in the structure that you wish to replace and the substitution will be made.



SMILES for metabolite is entered into EDITOR. Add metabolite name to Chemical Name and check affiliation box of parent structure for this metabolite. Hit Submit to accept.

Check box here to denote connectivity of structure 2 (5-Hydroxy-Mesotriione), the metabolite of the parent structure 1 (Mesotriione).

Then hit submit.

Note: In more complex maps the same metabolite may originate from more than one source.

Continue filling in structures with connectivity information until the resulting table is sufficiently completed to represent the metabolic map.

Editing button to insert a row – highlight row for location and click and insert

Editing button to delete a row – highlight row for deletion and click

Button to edit an existing row – highlight row and click to edit – then make and accept changes

Option to list metabolites, degrades or residues with connectivity (Tree) or simply as a list of those found (List) within a study.

Completed Appendix 2 Metabolite inventory table with structure ID number, name, SMILES and connectivity.

| ID | Common Name / Code | Chemical Name | SMILES | Parent(s) | Expertise |
|----|----------------------|-----------------------|-----------------------------------|-----------|-----------|
| 1 | Mesotriione | Mesotriione (ZA1296) | CS(=O)(=O)c1ccc(C(=O)C2C(=O)O)cc1 | | |
| 2 | 5-Hydroxy-Mesotri... | 5-Hydroxy-Mesotriione | CS(=O)(=O)c1ccc(C(=O)C2C(=O)O)cc1 | 1 | |
| 3 | 4-Hydroxy-Mesotri... | 4-Hydroxy-Mesotriione | CS(=O)(=O)c1ccc(C(=O)C2C(=O)O)cc1 | 1 | |
| 4 | MNSA | MNSA | CS(=O)(=O)c1ccc(C(=O)C2C(=O)O)cc1 | 1 | |
| 5 | Intermediate | Intermediate | CS(=O)(=O)c1ccc(C(=O)C2C(=O)O)cc1 | 1 | by Author |
| 6 | AMBA | AMBA | CS(=O)(=O)c1ccc(C(=O)C2C(=O)O)cc1 | 4,5 | |

Note: Structure #5 is labeled as intermediate and is listed as "Assumed By Author" under expertise which denotes that the metabolite was not found in the study but was implied by the study authors as an intermediate in the metabolic map.

Note: Other expertise may be entered to specify why a given structure was drawn. Example might be unspecified location for ring-hydroxylation that was drawn as a most likely position. Or perhaps a site of glucuronidation on a given structure with an explanation of why it is the most probable.

| ID | Common Name / Code | Expertise |
|----|--------------------|----------------------|
| 1 | Mesotrione | |
| 2 | 5-Hydroxy-Meso | |
| 3 | 4-Hydroxy-Meso | |
| 4 | MNBA | |
| 5 | Intermediate | Assumed by author(s) |
| 6 | AMBA | |

2.6. Material and methods – Study design and methods

Next go back to **II. Materials and methods** tab & sub-tab **B. Study design and methods** and fill in narrative text sections under **1. Group arrangements** and **2. Dosing and sample collection**. Tables 1a auto-populates from Appendix 1.

DER Composer v5.2 (Rat/Livestock)
Developed by LMC/Bourgas in Collaboration with US EPA/ORD/NERL-NHEERL

I. General info II. Materials and methods III. Results IV. Discussion and conclusions V. Appendix VI. Attachments

A. Materials B. Study design and methods

1. Group arrangements
Animals were assigned to the test groups noted in Table 1

| Treatment Group | Sex | Number | Dose Route | Dose (nominal) | Dose (measured) | Dose Type | Remarks |
|-----------------|--------|--------|------------|----------------|-----------------|-----------|------------------------------|
| 6 | Female | 5 | Oral | 1.0mg/kg | 1.02mg/kg | multiple | Feces,Tissue,Urine; "72 hrs" |
| 7 | Male | 5 | I.V. | 1.0mg/kg | 0.99mg/kg | single | Feces,Tissue,Urine; "72 hrs" |
| 8 | Female | 5 | I.V. | 1.0mg/kg | 1.02mg/kg | single | Feces,Tissue,Urine; "72 hrs" |
| 9 | Male | 2 | Oral | 50.0mg/kg | 49.4mg/kg | single | Bile,Feces,Urine; "48 hrs" |
| 10 | Female | 2 | Oral | 50.0mg/kg | 48.5mg/kg | single | Bile,Feces,Urine; "48 hrs" |
| 11 | Male | 2 | Oral | 100.0mg/kg | 104.8mg/kg | single | Feces,Urine; "48 hrs" |
| 12 | Female | 2 | Oral | 100.0mg/kg | 110.7mg/kg | single | Feces,Urine; "48 hrs" |

2. Dosing and sample collection
Briefly describe dosing methods and sample collection

Table 2a

| Treatment Group | Matrix | Sample Time | Major Method | Conjugate Analysis | Analytical Separation | Analytical Detection | Remarks |
|----------------------------|--------|-------------|--------------|--------------------|-----------------------|----------------------|---------|
| 10A, 11A, 12A, 13A, 2A | Urine | | | | | | |
| 10B, 11B, 12B, 13B, 2B | Feces | | | | | | |
| 10C, 11C, 12C, 13C, 5C, 6C | Tissue | | | | | | |
| 10C, 9C | Bile | | | | | | |

Add narrative text throughout within this section.

Down further in **II. Materials and methods** tab & sub-tab **B. Study design and methods** Tables 2a auto-populates part way from Appendix 1.

DER Composer v5.2 (Rat/Livestock)
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I. General info II. Materials and methods III. Results IV. Discussion and conclusions V. Appendix VI. Attachments

A. Materials B. Study design and methods

a. Pharmacokinetic studies
[Briefly describe how samples were handled after harvesting (shipment, storage, etc.) and any preparation that was done prior to extraction.]
[If warranted, include a graphic (i.e., flowchart) of the extraction and fractionation schemes and omit following textual description.]
[Briefly describe the extraction, fractionation and hydrolysis strategies for each tissue. The description should include solvents used (ratios), the order of their use, the extraction procedures employed (i.e., blending, maceration, Soxhlet, etc.) and procedures used to release bound and conjugated residues (i.e., acid, base, or enzyme hydrolysis, exhaustive extraction, etc.). Has the petitioner justified the use of severe conditions (e.g., strong acid hydrolysis)?]

b. Metabolite characterization studies
[Briefly describe the principle of the methods used for identification/characterization of the residues. Specify instrumentation (LSC, TLC, GLC, HPLC, etc.) and detection method used (UV, ECD, FID, etc.). Specify any other methods used to identify and/or confirm bound residues as in protein or lipid fractions.]

3
[The Reviewer considers the analyses used to be appropriate. If inappropriate, provide alternative/rationale]

Modified Rat

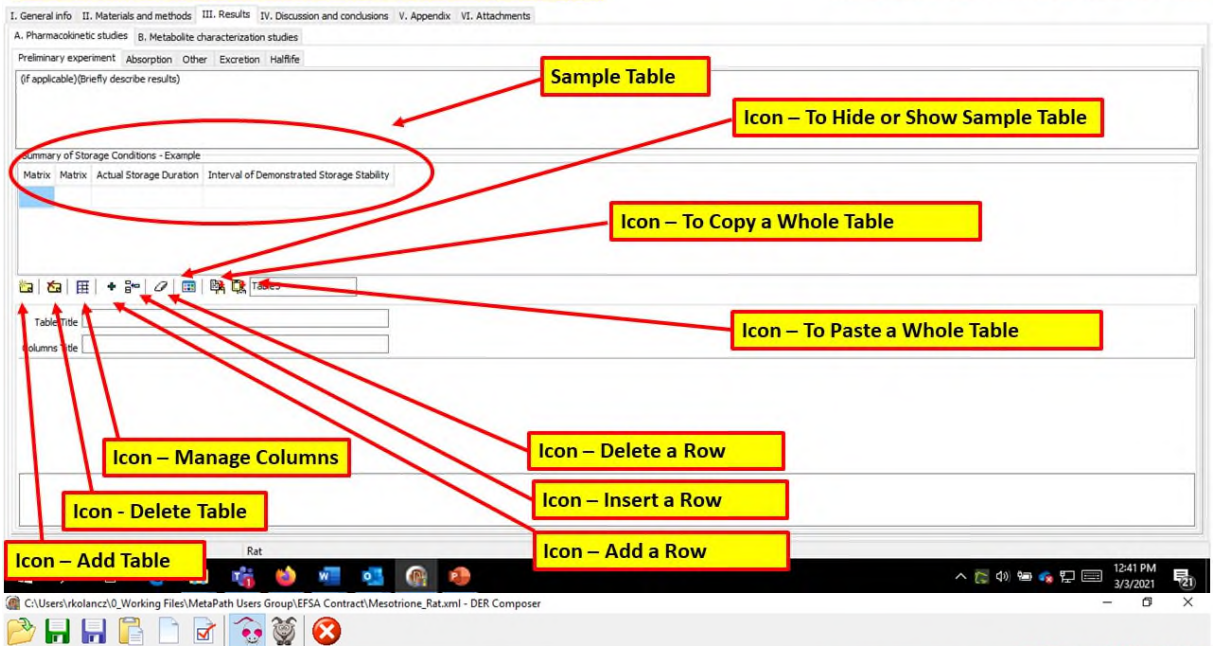
To finish filling out information in Table 2a, move cursor to line in table to be edited and click this EDIT button. The blue-box Table 2 EDITOR will come up.

Make edits and click Submit.

Finish adding text

2.7. Results – Pharmacokinetic Studies

III. Results tab & sub-tab A. Pharmacokinetic studies. There are sub-tabs for preliminary experiment, Absorption, Other, Excretion, and Half-life. Each will display a sample table and table construction will essentially follow the same process for each tab. Below are functions of button bar icons.



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Sample Table

Icon – To Hide or Show Sample Table

Icon – To Copy a Whole Table

Icon – To Paste a Whole Table

Icon – Manage Columns

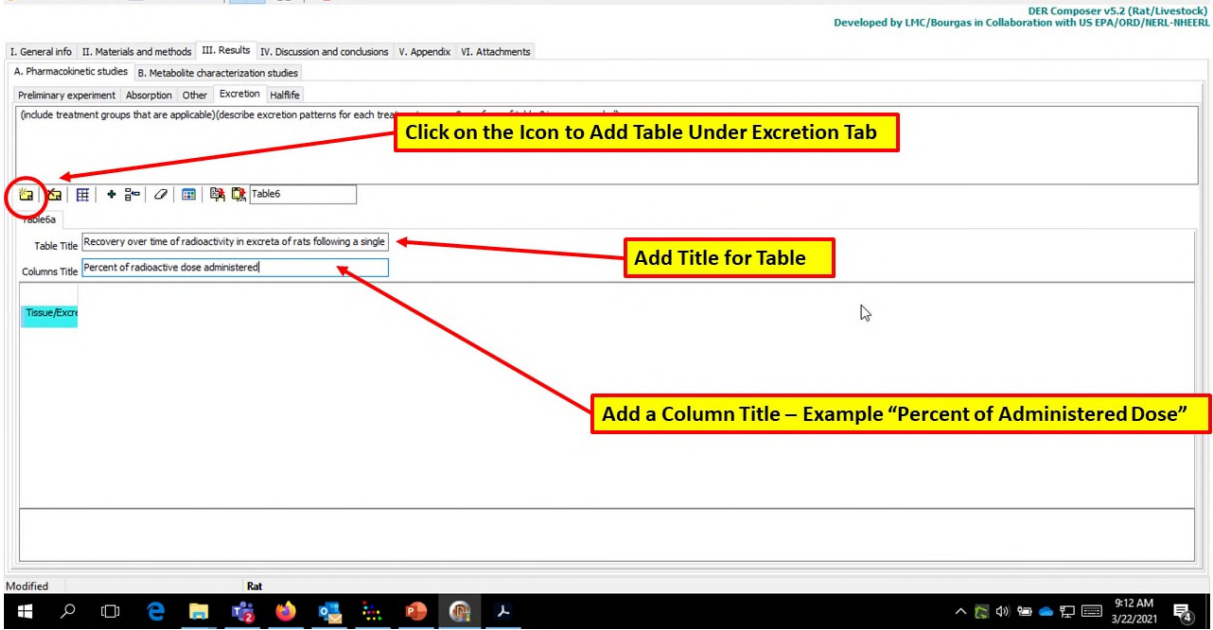
Icon – Delete a Row

Icon – Insert a Row

Icon – Add a Row

Icon – Delete Table

Icon – Add Table



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Click on the Icon to Add Table Under Excretion Tab

Add Title for Table

Add a Column Title – Example “Percent of Administered Dose”

| Tissue/Excr | Percent of radioactive dose administered |
|-------------|------------------------------------------|
| | |

C:\Users\vkolancz\0_Working Files\MetaPath Users Group\EFSA Contract\Mesotrione_Rat.xml - DER Composer

DER Composer v5.2 (Rat/Livestock)
Developed by LMC/Bourgas in Collaboration with US EPA/ORD/NERL-1NHEERL

I. General info II. Materials and methods III. Results IV. Discussion and conclusions V. Appendix VI. Attachments

A. Pharmacokinetic studies B. Metabolite characterization studies

Preliminary experiment Absorption Other Excretion Half-life

(include treatment groups that are applicable)(describe excretion patterns for each treatment group)

Click on Manage Column Icon – Brings up Editor Box

Columns Editor

Entered tests

| Test | Matrix | Column | General Label |
|------|--------|--------|---------------|
| | | 6 hr | male |

Custom Column: 12 hr Add

General Column Label: male Set

Add Custom Column Ex/ "12 hr" and Click Add

Add General Column Label Ex/ "male" by Clicking on Custom Column Above and then Set to Affix Label

Continue by Adding Custom Columns & Labels Until the Time Points 6, 12, 24, 36, 48, 72 hrs and Total are Created for Both Males and Females

Modified Rat

C:\Users\vkolancz\0_Working Files\MetaPath Users Group\EFSA Contract\Mesotrione_Rat.xml - DER Composer

DER Composer v5.2 (Rat/Livestock)
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I. General info II. Materials and methods III. Results IV. Discussion and conclusions V. Appendix VI. Attachments

A. Pharmacokinetic studies B. Metabolite characterization studies

Preliminary experiment Absorption Other Excretion Half-life

(include treatment groups that are applicable)(describe excretion patterns for each treatment group)

Completed Addition of Custom Columns & Labels for the Time Points 6, 12, 24, 36, 48, 72 hrs and Total for Both Males and Females

Columns Editor

| Test | Matrix | Column | General Label |
|------|--------|--------|---------------|
| | | 24 hr | female |
| | | 36 hr | female |
| | | 48 hr | female |
| | | 72 hr | female |
| | | Total | female |

Custom Column: Add

General Column Label: female Set

Click Close When Done with Editor

Modified Rat

C:\Users\rkolancz\0_Working Files\MetaPath Users Group\EFSA Contract\Mesotrione_Rat.xml - DER Composer

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I. General info II. Materials and methods III. Results IV. Discussion and conclusions V. Appendix VI. Attachments

A. Pharmacokinetic studies B. Metabolite characterization studies

Preliminary experiment Absorption Other Excretion Halflife

(include treatment groups that are applicable)(describe excretion patterns for each treatment group. Some form of table 3 is recommended)

Table6

Table Title Recovery over time of radioactivity in excreta of rats following a single

Columns Title Percent of radioactive dose administered

| Tissue/Excr | male 6 hr | male 12 hr | male 24 hr | male 36 hr | male 48 hr | male 72 hr | male Total | female 6 hr | female 12 hr | female 24 hr | female 36 hr | female 48 hr | female 72 hr | female Total |
|-------------|--------------|---------------|---------------|---------------|---------------|---------------|---------------|----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|-------------|--------------|---------------|---------------|---------------|---------------|---------------|---------------|----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|

Add Rows to Table

Modified Rat

C:\Users\rkolancz\0_Working Files\MetaPath Users Group\EFSA Contract\Mesotrione_Rat.xml - DER Composer

DER Composer v5.2 (Rat/Livestock)
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I. General info II. Materials and methods III. Results IV. Discussion and conclusions V. Appendix VI. Attachments

A. Pharmacokinetic studies B. Metabolite characterization studies

Preliminary experiment Absorption Other Excretion Halflife

(include treatment groups that are applicable)(describe excretion patterns for each treatment group. Some form of table 3 is recommended)

Table6

Table Title Recovery over time of radioactivity in excreta of rats following a single

Columns Title Percent of radioactive dose administered Enter a single numerical entry or "+"

| Tissue/Excreta | male 6 hr | male 12 hr | male 24 hr | male 36 hr | male 48 hr | male 72 hr | male Total | female 6 hr | female 12 hr | female 24 hr | female 36 hr | female 48 hr | female 72 hr | female Total |
|----------------|--------------|---------------|---------------|---------------|---------------|---------------|---------------|----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Urine | 44.02 | 7.16 | 1.77 | 0.51 | 0.33 | 0.36 | 54.15 | 44.49 | 5.63 | 3.05 | 0.97 | 0.84 | 0.90 | 55.88 |
| Feces | | 12.12 | 9.23 | 1.94 | 0.72 | 0.50 | 24.50 | 8.92 | 11.29 | 2.15 | 0.82 | 0.62 | 0.62 | 23.80 |
| Total | 44.02 | 19.28 | 11.00 | 2.45 | 1.05 | 0.86 | 78.65 | 44.49 | 14.55 | 14.34 | 3.12 | 1.66 | 1.52 | 79.68 |

Population of Values to Complete the Table

Rows Added to Table

Modified Rat

10:44 AM
3/22/2021

C:\Users\kolancz\0_Working Files\MetaPath Users Group\EFSA Contract\Mesotrione_Rat.xml - DER Composer

DER Composer v5.2 (Rat/Livestock)
Developed by LMC/Bourgais in Collaboration with US EPA/ORD/NERL-NHEERL

I. General info II. Materials and methods III. Results IV. Discussion and conclusions V. Appendix VI. Attachments

A. Pharmacokinetic studies B. Metabolite characterization studies

Preliminary experiment Absorption Other Excretion Half-life

Absorption and excretion - Following a single oral dose of [¹⁴C- aromatic]mesotrione at 5.0 mg/kg, excretion in the urine for the males was rapid with 54.1-58.6% of the dose being excreted in the urine within 6 hours of dosing (Table 2), equivalent to 75-88% of the total urinary excretion. In the single male kept to 48 hours, overall excretion in urine and feces, was essentially complete within 24 hours and accounted for 90.2% of the dose, equivalent to 97% of the total excretion. Following oral dosing of [¹⁴C- aromatic]mesotrione at 5.0 mg/kg, excretion in the urine for the females was slower than the males with only 19.3-20.9% of the dose being excreted in the urine within 6 hours of dosing, equivalent to 39-46% of the total urinary excretion. In the single female kept to 48 hours, overall excretion in urine and feces, was essentially complete within 24 hours and accounted for 48.1% of the dose, equivalent to 64% of the total excretion. Recovery of total radioactivity was lower in females when compared to males with only 52.9-75.6% of the total administered dose recovered for the females vs 92.8-100.9% of the dose recovered for the males. Less than 0.1% of the dose was recovered from exhaled air in both sexes.

Tables

Table 5a Table 5b Table 5c Table 5d

Table Title: Recovery over time of radioactivity in excreta of rats following a single

Columns Title: Percent of radioactive dose administered

| | male | male | male | male | male | male | male | female | female | female | female | female | female | female |
|----------------|-------|-------|-------|-------|-------|-------|-------|--------|--------|--------|--------|--------|--------|--------|
| Tissue/Excreta | 6 hr | 12 hr | 24 hr | 36 hr | 48 hr | 72 hr | Total | 6 hr | 12 hr | 24 hr | 36 hr | 48 hr | 72 hr | Total |
| Urine | 70.68 | 5.85 | 1.65 | 0.62 | 0.40 | 0.19 | 79.39 | 75.06 | 4.75 | 2.15 | 1.14 | 0.59 | 0.45 | 84.14 |
| Feces | 2.61 | 3.05 | 0.69 | 0.28 | 0.24 | 6.77 | | 0.71 | 1.08 | 0.21 | 0.19 | 0.16 | 2.35 | |
| Total | 70.68 | 8.46 | 4.70 | 1.21 | 0.68 | 0.43 | 86.16 | 75.06 | 5.46 | 3.23 | 1.35 | 0.78 | 0.61 | 86.49 |

Population of Text

Addition of Multiple Tables

Modified Rat

Windows Taskbar: 3:04 PM 3/22/2021

2.8. Results – Metabolite Characterization Studies

C:\Users\lrolanca\0_Working Files\MetaPath Users Group\EFSA Contract\Mesotrione_Rat.xml - DER Composer

DER Composer v5.2 (Rat/Livestock)
Developed by LMC/Bourgais in Collaboration with US EPA/ORD/NERL-NHEERL

I. General info II. Materials and methods III. Results IV. Discussion and conclusions V. Appendix VI. Attachments

A. Pharmacokinetic studies B. Metabolite characterization studies

aromatic) mesotrione either iv at a target dose of 1.00 mg/kg or orally (gavage) at target doses of 1.00 or 100 mg/kg or 1.00 mg/kg/day. A group composed for bile-duct cannulated rats (2/sex) were also dosed once orally with [14C-aromatic]mesotrione at 50 mg/kg to examine biliary excretion. To assess the effect of 14C-label position within the molecule on metabolism and excretion, a final group of bile-duct cannulated rats (2/sex) was dosed once orally with [14C-dione]mesotrione at a target dose of 50 mg/kg.

Animals were randomly assigned to dose groups. Actual average doses for each test group are presented in Table 1 and were within 96-102% of the nominal 1.00 mg/kg dose, 94-99% of the nominal 50.0 mg/kg dose, and 99-111 % of the nominal 100 mg/kg dose.

Also is Critical to Use the Treatment Groups as Described in Appendix 1. We Need to Conserve the Relationship Between Treatment Group and Metabolite in the Interest of Maintaining the Highlight Treatment Group Function. Click on this Icon for Access to a Listing of Potential Columns when Constructing the Table(s).

Under Metabolite Characterization Tab – When a New Table is Added a List of Metabolites (From Appendix 2) Are Automatically Populated. This is Important as These Exact Names are Critical for the Eventual Import into MetaPath Regarding the “Highlight Treatment Group” Function.

Modified Rat

Metabolic Pathways - application ver.3.20.8, database ver.3.1.0 - Regulatory06_771_June 2020_v3.3.0.MTB, logged in as "administrator"

Developed by LMC Bourgais in collaboration with US EPA / ORD / NERL-NHEERL

Locked by: administrator

Regulatory ID quick search

Value

1. 220899-03-6; Metrafenone [B] 2. 220899-03-6; Metrafenone [I] 3. 148677-41-8; Bifenazate [14C] 4. 28057-48-9; d-Trans-Allethrin 5. 28057-48-9; d-Trans-Allethrin 6. 150114-71-9; Amisopryal [p] 7. 57960-19-7; Acequinolol [sds] 8. 57960-19-7; Acequinolol [she] 9. 741-58-2; Bensulide [phenyl/r] 10. 335104-84-2; Tembotrione [I] 11. 335104-84-2; Tembotrione [I] 12. 420-04-2; Clovamide [C-14] 13. 8018-01-7; Mancozeb [14C-e] 14. 239110-15-7; Flupoxazole [1v] 15. 239110-15-7; Flupoxazole [p] 16. 272451-65-7; Flubendazole 17. 272451-65-7; Flubendazole 18. 272451-65-7; Flubendazole

ILPAC name Metrafenone; [3-bromo-6-me Name Metrafenone [Bromophenyl-6 CAS 220899-03-6 SMILES Cc1cc(OCC)c(OCC)c1C=C

Double-click for display options

Tree Results, met. Results, PK

CAS:220899-03-6; Metrafenone [Bromophenyl-6-14C] [BAS 560F] Rat, in vivo (x8)

Metrafenone (BAS 560F)

CL 3000402 CL 378991 CL 437423 CL 377160 1Xnterm to CL1500700

CL 1023427 CL 1500701 CL 1500699 CL 377096 CL 1500698 CL 1500700

CL 1500702 CL 1500697

Metabolic Pathways - Highlight treatment groups

Common fields: Rat; in vivo; oral; 10 mg/kg; nominal measured dose; radiolabeled parent; single dose; Sprague-Dawley (Cr:CD BR); single oral low dose; 168 h

Coloring and specifics:

- [a] male; urine
- [b] male; feces
- [c] male; cage wash
- [d] male; tissues
- [e] female; urine
- [f] female; feces
- [g] female; cage wash

Treatment group: Rat; Female; in vivo; feces; oral; 10 mg/kg; single dose (radiolabeled), Sprague-Dawley (Cr:CD BR), 168 h

Citations: Hillquist, N.M. (2002) BAS 560F (AC 375839): absorption, distribution, metabolism, and excretion study in the rat. BASF Corporation, BASF Agro Research, Princeton, NJ, and Xenobiotic Laboratories, Inc., Parsippany, NJ. Laboratory Project Identification: 98025, April 30, 2002. MRID 46415747. Unpublished.

Subjects:

- Species - Rat
- Gender - Female (5 subjects)
- Weight - Between 150 - 350 grams (female)
- Age - Between 5 - 10 weeks old
- Strain - Sprague-Dawley (Cr:CD BR)
- Source - Charles River Laboratories (Kingston, NY) for normal animals; Hilltop Lab Animals (Scottsdale, PA) for bile-duct cannulated animals
- Housing - For the preliminary excretion study, rats were housed individually in glass metabolism cages. For all other studies, rats were housed individually in stainless steel metabolism cages
- Diet - Lab Diet 5002 certified rodent diet (PMI Nutrition, St. Louis, MO), ad libitum
- Water - Tap water, ad libitum

Environmental conditions:

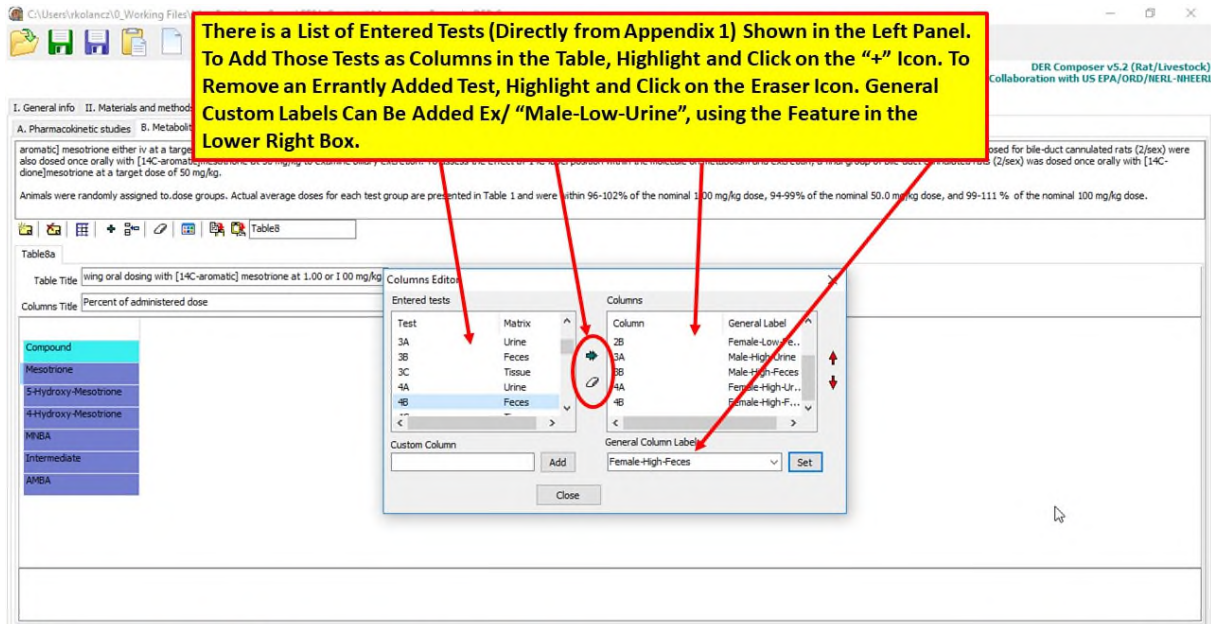
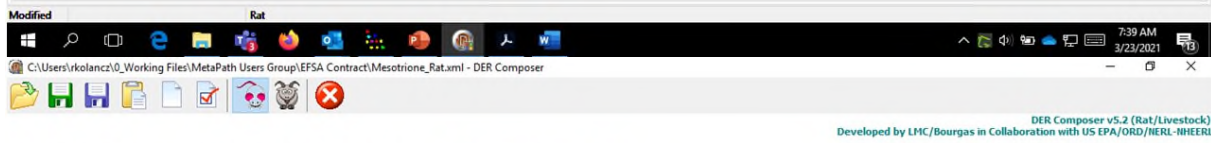
- Env. temperature - Between 16 - 24 °C
- Humidity - Between 30 - 70 %
- Air changes - Not provided
- Photoperiod - 12 h light/12 h dark

In vivo / in vitro:

- In vivo
- Excer. descriptors (General) - single oral low dose

Critical to Use the Treatment Groups as Described in Appendix 1. We Need to Conserve the Relationship Between Treatment Group and Metabolite in the Interest of Maintaining the Highlight Treatment Group Function in MetaPath.

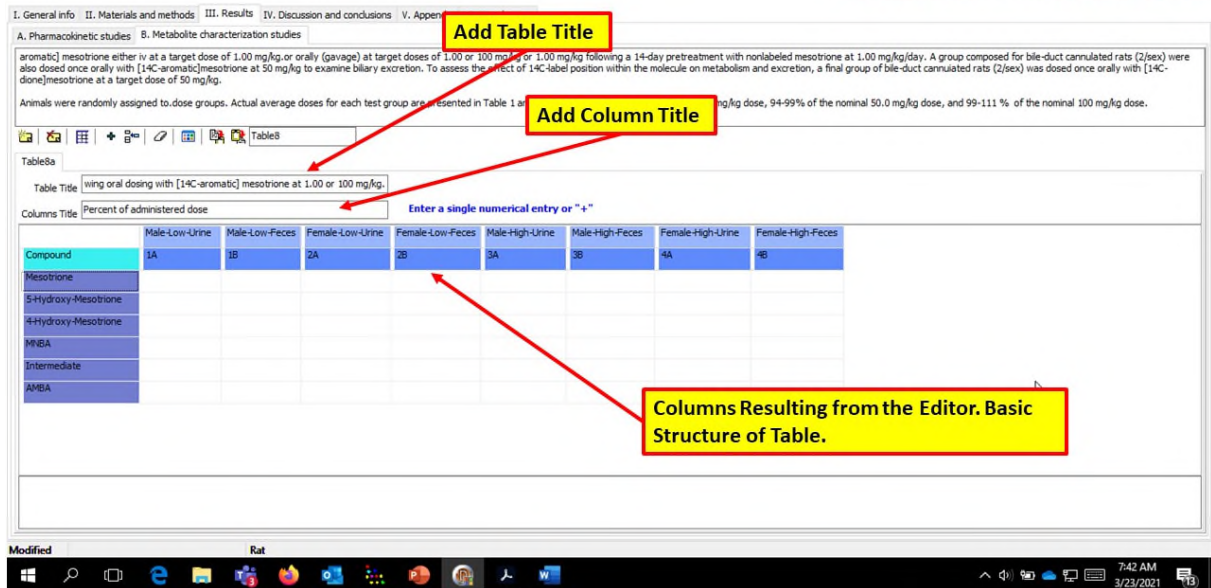
There is a List of Entered Tests (Directly from Appendix 1) Shown in the Left Panel. To Add Those Tests as Columns in the Table, Highlight and Click on the “+” Icon. To Remove an Errantly Added Test, Highlight and Click on the Eraser Icon. General Custom Labels Can Be Added Ex/ “Male-Low-Urine”, using the Feature in the Lower Right Box.

Add Table Title

Add Column Title

Columns Resulting from the Editor. Basic Structure of Table.



| Compound | Male-Low-Urine 3A | Male-Low-Feces 3B | Female-Low-Urine 2A | Female-Low-Feces 2B | Male-High-Urine 3A | Male-High-Feces 3B | Female-High-Urine 4A | Female-High-Feces 4B |
|----------------------|----------------------|----------------------|------------------------|------------------------|-----------------------|-----------------------|-------------------------|-------------------------|
| Mesotrione | | | | | | | | |
| 5-Hydroxy-Mesotrione | | | | | | | | |
| 4-Hydroxy-Mesotrione | | | | | | | | |
| MNBA | | | | | | | | |
| Intermediate | | | | | | | | |
| AMBA | | | | | | | | |

C:\Users\kolancz\0_Working Files\MetaPath Users Group\EFSA Contract\Mesotriene_Rat.xml - DER Composer

DER Composer v5.2 (Rat/Livestock)
Developed by LMC/Bourgas in Collaboration with US EPA/ORD/NERL-NHEERL

I. General info II. Materials and methods III. Results IV. Discussion and conclusions V. Appendix VI. Attachments

A. Pharmacokinetic studies B. Metabolite characterization studies

aromatic] mesotriene either iv at a target dose of 1.00 mg/kg or orally (gavage) at target doses of 1.00 or 100 mg/kg or 1.00 mg/kg following a 14-day pretreatment with nonlabeled mesotriene at 1.00 mg/kg/day. A group composed for bile-duct cannulated rats (2/sex) were also dosed once orally with [14C-aromatic]mesotriene at 50 mg/kg to examine biliary excretion. To assess the effect of 14C-label position within the molecule on metabolism and excretion, a final group of bile-duct cannulated rats (2/sex) was dosed once orally with [14C-dione]mesotriene at a target dose of 50 mg/kg.

Animals were randomly assigned to dose groups. Actual average doses for each test group are presented in Table 1 and were within 96-102% of the nominal 1.00 mg/kg dose, 94-99% of the nominal 50.0 mg/kg dose, and 99-111 % of the nominal 100 mg/kg dose.

TableSa

Table Title: [wing oral dosing with [14C-aromatic] mesotriene at 1.00 or 100 mg/kg.]

Columns Title: Percent of administered dose

Enter a single numerical entry or "+"

| Compound | Male-Low-Urine | | Male-Low-Feces | | Female-Low-Urine | | Female-Low-Feces | | Male-High-Urine | | Male-High-Feces | | Female-High-Urine | | Female-High-Feces | |
|----------------------|----------------|----|----------------|----|------------------|----|------------------|----|-----------------|----|-----------------|----|-------------------|----|-------------------|----|
| | 1A | 1B | 2A | 2B | 3A | 3B | 4A | 4B | 5A | 5B | 6A | 6B | 7A | 7B | 8A | 8B |
| Mesotriene | 47 | 3 | 53 | 7 | 56 | 8 | 59 | 3 | | | | | | | | |
| 5-Hydroxy-Mesotriene | | 2 | | | | 2 | | | | | | | | | | 2 |
| 4-Hydroxy-Mesotriene | 5 | | 1 | | | 3 | | | | | | | | | | |
| MNBA | | 1 | 1 | 2 | 1 | 2 | 1 | 1 | | | | | | | | 1 |
| Intermediate | | | | | | | | | | | | | | | | |
| AMBA | 1 | 2 | | 5 | | 5 | | | | | | | | | | 12 |

If a Metabolite is **NOT** found in a Treatment Group, Leave the Cell Blank. **DO NOT** Populate with a N.D. or "-".

Wherever a Value (Numerical) is Placed within a Cell, it Indicates an Established Correspondence Between Treatment Group and Metabolite. This will then Pass into MetaPath upon Import defining the "Highlight Treatment Group" Function.

Modified Rat

C:\Users\kolancz\0_Working Files\MetaPath Users Group\EFSA Contract\Mesotriene_Rat.xml - DER Composer

DER Composer v5.2 (Rat/Livestock)
Developed by LMC/Bourgas in Collaboration with US EPA/ORD/NERL-NHEERL

I. General info II. Materials and methods III. Results IV. Discussion and conclusions V. Appendix VI. Attachments

A. Pharmacokinetic studies B. Metabolite characterization studies

aromatic] mesotriene either iv at a target dose of 1.00 mg/kg or orally (gavage) at target doses of 1.00 or 100 mg/kg or 1.00 mg/kg following a 14-day pretreatment with nonlabeled mesotriene at 1.00 mg/kg/day. A group composed for bile-duct cannulated rats (2/sex) were also dosed once orally with [14C-aromatic]mesotriene at 50 mg/kg to examine biliary excretion. To assess the effect of 14C-label position within the molecule on metabolism and excretion, a final group of bile-duct cannulated rats (2/sex) was dosed once orally with [14C-dione]mesotriene at a target dose of 50 mg/kg.

Animals were randomly assigned to dose groups. Actual average doses for each test group are presented in Table 1 and were within 96-102% of the nominal 1.00 mg/kg dose, 94-99% of the nominal 50.0 mg/kg dose, and 99-111 % of the nominal 100 mg/kg dose.

TableSa

Table Title: [1.00 or 100 mg/kg.]

Columns Title: Percent of administered dose

| Compound | Male-Low-Urine | | Male-Low-Feces | | Female-Low-Urine | | Female-Low-Feces | | Male-High-Urine | | Male-High-Feces | | Female-High-Urine | | Female-High-Feces | |
|--------------------------|----------------|----|----------------|----|------------------|----|------------------|----|-----------------|----|-----------------|----|-------------------|----|-------------------|----|
| | 1A | 1B | 2A | 2B | 3A | 3B | 4A | 4B | 5A | 5B | 6A | 6B | 7A | 7B | 8A | 8B |
| 5-Hydroxy-Mesotriene | | 2 | | | | 2 | | | | | | | | | | 2 |
| 4-Hydroxy-Mesotriene | 5 | | 1 | | | 3 | | | | | | | | | | |
| MNBA | | 1 | 1 | 2 | 1 | 2 | 1 | 1 | | | | | | | | 1 |
| Intermediate | | | | | | | | | | | | | | | | |
| AMBA | 1 | 2 | | 5 | | 5 | | | | | | | | | | 12 |
| Unidentified Metabolites | | | | | | | | | | | | | | | | |
| Tissues | | | | | | | | | | | | | | | | |
| Cage Wash | | | | | | | | | | | | | | | | |
| Total Accounted For | | | | | | | | | | | | | | | | |

Use These Icons to Add or Insert a New Row

To Finish the Table, Additional Rows can be Added to Describe for Ex/ "Unidentified Metabolites", "Tissues", "Cage Wash", and "Total Accounted For", etc....

Modified Rat

C:\Users\kolancz\0_Working Files\MetaPath Users Group\EFSA Contract\Mesotriene_Rat.xml - DER Composer

DER Composer v5.2 (Rat/Livestock)
Developed by LMC/Bourgas in Collaboration with US EPA/ORD/NERL-NHEERL

2.9. Conclusions, XML saving and Report generator

Please respect the following nomenclature when naming the DER XML file:

- Mammalian toxicology metabolism studies: id_activesubstance_mt_species_vX.xml (e.g. id_quinmerac_mt_rat_v1).

Please noted that id means identification number. The applicant might decide to give a specific identification number to the file. EFSA will allocate an id called CardNo to the file once integrated into the regulatory MetaPath database.

C:\Users\kalin\OneDrive\Working Files\MetaPath Users Group\EFSA Contract\Mesotriene_Rat.xml - DER Composer

DER Composer v5.2 (Rat/Livestock)
Developed by LMC/Bourgas in Collaboration with US EPA/ORD/NREL-NHEERL

I. General info II. Materials and methods III. Results IV. Discussion and conclusions V. Appendix VI. Attachments

A. Pharmacokinetic studies B. Metabolite characterization studies

B. Study Design - These studies were designed to determine the absorption, metabolism, distribution, and excretion of [14C]mesotriene in rats as a function of single or repeated oral dosing, or a single intravenous dose. A preliminary study consisted of two groups of Alpk:APISD rats (2/sex/dose group) that were dosed once with [14C-aromatic]mesotriene or [14C-dione]mesotriene at a target dose of 5 mg/kg. The main mass balance study consisted of four groups of Alpk:APISD rats (5/sex/dose group) that were dosed once with [14C-aromatic] mesotriene either iv at a target dose of 1.00 mg/kg, or orally (gavage) at target doses of 1.00 or 10.0 mg/kg. A group composed of bile-duct cannulated rats (2/sex) were also dosed once orally with [14C-aromatic]mesotriene at 50 mg/kg to examine biliary excretion. To assess the excretion of [14C-dione]mesotriene at a target dose of 50 mg/kg, a final group of bile-duct cannulated rats (2/sex) was dosed once orally with [14C-

Save or Save As the XML

Might be a good idea to do frequent saves of your work during the data capture process.

TableSa

Table Title: 1.00 or 100 mg/kg.

Columns Title: Percent of administered dose

| Compound | Male-Low-Urine | | Male-Low-Feces | | Female-Low-Urine | | Female-High-Feces | |
|--------------------------|----------------|----|----------------|----|------------------|----|-------------------|----|
| | 1A | 1B | 2A | 2B | 3A | 3B | 4A | 4B |
| 5-Hydroxy-Mesotriene | | 2 | | | | | 2 | 2 |
| 4-Hydroxy-Mesotriene | 5 | 1 | | | | 3 | | |
| MNBA | | 1 | 1 | 2 | 1 | 2 | 1 | 1 |
| Intermediate | | | | | | | | |
| AMBA | 1 | 2 | | 5 | | 5 | | 12 |
| Unidentified Metabolites | 12 | 8 | 11 | 1 | 6 | 4 | 5 | 5 |
| Tissues | 7 | | 6 | | 9 | | 3 | |
| Cage Wash | 7 | | 12 | | 5 | | 8 | |
| Total Accounted For | 79 | 17 | 83 | 15 | 80 | 21 | 76 | 23 |

Modified: Rat

I. General info II. Materials and methods III. Results IV. Discussion and conclusions V. Appendix VI. Attachments

Appendix 1a

| Test# | Sex | Number | Dose Route | Dose (nominal) | Dose (measured) | Dose Type | Test Duration | Matrix | Experimental Descriptor | Remarks |
|-------|--------|--------|------------|----------------|-----------------|-----------|---------------|--------|-------------------------|----------------------------------------|
| 1A | Male | 5 | Oral | 100 mg/kg | 100.11 mg/kg | single | 72 hrs | Urine | | pooled samples of urine and feces from |
| 1B | Male | 5 | Oral | 100 mg/kg | 100.11 mg/kg | single | 72 hrs | Feces | | pooled samples of urine and feces from |
| 1C | Male | 5 | Oral | 100 mg/kg | 100.11 mg/kg | single | 72 hrs | Tissue | | pooled samples of urine and feces from |
| 2A | Female | 5 | Oral | 100 mg/kg | 98.79 mg/kg | single | 72 hrs | Urine | | pooled samples of urine and feces from |
| 2B | Female | 5 | Oral | 100 mg/kg | 98.79 mg/kg | single | 72 hrs | | | |
| 2C | Female | 5 | Oral | 100 mg/kg | 98.79 mg/kg | single | 72 hrs | | | |
| 3A | Male | 5 | Oral | 1.0 mg/kg | 1.0 mg/kg | single | 72 hrs | | | |
| 3B | Male | 5 | Oral | 1.0 mg/kg | 1.0 mg/kg | single | 72 hrs | | | |

Appendix 2

| ID | Common Name / Code | Chemical Name | SMILES | Par |
|----|----------------------|----------------------|---------------------------------|-----|
| 1 | Mesotriene | Mesotriene (Z11296) | CS(=O)(=O)c1ccc(C(=O)C2C(=O)... | |
| 2 | 5-Hydroxy-Mesotri... | 5-Hydroxy-Mesotriene | CS(=O)(=O)c1ccc(C(=O)C2C(=O)... | 1 |
| 3 | 4-Hydroxy-Mesotri... | 4-Hydroxy-Mesotriene | CS(=O)(=O)c1ccc(C(=O)C2C(=O)... | 1 |
| 4 | MNBA | MNBA | CS(=O)(=O)c1ccc(C(=O)C2C(=O)... | 1 |
| 5 | Intermediate | Intermediate | CS(=O)(=O)c1ccc(C(=O)C2C(=O)... | 1 |
| 6 | AMBA | AMBA | CS(=O)(=O)c1ccc(C(=O)C2C(=O)... | 4,5 |

Save As

Organize ▾ New folder

Name: Mesotriene_Rat.xml

Date modified: 4/13/2021 10:24 AM

Type: XML Document

Size: 54

File name: D:\0_Working Files\MetaPath Users Group\EFSA Contract\Mesotriene_Rat.xml

Save as type: XML File (*.xml)

Save Cancel

Rat

C:\Users\vkolancz\OneDrive\Working Files\MetaPath Users Group\EFSA Contract\Mesotrione_Rat.xml - DER Composer

DER Composer v5.2 (Rat/Livestock)
Developed by LMC/Bourgas in Collaboration with US EPA/ORD/NERL-NHEERL

I. General info II. Materials and methods III. Results IV. Discussion and conclusions V. Appendix VI. Attachments

A. Pharmacokinetic studies B. Metabolite characterization studies

B. Study Design - These studies were designed to determine the absorption, metabolism, distribution, and excretion of [14C]mesotrione in rats as a function of single or repeated oral dosing, or a single intravenous dose. A preliminary study consisted of two groups of Alpk:APSD rats (2/sex/dose group) that were dosed once with [14C-aromatic]mesotrione or [14C-dione]mesotrione at a target dose of 5 mg/kg. The main mass balance study consisted of four groups of Alpk:APSD rats (5/sex/dose group) that were dosed once with [14C-aromatic] mesotrione either iv at a target dose of 1.00 mg/kg or orally (gavage) at target doses of 1.00 or 5.00 mg/kg. A group composed of biliary excretion. To assess the excretion of [14C-dione]mesotrione at a target dose of 50 mg/kg, a final group of bile-duct cannulated rats (2/sex) was dosed once orally with [14C-dione]mesotrione at a target dose of 50 mg/kg.

Generate the WORD Document.
The WORD Document can then be Modified as you would any WORD Document to Conform to Report Style and Content.

| Compound | Male-Low-Urine | | Male-Low-Feces | | Female-Low-Urine | | Female-Low-Feces | |
|--------------------------|----------------|----|----------------|----|------------------|----|------------------|----|
| | 1A | 1B | 2A | 2B | 3A | 3B | 4A | 4B |
| 5-Hydroxy-Mesotrione | | 2 | | | | 2 | | 2 |
| 4-Hydroxy-Mesotrione | 5 | 1 | | | 3 | | | |
| MNBA | | 1 | 1 | 2 | 1 | 2 | 1 | 1 |
| Intermediate | | | | | | | | |
| AMBA | 1 | 2 | | 5 | | 5 | | 12 |
| Unidentified Metabolites | 12 | 8 | 11 | 1 | 6 | 4 | 5 | 5 |
| Tissues | 7 | | 6 | | 9 | | 3 | |
| Cage Wash | 7 | | 12 | | 5 | | 8 | |
| Total Accounted For | 79 | 17 | 83 | 15 | 80 | 21 | 76 | 23 |

Modified Rat

AutoSave rendered:docx - Compatibility Mode - Saved to this PC Kolarczyk, Richard 1:24 PM 3/23/2021

File Home Insert Draw Design Layout References Mailings Review View Help Acrobat

Clipboard Font Paragraph Styles Editing

DATA EVALUATION RECORD

STUDY TYPE: Metabolism rat; OPPTS 870.7485[85-1]; OECD 417

AGENCY CODE(S): (CAS NUMBER) 104206-82-8, (US EPA PC CODE) 122990
DP BARCODE:
SUBMISSION NO.:

TEST MATERIAL COMMON NAME: Mesotrione

TEST MATERIAL PURITY: >98.1 %

IUPAC NAME: 2-[4-(Methylsulfonyl)-2-nitrobenzoyl]cyclohexane-1,3-dione

SYNONYMS: ZA1296;

END-USE PRODUCT:

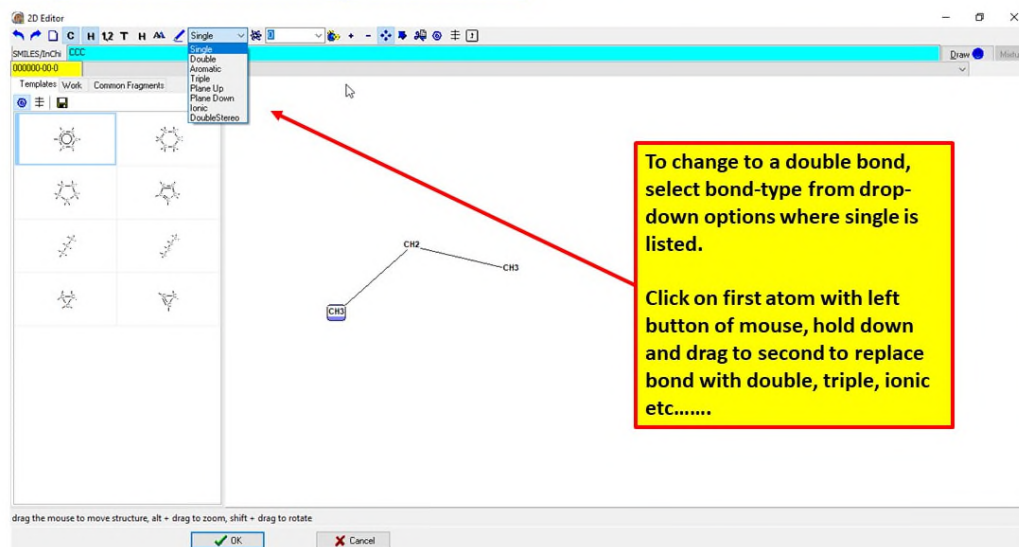
| Reference | MRID |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| (1995) ZA1296: Whole body autoradiography study in the rat following a single oral dose (mg/kg). Central Toxicology Laboratory, Cheshire, UK. Laboratory Report Study No. CTL-P-4666/PRO990, September 19, 1995. Unpublished. | 44505101 |
| (1996) ZA1296: Excretion and tissue retention of a single oral dose (100 mg/kg) in the rat. Central Toxicology Laboratory, Cheshire, UK. Laboratory Report Study No. CTL-P-4927/UR0501, May 17, 1996. Unpublished. | 44505102 |
| (1996) ZA1296: Biotransformation in the rat. Central Toxicology Laboratory, Cheshire, UK. Laboratory Report Study No. CTL-P-4930/UR0442, June 3, 1996. Unpublished. | 44505103 |
| (1996) ZA1296: Excretion and tissue retention of a single oral dose (1 mg/kg) in the rat. Central Toxicology Laboratory, Cheshire, UK. Laboratory Report Study No. CTL-P-4948/UR0502, May 20, 1996. Unpublished. | 44505104 |
| (1996) ZA1296: Excretion and tissue retention of a single intravenous dose (1 mg/kg) in the rat. Central Toxicology Laboratory, Cheshire, UK. Laboratory Report Study No. CTL-P-4976/UR0523, May 29, 1996. Unpublished. | 44505105 |
| (1996) ZA1296: Excretion and tissue retention of a single oral dose (1 mg/kg) in the rat following repeat dosing. Central Toxicology Laboratory, Cheshire, UK. Laboratory Report Study No. CTL-P-4995/UR0523, May 24, 1996. Unpublished. | 44505106 |

Page 1 of 19 4291 words 8:48 AM 4/14/2021

2.10. Drawing Tools, Structure Editor

STRUCTURE EDITING

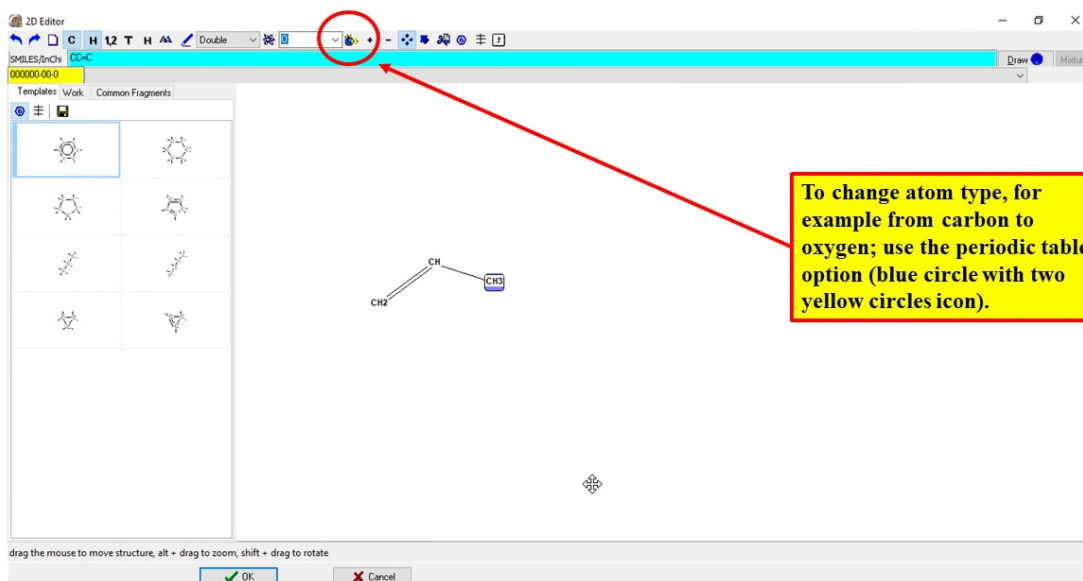
The following screen-shots illustrate some other functions of the STRUCTURE DRAWING package that may be used to modify/edit/draw 2-D structures of parent/metabolites.



To change to a double bond, select bond-type from drop-down options where single is listed.

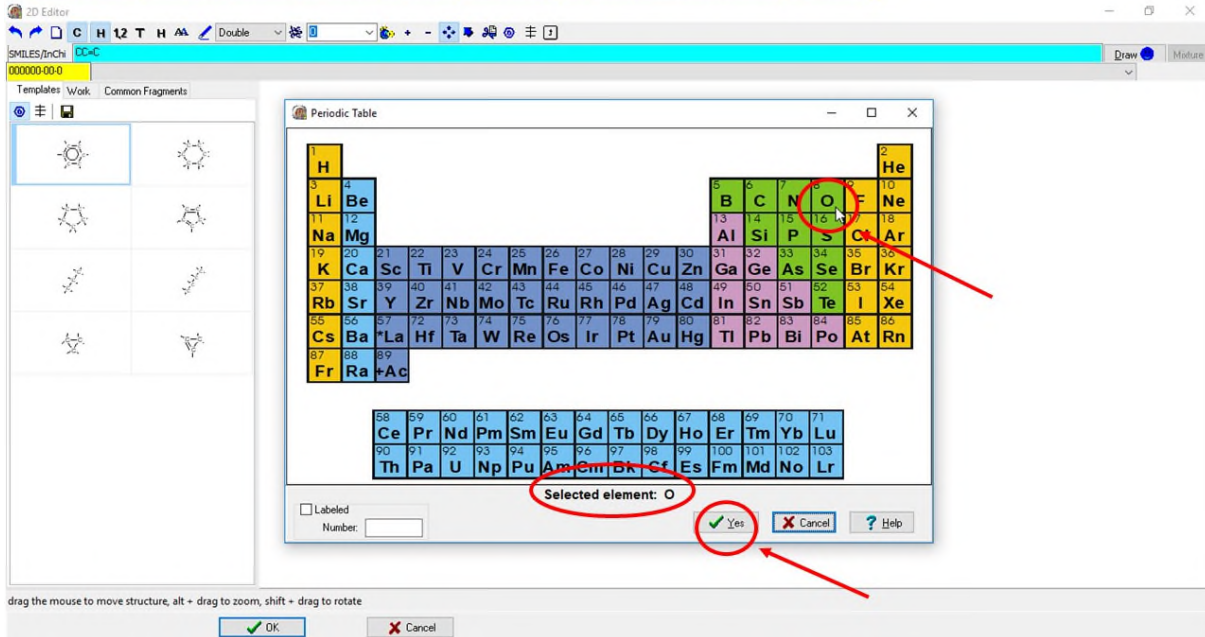
Click on first atom with left button of mouse, hold down and drag to second to replace bond with double, triple, ionic etc.....

To change atom type, for example from carbon to oxygen; use the periodic table option (blue circle with two yellow circles icon).

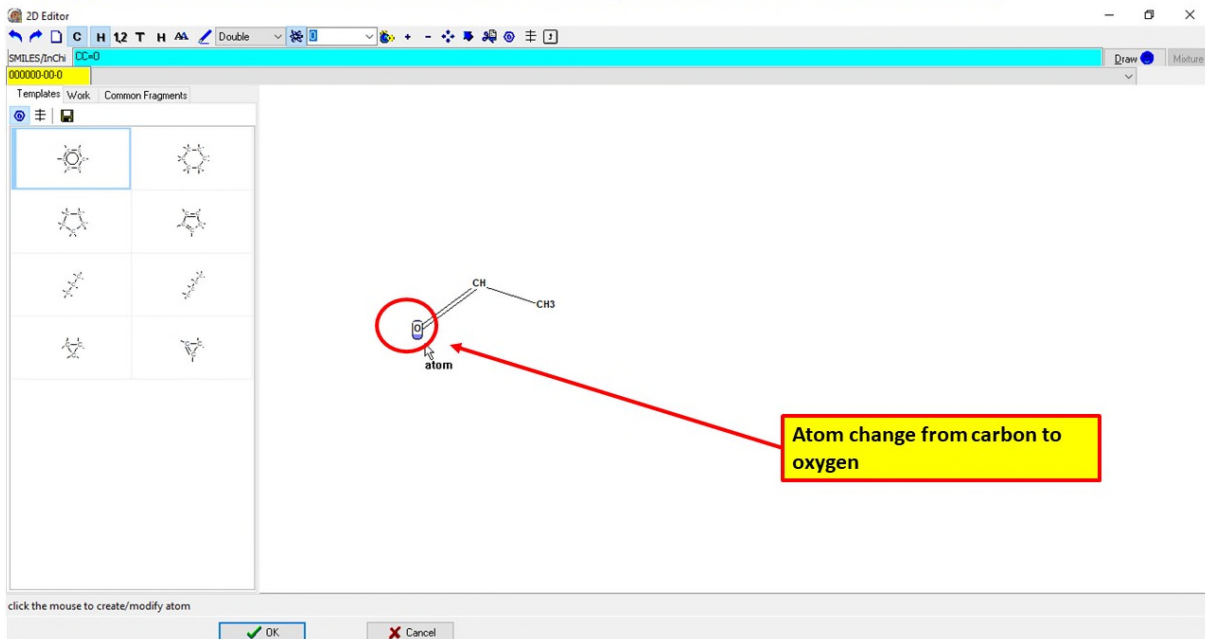


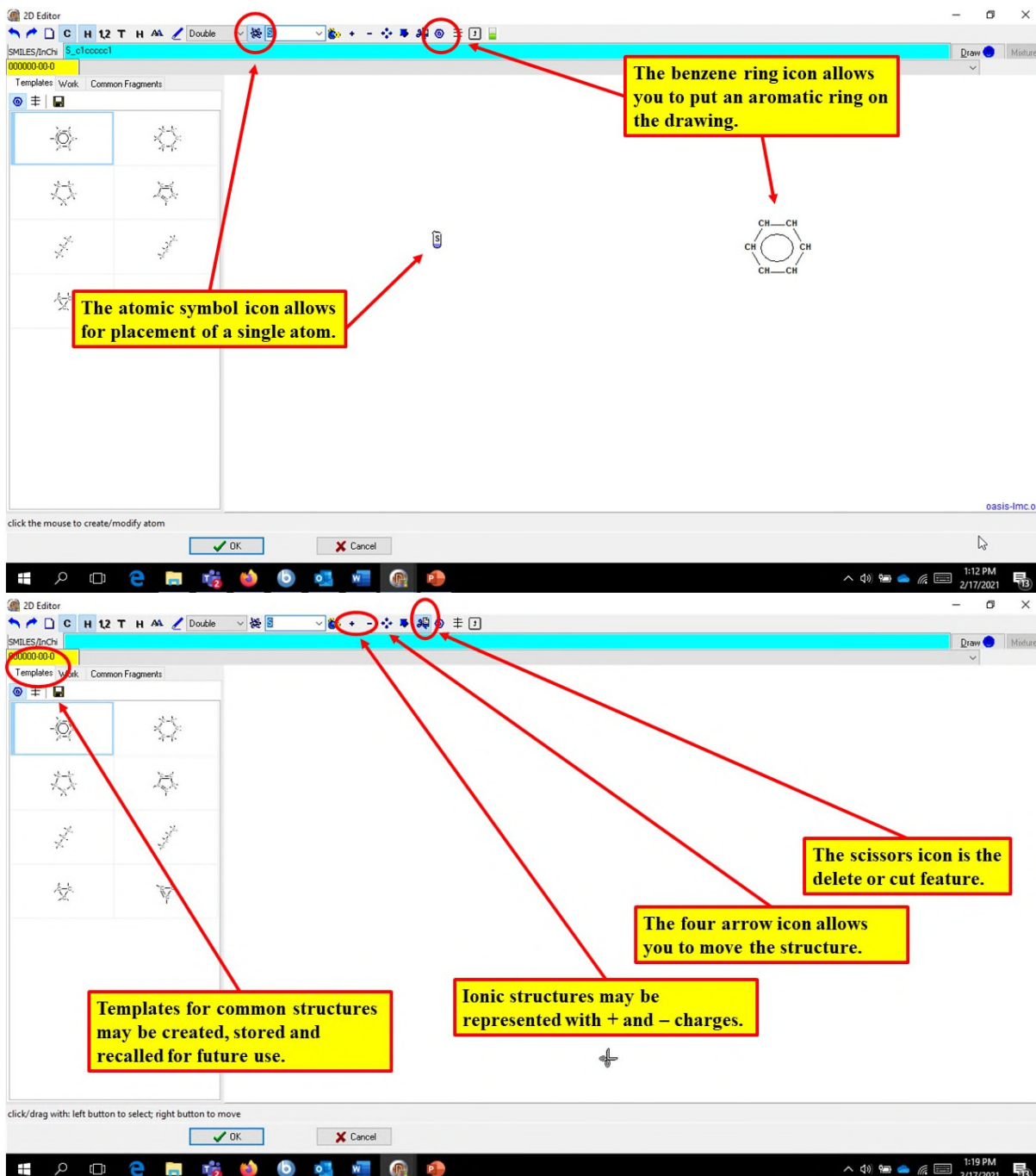
To change atom type, for example from carbon to oxygen; use the periodic table option (blue circle with two yellow circles icon).

The table opens, click on atom choice, click yes to accept choice and the table goes away.



Simply click on the atom in the structure that you wish to replace and the substitution will be made.





The screenshots show the 2D Editor interface. The top screenshot highlights the benzene ring icon in the toolbar and the atomic symbol icon in the templates panel. The bottom screenshot highlights the scissors icon, the four arrow icon, and the templates panel.

The benzene ring icon allows you to put an aromatic ring on the drawing.

The atomic symbol icon allows for placement of a single atom.

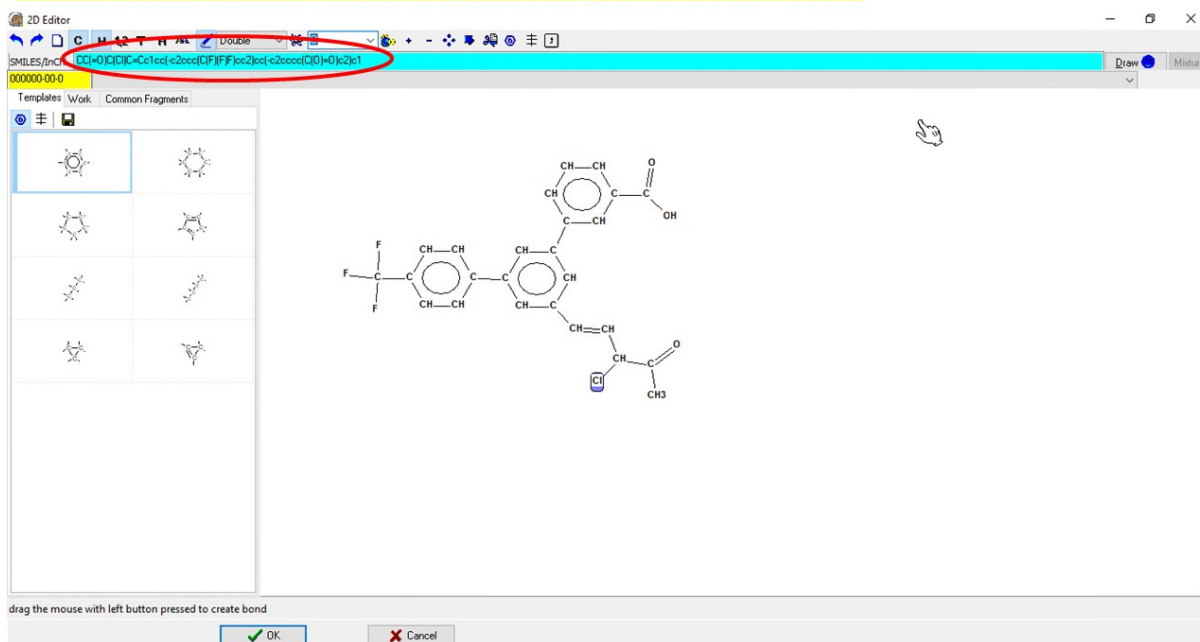
The scissors icon is the delete or cut feature.

The four arrow icon allows you to move the structure.

Templates for common structures may be created, stored and recalled for future use.

Ionic structures may be represented with + and - charges.

Once a structure is drawn, the SMILES string will be auto-generated for that structure.



3. Instructions for the Mandatory Data Evaluation Record (DER) Composer Fields.

Toxicokinetics studies should be submitted in IUCLID by using "Basic toxicokinetics – Endpoint study record" template implementing OECD Harmonised Template (OHT) 58. DER Composer XML should be attached in the LITERATURE object of this template (EFSA MRL Manual v1).

EFSA recommends the applicant to fulfil all fields of the DER Composer. However, EFSA understands that some of the fields are common to OHT 58 template implemented in IUCLID for toxicokinetic studies and therefore implies duplication of the work. Therefore EFSA asked the applicant to provide at least the fields relevant for correct functioning for the metabolism layer of the MetaPath software. EFSA noted that implementation of the kinetic layer of the MetaPath software will be soon available and therefore results regarding toxicokinetic parameters are strongly recommended to fill in the DER Composer but are not currently mandatory.

Only those studies addressing metabolism are currently needed to be entered into the Composer. Other toxicokinetic studies investigating other Absorption Distribution and Excretion endpoints, e.g. oral absorption are not currently mandatory to be reported by using the DER composer.

The instructions for the DER Composer fields that are mandatory for correct functioning for the metabolism layer of the MetaPath software are included in table 1.

Table 1: Instructions for the mandatory DER Composer Fields

| Data entry flow | Type | Field | Instructions |
|-----------------|----------------------|-----------------------|-------------------------------------------------------------|
| 1 | Header | I GENERAL INFO | |
| | Field text | STUDY TYPE | Pre-filled: Metabolism rat; OPPTS 870.7485[85-1]); OECD 417 |
| | Field text. Picklist | AGENCY CODE(S): | Please select EFSA number |

| | | |
|-----------------|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Field text | Agency Code value | Please insert EFSA PARAM term code for the active substance available in EFSA, 2020. doi. 10.5281/zenodo.4495166, e.g. for quinmerac the code is RF-0381-001-PPP. Please open the DCF catalogue "PARAM excel file", go to "term" tab and search for the active substance name. |
| Field text | TEST MATERIAL COMMON NAME: | e.g. quinmerac |
| Numerical value | TEST MATERIAL PURITY: | e.g. 97% |
| Field text | IUPAC NAME: | e.g. 7-Chloro-3-methylquinoline-8-carboxylic acid |
| Field text | SYNONYMS: | e.g. BASF 518 H |
| Field text | Citation | Please include study titles. Multiple references may be included in a single XML composer. Just needs to be the same active substance (where different labels might be included) and same species. |
| Field text | Sponsor: | e.g. BASF |
| Header | II. MATERIALS AND METHODS | |
| Header | A. MATERIALS: | |
| Header | 1. Test compound: | |
| Button | ADD/DEL | To add or delete radio-labeled test materials. More than one radio-labeled can be included in a single XML composer but there is also the possibility to have separate XML composer for each radio-label. |
| Field text | Radio-labeled test material: | Follow Nomenclature recommended by ANSES, 2020 |
| Numerical value | Radio-labeled purity: | |
| Numerical value | Specific activity: | |
| Field text | Lot/batch #: | |
| Smiles code | Structure: | Follow Drawing instructions for radiolabeled material as described by ANSES 2020. |
| Field text | Non-radio-labeled test material: | |
| Field text | Lot/batch #: | |
| Numerical value | Purity: | |
| Field text | CAS# of TGAI: | |

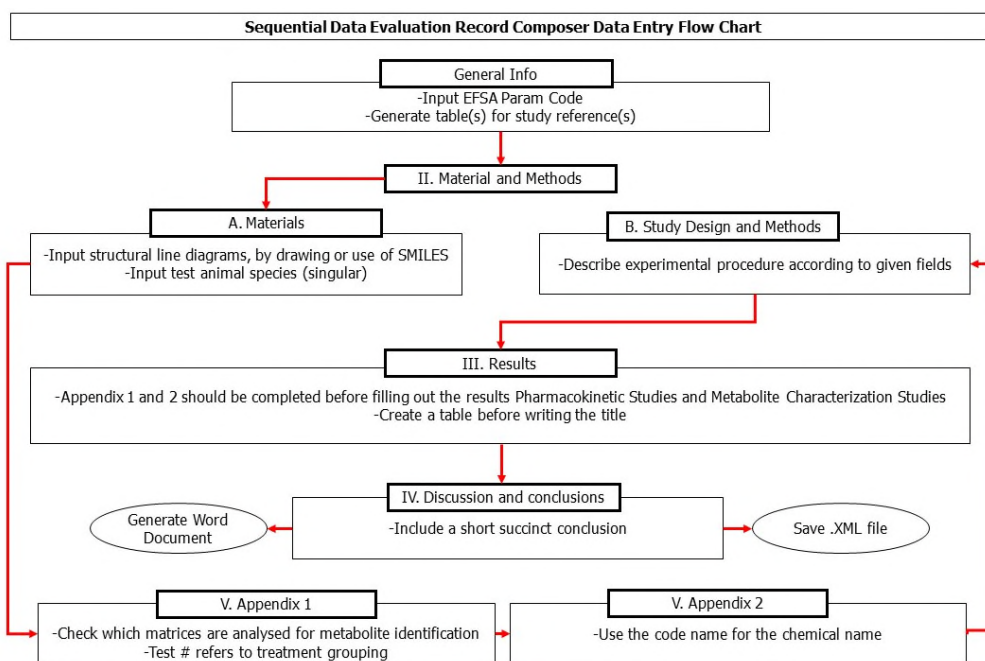
| | | | |
|----------|-----------------------------------------------------|-------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | Smiles code | Structure: | Follow Drawing instructions for non-radio-labeled material as described by ANSES 2020. |
| | Header Text field: Piclist | 3. Test animals: Species: | e.g. rat (Please use singular) |
| 4 | Header | B. STUDY DESIGN AND METHODS: | |
| | Field text | 1. Group arrangements: | Pre-filled text: Animals were assigned to the test groups noted in Table1 |
| | HTML table | metaboliteStudies Table 1a | This table is auto populated with appendix 1a |
| 5 | Header Header | III. RESULTS: B. Metabolite characterization studies: | |
| | Matrix HTML table(s) (repeated block of fields) | Table(s) 8 | <p>The first column of a table is auto populated with information coming from Appendix 2. The auto populated names must not be changed.</p> <p>The tables should be summarising the occurrence of parent and metabolites in the different body fluids and tissues: i.e. the link to treatment groups should be established by using treatment groups from the appendix 1 for the column headers.</p> <p>Please note that where a numerical entry is present in the matrix (table) created between Columns (treatment groups) and Rows (metabolite names) establishes that correlation.</p> <p>Avoid use of non-numerical entries in the cells. If there is no correspondence – leave cell blank.</p> <p>If there is the need to add the standard deviation the coder would consider adding a custom column to the table next to that for the reporting value and label it as S.D.</p> |
| 2 | Header Header (repeated block of fields) | V. APPENDIX: APPENDIX 1a Summary of all treatment groups | A matrix with all the different treatment groups and combination should be set. |

| | | | | | | | | | | | | | | | |
|----------|------------------------------------------|--------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|-------------------------|----|-------------------------|----|------------------------|----|---------------------------|----|---------------------------|----|----------|
| | Text field | Test # | <p>There is not fixed nomenclature for the test #.</p> <p>The nomenclature should clearly define groups in appendix 1 and the results tables treatment group identifier should be understandable.</p> <p>Examples: Lo-M-Urine for Low Dose in Male Rat Urine. Or low dose male rats as (1) and urine standardized as (a), feces (b), bile (c), thus: Thus</p> <table border="0"> <tr> <td>1a</td> <td>Low Dose Male Rat Urine</td> </tr> <tr> <td>1b</td> <td>Low Dose Male Rat Feces</td> </tr> <tr> <td>1c</td> <td>Low Dose Male Rat Bile</td> </tr> <tr> <td>2a</td> <td>Low Dose Female Rat Urine</td> </tr> <tr> <td>2b</td> <td>Low Dose Female Rat Feces</td> </tr> <tr> <td>2c</td> <td>etc.....</td> </tr> </table> | 1a | Low Dose Male Rat Urine | 1b | Low Dose Male Rat Feces | 1c | Low Dose Male Rat Bile | 2a | Low Dose Female Rat Urine | 2b | Low Dose Female Rat Feces | 2c | etc..... |
| 1a | Low Dose Male Rat Urine | | | | | | | | | | | | | | |
| 1b | Low Dose Male Rat Feces | | | | | | | | | | | | | | |
| 1c | Low Dose Male Rat Bile | | | | | | | | | | | | | | |
| 2a | Low Dose Female Rat Urine | | | | | | | | | | | | | | |
| 2b | Low Dose Female Rat Feces | | | | | | | | | | | | | | |
| 2c | etc..... | | | | | | | | | | | | | | |
| | Text field. Picklist | sex | | | | | | | | | | | | | |
| | Numerical value | number | | | | | | | | | | | | | |
| | Text field | dose route | | | | | | | | | | | | | |
| | Numerical value | dose nominal | | | | | | | | | | | | | |
| | Numerical value | dose measured | | | | | | | | | | | | | |
| | Text field. Picklist | dose type | | | | | | | | | | | | | |
| | Text field | matrix | | | | | | | | | | | | | |
| | Text field | descriptor | | | | | | | | | | | | | |
| | Text field | remarks | | | | | | | | | | | | | |
| 3 | Header (repeated block of fields) | APPENDIX 2 Summary of parent and all identified/detected metabolites and their relationship | Follow Appendix 2 instructions | | | | | | | | | | | | |
| | Text field | common name/code | Follow Nomenclature recommended by ANSES, 2020. | | | | | | | | | | | | |
| | Text field | chemical name | Follow Nomenclature recommended by ANSES, 2020. | | | | | | | | | | | | |
| | Smiles code | chemical structure | Follow Drawing instructions as described by ANSES 2020. | | | | | | | | | | | | |
| | Metabolic pathway description | parent | Link between parent and their metabolites should be established. Please start with the parent. | | | | | | | | | | | | |

Text field. Picklist expertise none; assumed by the author(s); tolerance expression; residue of concern; expert specified.

4. Sequential Data Entry Flow Chart

The data entry flow in the DER Composer follows a specific order as given under Steps chapter. The sequential data entry flow chart is summarised in figure 1. The figure is based on a previous Flow Chart developed for the former version 3r21 of the livestock DER composer (Cory McCurry, July 2010).



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The arrows and connectors of the flow chart are to represent the sequence by which a coder should input information.

Figure 1: Sequential Data Entry Flow Chart

5. Webinar: MetaPath – how to complete DER composers for pesticides mammalian toxicology metabolism studies - Q&A sessions

A webinar, hosted by EFSA, in cooperation with US EPA, took place 20th April 2021 and covered the following topic, Completing Data Evaluation Record (DER) for pesticide mammalian toxicology metabolism studies.

The webinar included a theoretical part and a live session to explain how to complete DER composers for pesticide mammalian toxicology metabolism studies¹.

Q&A sessions were also held to answer attendees' questions.

| Number | Question | Answer |
|-----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| General information | | |
| 1. | <i>Will the DER Composer be replaced by a much more user-friendly MSS Composer?</i> | Through contracts NP/EFSA/PREV/2020/01 and NP/EFSA/PRES/2020/01 EFSA intended to update the DER Composer to a user-friendly MSS Composer. |
| 2. | <i>Will the DER composer be freely downloadable, or will a paid license be required?</i> | Both MetaPath and DER composer could be downloaded for free at https://oasis-lmc.org/products/software/metapath.aspx . |
| 3. | <i>Which citations should be included in the General Info?</i> | Reference of ADME experimental studies. |
| 4. | <i>How will redaction of author names of mammalian studies be handled in DER Composers?</i> | The names of the authors should be reported by the applicant when submitting a study with the DER composer. Before sharing the final version of the file in a public database, EFSA prepare a sanitized version, removing the confidential information. |
| 5. | <i>Is there a certain style that needs to be used for citations?</i> | There is no specific style, the citation should allow the risk assessor to identify properly the study or studies they are referring to. |
| Material and methods | | |
| 6. | <i>Will there be the possibility in near future to put in an InChI code or a structure?</i> | That capability is already included in the Composer. Options for structure generation include submission of InChI, submission of SMILES or use of the drawing tools included in the Structure Editor. |
| 7. | <i>Open 2D Structure Editor - means - free tool (integrated into the MetaPath Program Supply); if only CAS number are inserted is it enough to have comprehended data on all molecule properties?</i> | Yes, the tool is free and included in DER Composer. Insertion of CAS number will not automatically produce a 2-D structure. Insertion of SMILES, InChI, or use of the drawing tools will produce the structure. The structure identification is derived from the experimental study. CAS numbers have been selected to track the active ingredient because they are very specific for the structure; however, they might not be available for metabolites. |
| 8. | <i>Do you need to include e.g. % when filling in the environmental condition's fields?</i> | This is not a mandatory field. See Chapter 3 of the Manual. |

¹ <https://www.efsa.europa.eu/en/events/webinar-metapath-how-complete-der-composers-pesticides-mammalian-toxicology-metabolism>

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|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 9. | <i>How to deal with isomers in this composer? Do active substances as well as metabolites must be included separately? Is the drawing program able to specify the different isomers?</i> | Within the structure drawing package there are features for drawing the stereoisomers, this is extensively explained in MSS composer manual by ANSES, 2020. Metabolites need to be included in the metabolic pathway. Please noted that the structure drawing package is the same in DER and MSS composers. |
| 10. | <i>How can I add a new species to point 3 "Test animals"? I have only 3 species (i.e. Goat, Hen, Cow)</i> <i>Within # 3. Test animals, the pull down did not show Rat or Dog. It was possible to add the text however. Will that be okay?</i> | The name of the new species could be typed in. Please remember to use singular common name e.g., Rat, Mouse, Rabbit, Monkey, Dog, etc... |
| 11. | <i>What about formatting within text blocks (narrative descriptions): e. g. Font type and size (of pasted text); e. g. italics for Latin names, bold words, underlining, etc. Does this formatting matter or stay as it has been inserted, or can it cause problems?</i> | Format does not matter. There are limitations in the ability to format that will be enhanced in the new MSS style Composer upgrade that is planned. The formats and special characters are available via copy and paste. |
| 12. | <i>The DER composer is appropriate for in vivo metabolism studies, what about the in vitro comparative metabolism studies which are now required under the 1107/2009?</i> | To report comparative <i>in vitro</i> metabolism studies by using the DER composer is not mandatory. See Chapter 3 of the Manual. |
| Appendix 1 and 2 | | |
| 13. | <i>Is it possible to prepare a separate table for the quantification of stereoisomers, e.g enantiomers of the parent compound (which is also quantitated in total)?</i> | It is possible. |
| 14. | <i>Should the data be included study by study or should the studies for one species be summarised in one entry?</i> | Studies for one species can be summarised in one Composer file unless clear differences in metabolism are observed between two or more studies. A separate XML/entry should be created for one species and one active ingredient. |
| 15. | <i>Is there a certain way to name the Appendix1 Test#, e.g. similar to the one used in the MSS Composers?</i> | For the treatment group nomenclature there is no fixed criteria. See Chapter 3 of the Manual. |
| 16. | <i>Presumably you define different radiolabel positions in Appendix 1 as well to generate data entry tables for different labels in III, results. Is this correct?</i> | Yes. See also replies under 17 and 19. |
| 17. | <i>If the molecule is radiolabelled in 2 different parts, should I report it only once? Or should we fill in two composer xml files?</i> | It is possible to separate XML for each radio-label and each XML will import as a separate folder/map into MetaPath. However, the DER Composer also allows for the option of combining more than one radio-label. Also, remember that MetaPath allows the user to combine the two later if so desired by using the map merge function. |
| 18. | <i>Is there a limit to the number of treatment groups?</i> | There is no limit. |
| 19. | <i>I guess in Appendix V 1st Table two different labels must also be included separately? Which means two times the same matrices/single oral etc.?</i> | A second radiolabelled molecule could be added under > II. Material and methods > 1. Test Compound > click on "ADD" button to include a second molecule. In this specific case, in the "Radio-labelled test material" box, it is important to specify the site of label. Then two options are available: |

| | | |
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| | | <ol style="list-style-type: none"> 1. In the <i>Appendix Ia</i> the <i>Test#</i> could be adapted to specify the Radio-labelled test material they are referring to. 2. An additional reference could be added in the citation box (under <i>General Info</i>) to cover the different radiolabelling. In this case a second <i>Appendix Ib</i> will appear under <i>V. Appendix</i>. |
| 20. | <i>While inserting the information in the appendix regarding the treatment groups, do we need to insert information regarding organs and tissues under the filed Matrix?</i> | The information to be included in Appendix 1 are the ones related to body fluids and tissues in which metabolite identification has been done. At a minimum the guideline study looks at excreta, but some will include Bile studies as well as investigation of metabolites in tissues. |
| 21. | <i>How to handle generic structures?</i> | It should be described under Appendix 2 Editor > Expertise > Expertly Specified. Two approaches could be taken: <ol style="list-style-type: none"> 1. Include the more logical position (based on chemistry, hindrance). 2. Draw both metabolites' structures and include all the position in the drawing. |
| 22. | <i>What about "generic structures" of metabolites, e. g. the position of hydroxylation (or conjugation) has several possibilities?</i> | See reply n.21. |
| 23. | <i>What to do if position of hydroxylation is not identified and there is no information to make expert judgment?</i> | See reply n.21. |
| 24. | <i>In your example of ring hydroxylation, you suggested to use expert judgement. Is there a way to use generic structures instead, since for many chemicals the hydroxylation probability is high at multiple positions, and it is likely that all occur to a limited extend?</i> | See reply n.21. |
| 25. | <i>If you add all possible structure where you don't know the exact position of the OH, how do you make it clear in the pathway that you did not have all of these metabolites as discrete metabolites (i.e. that they are all possibilities for the same metabolite?)</i> | See reply n.21. |
| 26. | <i>What about isotope labels without radioactivity (e. g. 13C, ...) ?; List them under "radiolabel" ?</i> | Stable isotope labels (e.g., 13C) could be included under the radio-label test material(s). They could also give rise to specific treatment groups where the stable isotope was utilized as test material. |
| 27. | <i>What if you do not know the exact structure of the metabolite. For example, the position of an OH group on your metabolite so there are several possible isomers and there is no expert view on which is most likely, or all are equally likely. How would you enter a structure when you do not know exactly what it is, but you know it is a metabolite?</i> | See reply n.21. |
| 28. | <i>I noticed there were templates in the structure editor - will these be covered in the session after the break?</i> | In this regard, please see the information reported under "2.10. Drawing tools, Structure Editor" |
| Results – Pharmacokinetic studies | | |
| 29. | <i>Can you paste data from excel or word tables into the result tables?</i> | Currently not. Through contracts NP/EFSA/PREV/2020/01 and NP/EFSA/PRES/2020/01 EFSA intended to update the DER Composer and this useful functionality can be indeed explored. |

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| 30. | <i>Can you import whole tables from excel?</i> | No. See reply n. 29. |
| 31. | <i>If at one timepoint no value is given, is there a special type to fill-in "not given" or "not detected"? And where to put such abbreviations? In the text above?</i> | Yes, for the results under "Pharmacokinetic studies". In this section there is the possibility to include "ND" or "NS", adding guidance (e.g. ND= not detected) in the free text box below. It should be avoided in the case of "Metabolites characterization studies". |
| 32. | <i>Is there any template that can be used to upload all the data rather than doing this manually?</i> | No. See reply n. 29. |
| 33. | <i>Is there a possibility to paste tables or table rows from a file as a whole, without the necessity to insert each cell separately?</i> | No. See reply n. 29. |
| 34. | <i>Would the 'other' tab be used also for distribution data?</i> | Yes, the "Other" tab under III. Results > A. Pharmacokinetic studies > Other, can be used e.g. for distribution data, bio-accessibility and enzyme activity if needed.. |
| 35. | <i>Will it be possible to save table layouts if there are many such tables to include?</i> | Currently not. Best option is to use the copy/paste table function. Through contracts NP/EFSA/PREV/2020/01 and NP/EFSA/PRES/2020/01 EFSA intended to update the DER Composer and this useful functionality can be indeed explored. |
| 36. | <i>Is there a possibility to import tables from e.g. xls files?</i> | See reply n. 29. |
| 37. | <i>Is there any consideration given to build templates so that data can be uploaded, or we can implement simple copy paste functions in the future?</i> | Currently not. See reply n. 29 & 35. |
| Results - Metabolite characterization studies | | |
| 38. | <i>If all of these have been done for one active substance; can this can be re-utilised subsequently (a few months later) for another active as a template to save re-entering the general info, tables, etc.. as the study designs are often the same? If we cannot re-use the work of a previous active substance as a template, does this mean we have to start from scratch for a new active substance ?</i> | By using the SAVE AS command an XML created for one active could be re-used for another but there would be changes to be made considering the new active, structures & descriptors, test animal characteristics, all of the metabolites, values in tables would be different, etc... Our assessment would be that for all the required modifications it would be best to start from scratch. Rather than a template we would consider the first study as an example for completing subsequent studies. Whereas, in the case of a different species with the same active substance the document could be slightly modified accordingly. However, through contracts NP/EFSA/PREV/2020/01 and NP/EFSA/PRES/2020/01 EFSA intended to update the DER Composer and the inclusion of predefine tables can be indeed explored. |
| 39. | <i>Do the rows update automatically when updating the Appendix?</i> | No, therefore a specific way to enter the data (specific flow) is needed. A new metabolite could be included in the |

| | | |
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| | | "Metabolite Characterization Tab" table; however, the name should be entered into the table exactly the same as the name of the metabolite reported in the Appendix. |
| 40. | <i>Does MetaPath include "identified" metabolites under "characterization" ? - while the guidelines differentiate between "identified" and "characterized" ?</i> | In MetaPath they are treated as synonymous. If a metabolite is identified but not quantified, a code might be used in the results table to explain it (e.g. 111111) and then explanation could be given in the free text box below as a footnote (e.g. 111111 = metabolites observed but not quantified) . |
| 41. | <i>What if, if the metabolites are only postulated by the author but not find in the samples? Can we left the table related to these empty?</i> | Yes, to allow for a clean look to the Table, delete the rows (metabolites) with no value to report. |
| 42. | <i>Does the metabolite quantitation table accept range values?</i> | No. |
| 43. | <i>Can you use less than (<) symbol? Do the symbols "<" and ">" cause irritations in Metapath because they could mean "open/close brackets" in xml?</i> | The < symbol does make the value disappear as well as the ≤ symbol. In addition to this, for metabolites that were observed but not quantified it was initially recommended that a "+" be used in the characterization table(s). In addition to numbers, the "+" allows for maintaining correspondence between treatment and metabolite. However, the "+" symbol is not imported into MetaPath on the depicted table. Therefore, as already explained under reply n. 40, the use of a code, e.g. 11111 to denote presence of metabolite with an explanation as footnote, is currently the option recommended. |
| 44. | <i>In the example table ppm and TRR are provided together. Would you propose to sperate theses values in different tables? And what are the rules to separate information, like treatment groups or matrices or labels?</i> | The preferred option is to be separated; however, it is a matter of preference. Both can be entered as long as the units are described in each column. By using the "General Column Label". |
| 45. | <i>Is there a restricted number of tables (only three?)?</i> | No. |
| 46. | <i>I notice that there is no build pathway option as with MSS. So, there is no way to check visually that your pathway looks right before it ends up in Metapath?</i> | There is no immediate screen of the proposed metabolic pathway. Through contracts NP/EFSA/PREV/2020/01 and NP/EFSA/PRES/2020/01 EFSA intended to update the DER Composer to a user-friendly MSS Composer on which this functionality will be available. |
| 47. | <i>Is it possible to include < LOQ or <0.001 ppm?</i> | See reply n. 43. |
| 48. | <i>If you added a table by mistake, how can you delete it?</i> | There is a delete function. |
| 49. | <i>How to handle coeluting minor metabolites?</i> | Keep them separate, maybe add a footnote to explain it. Possible to split the reported quantity between the two (or more) co-eluting metabolites; just indicate as a footnote. |
| 50. | <i>Is it possible to prepare a separate table for the quantification of stereoisomers, e.g enantiomers of the parent compound (which is also quantitated in total)?</i> | There is no need to add a separate table if the stereoisomers are included as separate metabolite. |

| | | |
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| 51. | <i>Is there a word limit on the discussion?</i> | There is not a limit. |
| 52. | <i>What would happen if the metabolite name or codes changed through the lifetime of the active substance?</i> | Even during the assessment of a substance different applicants could name the metabolite differently. This is countered in MetaPath by using the structure represented by SMILES of the metabolite instead of the name of the metabolite for searching for a specific metabolite. |

6. *In vitro* metabolism studies

Comparative *in vitro* metabolism are requested according to the EU data requirements on pesticides². Currently, comparative *in vitro* metabolism studies should be reported under 5.8 Other toxicological studies (ENDPOINT_STUDY_RECORD.AdditionalToxicologicalInformation -v.6.3) as described in the EFSA MRL Application Manual (EFSA, 2021).

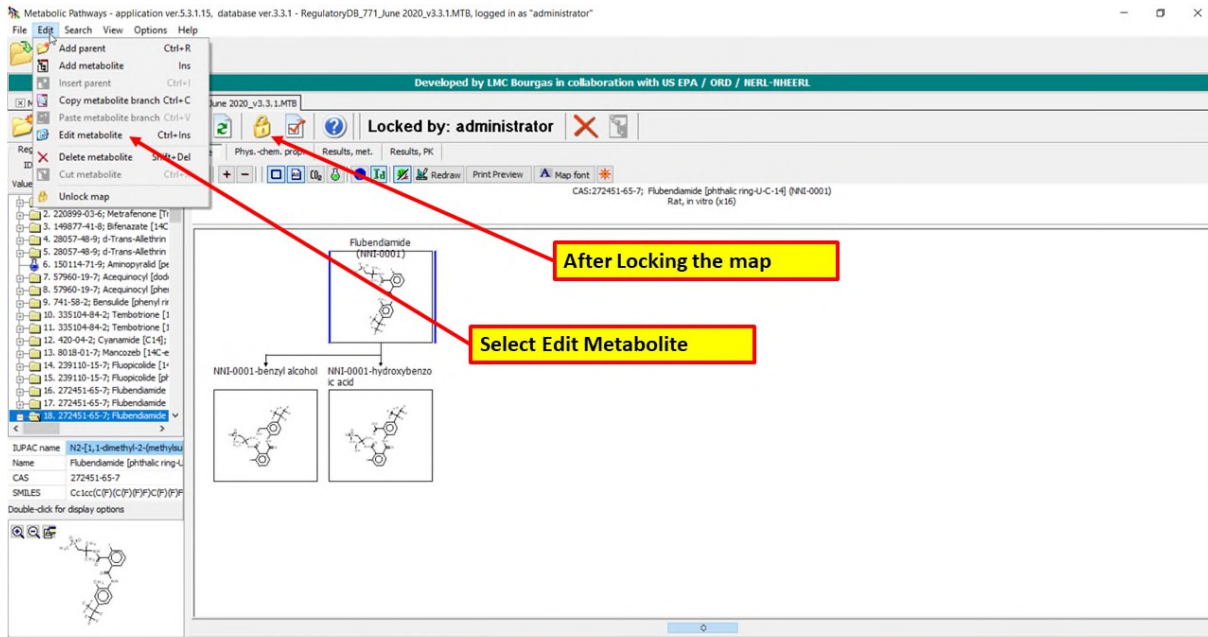
If metabolite identification has been conducted in the comparative *in vitro* metabolism study it is possible to use the DER composer to report the metabolic pathway in these studies. However, the DER composer currently does not allow distinction at the *in vitro* /*in vivo* level. When setting up treatment groups in Appendix 1 the coder should describe the matrix appropriately, e.g., liver microsomes. Once the XML is imported into MetaPath, there would be the need to edit and modify the treatment groups to reflect the *in vitro* study in MetaPath. The following step-by-step guide describes instructions on how to do it, however, currently it is not mandatory to report *in vitro* metabolism studies by using the DER composer and further editing in MetaPath.

² Commission Regulation (EU) No 283/2013 of 1 March 2013 setting out the data requirements for active substances, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market Text with EEA relevance OJ L 93, 3.4.2013, p. 1–84

Steps for Finishing Entry of In Vitro Studies within MetaPath – Need to Apply Descriptors for (1) In Vitro (2) Experimental System (3) Organ/Tissue After the Import of the DER Composer XML

The screenshot shows the MetaPath application window. The title bar indicates the application version (5.3.1.15) and the database version (3.3.1). The interface includes a menu bar (File, Edit, Search, View, Options, Help), a toolbar with various icons, and a main workspace. On the left, there is a 'Regulatory ID quick search' panel with a list of compounds. The main workspace displays a chemical map for Flubendamide (CAS: 272451-65-7) with its chemical structure and two sub-structures: NHI-0001-benzyl alcohol and NHI-0001-hydroxybenzoic acid. A red arrow points to a lock icon in the toolbar, labeled 'Lock the map'. Another red arrow points to a newly added chemical structure in the map, labeled 'New added map - selected'. The bottom status bar shows the system time as 10:13 AM on 5/5/2021.

Metabolic Pathways - application ver.5.3.1.15, database ver.3.3.1 - RegulatoryDB_771_June 2020_v3.3.1.MTB, logged in as "administrator"



Developed by LMC Bourgas in collaboration with US EPA / ORD / NERL/NHEERL

Locked by: administrator

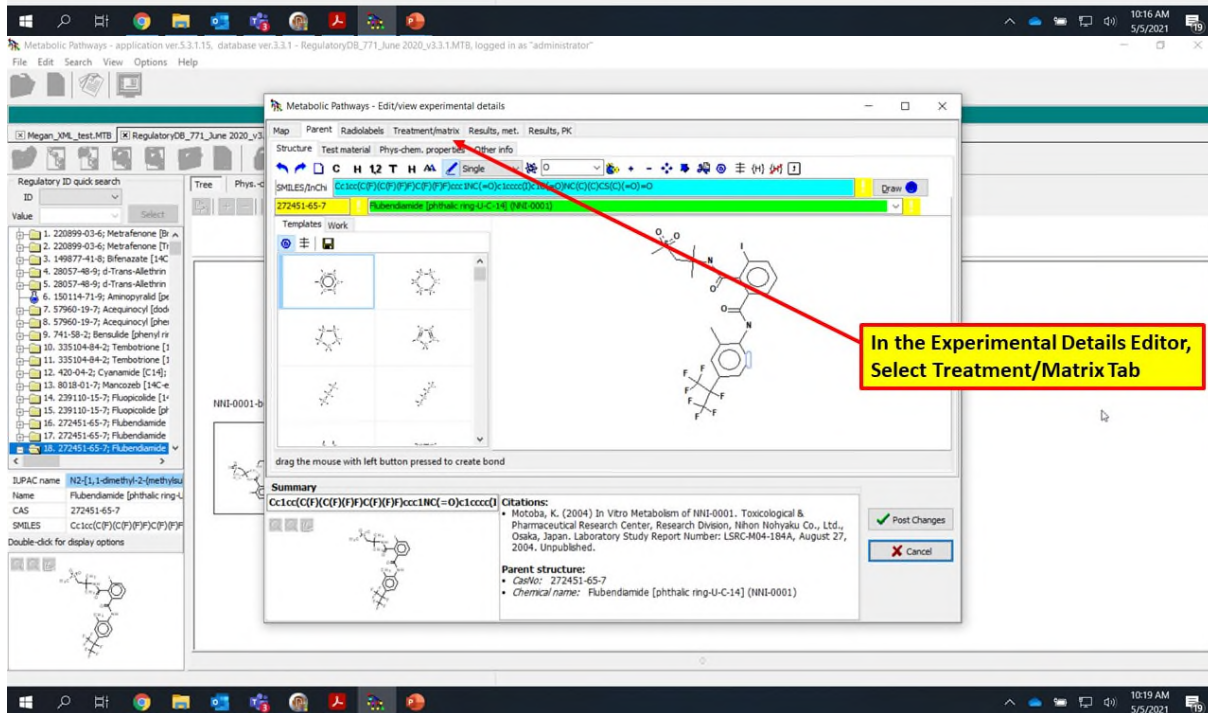
CAS: 272451-65-7; Flubendamide [phtalac ring-U-C-14] (NNI-0001)
Rat, in vitro (x16)

Flubendamide (NNI-0001)

NIH-0001-benzyl alcohol NNI-0001-hydroxybenzoic acid

ILPAC name N2-(1,1-dimethyl-2-(methylsulfonyl)ethyl)benzamide
Name Flubendamide [phtalac ring-U-C-14]
CAS 272451-65-7
SMILES Cc1cc(C(F)(F)F)C(F)(F)F

Metabolic Pathways - application ver.5.3.1.15, database ver.3.3.1 - RegulatoryDB_771_June 2020_v3.3.1.MTB, logged in as "administrator"



Metabolic Pathways - Edit/view experimental details

Map Parent Radiolabels Treatment/matrix Results, met. Results, PK

Structure Test material Phys-chem, properties Other info

SMILES/InChI Cc1cc(C(F)(F)F)C(F)(F)F Cc1cc(C(F)(F)F)C(F)(F)F Cc1cc(C(F)(F)F)C(F)(F)F

272451-65-7 Flubendamide [phtalac ring-U-C-14] (NNI-0001)

Templates Work

drag the mouse with left button pressed to create bond

Summary

CC1cc(C(F)(F)F)C(F)(F)FCC1NC(=O)C1CCCC1

Citations:

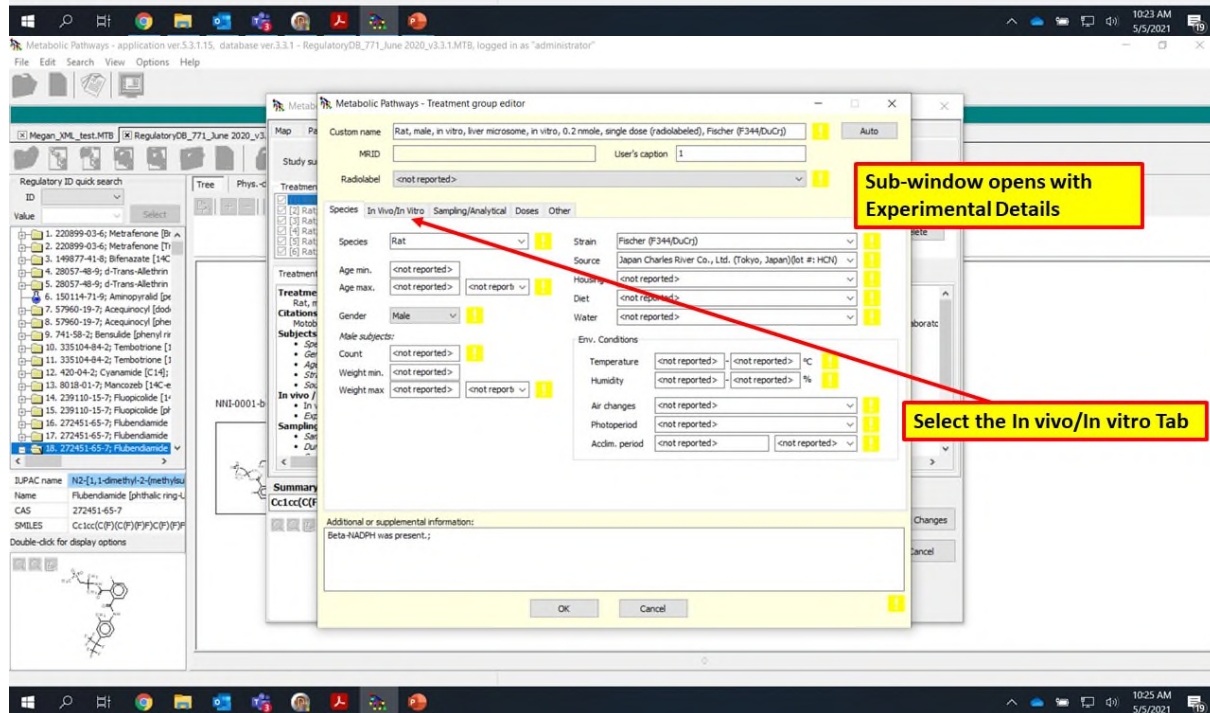
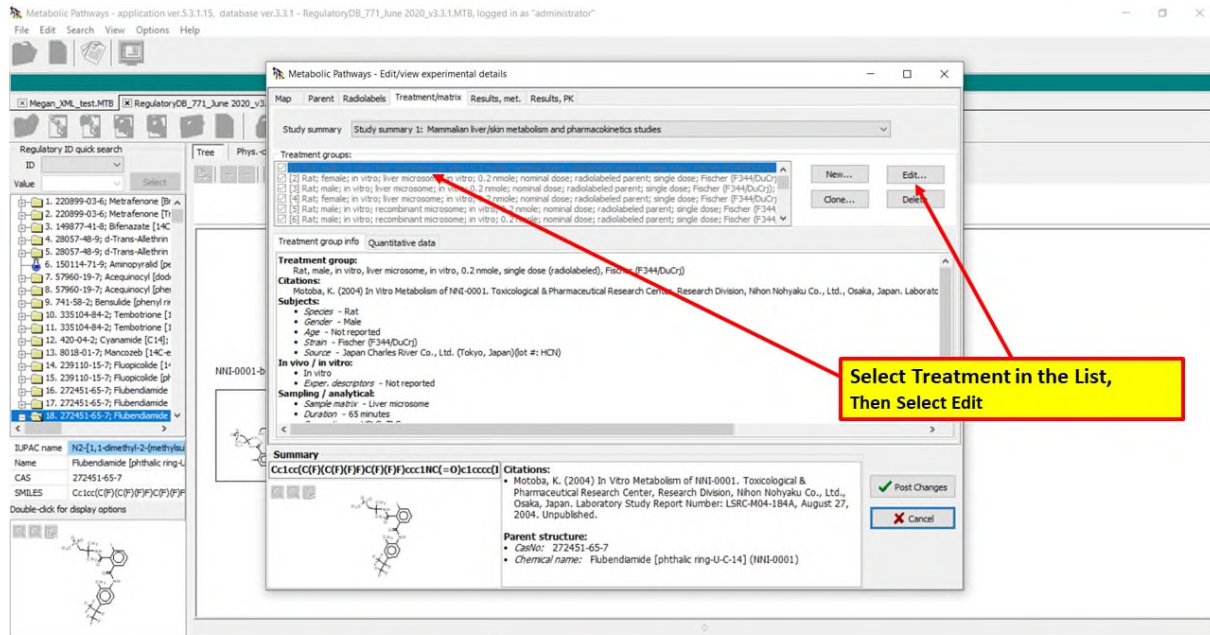
- Motoba, K. (2004) In Vitro Metabolism of NNI-0001. Toxicological & Pharmaceutical Research Center, Research Division, Nihon Nohyaku Co., Ltd., Osaka, Japan. Laboratory Study Report Number: LSRC-M04-184A, August 27, 2004. Unpublished.

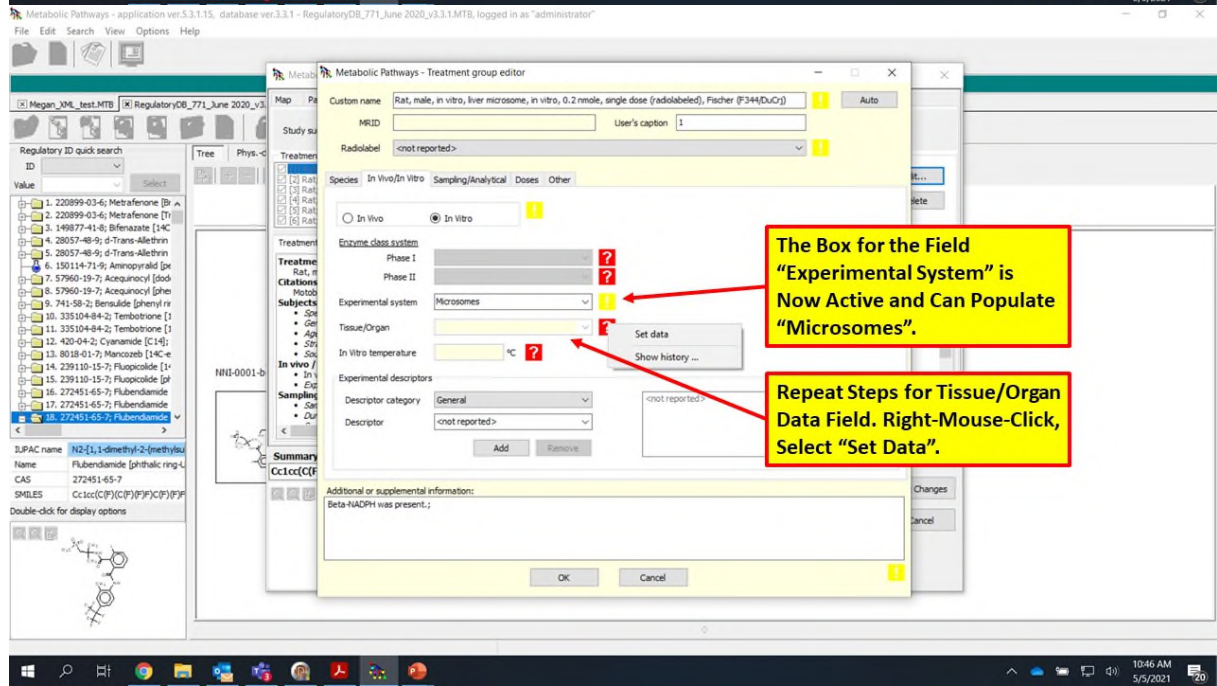
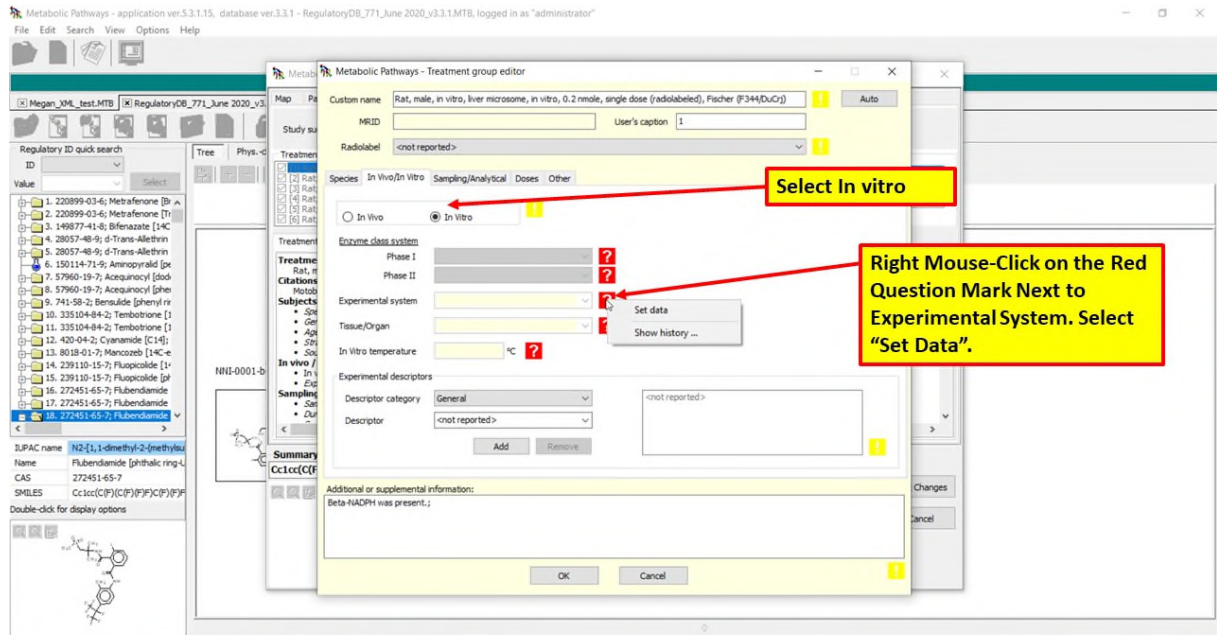
Parent structure:

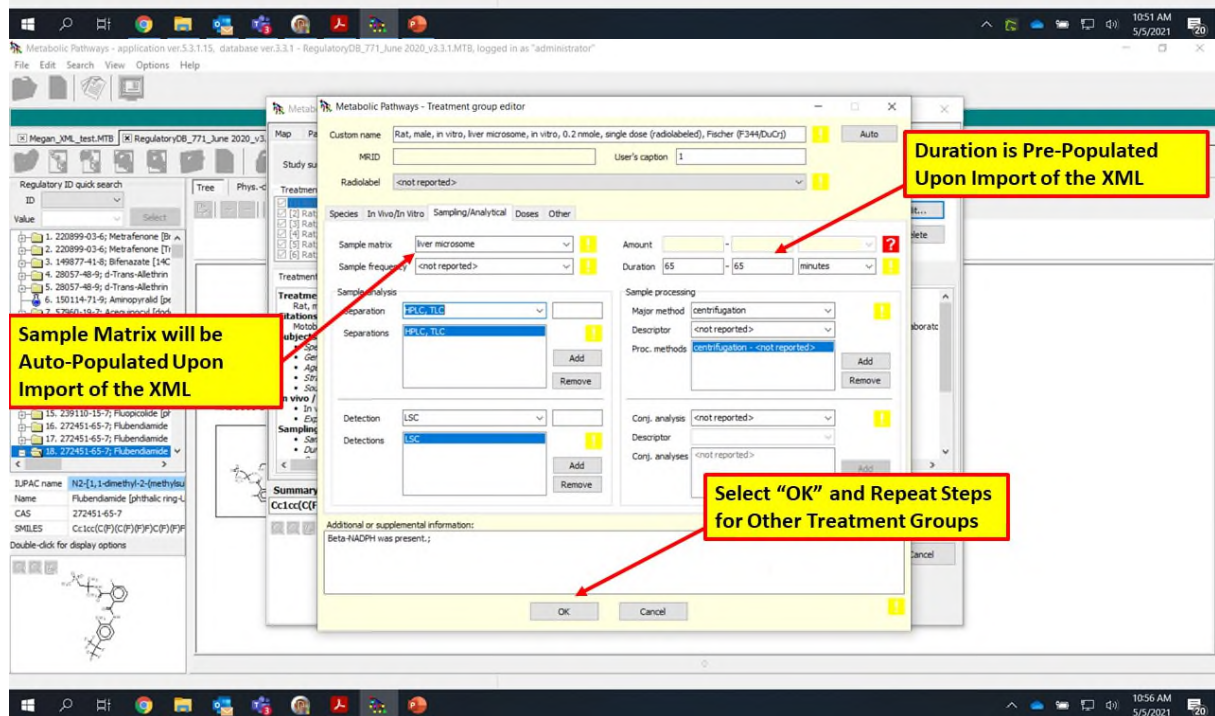
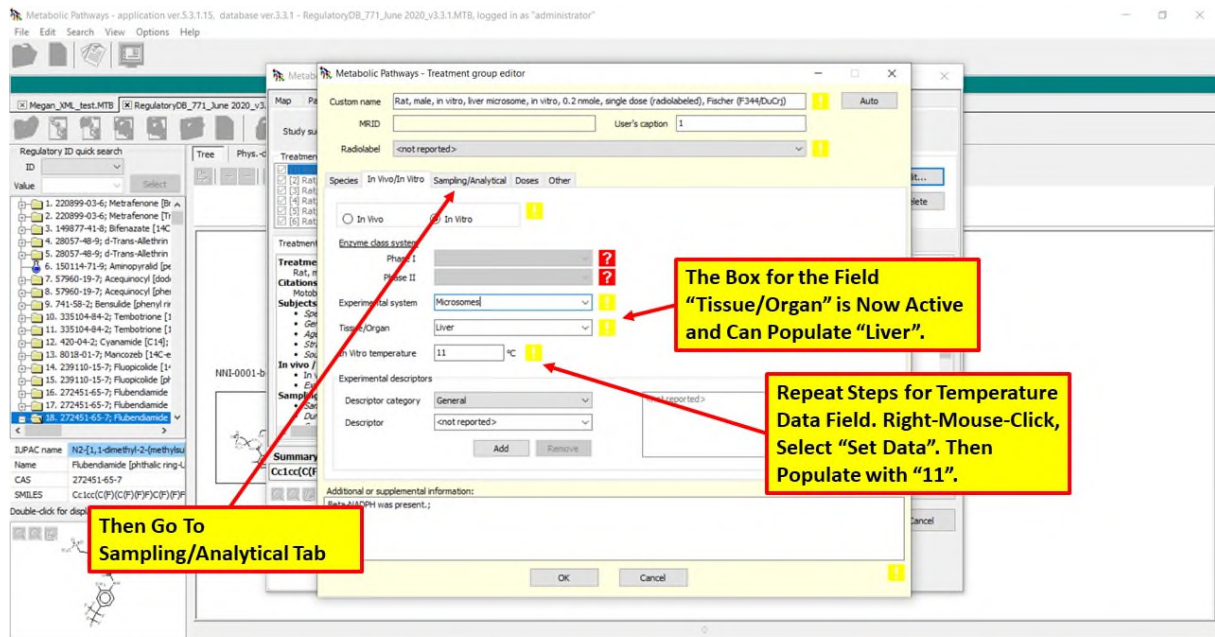
- CasNo: 272451-65-7
- Chemical name: Flubendamide [phtalac ring-U-C-14] (NNI-0001)

Post Changes

Cancel







References

- ANSES, 2020. MSS Composer Manual (MSS COMPOSERS ADVISORY NOTICE). Available online at: <https://www.efsa.europa.eu/sites/default/files/2021-03/mss-composers-manual.pdf>
- Cory McCurry, July 2010. Sequential Data Entry Flow Chart. Not published.
- European Food Safety Authority. (2020). Harmonized terminology for scientific research [Data set]. Zenodo. <http://doi.org/10.5281/zenodo.3243215>
- European Food Safety Authority. (2021, March 23). MRL Application manual. Zenodo. <http://doi.org/10.5281/zenodo.4630194>