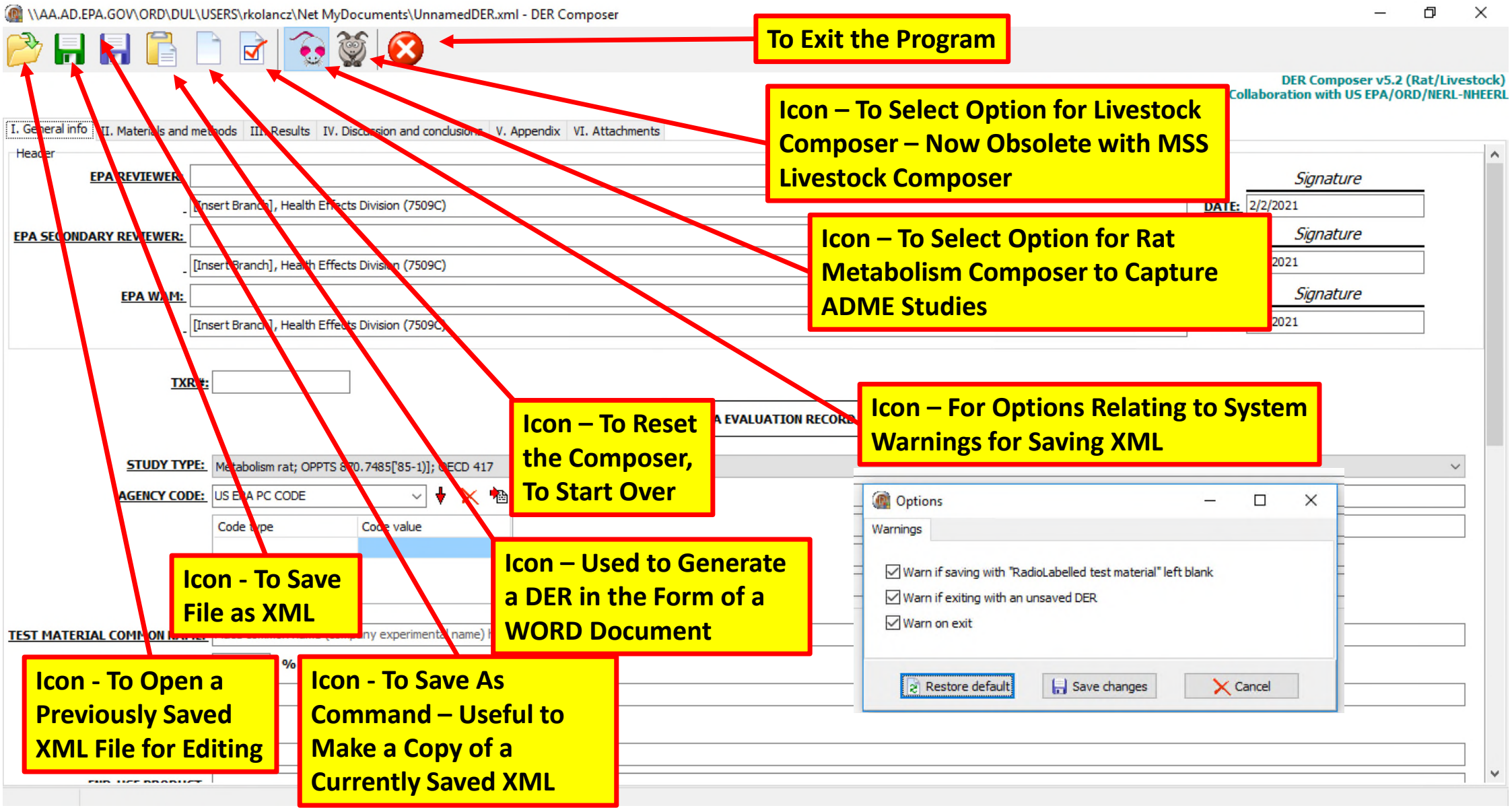
Guideline For The Use Of Der/Xml Composer – Rat Metabolism v.5.2

Prepared for use with DER Composer, a product resulting from the joint cooperation between the U.S. Environmental Protection Agency (USEPA) and the Laboratory of Mathematical Chemistry (LMC-Bourgas, Bulgaria).

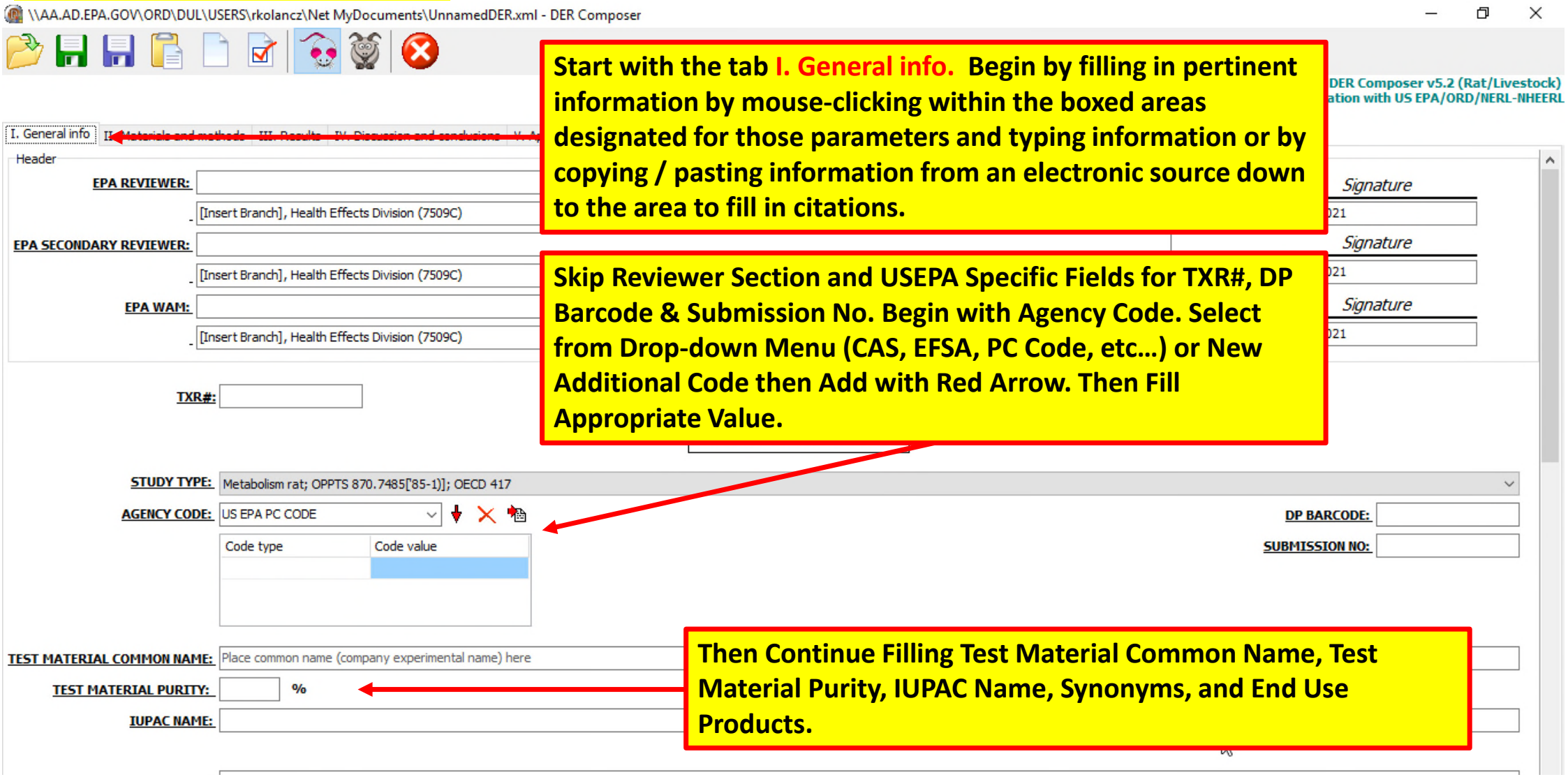
Part 1:

- **Opening DER Composer**
- **General info**
- **Material and methods**

Open the program – start up will appear as follows:



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.

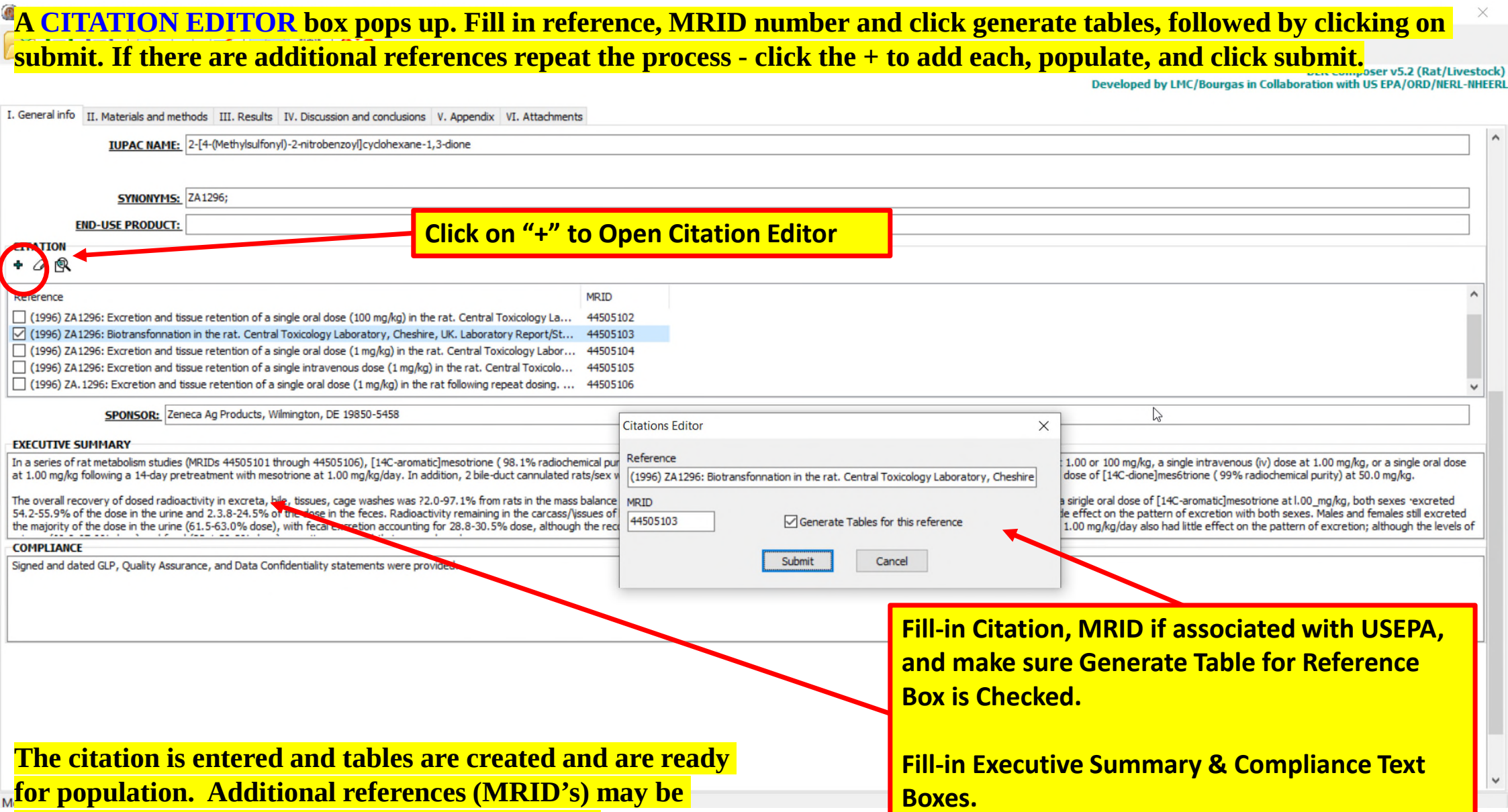


Start with the tab I. General info. Begin by filling in pertinent information by mouse-clicking within the boxed areas designated for those parameters and typing information or by copying / pasting information from an electronic source down to the area to fill in citations.

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.

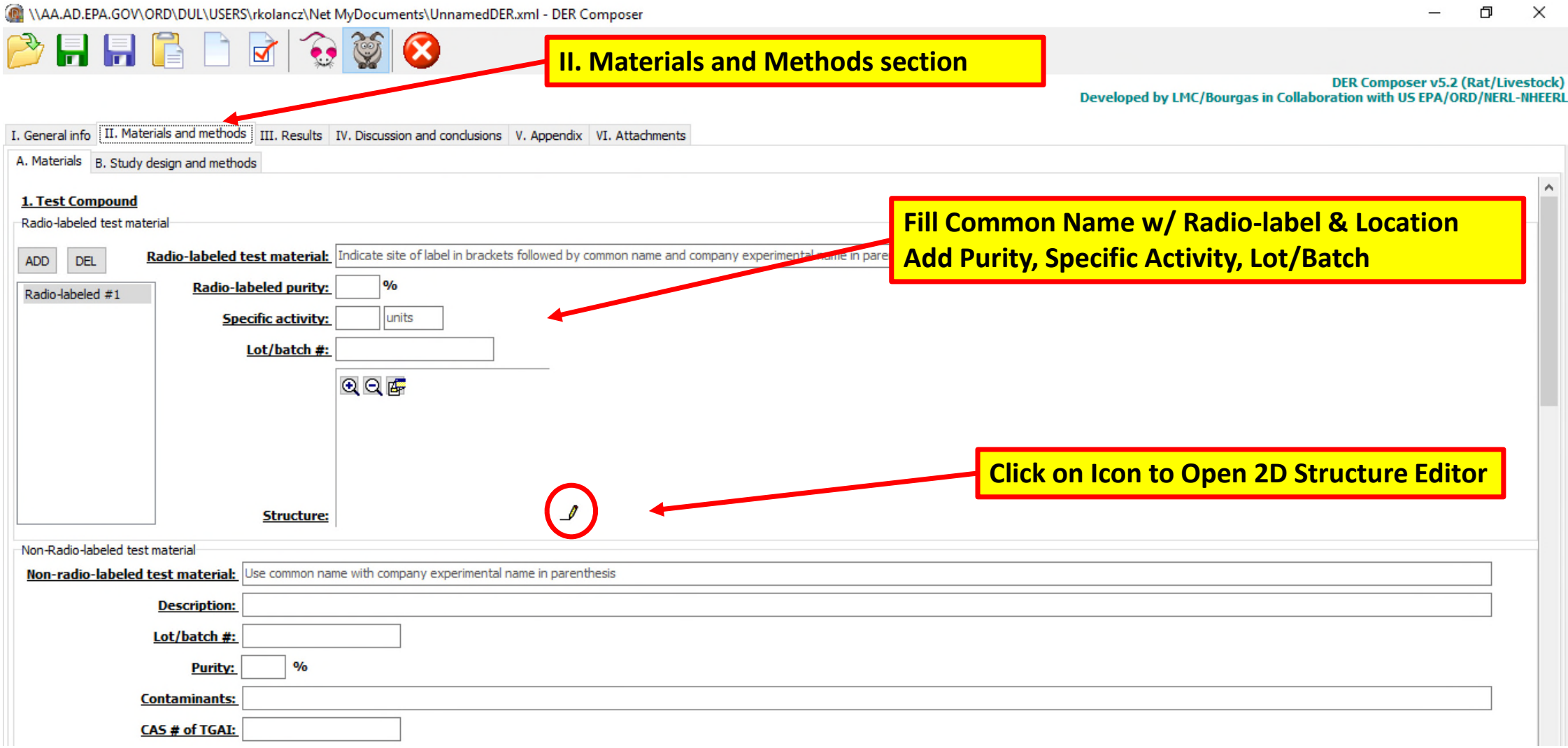
Then Continue Filling Test Material Common Name, Test Material Purity, IUPAC Name, Synonyms, and End Use Products.

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.

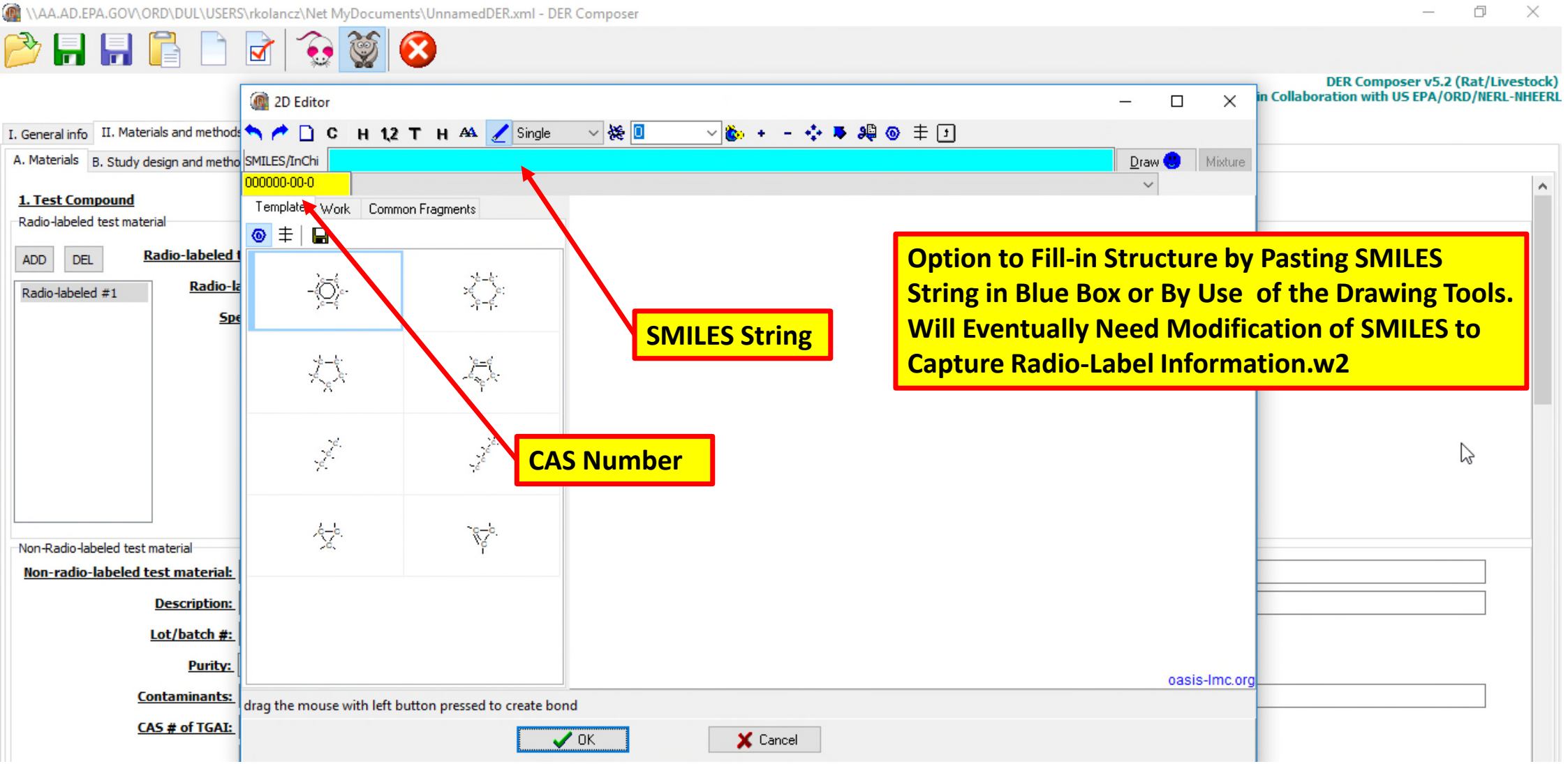


The citation is entered and tables are created and are ready for population. Additional references (MRID's) may be entered by repeat of the afore mentioned process

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:

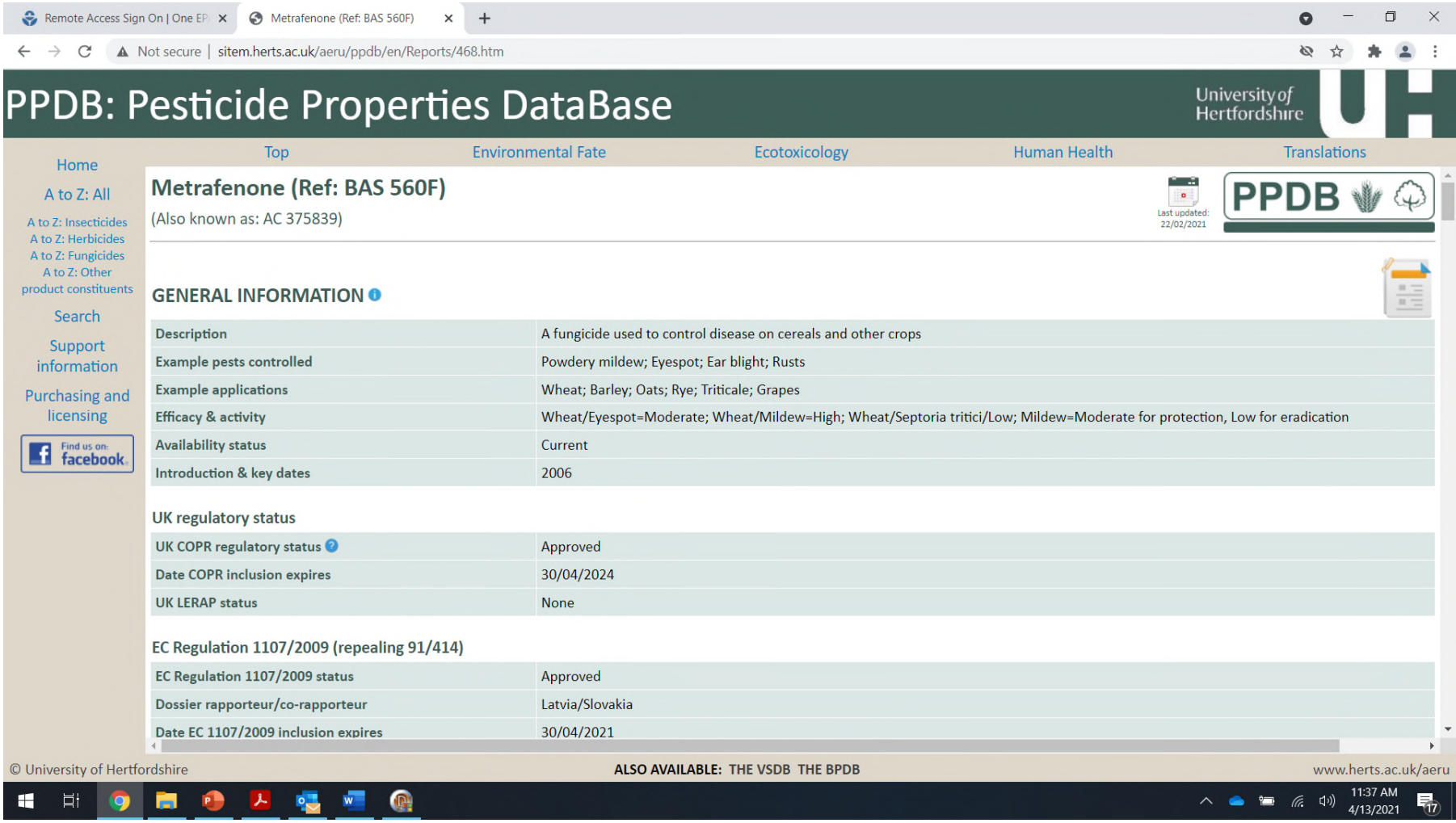


Below is a graphic of the STRUCTURE DRAWING editor pop-up box. The large white area is the drawing workspace, the light-blue box is where a SMILES string may be entered or displayed, and the yellow box is where a CAS number can be entered. Scrolling over the top of the icons will give some indication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

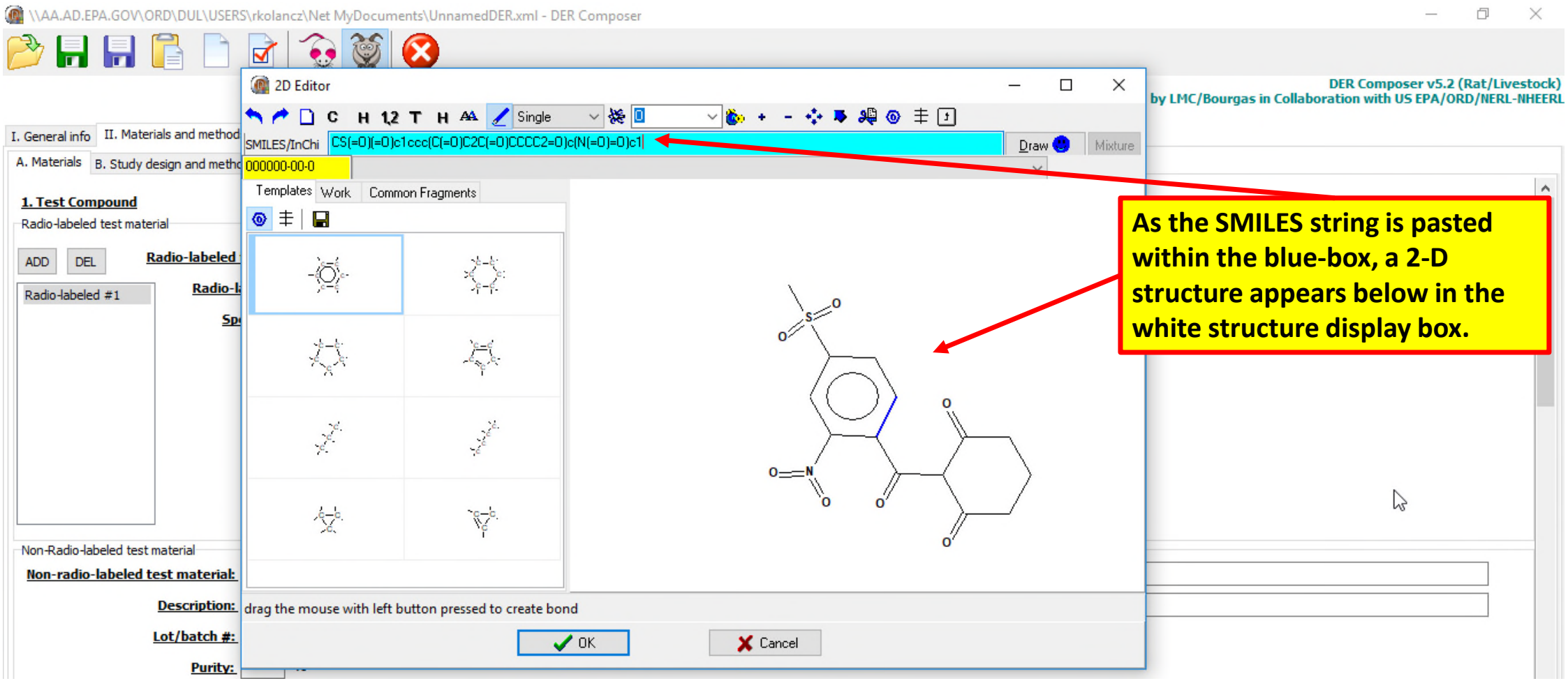


To get started a good source of parent nomenclature, 2-D structures represented as linear "SMILES strings", etc are available on the Pesticide Properties Database (PPDB) of the University of Hertfordshire web-site.

http://sitem.herts.ac.uk/aeru/ppdb/en/index.htm



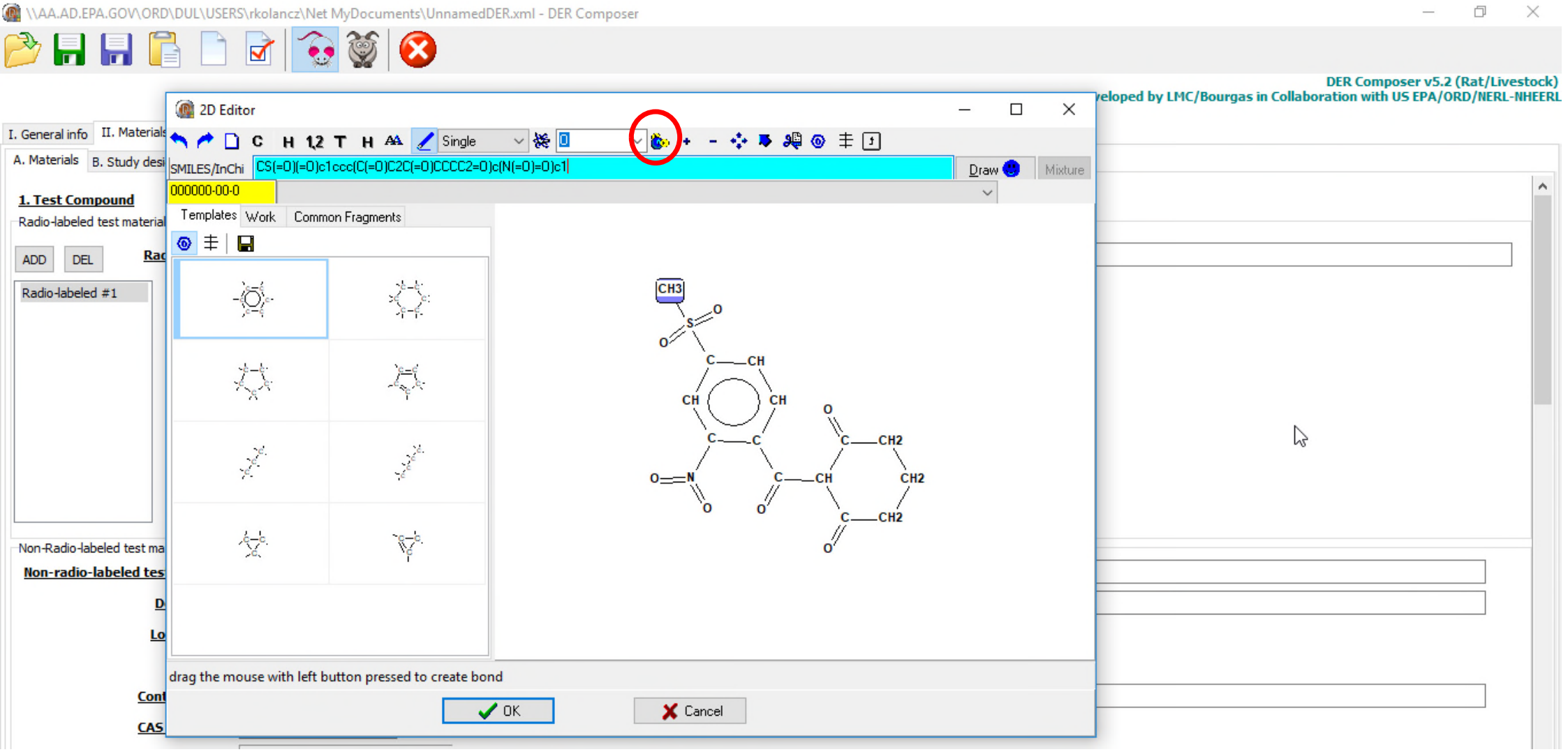
Perform a right-hand click of the mouse in the light-blue box of the STRUCTURE DRAWING package and select paste to enter the parent structure.



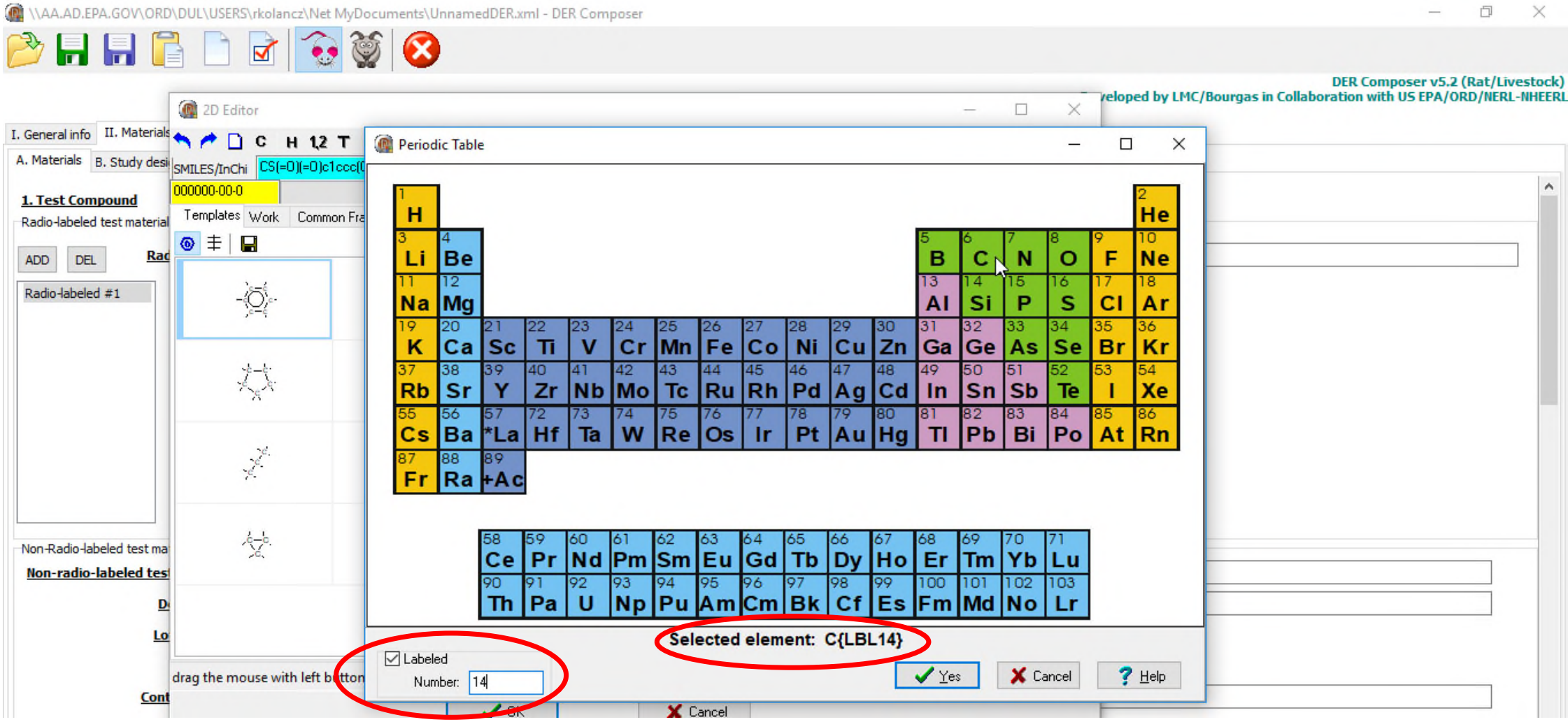
The parent structure (now present in the STRUCTURE DRAWING editor) may be modified utilizing tools within the editor. Specifically a label may be introduced in the structure of the radio-labeled parent.

Radio labeling of atoms

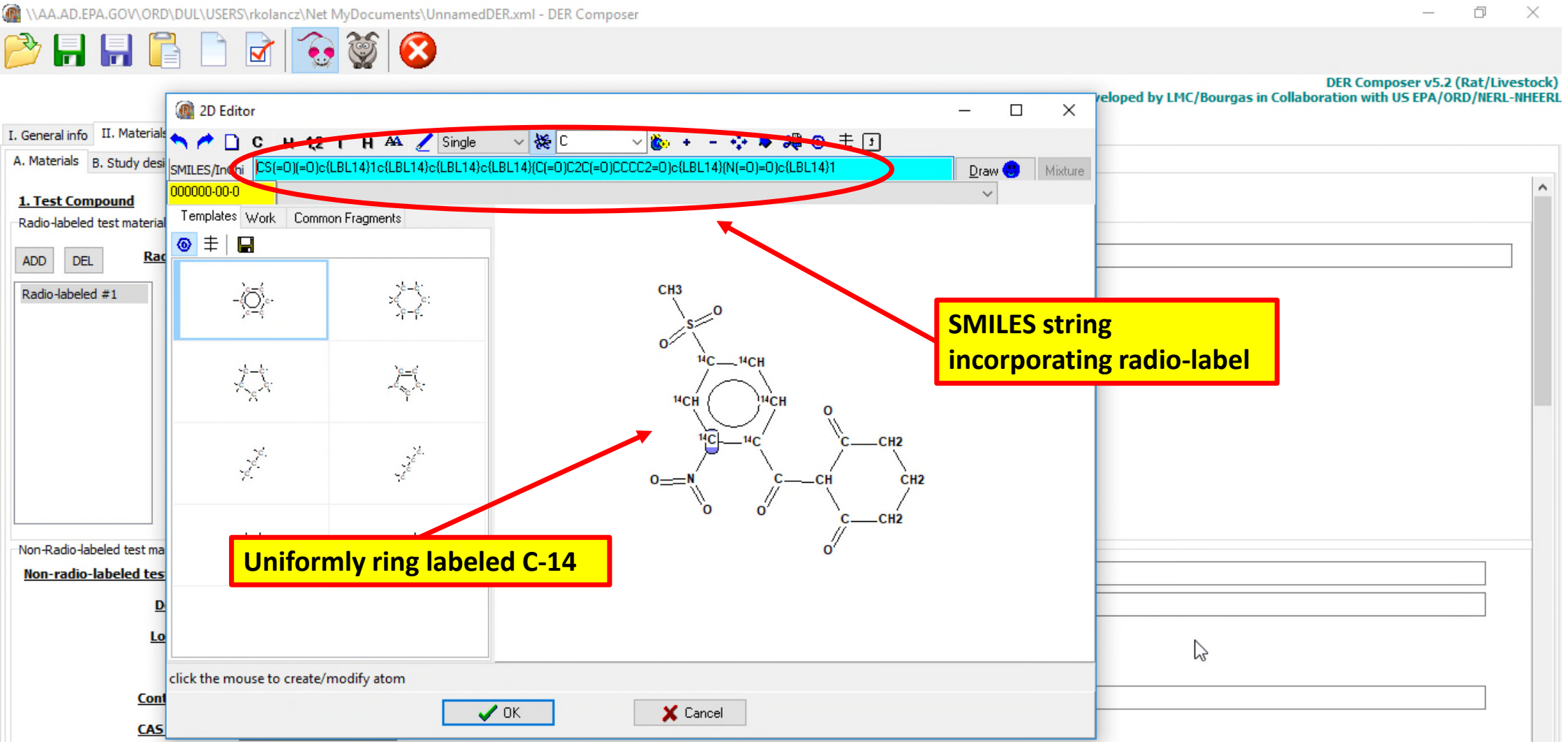
Within the STRUCTURE DRAWING window, open the periodic table by selecting the icon as circled in the figure below.



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.



\\AA.AD.EPA.GOV\ORD\DUL\USERS\rkolancz\Net MyDocuments\UnnamedDER.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

ADD DEL

Radio-labeled #1

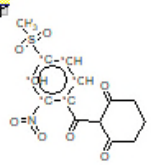
Radio-labeled test material: Mesotrione [14C-aromatic]

Radio-labeled purity: 97 %

Specific activity: 1.12-1 GBq/mmol

Lot/batch #: Y06684/159 or Y06684/011

Structure:



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

Non-Radio-labeled test material

Non-radio-labeled test material: Use common name with company experimental name in parenthesis

Description:

Lot/batch #:

Purity: %

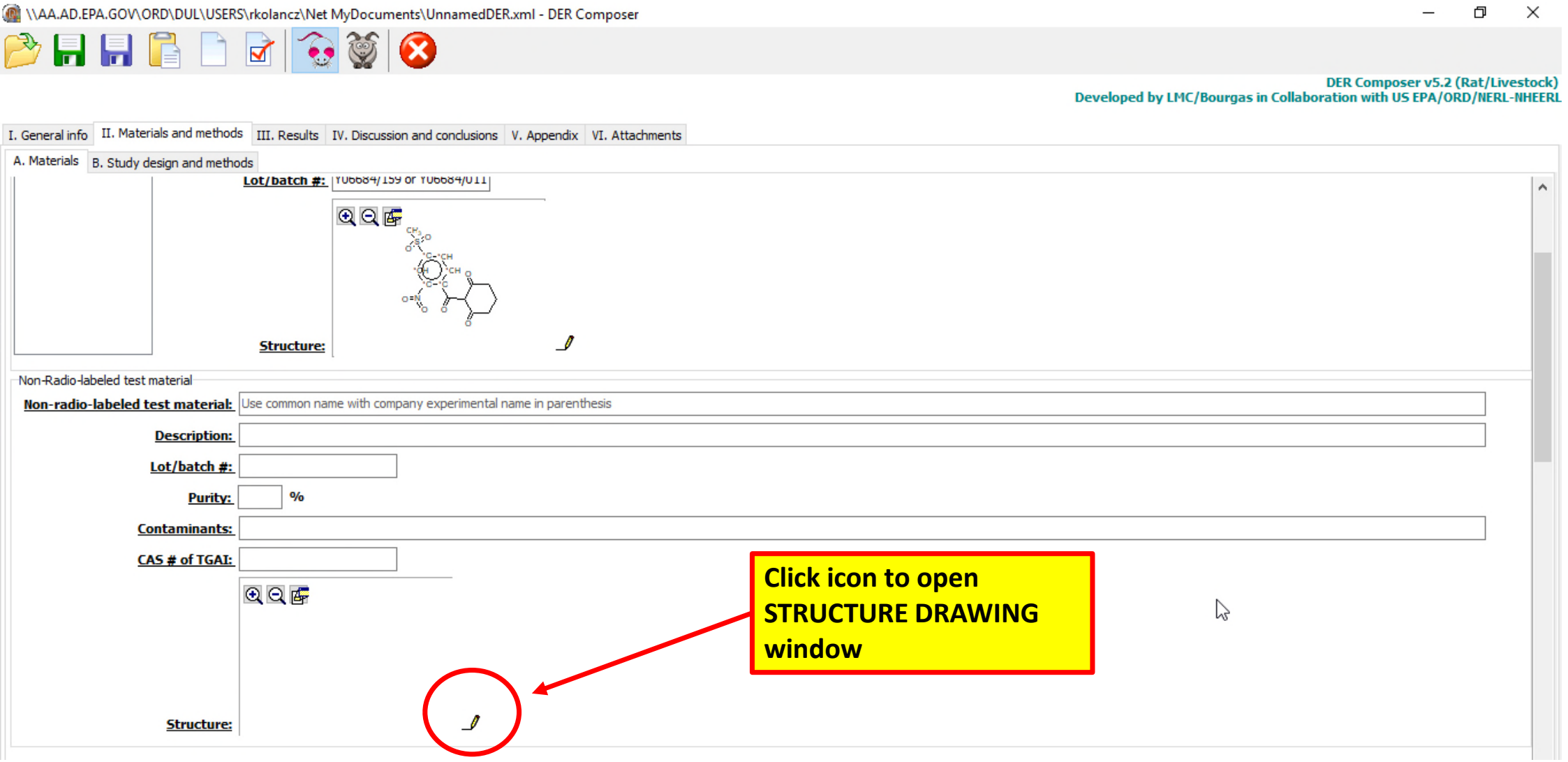
Contaminants:

CAS # of TGAI:

Modified | Rat

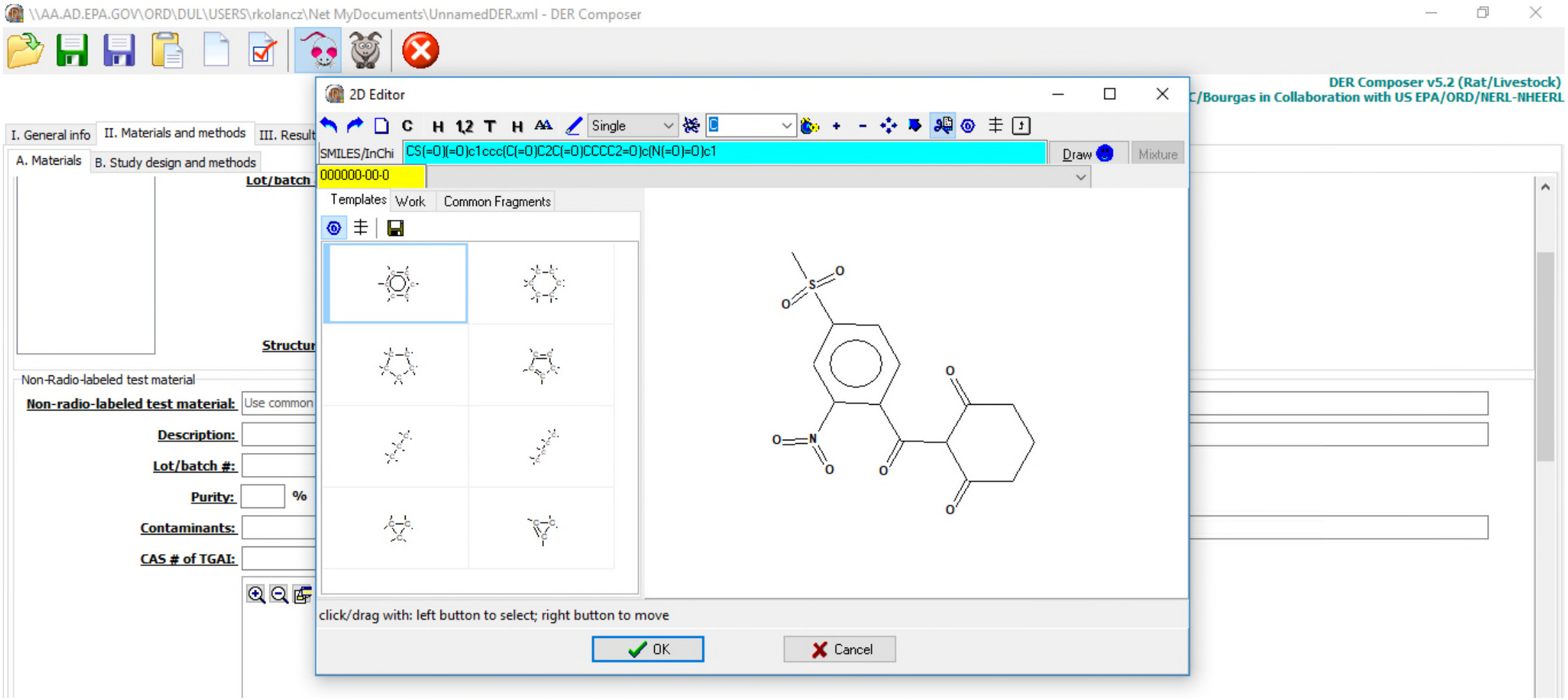
8:42 AM
2/17/2021

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



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.



\\AA.AD.EPA.GOV\ORD\DUL\USERS\rkolancz\Net MyDocuments\UnnamedDER.xml - DER Composer

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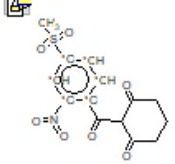
I. General info | II. Materials and methods | III. Results | IV. Discussion and conclusions | V. Appendix | VI. Attachments

A. Materials | B. Study design and methods

Lot/batch #: Y06684/159 or Y06684/011

Structure:



Non-Radio-labeled test material

Non-radio-labeled test material: Mesotrione

Description: Cream solid or off-white powder

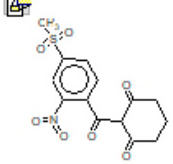
Lot/batch #: Y06684/008 or Y06684/005

Purity: >99.3 %

Contaminants: not specified

CAS # of TGAI: 104206-82-8

Structure:



Note: 2-D Structure for Non-radio-label Test Material. Finish Filling Test Material Including Common Name, Description of Material, Lot/Batch, Purity, Any Contaminants, and CAS #.

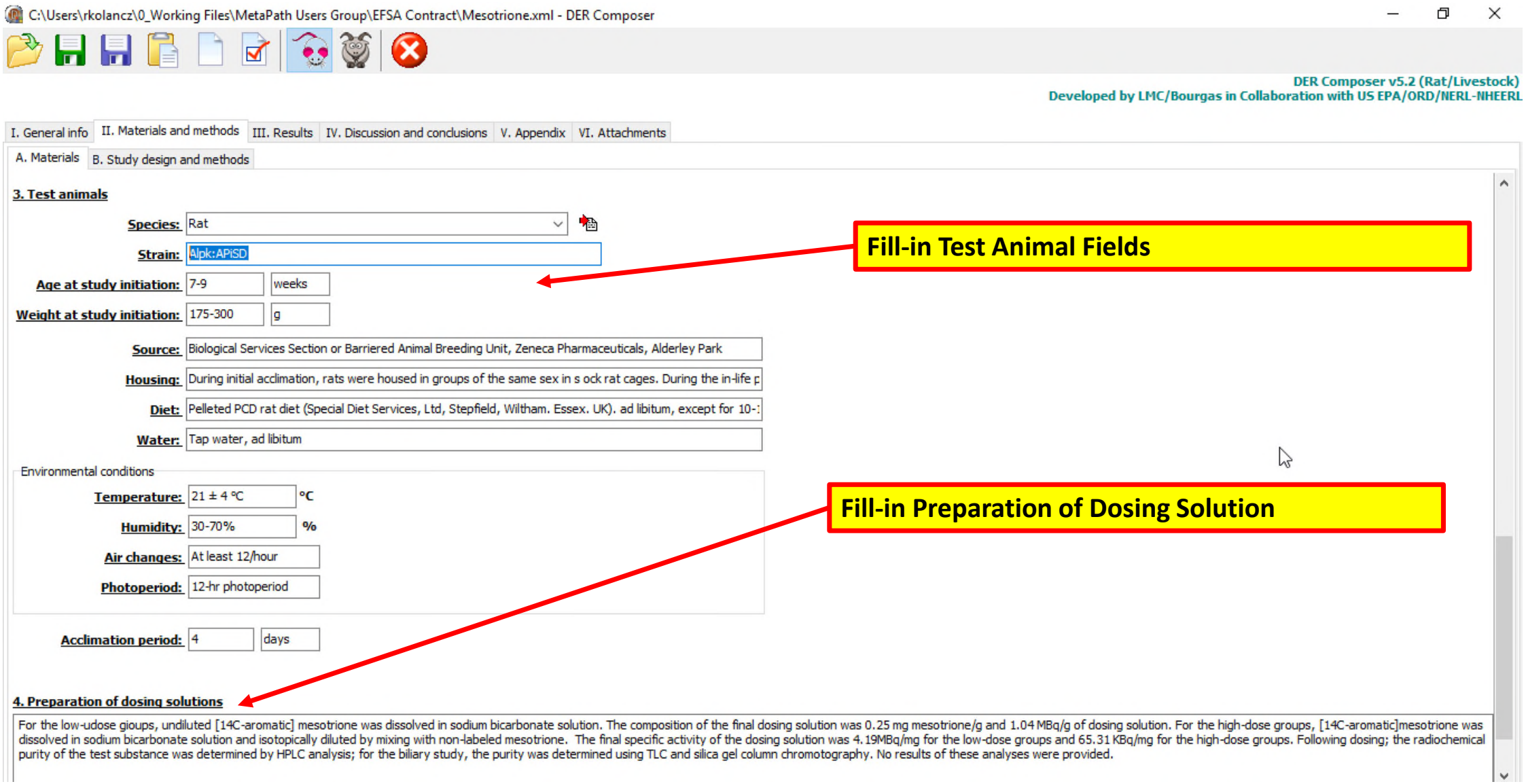
Physicochemical Properties

Parameter	Note	Value	Reference

Modified | Rat

9:04 AM
2/17/2021

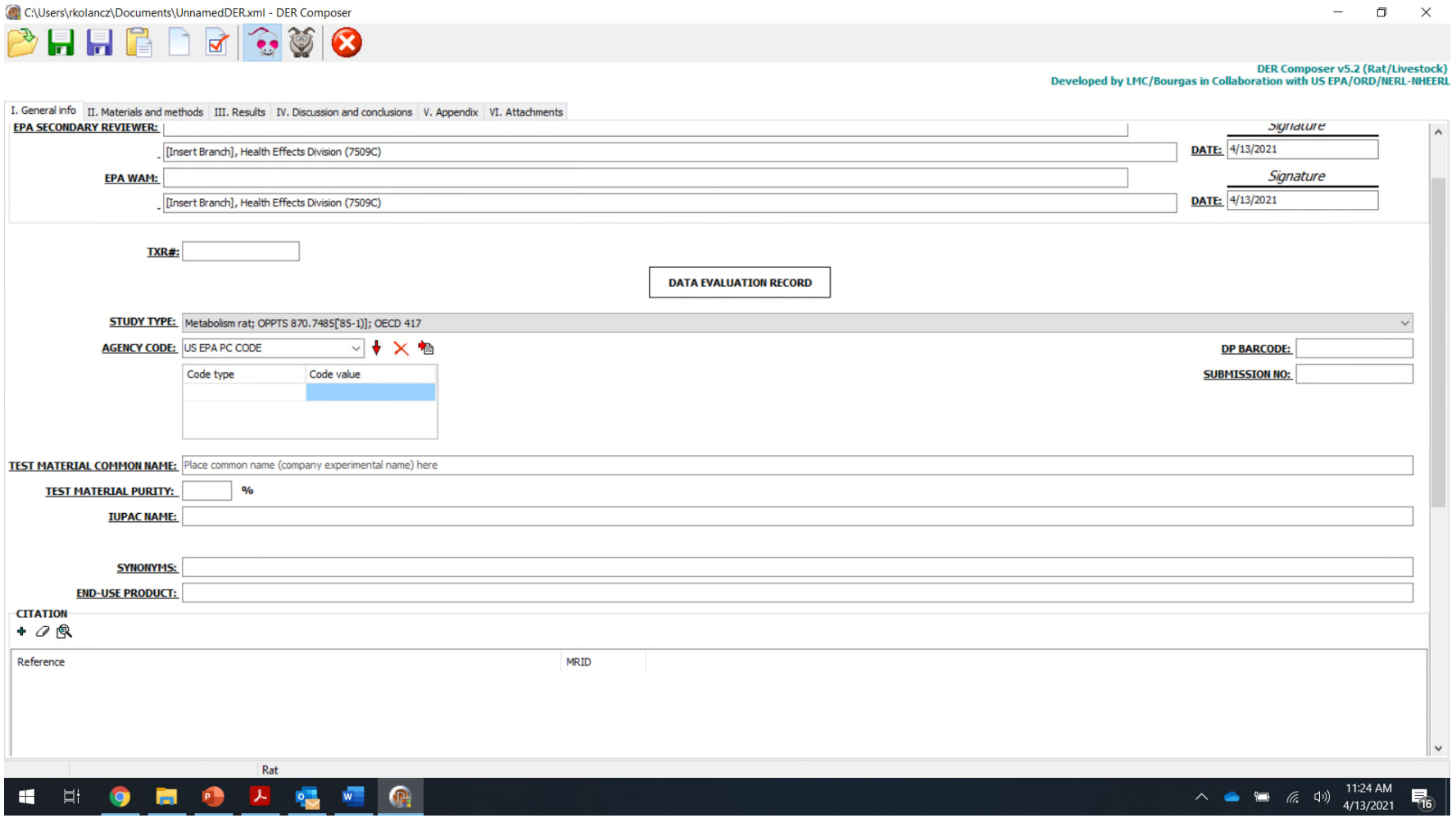
Continue filling out the rest of II. Material and methods A. Materials



Fill-in Test Animal Fields

Fill-in Preparation of Dosing Solution

Go To Live Demo

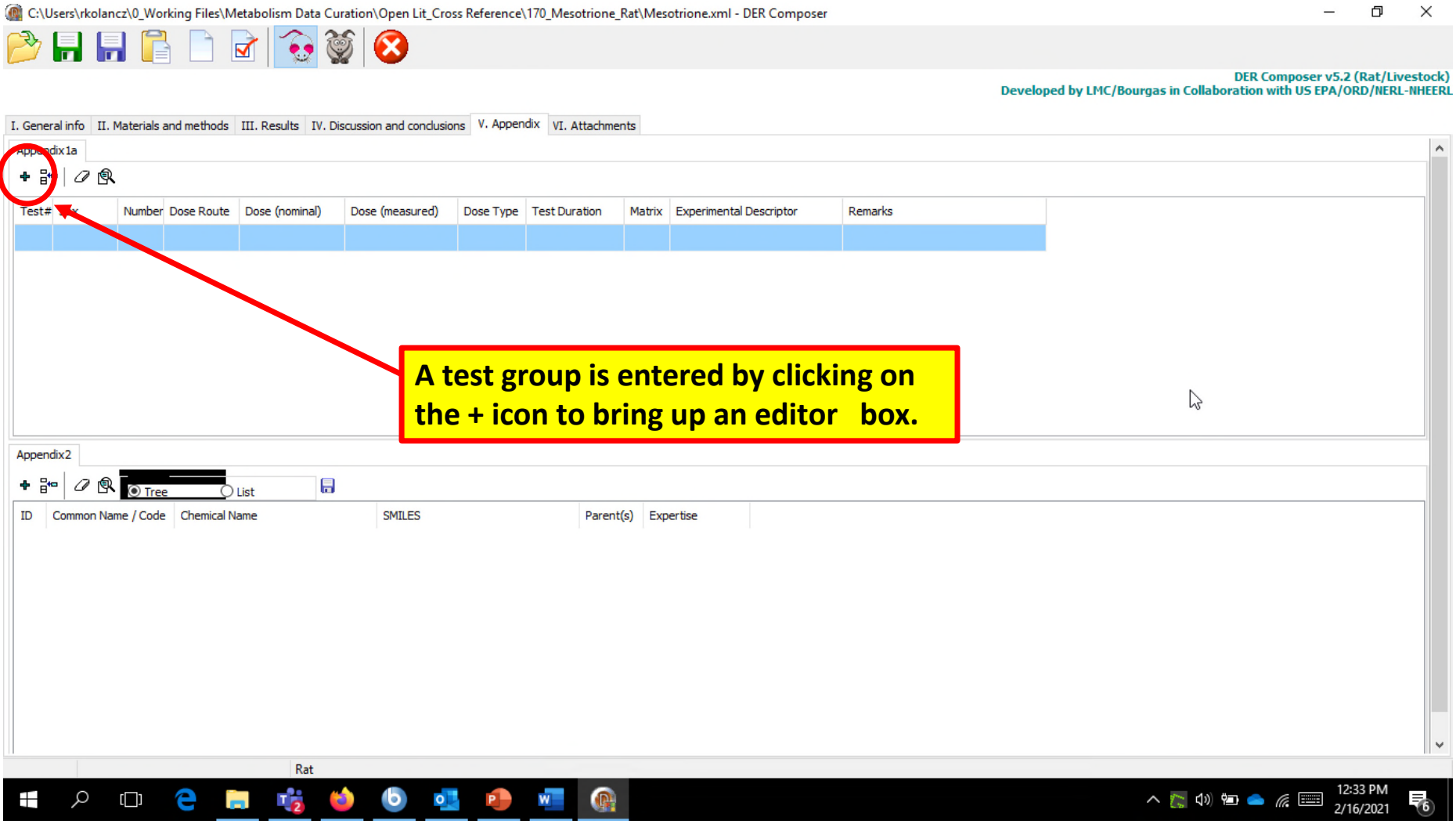


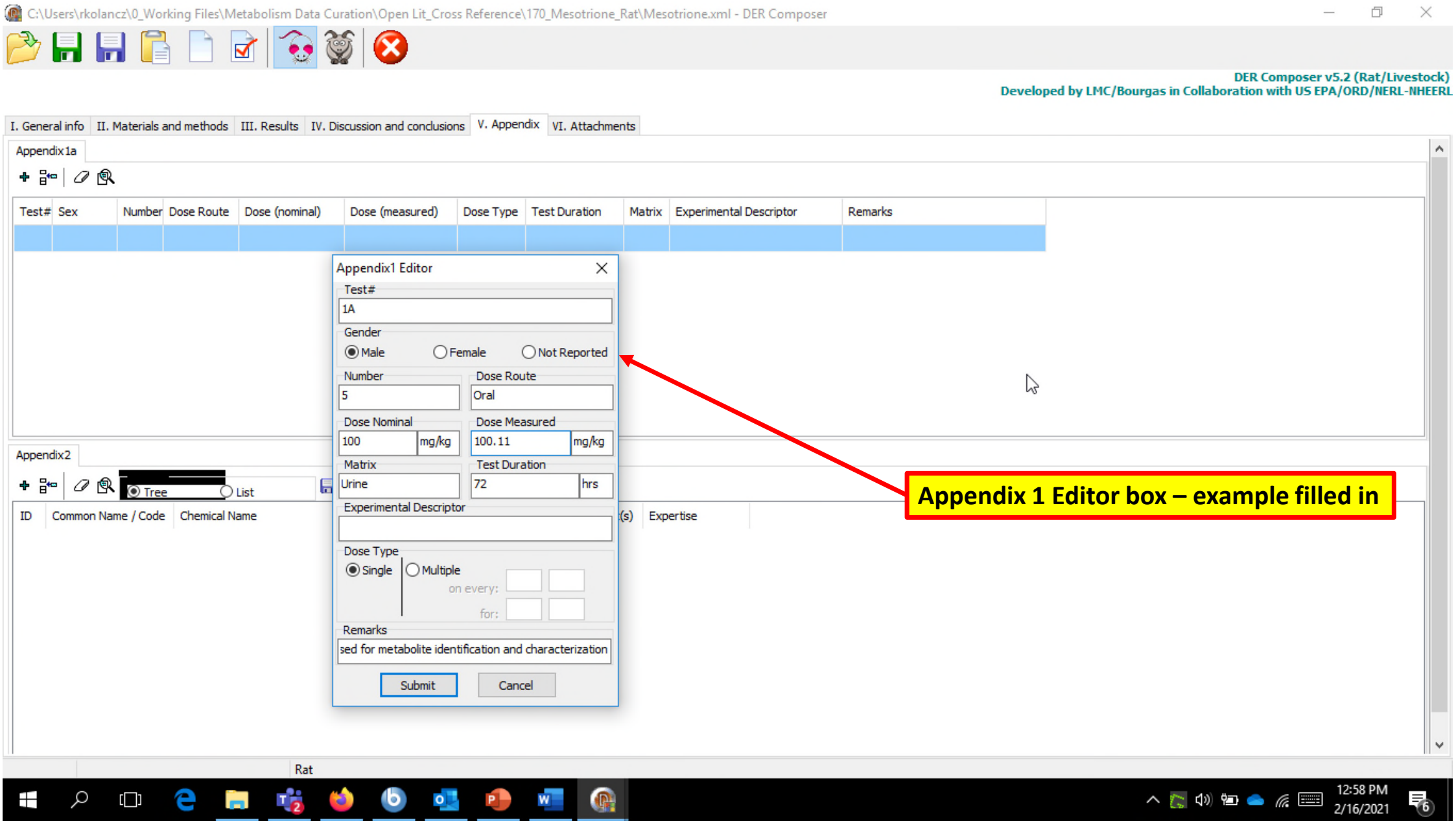
Questions ???
&
Answers

Part 2:

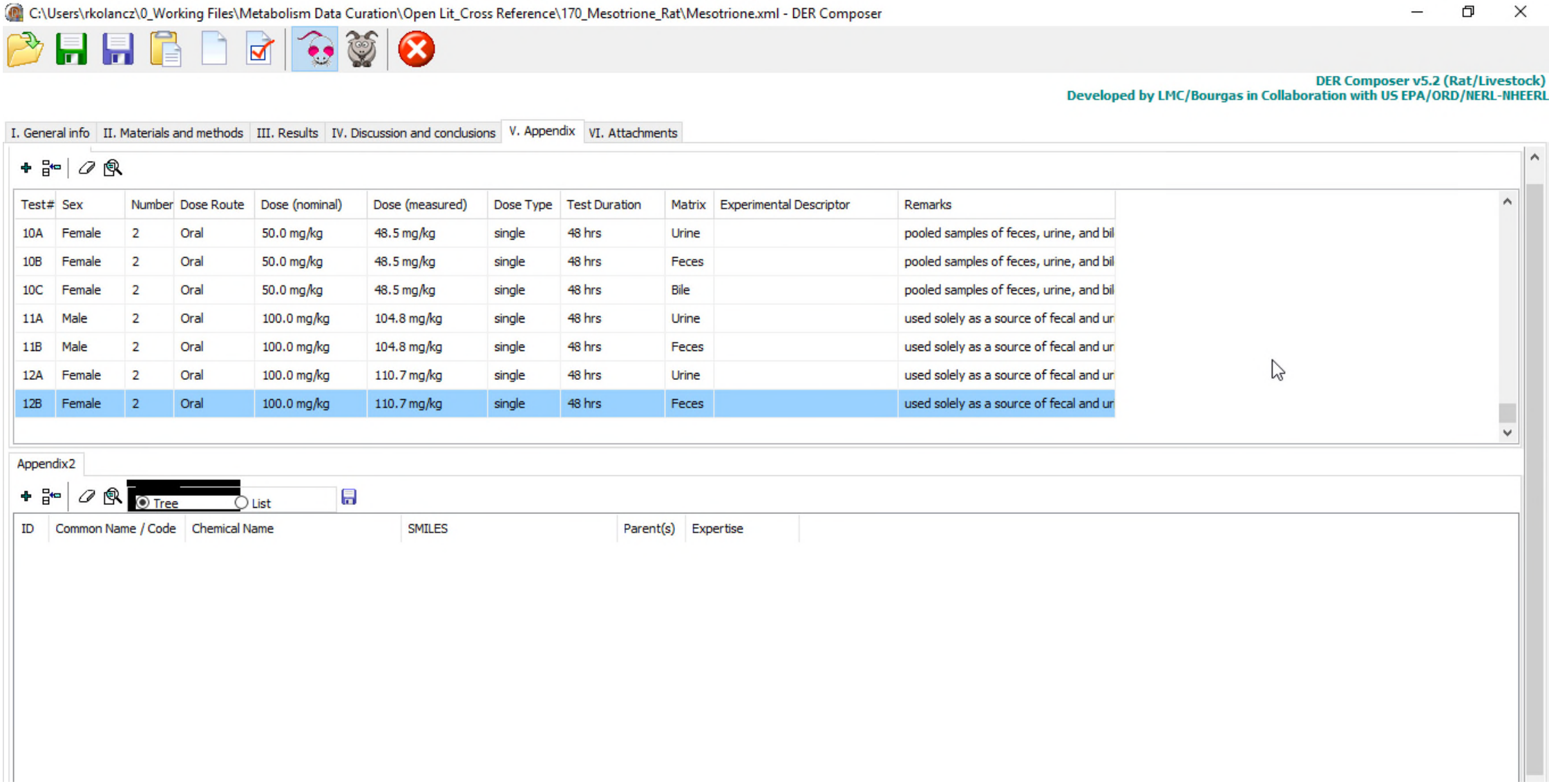
- **Appendix 1**
- **Appendix 2**
- **Material and methods**
- **Study design**

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).

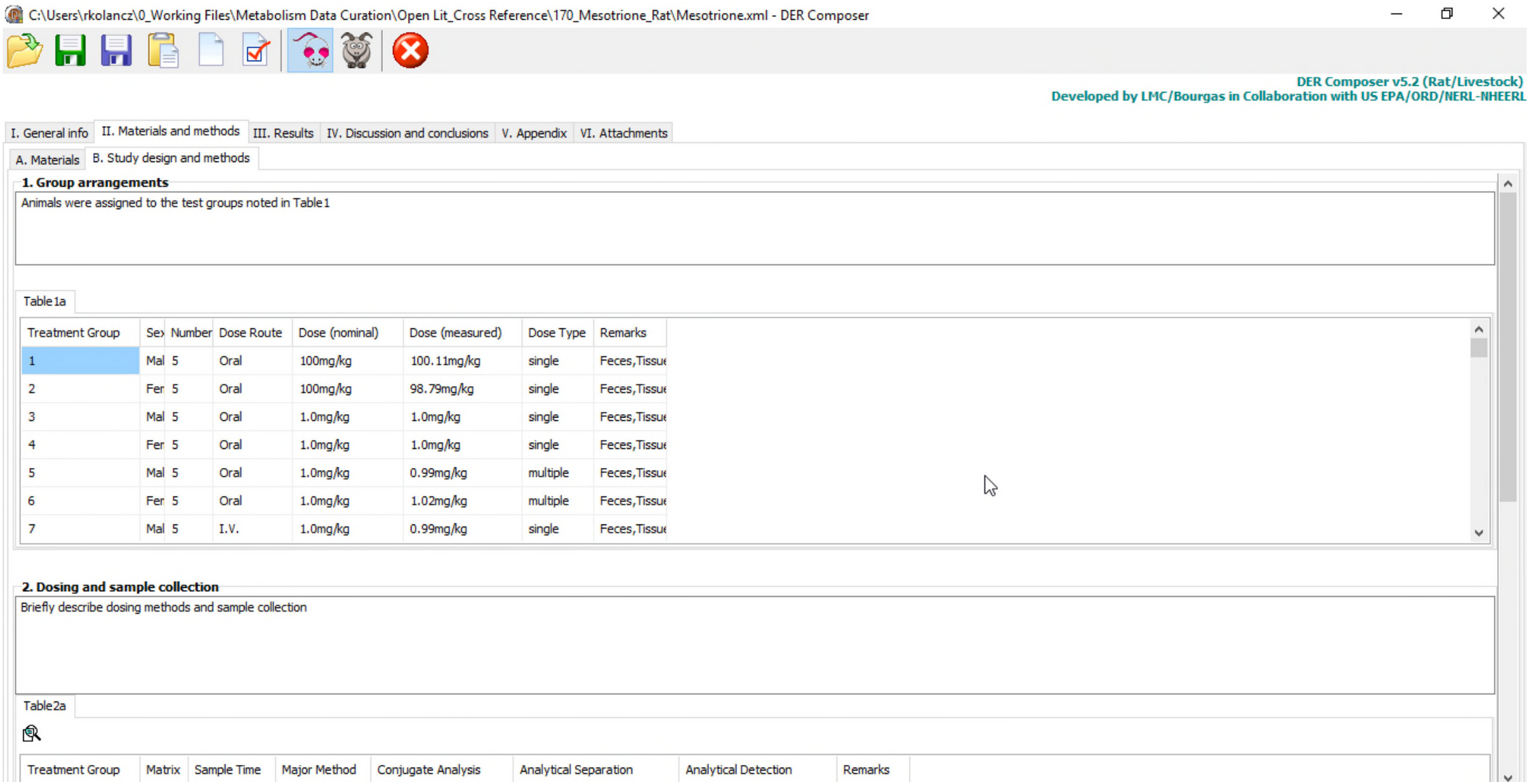



C:\Users\rkolancz\0_Working Files\Metabolism Data Curation\Open Lit_Cross Reference\170_Mesotrione_Rat\Mesotrione.xml - DER Composer
DER Composer v5.2 (Rat/Livestock)
Developed by LMC/Bourgas in Collaboration with US EPA/ORD/NERL-NHEERL
I. General info
II. Materials and methods
III. Results
IV. Discussion and conclusions
V. Appendix
VI. Attachments
Appendix 1a
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
Experimental Descriptor
Dose Type
Single
Multiple
on every:
for:
Remarks
sed for metabolite identification and characterization
Submit
Cancel
Appendix 1 Editor box – example filled in
Appendix2
Tree
List
ID
Common Name / Code
Chemical Name
Expertise
Rat
12:58 PM
2/16/2021

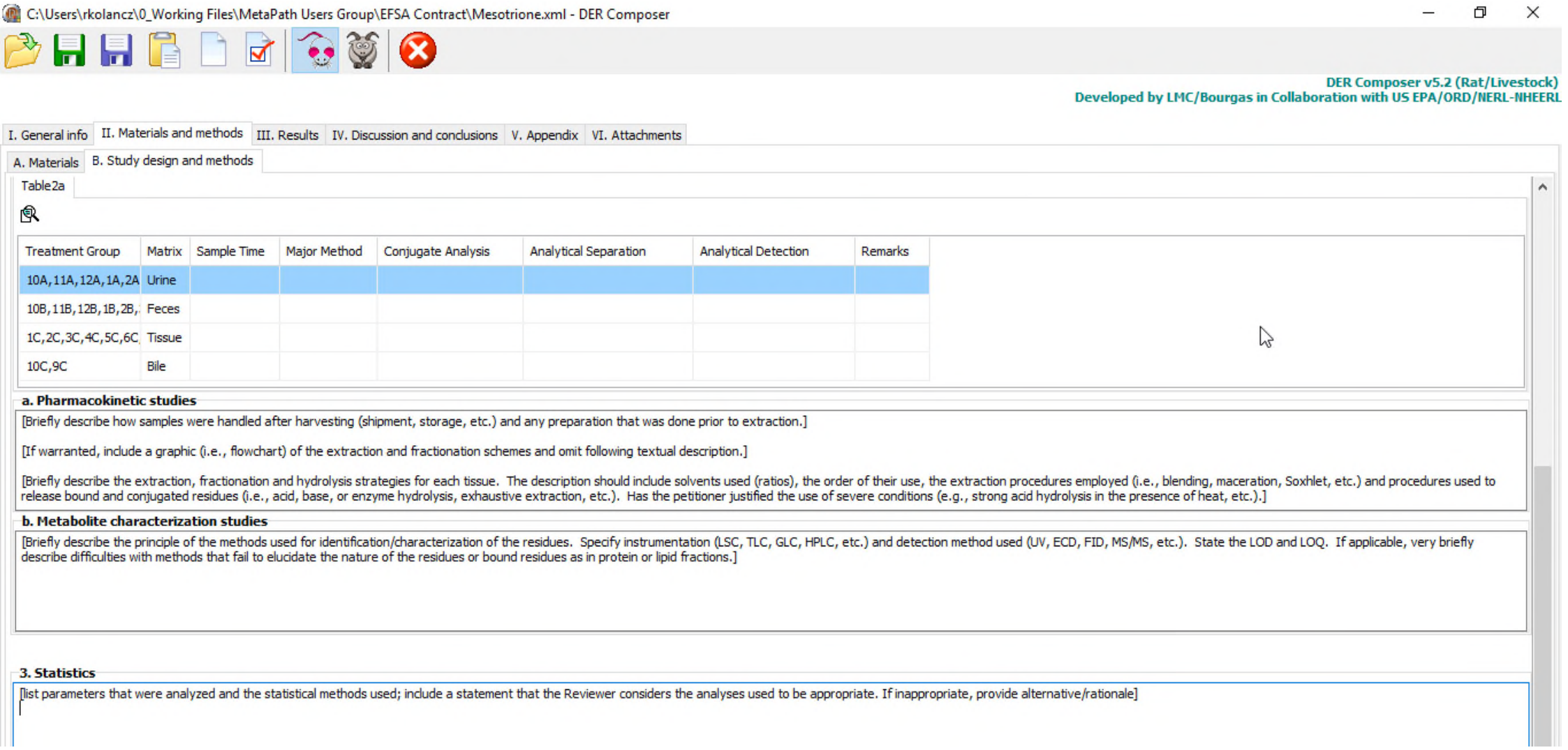
Click on submit to accept test – continue to add new tests via the same process until completed. Screen should appear as below:



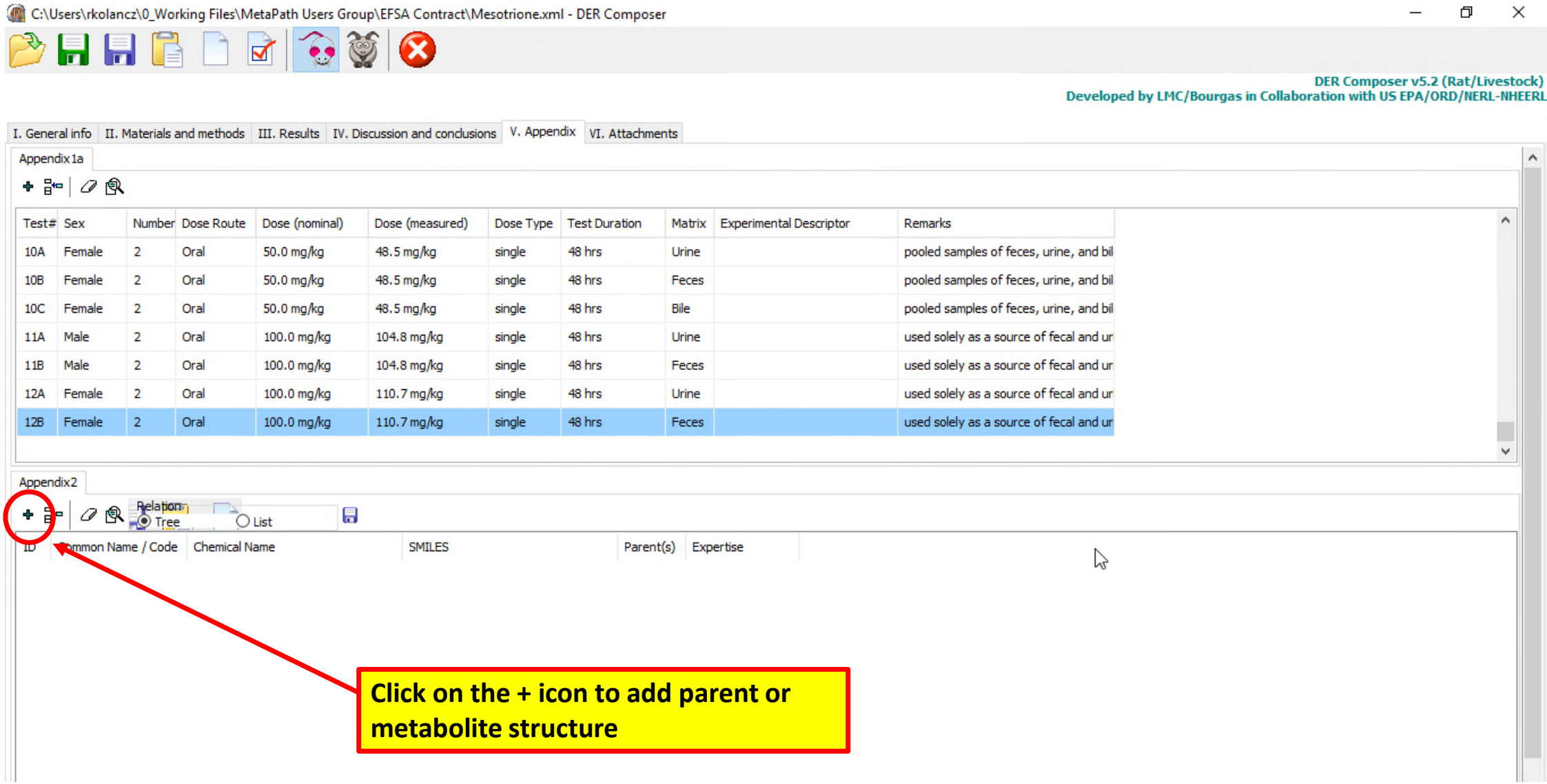
The completed Appendix 1 will automatically populate the group arrangements Table 1 of section/tab II. Materials and methods sub-tab B. Study design and methods. This may be observed by clicking on the appropriate tabs.

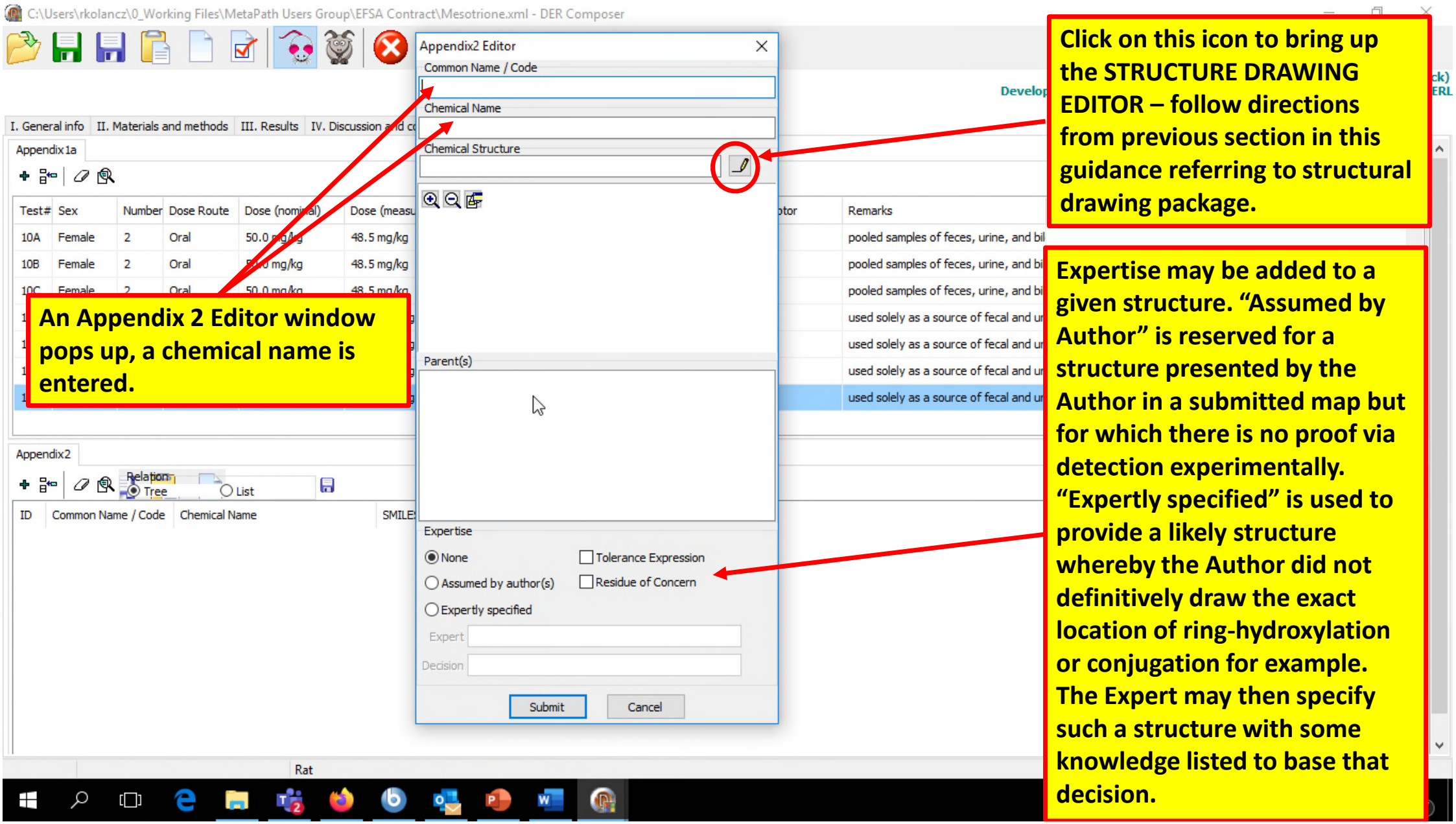


In addition, an automatic partial entry of the dosing and sample collection Table 2 of section/tab II. Materials and methods sub-tab B. Study design and methods takes place. We will return to complete this table after completion of Appendix 2.

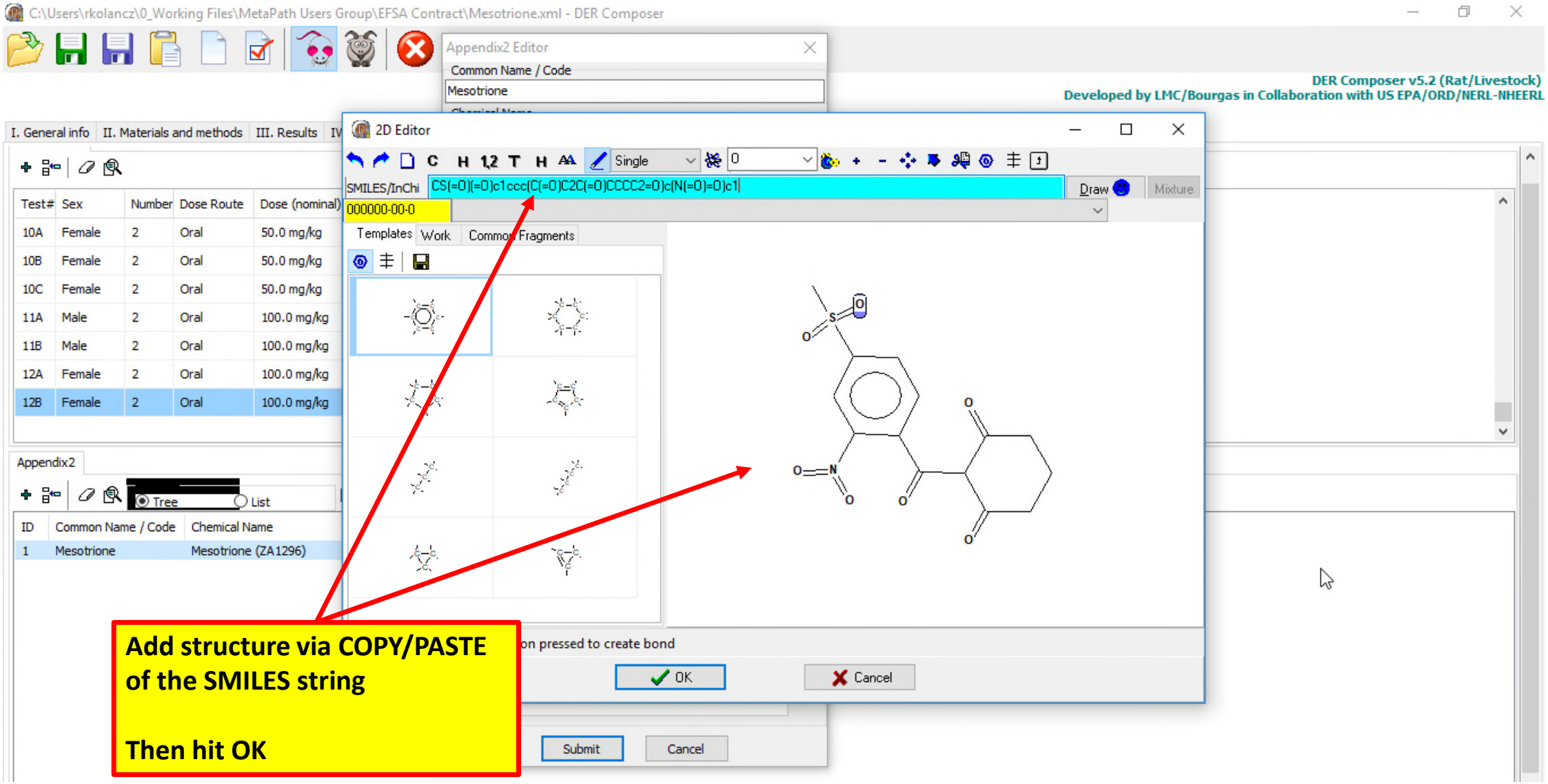


Next a Metabolite Inventory table should be completed as Appendix 2 of tab V. Appendix.



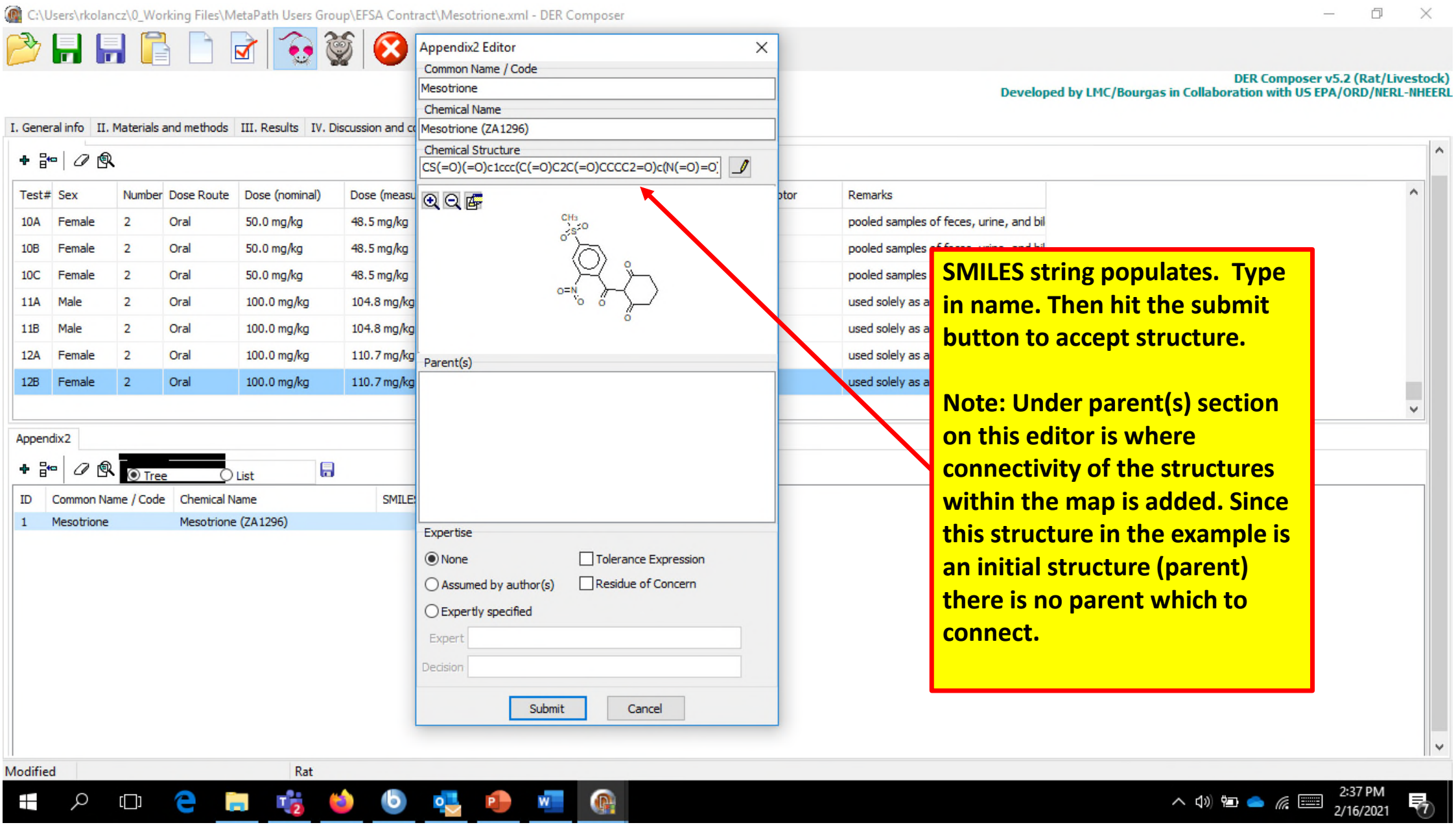

C:\Users\rkolancz\0_Working Files\MetaPath Users Group\EFSA Contract\Mesotrione.xml - DER Composer
Appendix2 Editor
Common Name / Code
Chemical Name
Chemical Structure
Parent(s)
Expertise
None
Assumed by author(s)
Expertly specified
Tolerance Expression
Residue of Concern
Expert
Decision
Submit
Cancel
I. General info
II. Materials and methods
III. Results
Appendix 1a
Test#
Sex
Number
Dose Route
Dose (nominal)
Dose (measu
Remarks
10A Female 2 Oral 50.0 mg/kg 48.5 mg/kg pooled samples of feces, urine, and bil
10B Female 2 Oral 48.5 mg/kg pooled samples of feces, urine, and bi
used solely as a source of fecal and ur
Appendix2
Relation
Tree
List
ID
Common Name / Code
Chemical Name
Rat
An Appendix 2 Editor window pops up, a chemical name is entered.
Click on this icon to bring up the STRUCTURE DRAWING EDITOR – follow directions from previous section in this guidance referring to structural drawing package.
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.

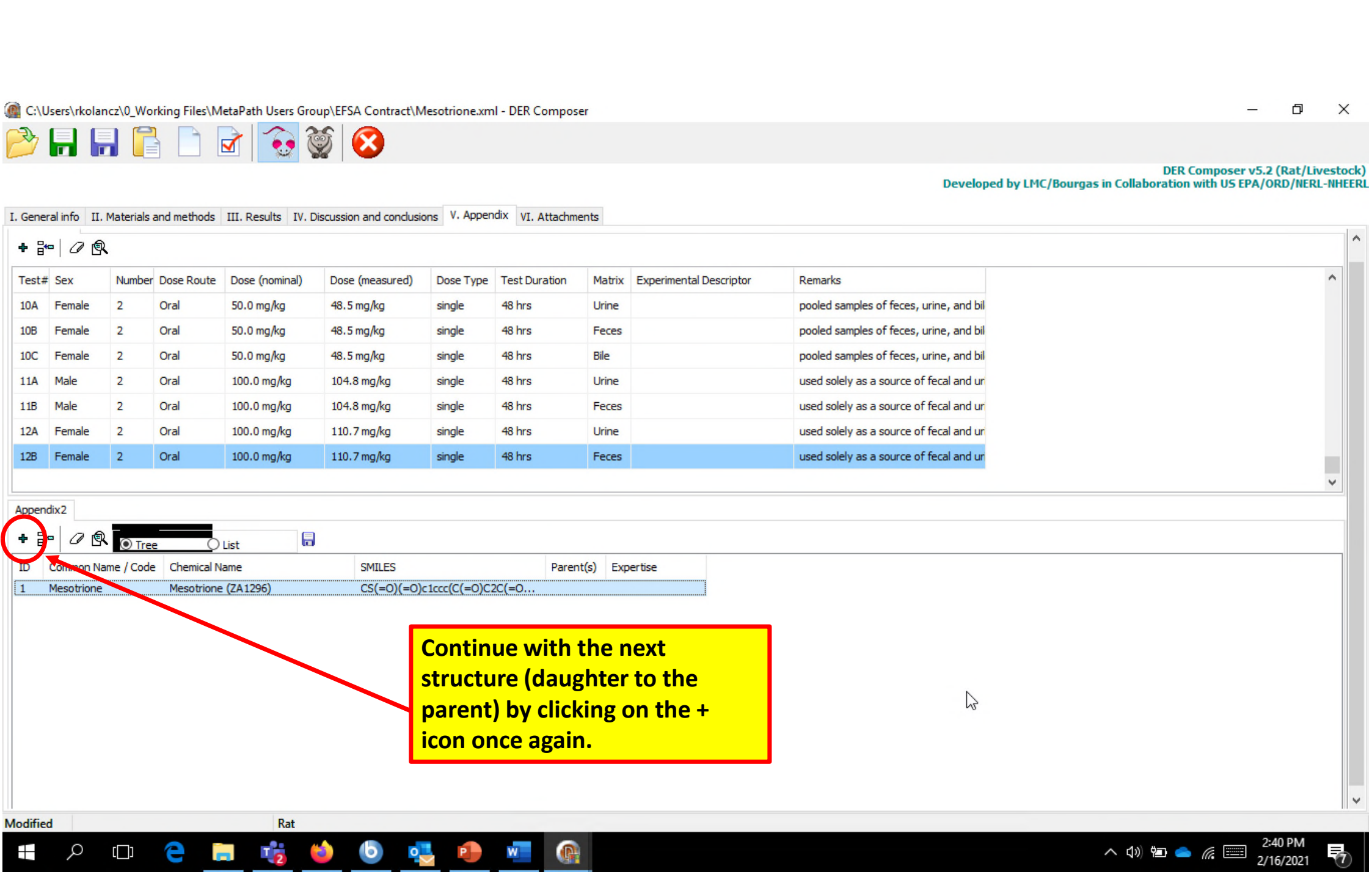
We will start by adding the parent structure – as was done in the materials & methods using COPY/PASTE of the SMILES string.

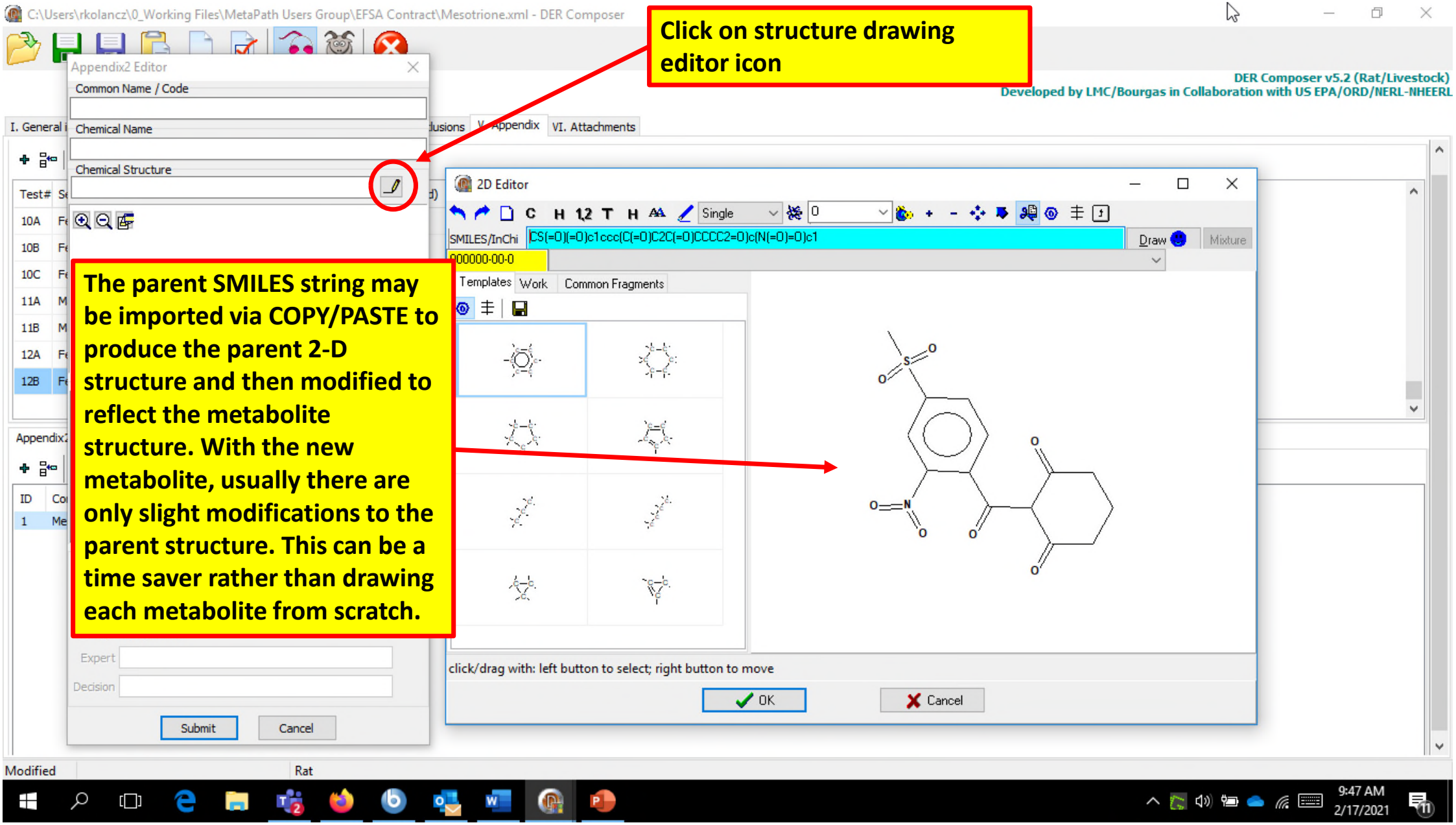


Add structure via COPY/PASTE of the SMILES string

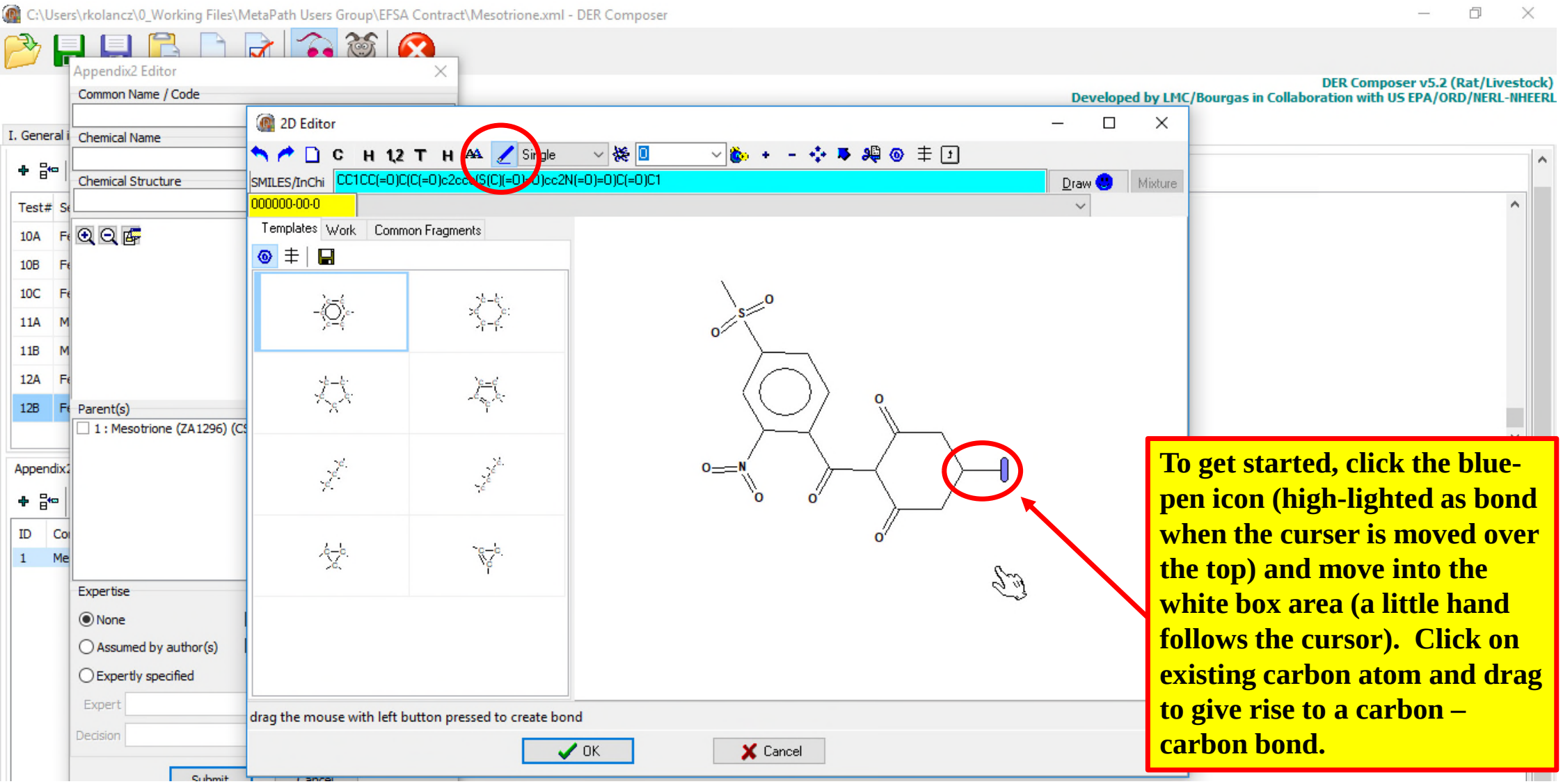
Then hit OK


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 c
Test#
Sex
Number
Dose Route
Dose (nominal)
Dose (measu
Remarks
10A Female 2 Oral 50.0 mg/kg 48.5 mg/kg pooled samples of feces, urine, and bil
10B Female 2 Oral 50.0 mg/kg 48.5 mg/kg pooled samples
10C Female 2 Oral 50.0 mg/kg 48.5 mg/kg pooled samples
11A Male 2 Oral 100.0 mg/kg 104.8 mg/kg used solely as a
11B Male 2 Oral 100.0 mg/kg 104.8 mg/kg used solely as a
12A Female 2 Oral 100.0 mg/kg 110.7 mg/kg used solely as a
12B Female 2 Oral 100.0 mg/kg 110.7 mg/kg used solely as a
Appendix2
Tree
List
ID
Common Name / Code
Chemical Name
SMILES
1 Mesotrione Mesotrione (ZA1296)
Appendix2 Editor
Common Name / Code
Mesotrione
Chemical Name
Mesotrione (ZA1296)
Chemical Structure
CS(=O)(=O)c1ccc(C(=O)C2C(=O)CCCC2=O)c(N(=O)=O
Parent(s)
Expertise
None
Assumed by author(s)
Expertly specified
Tolerance Expression
Residue of Concern
Expert
Decision
Submit
Cancel
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.
Modified
Rat
2:37 PM
2/16/2021


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
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
Tree
List
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.
Modified
Rat
2:40 PM
2/16/2021

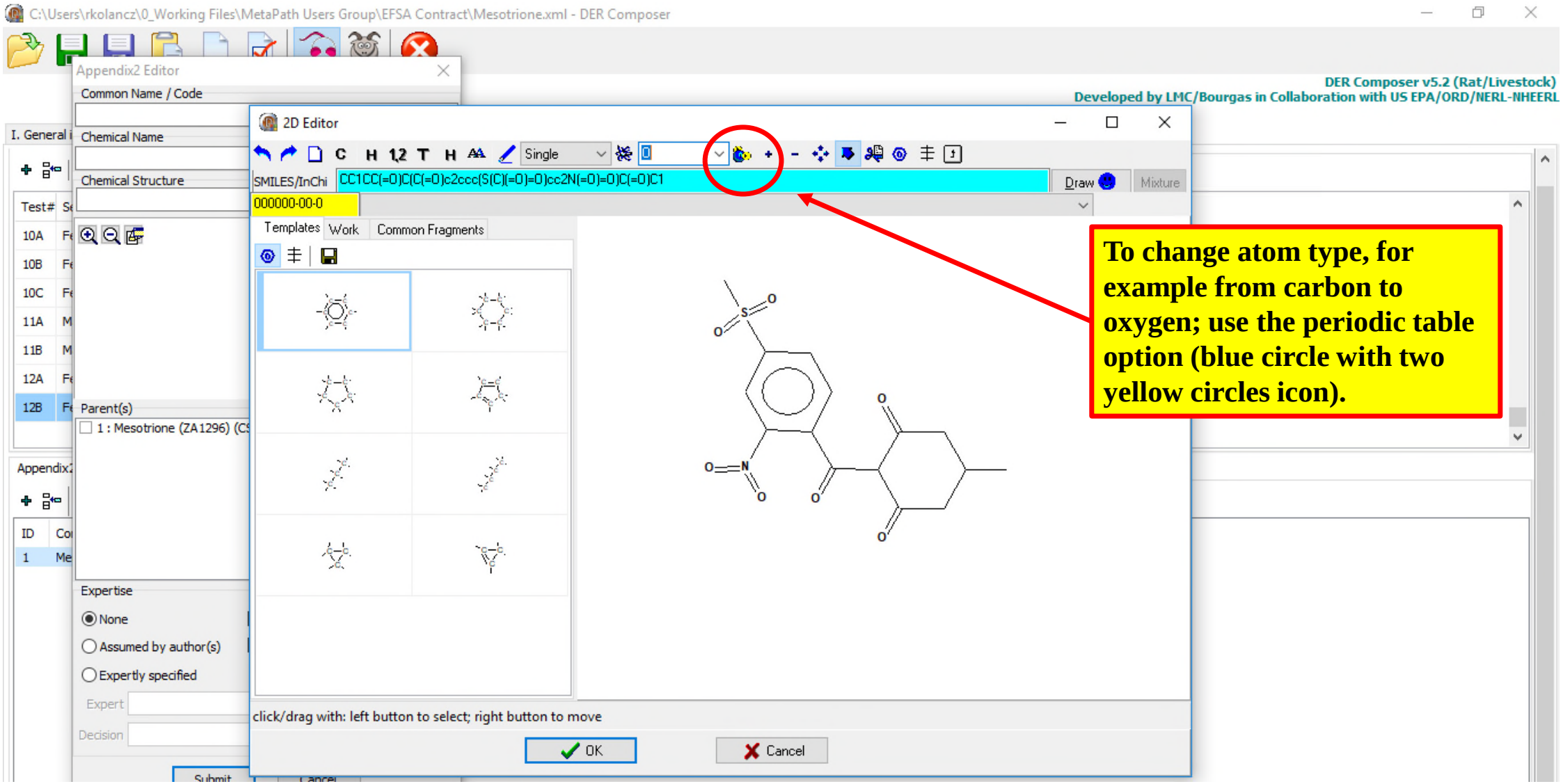

C:\Users\rkolancz\0_Working Files\MetaPath Users Group\EFSA Contract\Mesotrione.xml - DER Composer
Click on structure drawing editor icon
DER Composer v5.2 (Rat/Livestock)
Developed by LMC/Bourgas in Collaboration with US EPA/ORD/NERL-NHEERL
Appendix2 Editor
Common Name / Code
Chemical Name
Chemical Structure
I. General
V. Appendix
VI. Attachments
Test#
10A
10B
10C
11A
11B
12A
12B
ID
1
Expert
Decision
Submit
Cancel
2D Editor
Single
SMILES/InChi
CS(=O)(=O)c1ccc(C(=O)C2C(=O)CCCC2=O)c(N(=O)=O)c1
Draw
Mixture
Templates
Work
Common Fragments
click/drag with: left button to select; right button to move
OK
Cancel
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.
Modified
Rat
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.

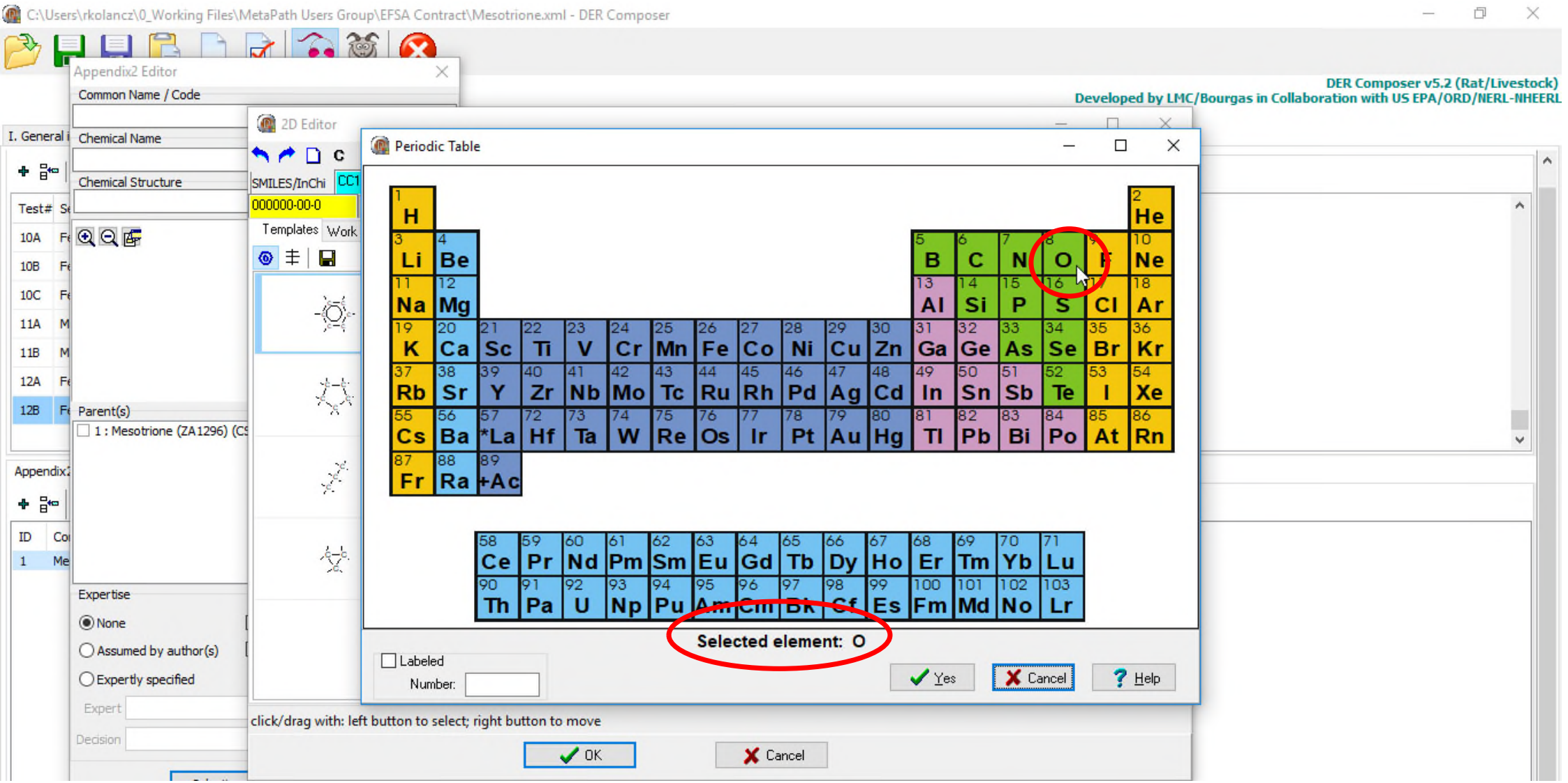


To get started, click the blue-pen icon (high-lighted as bond when the curser is moved over the top) and move into the white box area (a little hand follows the cursor). Click on existing carbon atom and drag to give rise to a carbon – carbon bond.

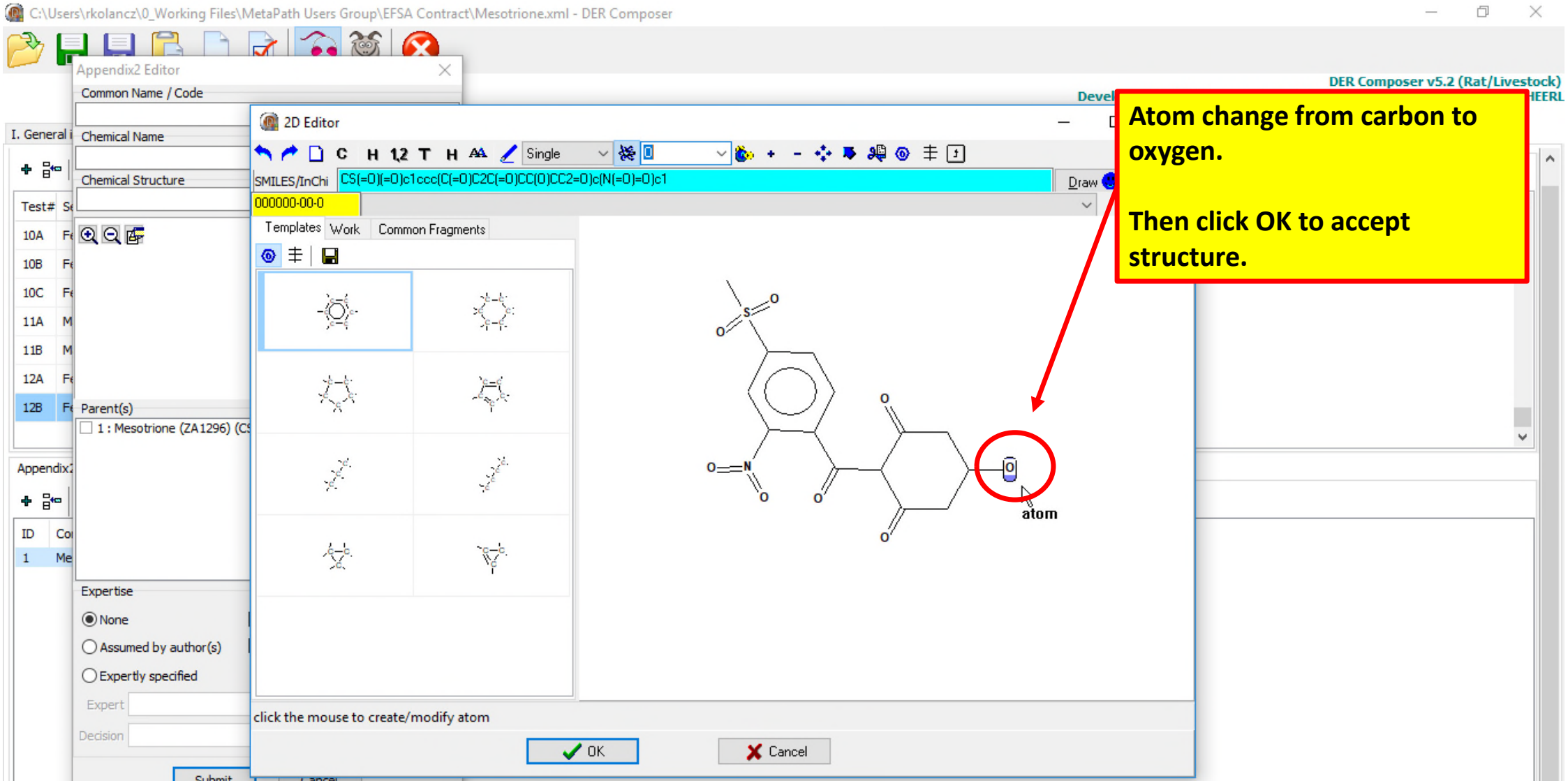
To change atom type, for example from carbon to oxygen; use the periodic table option (blue circle with two yellow circles icon).



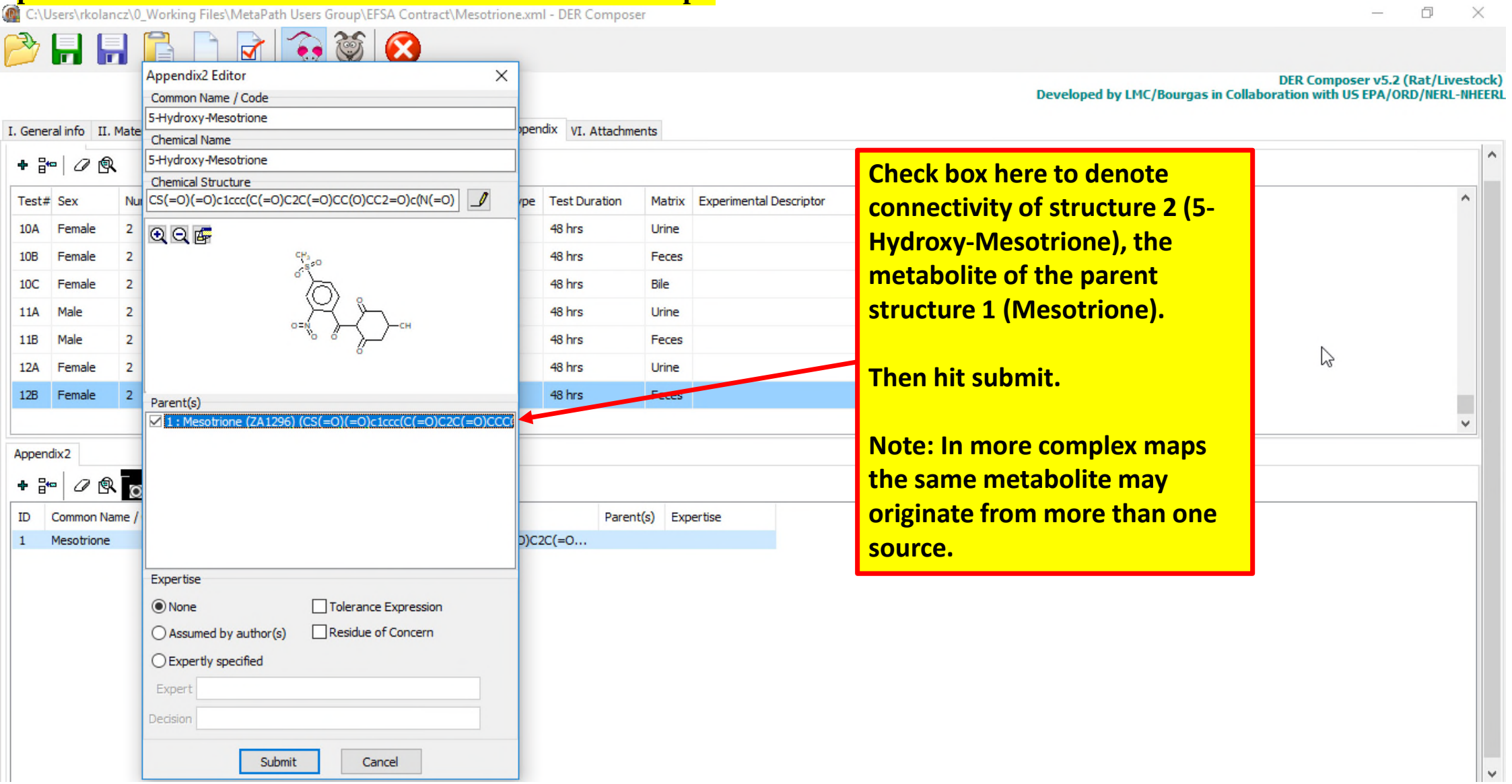
The periodic table opens, click on atom choice, click Yes to accept choice and the table goes away.



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.

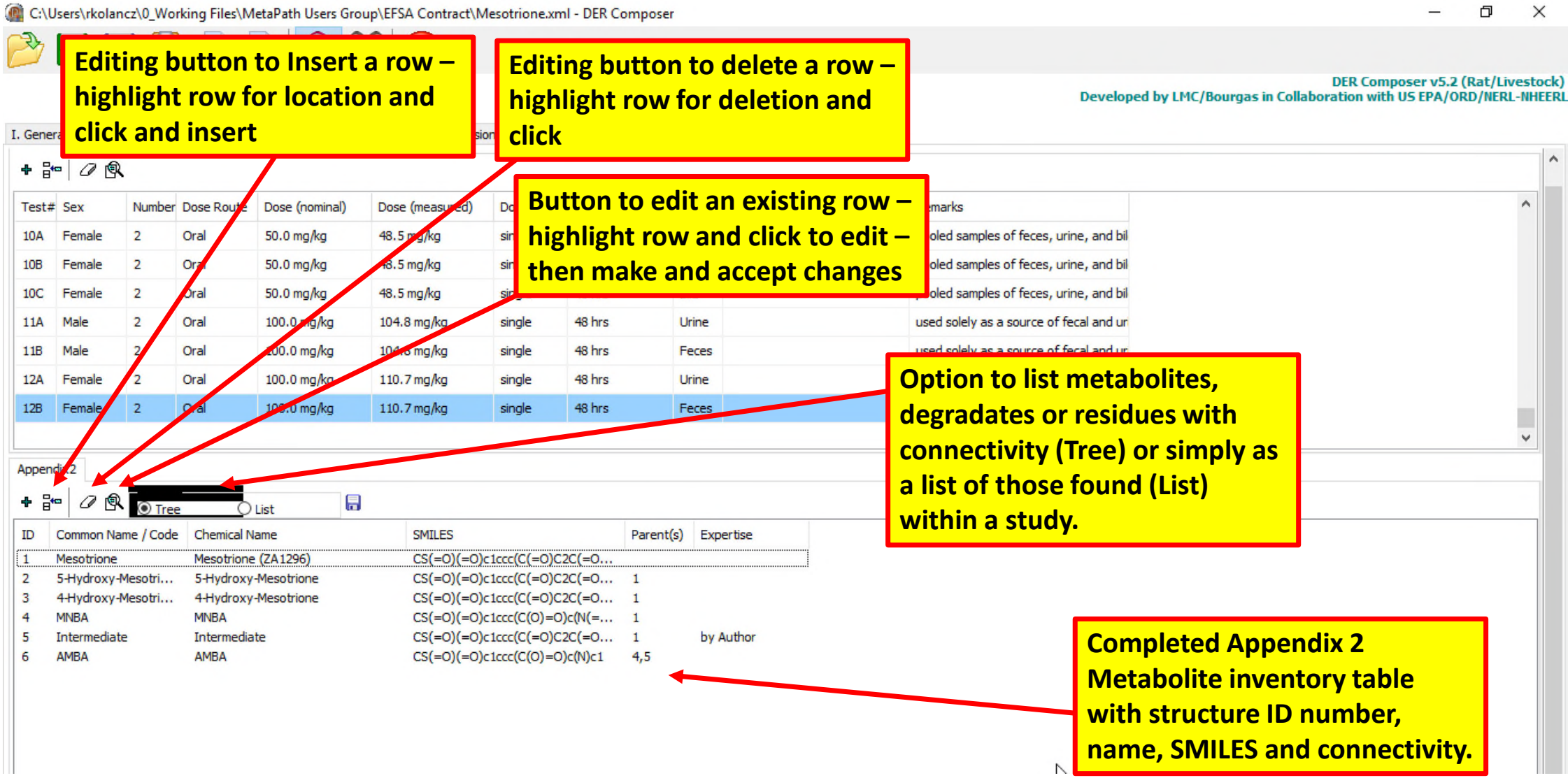


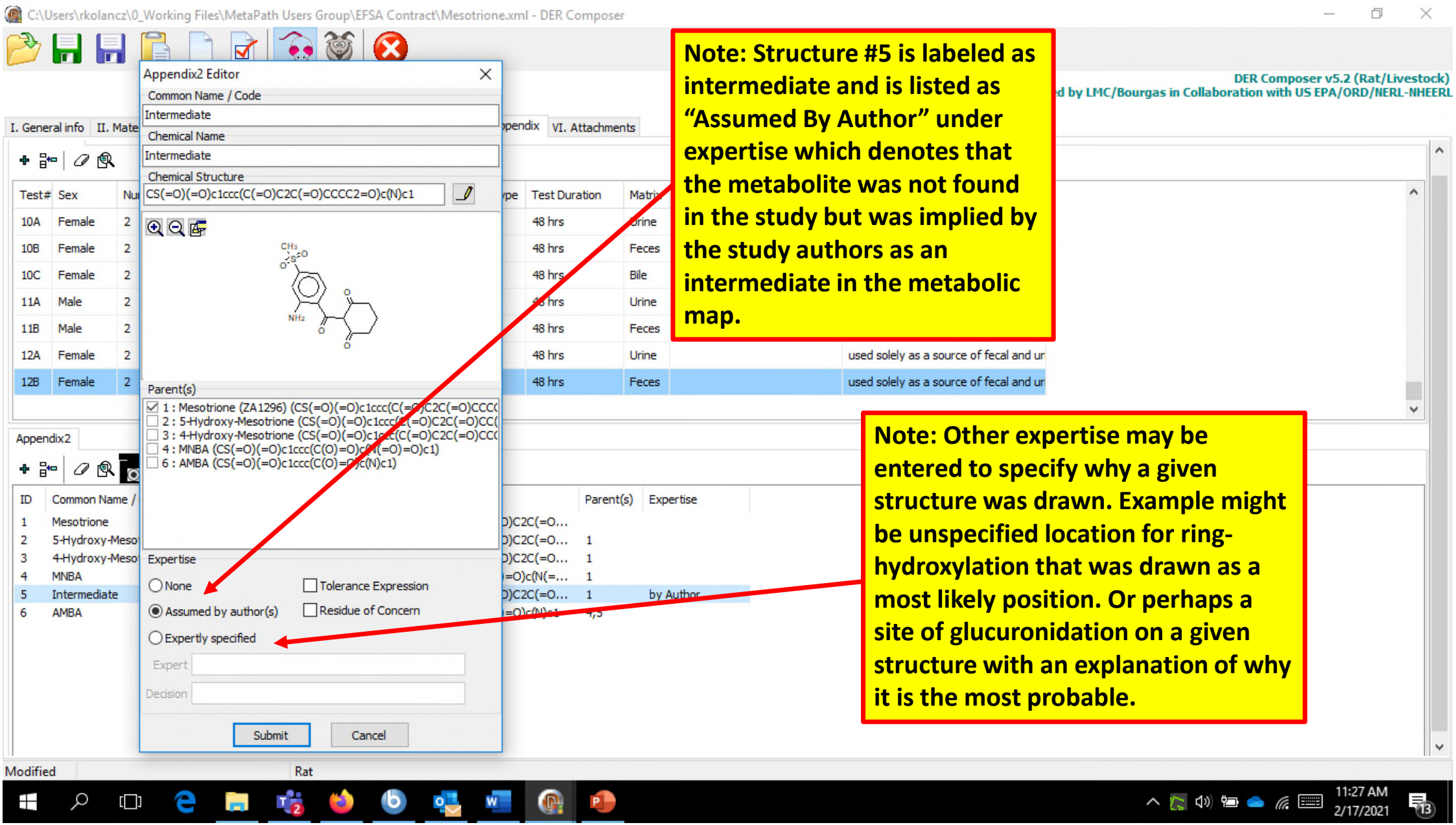
Check box here to denote connectivity of structure 2 (5-Hydroxy-Mesotrione), the metabolite of the parent structure 1 (Mesotrione).

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.

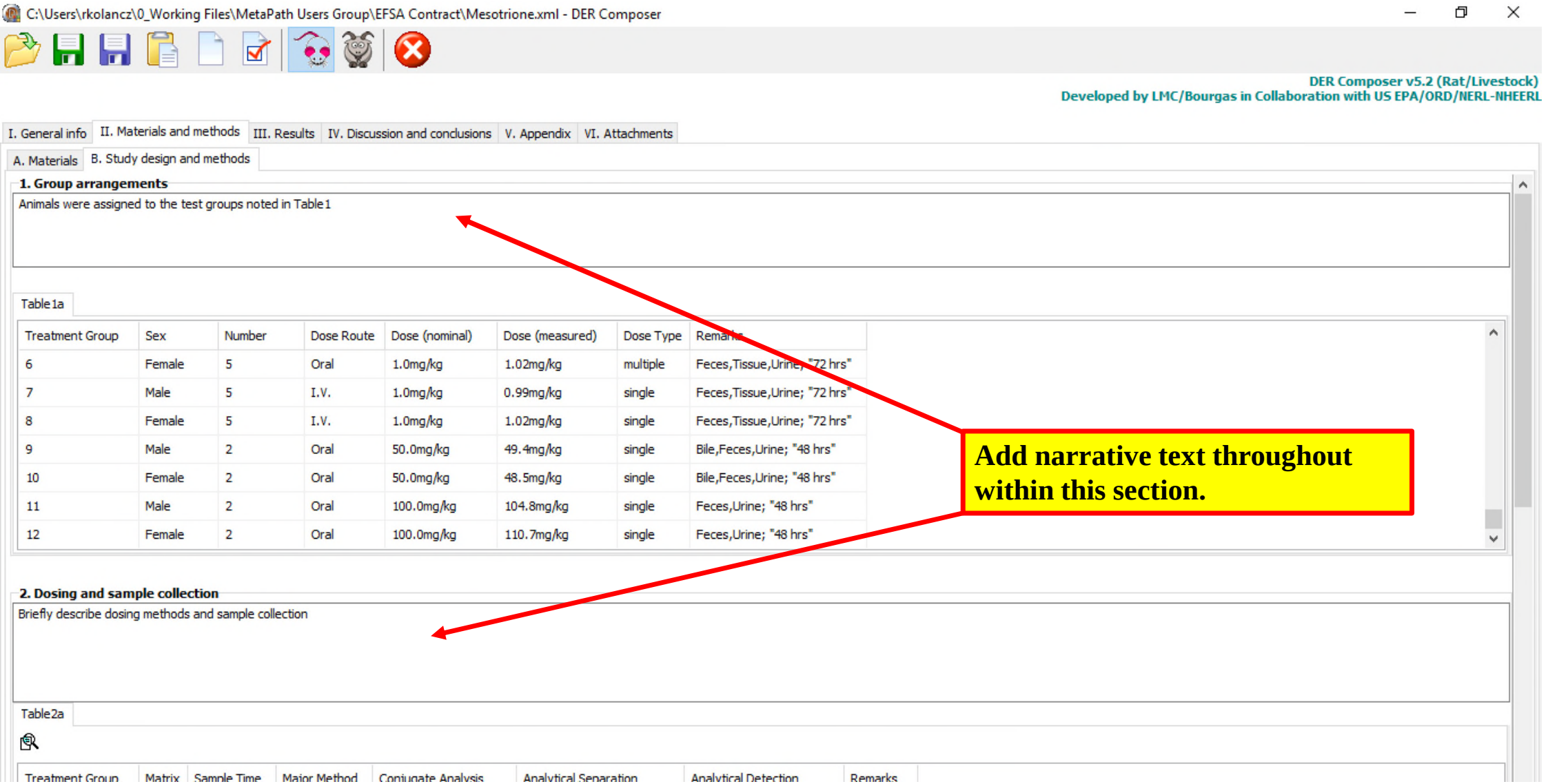




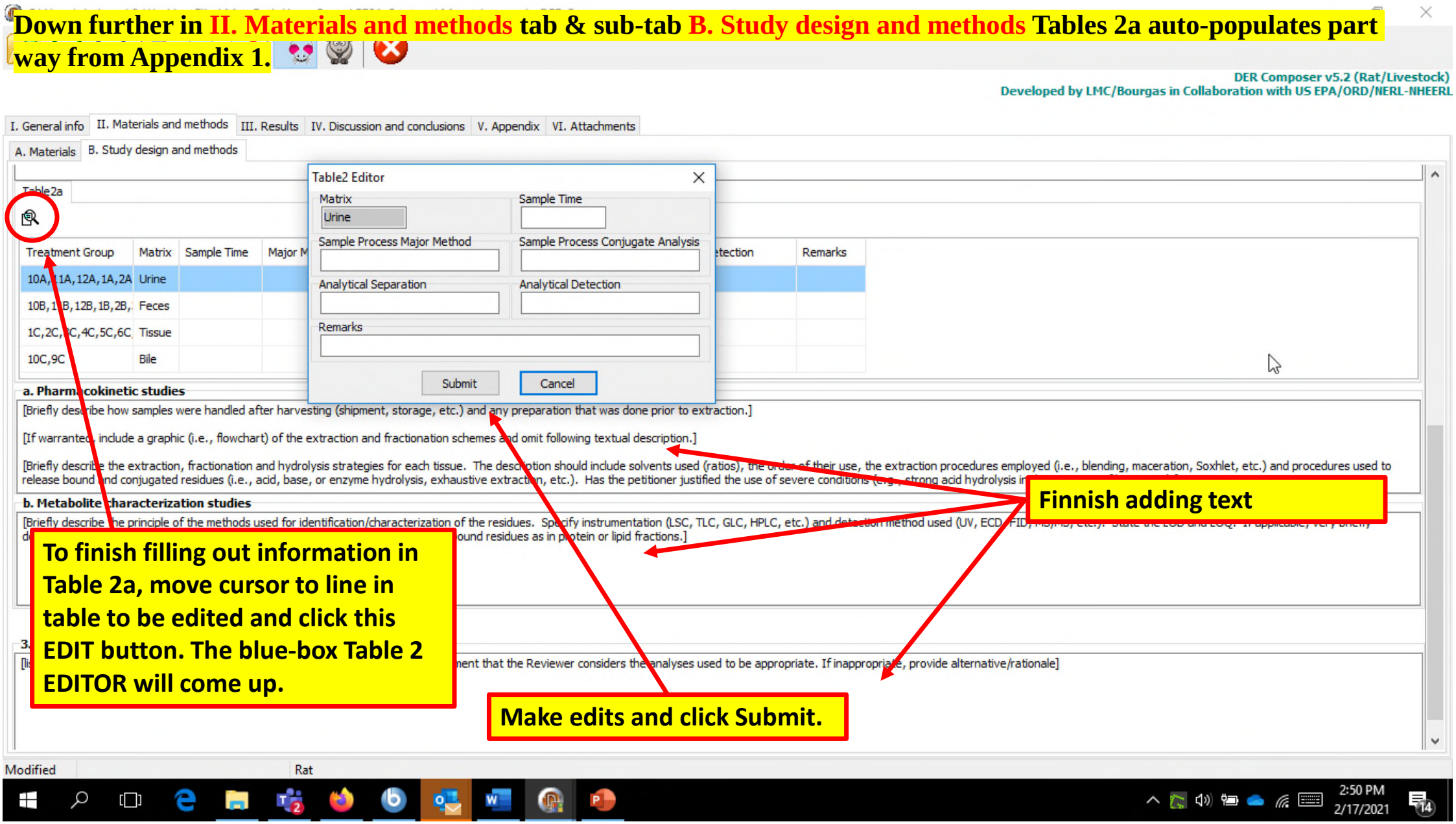
Note: Structure #5 is labeled as intermediate and is listed as "Assumed By Author" under expertise which denotes that the metabolite was not found in the study but was implied by the study authors as an intermediate in the metabolic map.

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.

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.



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

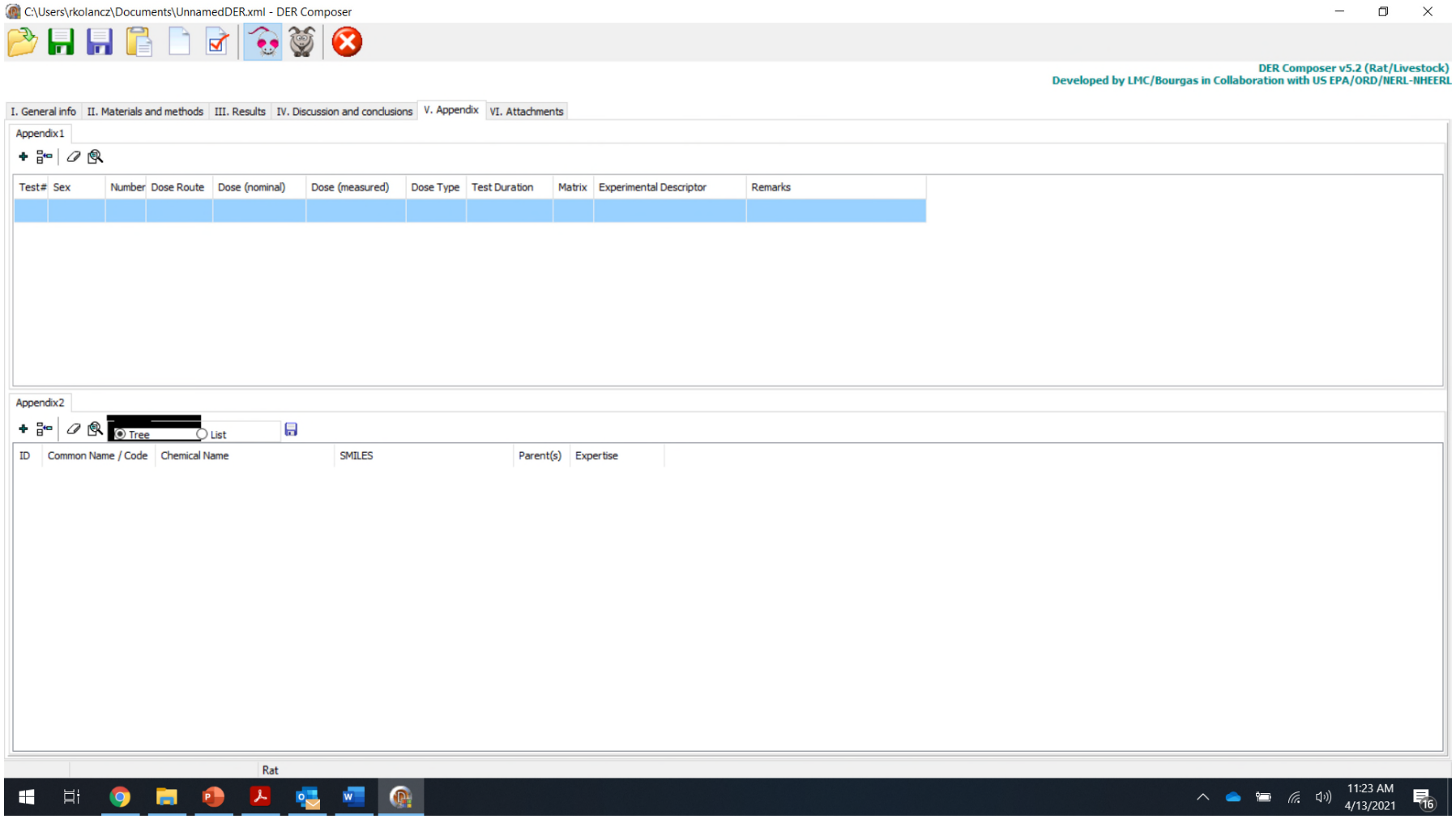


Finnish adding text

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.

Go To Live Demo



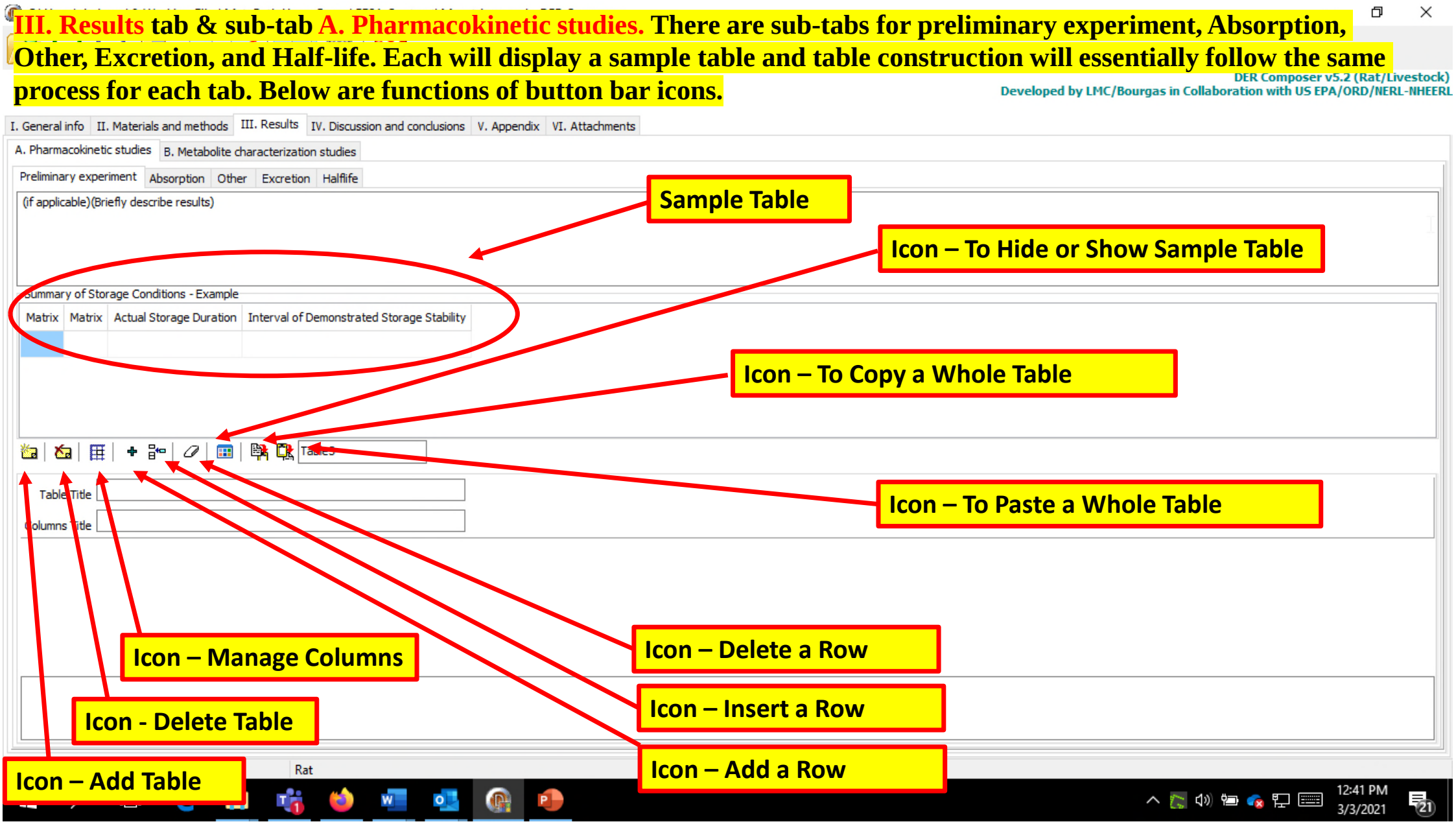
Questions ???
&
Answers

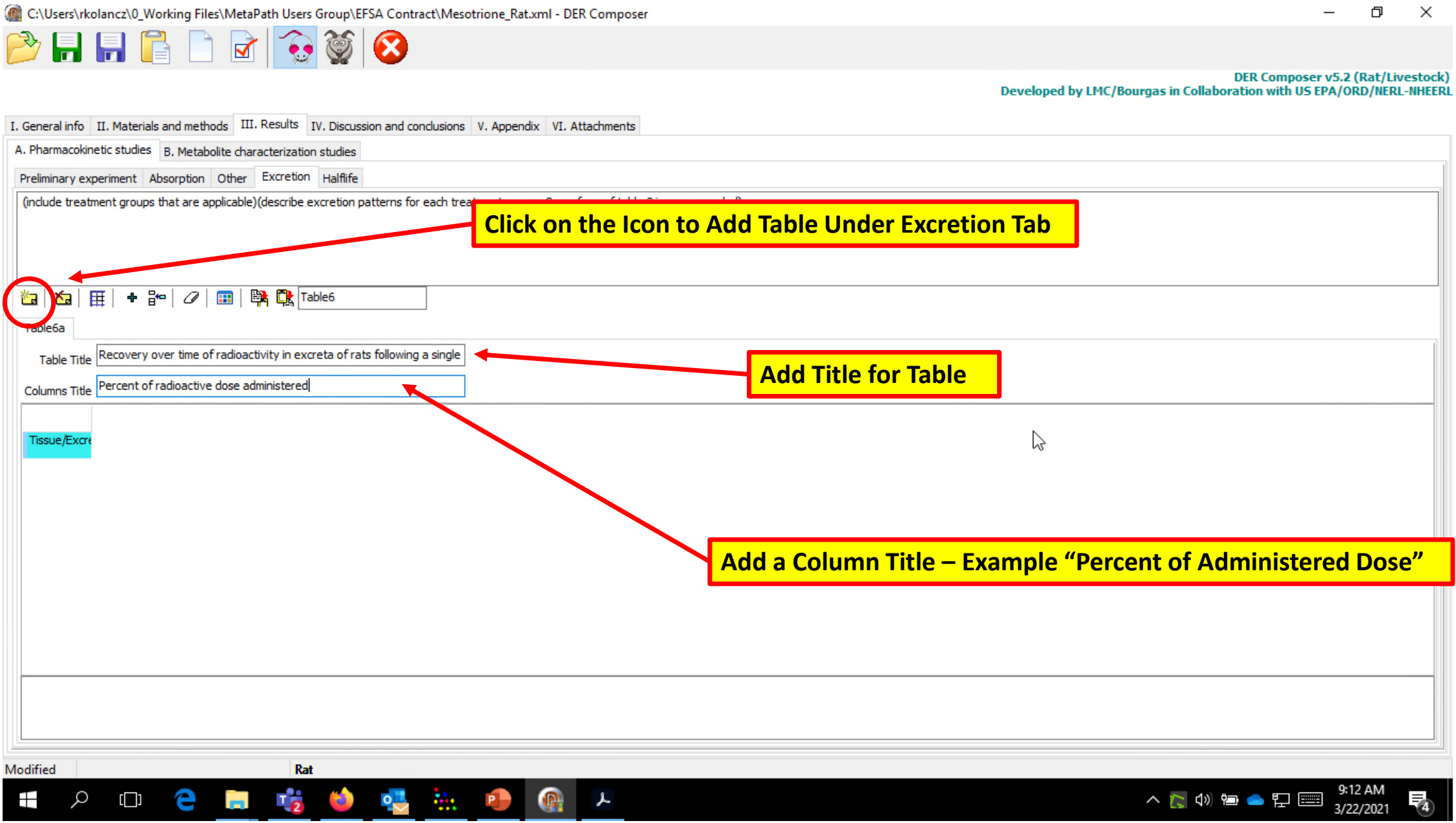
Part 3:

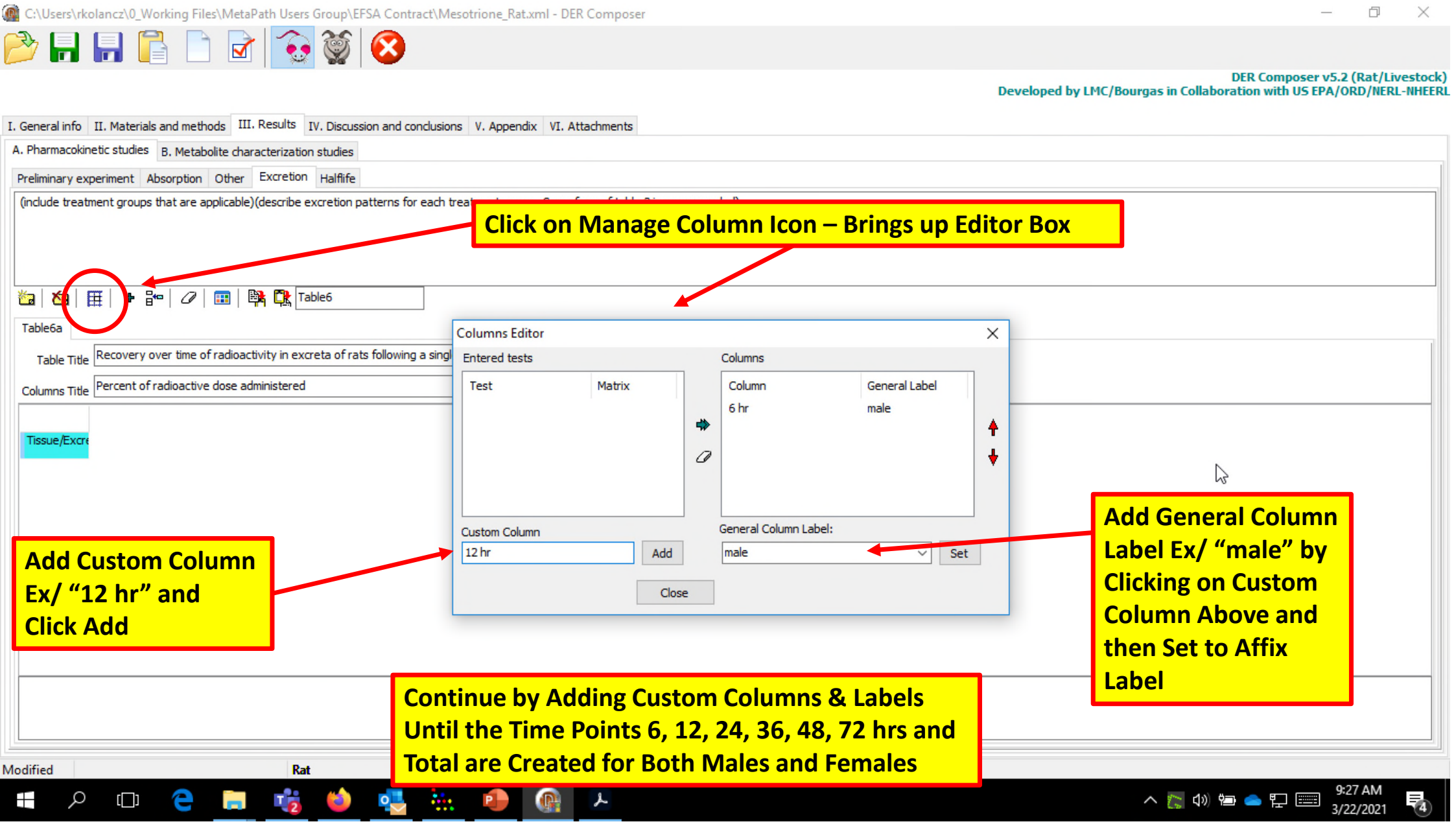
- **Results**

(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.




C:\Users\rkolancz\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-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
Halflife
(include treatment groups that are applicable)(describe excretion patterns for each trea
Table6
Table6a
Table Title
Recovery over time of radioactivity in excreta of rats following a single
Columns Title
Percent of radioactive dose administered
Tissue/Excr
Click on the Icon to Add Table Under Excretion Tab
Add Title for Table
Add a Column Title – Example “Percent of Administered Dose”
Modified
Rat
9:12 AM
3/22/2021


C:\Users\rkolancz\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-NHEERL
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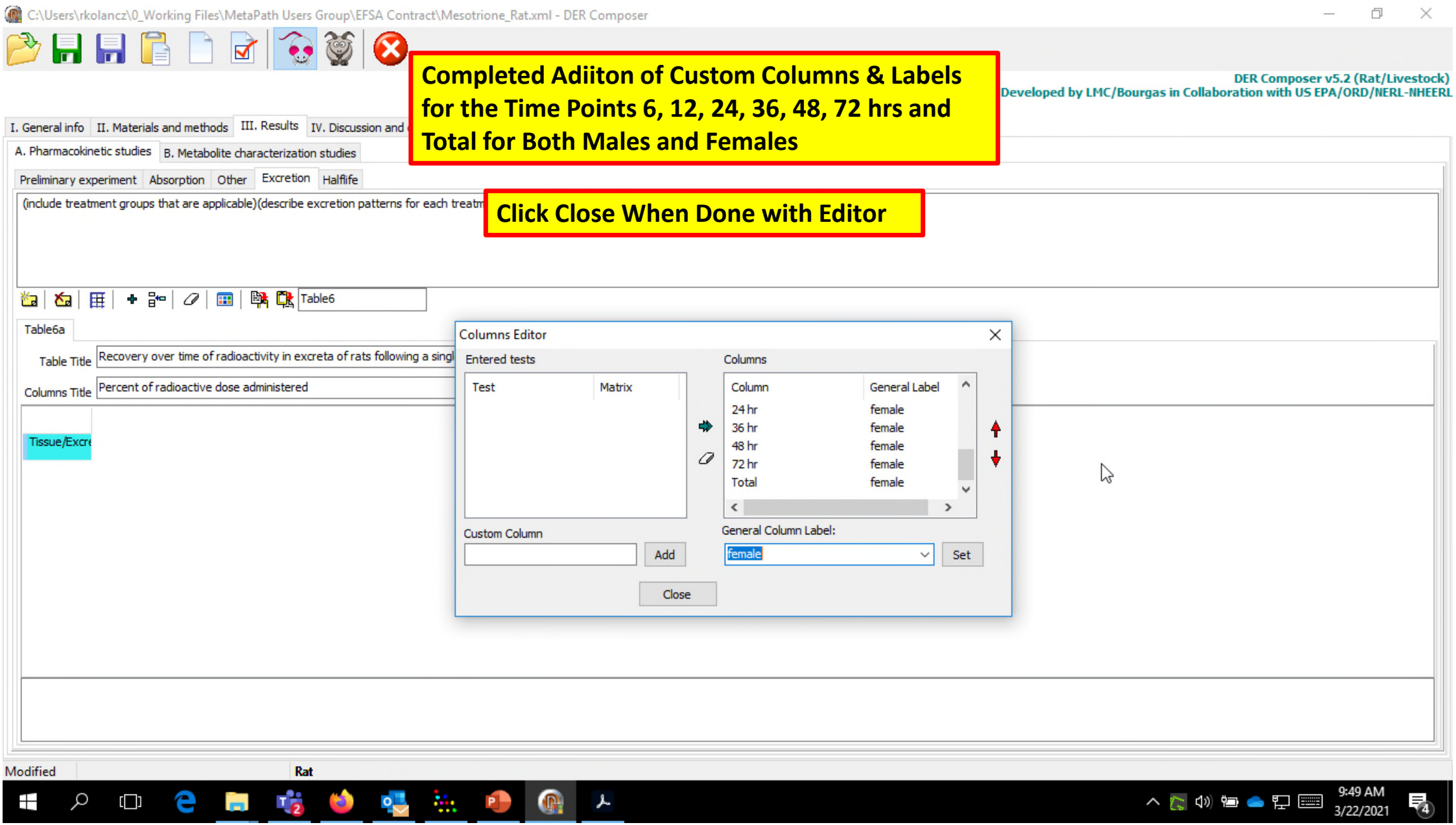
Preliminary experiment
Absorption
Other
Excretion
Halflife
(include treatment groups that are applicable)(describe excretion patterns for each trea
Table6
Table6a
Table Title
Recovery over time of radioactivity in excreta of rats following a singl
Columns Title
Percent of radioactive dose administered
Tissue/Excr
Click on Manage Column Icon – Brings up Editor Box
Columns Editor
Entered tests
Test
Matrix
Columns
Column
General Label
6 hr
male
Custom Column
12 hr
Add
General Column Label:
male
Set
Close
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
9:27 AM
3/22/2021


C:\Users\rkolancz\0_Working Files\MetaPath Users Group\EFSA Contract\Mesotrione_Rat.xml - DER Composer
Completed Adiiton of Custom Columns & Labels for the Time Points 6, 12, 24, 36, 48, 72 hrs and Total for Both Males and Females
DER Composer v5.2 (Rat/Livestock)
Developed by LMC/Bourgas in Collaboration with US EPA/ORD/NERL-NHEERL
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A. Pharmacokinetic studies
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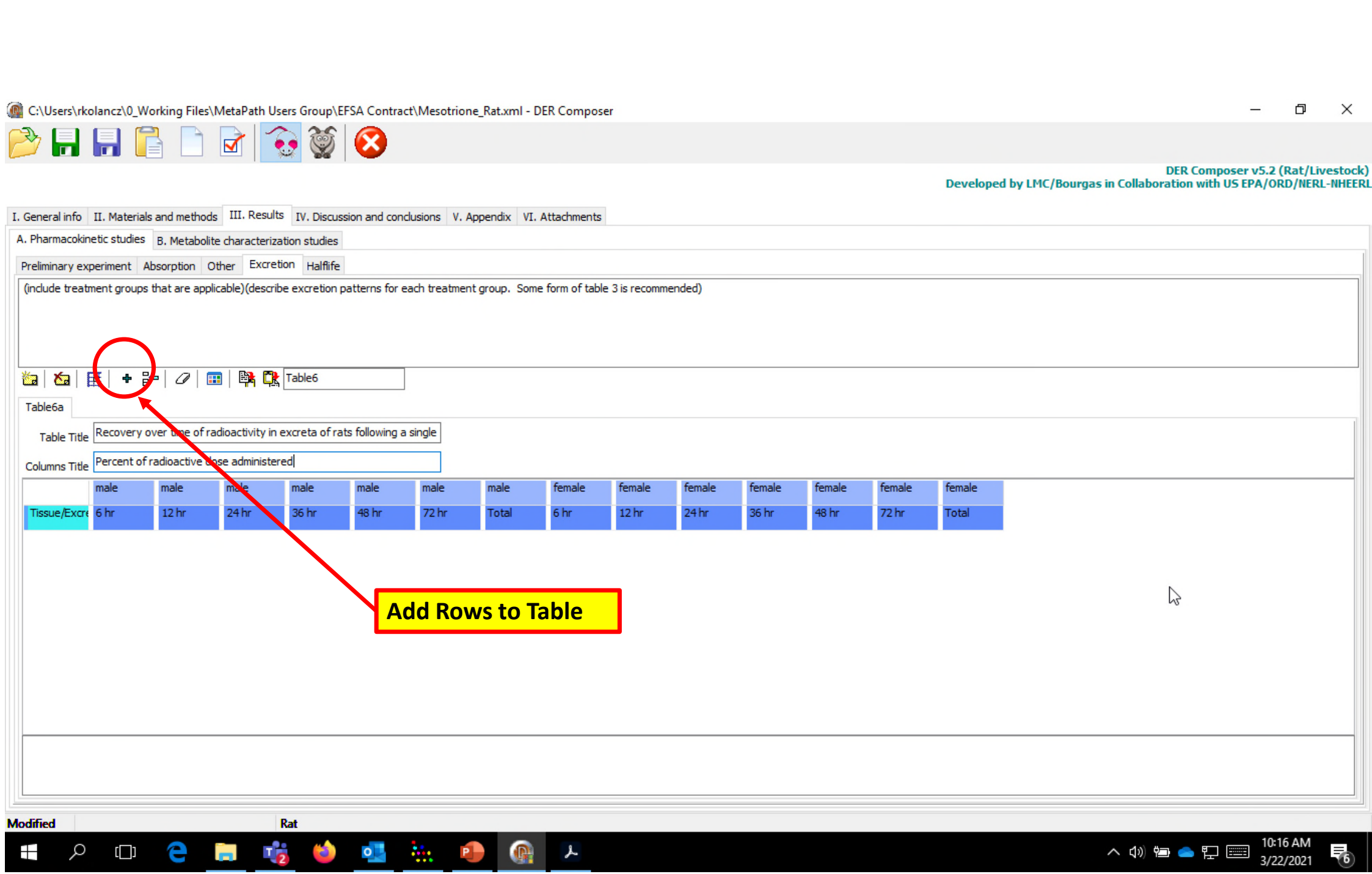
Preliminary experiment
Absorption
Other
Excretion
Halflife
(include treatment groups that are applicable)(describe excretion patterns for each treatm
Click Close When Done with Editor
Table6
Table6a
Table Title
Recovery over time of radioactivity in excreta of rats following a singl
Columns Title
Percent of radioactive dose administered
Tissue/Excr
Columns Editor
Entered tests
Test
Matrix
Columns
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
Close
Modified
Rat
9:49 AM
3/22/2021


C:\Users\rkolancz\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-NHEERL
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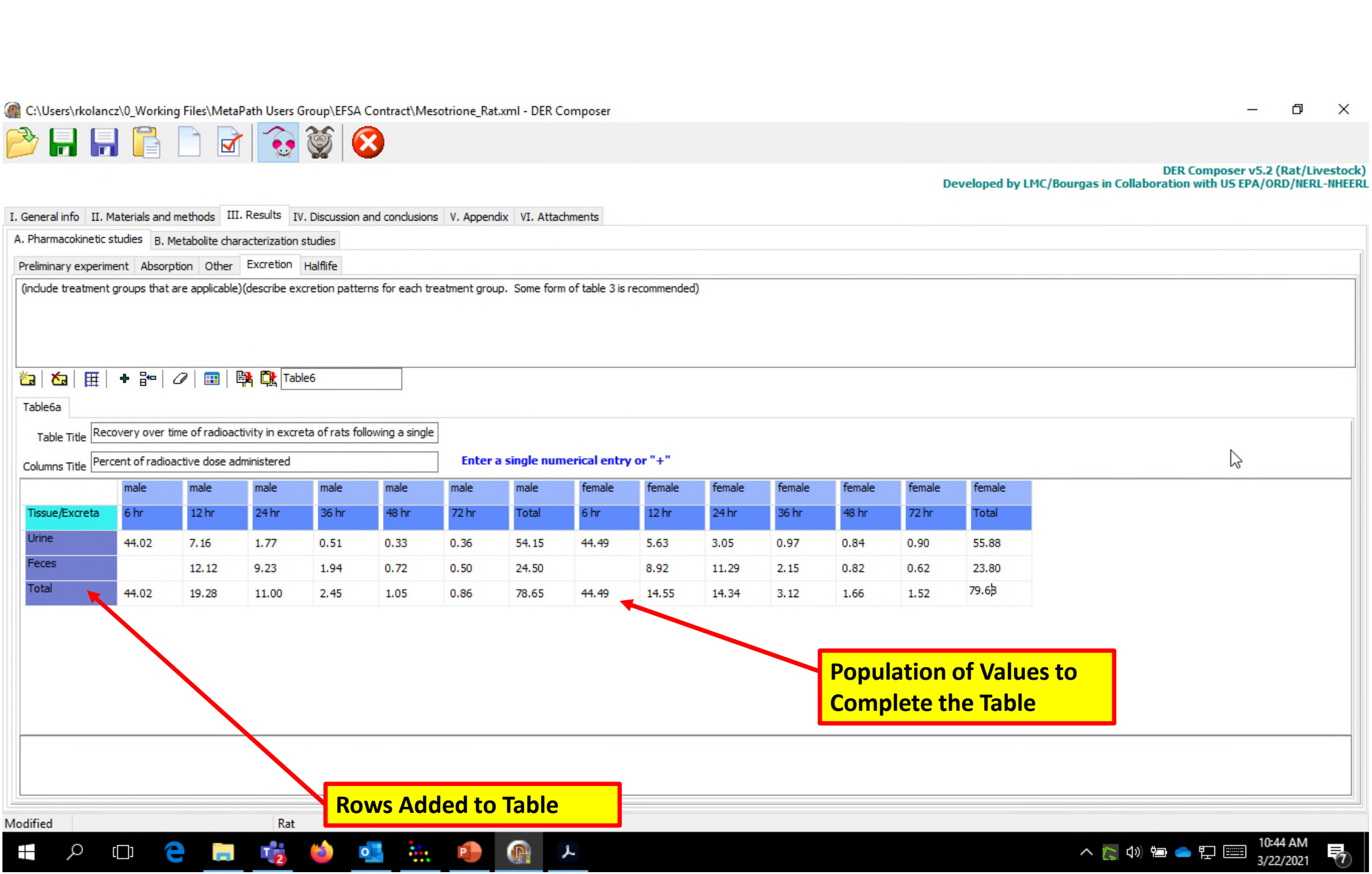
A. Pharmacokinetic studies
B. Metabolite characterization studies
Preliminary experiment
Absorption
Other
Excretion
Halflife
(include treatment groups that are applicable)(describe excretion patterns for each treatment group. Some form of table 3 is recommended)
Table6
Table6a
Table Title
Recovery over 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/Excre 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
Add Rows to Table
Modified
Rat
10:16 AM
3/22/2021


C:\Users\rkolancz\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-NHEERL
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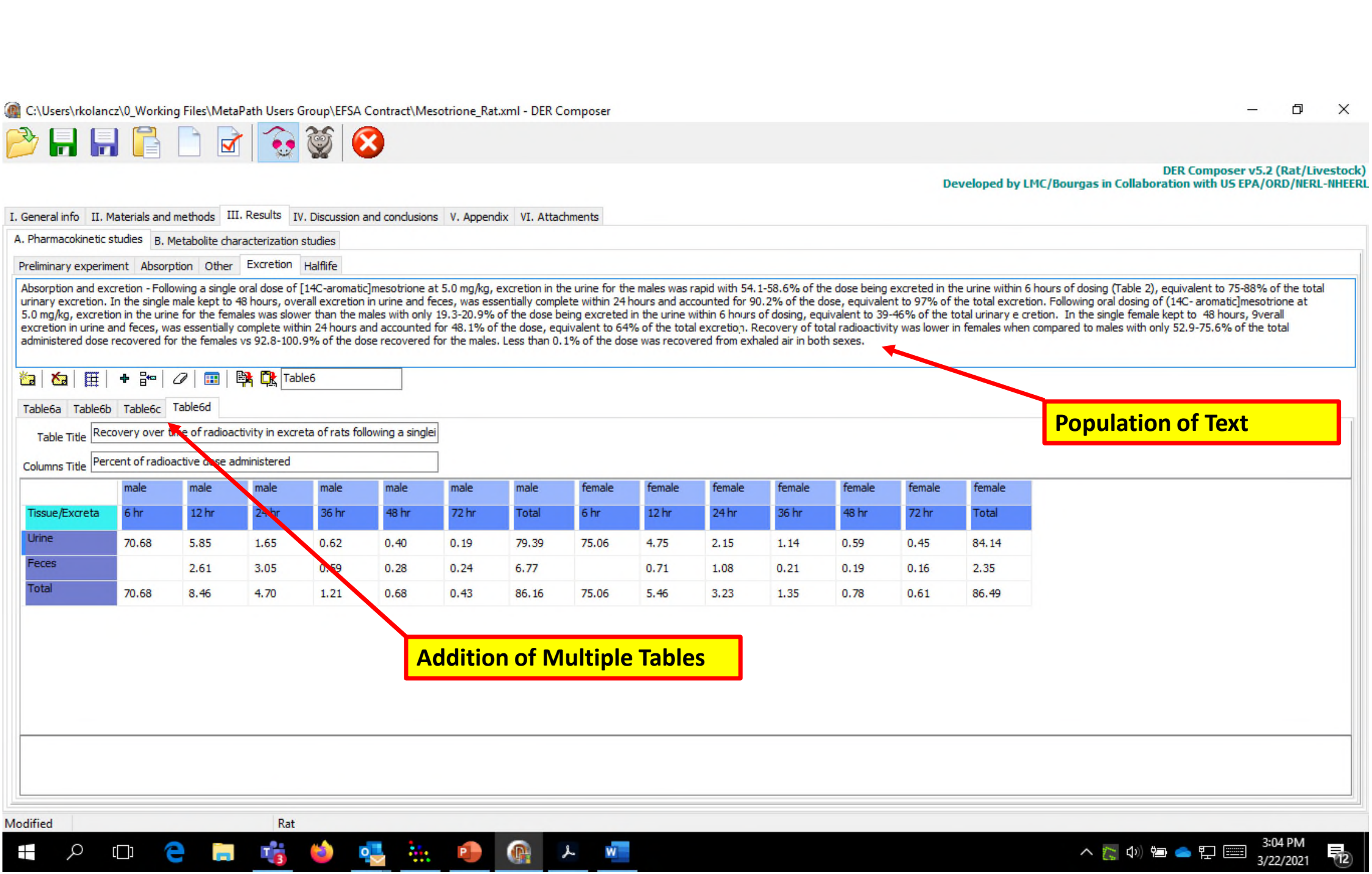
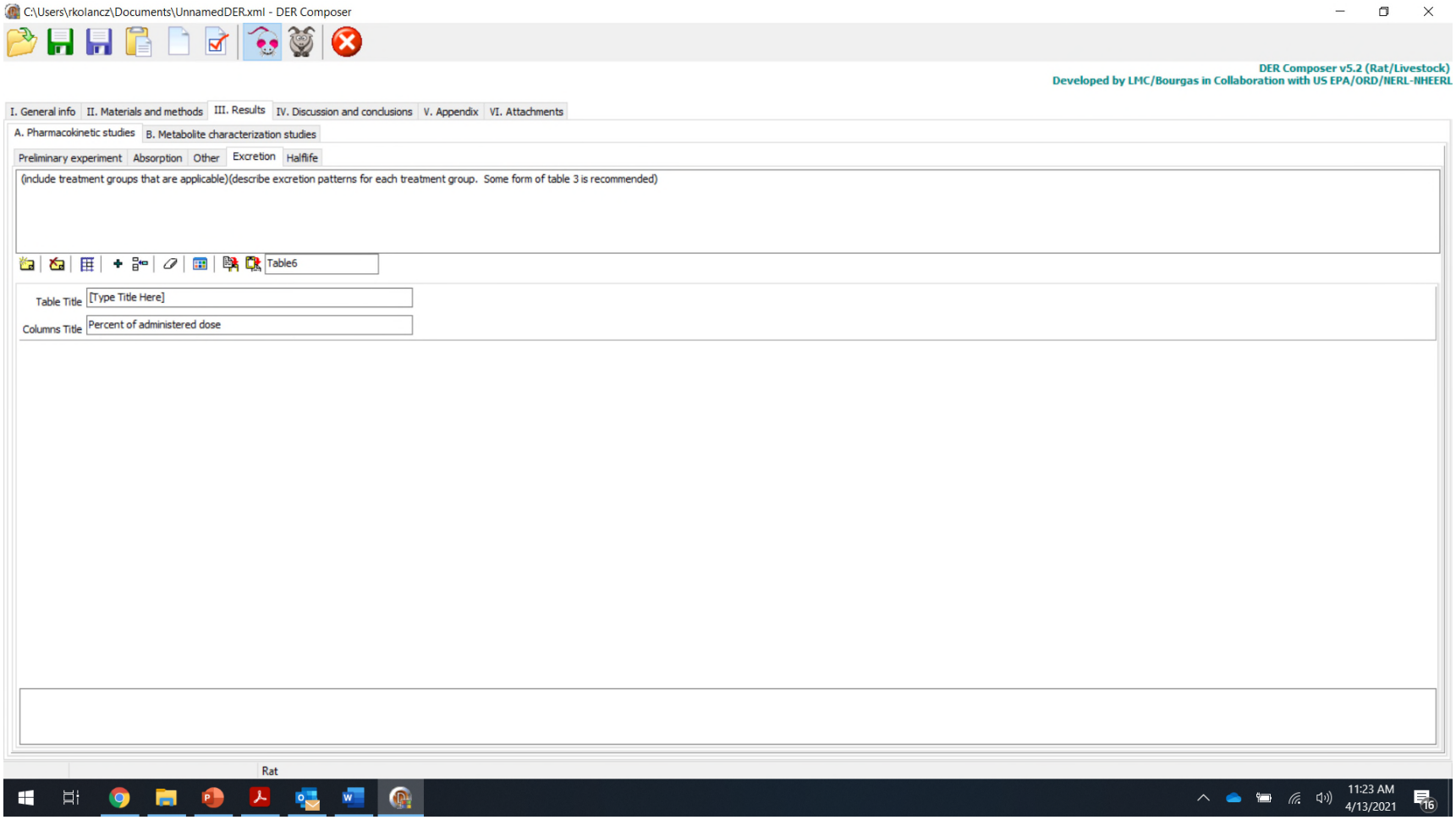
Preliminary experiment
Absorption
Other
Excretion
Halflife
(include treatment groups that are applicable)(describe excretion patterns for each treatment group. Some form of table 3 is recommended)
Table6
Table6a
Table Title
Recovery over time of radioactivity in excreta of rats following a single
Columns 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 | 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 | 79.63
Population of Values to Complete the Table
Rows Added to Table
Modified
Rat
10:44 AM
3/22/2021



	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	0.59	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

Go To Live Demo

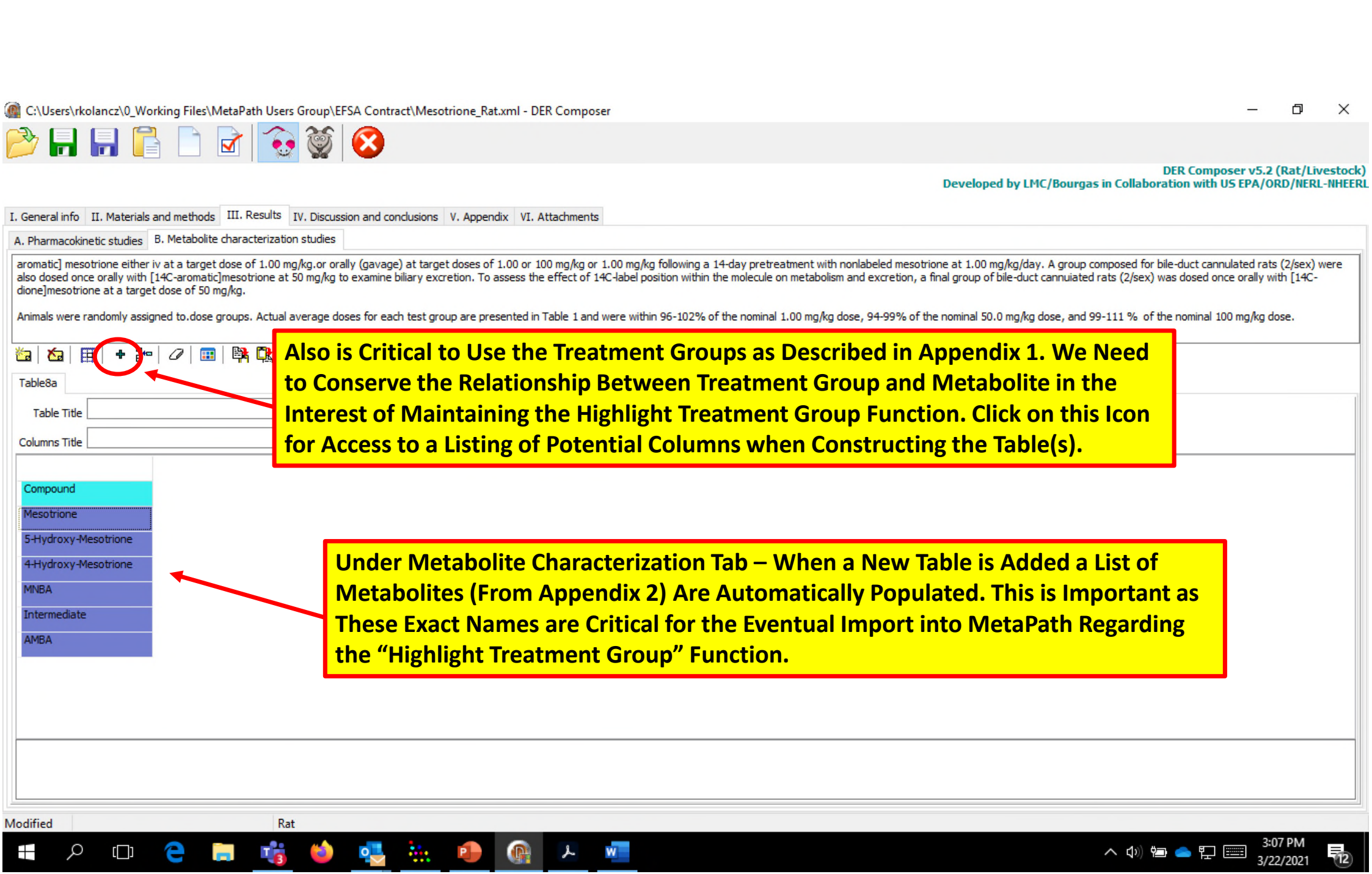


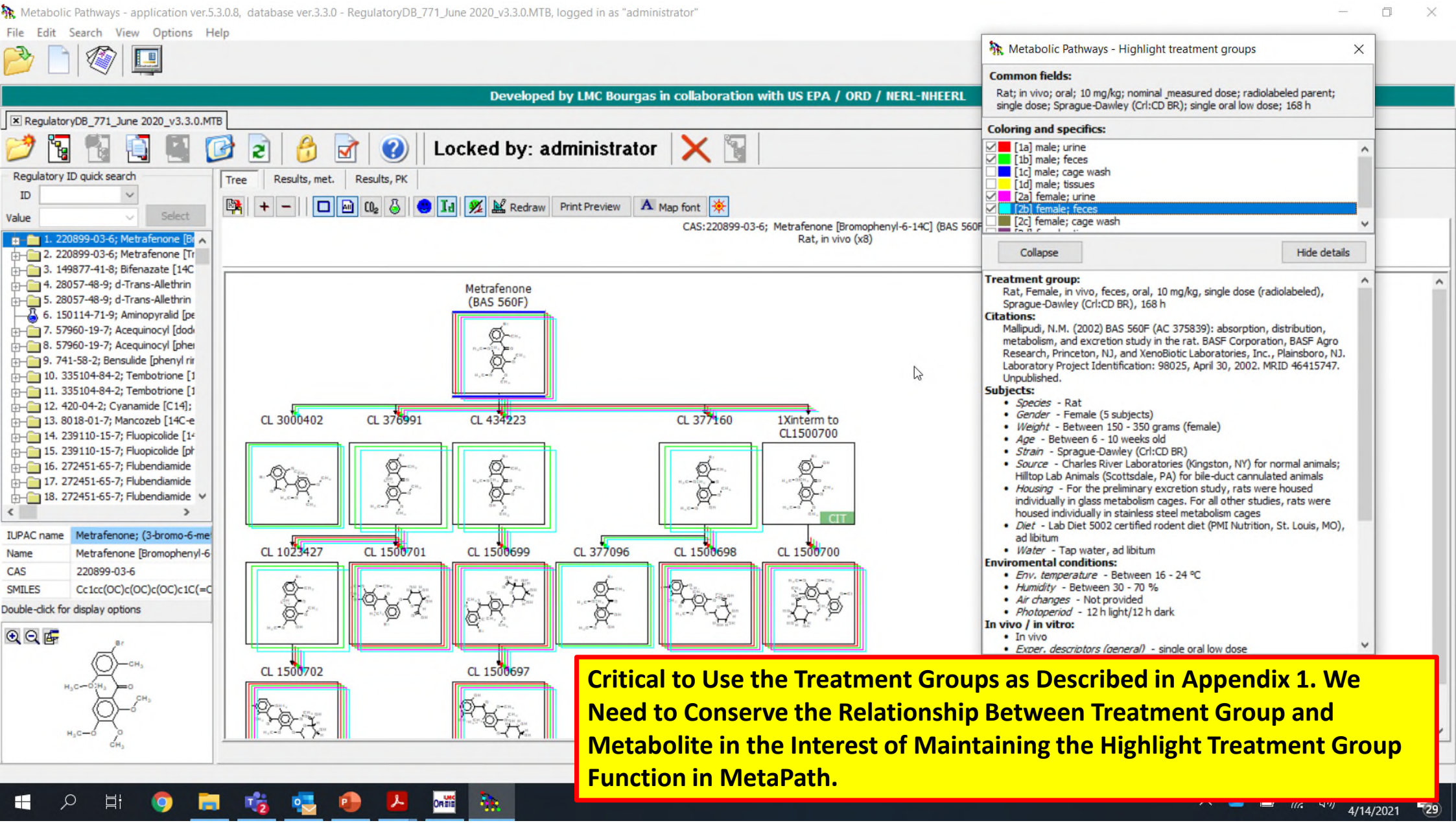
Questions ???
&
Answers

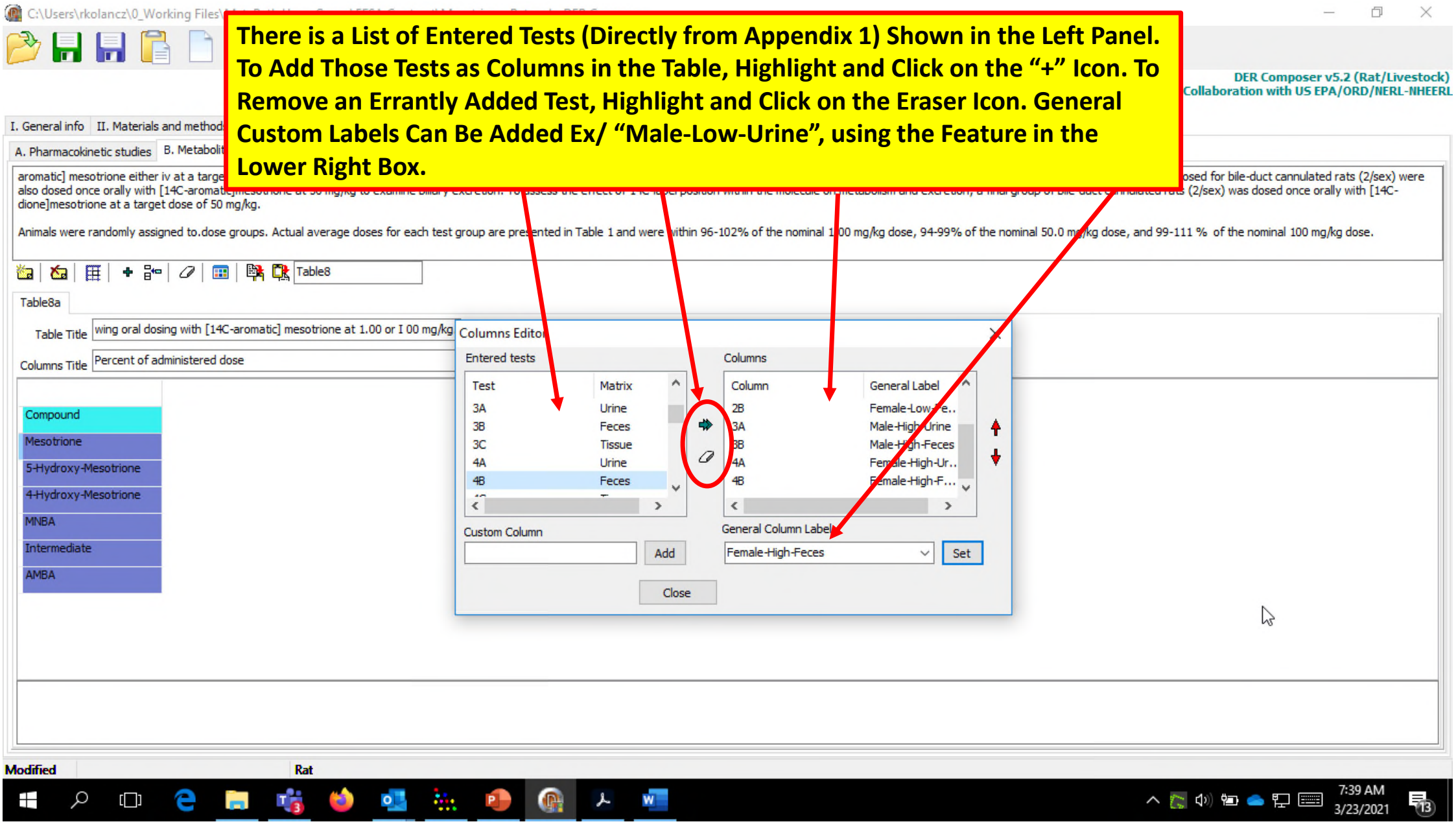
Part 4:

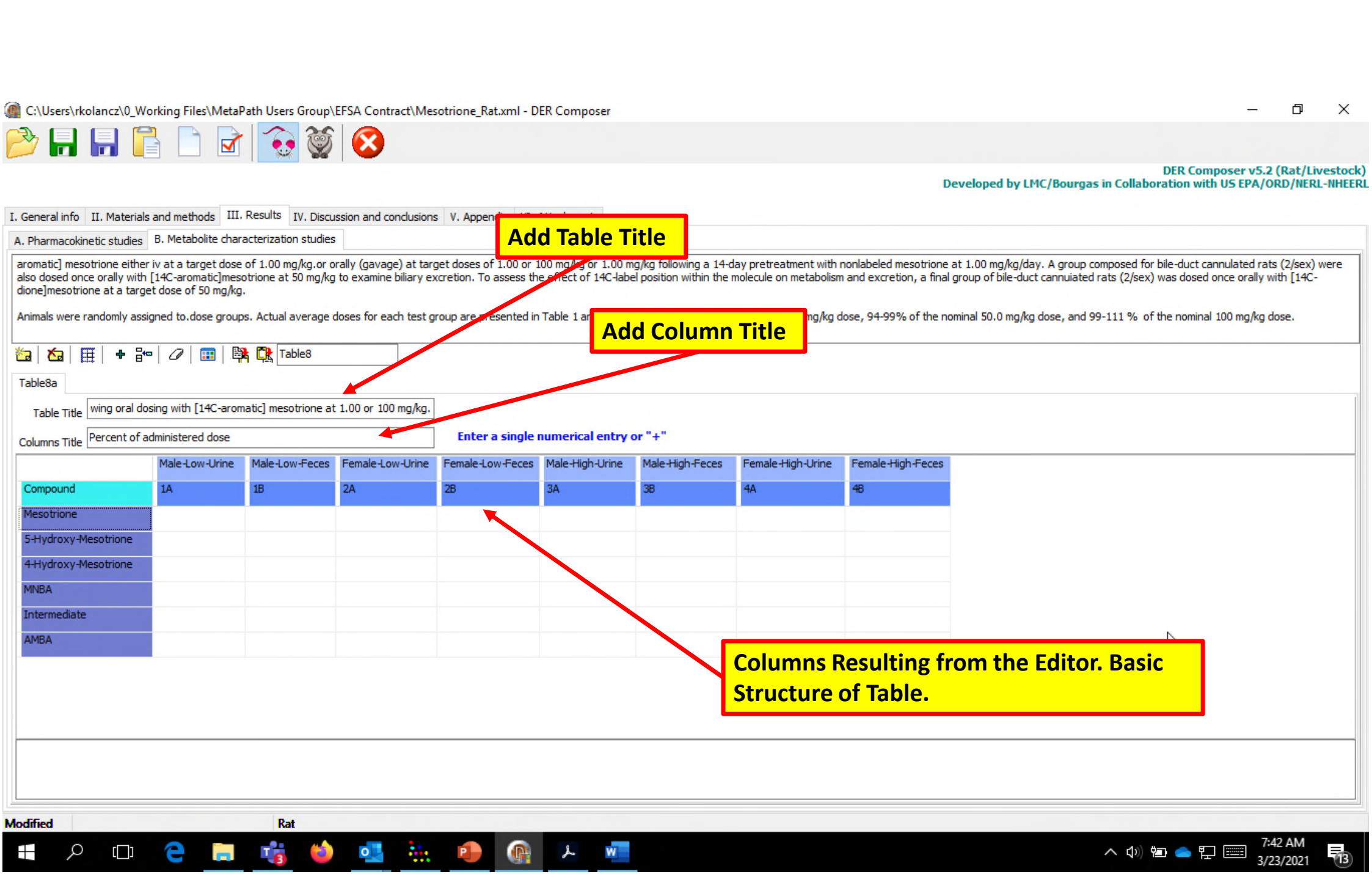
- **Results**

(Metabolite characterization studies)


C:\Users\rkolancz\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-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 following a 14-day pretreatment with nonlabeled mesotrione at 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 cannuiated 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).
Table8a
Table Title
Columns Title
Compound
Mesotrione
5-Hydroxy-Mesotrione
4-Hydroxy-Mesotrione
MNBA
Intermediate
AMBA
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
3:07 PM
3/22/2021


Metabolic Pathways - application ver.5.3.0.8, database ver.3.3.0 - RegulatoryDB_771_June 2020_v3.3.0.MTB, logged in as "administrator"
File Edit Search View Options Help
Developed by LMC Bourgas in collaboration with US EPA / ORD / NERL-NHEERL
RegulatoryDB_771_June 2020_v3.3.0.MTB
Locked by: administrator
Regulatory ID quick search
ID
Value
Select
Tree
Results, met.
Results, PK
Redraw
Print Preview
Map font
CAS:220899-03-6; Metrafenone [Bromophenyl-6-14C] (BAS 560F
Rat, in vivo (x8)
Metrafenone
(BAS 560F)
CL 3000402
CL 376991
CL 434223
CL 377160
1Xinterm to
CL1500700
CIT
CL 1023427
CL 1500701
CL 1500699
CL 377096
CL 1500698
CL 1500700
CL 1500702
CL 1500697
IUPAC name
Name
CAS
SMILES
Double-click for display options
Metabolic Pathways - Highlight treatment groups
Common fields:
Rat; in vivo; oral; 10 mg/kg; nominal _measured dose; radiolabeled parent; single dose; Sprague-Dawley (Crl:CD BR); single oral low dose; 168 h
Coloring and specifics:
[1a] male; urine
[1b] male; feces
[1c] male; cage wash
[1d] male; tissues
[2a] female; urine
[2b] female; feces
[2c] female; cage wash
Collapse
Hide details
Treatment group:
Rat, Female, in vivo, feces, oral, 10 mg/kg, single dose (radiolabeled), Sprague-Dawley (Crl:CD BR), 168 h
Citations:
Mallipudi, 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., Plainsboro, 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 6 - 10 weeks old
Strain - Sprague-Dawley (Crl: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
Enviromental 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
Exper. 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.
4/14/2021


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.
DER Composer v5.2 (Rat/Livestock)
Collaboration with US EPA/ORD/NERL-NHEERL
I. General info
II. Materials and method
A. Pharmacokinetic studies
B. Metaboli
aromatic] mesotrione either iv at a targe
also dosed once orally with [14C-aromat
dione]mesotrione at a target dose of 50 mg/kg.
osed for bile-duct cannulated rats (2/sex) were
(2/sex) was dosed once orally with [14C-
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.
Table8
Table8a
Table Title
wing oral dosing with [14C-aromatic] mesotrione at 1.00 or I 00 mg/kg
Columns Title
Percent of administered dose
Compound
Mesotrione
5-Hydroxy-Mesotrione
4-Hydroxy-Mesotrione
MNBA
Intermediate
AMBA
Columns Editor
Entered tests
Test
Matrix
3A
Urine
3B
Feces
3C
Tissue
4A
Urine
4B
Feces
Columns
Column
General Label
2B
Female-Low-Fe..
3A
Male-High-Urine
3B
Male-High-Feces
4A
Female-High-Ur..
4B
Female-High-F...
Custom Column
Add
General Column Label
Female-High-Feces
Set
Close
Modified
Rat
7:39 AM
3/23/2021


C:\Users\rkolancz\0_Working Files\MetaPath Users Group\EFSA Contract\Mesotrione_Rat.xml - DER Composer
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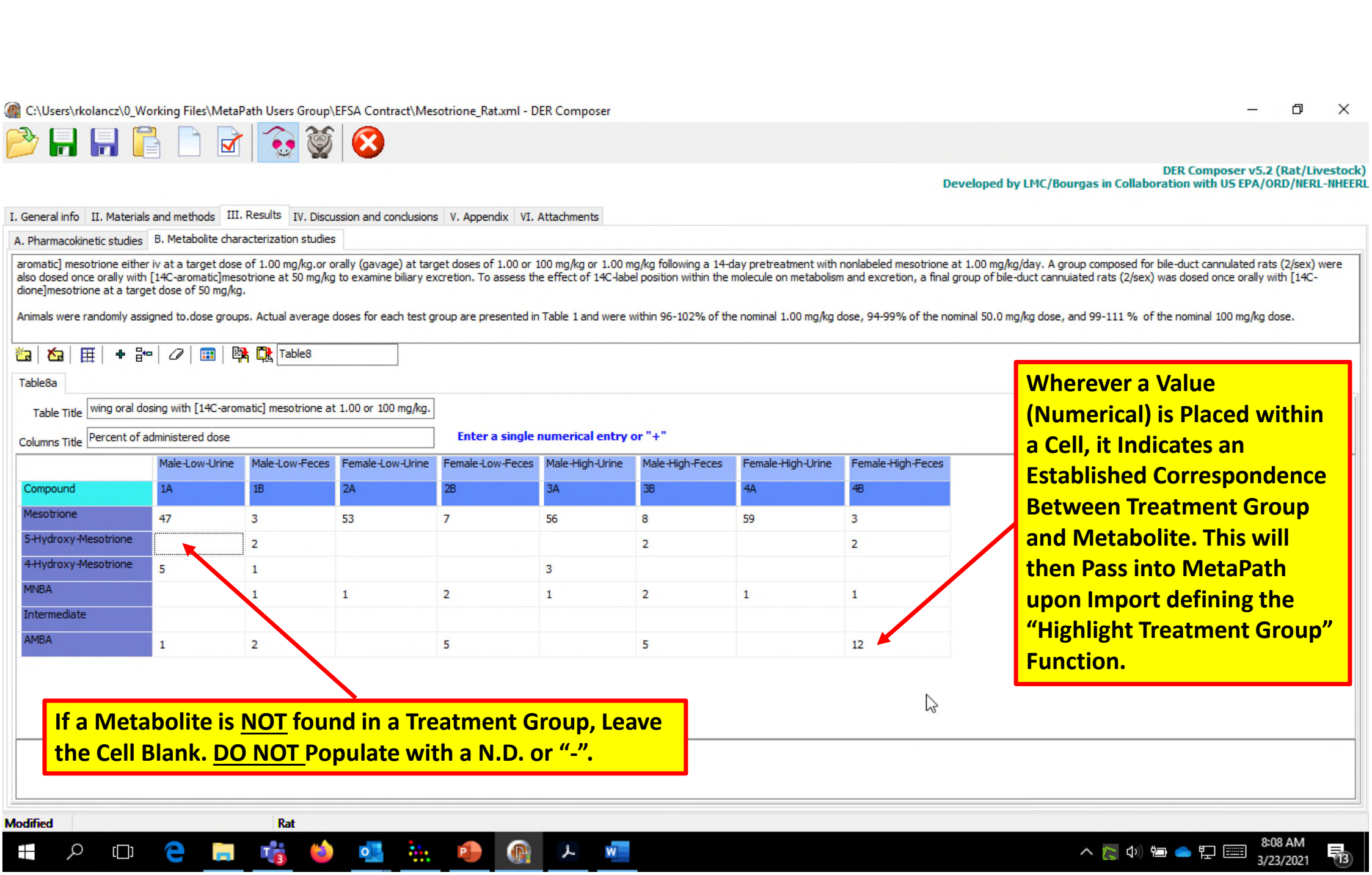
A. Pharmacokinetic studies
B. Metabolite characterization studies
aromatic] mesotrione either iv at a target dose of 1.00 mg/kg.or orally (gavage) at target doses of 1.00 or 100 mg/kg or 1.00 mg/kg following a 14-day pretreatment with nonlabeled mesotrione at 1.00 mg/kg/day. A group composed for bile-duct 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 cannuiated 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 ar
mg/kg dose, 94-99% of the nominal 50.0 mg/kg dose, and 99-111 % of the nominal 100 mg/kg dose.
Table8
Table8a
Table Title
wing oral dosing with [14C-aromatic] mesotrione at 1.00 or 100 mg/kg.
Columns Title
Percent of administered dose
Enter a single numerical entry or "+"
Male-Low-Urine
Male-Low-Feces
Female-Low-Urine
Female-Low-Feces
Male-High-Urine
Male-High-Feces
Female-High-Urine
Female-High-Feces
Compound
1A
1B
2A
2B
3A
3B
4A
4B
Mesotrione
5-Hydroxy-Mesotrione
4-Hydroxy-Mesotrione
MNBA
Intermediate
AMBA
Add Table Title
Add Column Title
Columns Resulting from the Editor. Basic Structure of Table.
Modified
Rat
7:42 AM
3/23/2021


C:\Users\rkolancz\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-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 following a 14-day pretreatment with nonlabeled mesotrione at 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 cannuiated 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.
Table8
Table8a
Table Title
wing oral dosing with [14C-aromatic] mesotrione at 1.00 or 100 mg/kg.
Columns Title
Percent of administered dose
Enter a single numerical entry or "+"
Male-Low-Urine
Male-Low-Feces
Female-Low-Urine
Female-Low-Feces
Male-High-Urine
Male-High-Feces
Female-High-Urine
Female-High-Feces
Compound
1A
1B
2A
2B
3A
3B
4A
4B
Mesotrione
47
3
53
7
56
8
59
3
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
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.
If a Metabolite is NOT found in a Treatment Group, Leave the Cell Blank. DO NOT Populate with a N.D. or "-".
Modified
Rat
8:08 AM
3/23/2021

C:\Users\rkolancz\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-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 following a 14-day pretreatment with nonlabeled mesotrione at 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 cannuiated 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 ... 94-99% of the nominal 50.0 mg/kg dose, and 99-111 % of the nominal 100 mg/kg dose.

Table8

Table8a

Table Title: 1.00 or 100 mg/kg.

Columns Title: Percent of administered dose

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

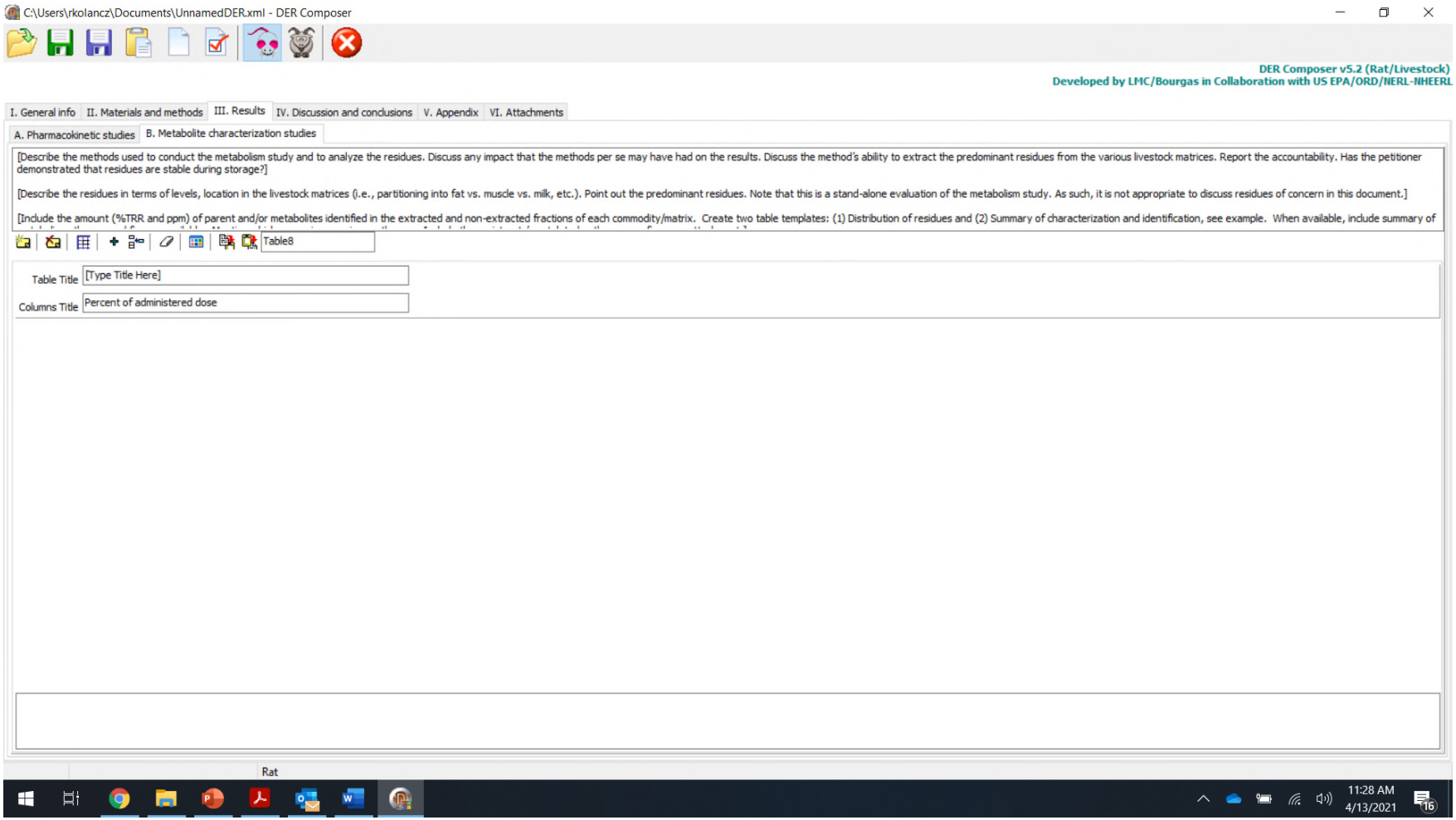
Use These Icons to Add or Insert a New Row

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

12:49 PM
3/23/2021

Go To Live Demo

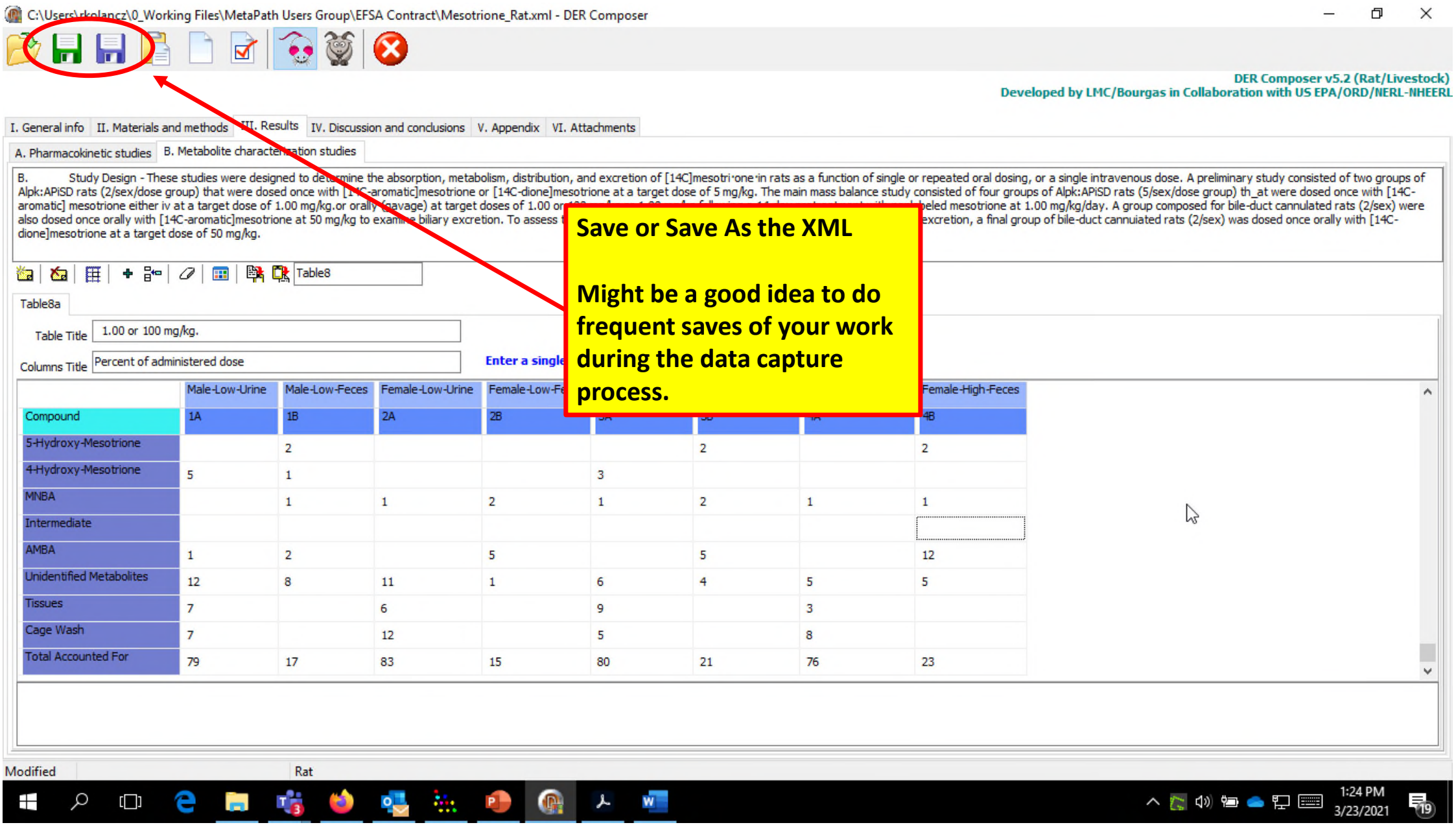


Questions ???
&
Answers

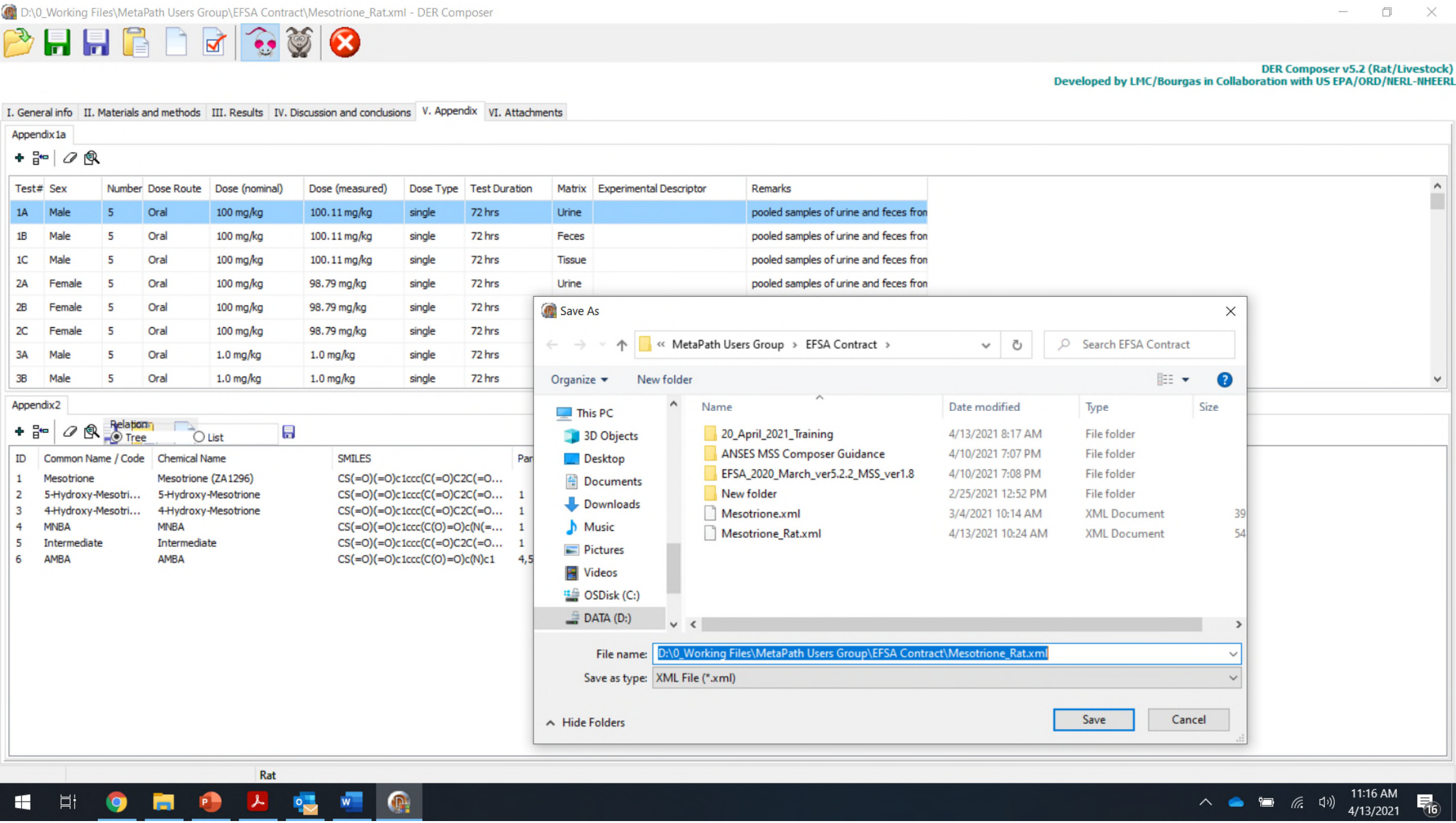
Part 5:

- **Conclusions**

- **XML**
- **.DOC File Generation of Report**



	Male-Low-Urine	Male-Low-Feces	Female-Low-Urine	Female-Low-Fe				Female-High-Feces
Compound	1A	1B	2A	2B				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


D:\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-NHEERL
I. General info
II. Materials and methods
III. Results
IV. Discussion and conclusions
V. Appendix
VI. Attachments
Appendix1a
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 fron
1B Male 5 Oral 100 mg/kg 100.11 mg/kg single 72 hrs Feces pooled samples of urine and feces fron
1C Male 5 Oral 100 mg/kg 100.11 mg/kg single 72 hrs Tissue pooled samples of urine and feces fron
2A Female 5 Oral 100 mg/kg 98.79 mg/kg single 72 hrs Urine pooled samples of urine and feces fron
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
Appendix2
Relation: Tree List
ID Common Name / Code Chemical Name SMILES
1 Mesotrione Mesotrione (ZA1296) CS(=O)(=O)c1ccc(C(=O)C2C(=O...
2 5-Hydroxy-Mesotri... 5-Hydroxy-Mesotrione CS(=O)(=O)c1ccc(C(=O)C2C(=O... 1
3 4-Hydroxy-Mesotri... 4-Hydroxy-Mesotrione CS(=O)(=O)c1ccc(C(=O)C2C(=O... 1
4 MNBA MNBA CS(=O)(=O)c1ccc(C(O)=O)c(N(=... 1
5 Intermediate Intermediate CS(=O)(=O)c1ccc(C(=O)C2C(=O... 1
6 AMBA AMBA CS(=O)(=O)c1ccc(C(O)=O)c(N)c1 4,5
Save As
MetaPath Users Group › EFSA Contract ›
Search EFSA Contract
Organize
New folder
This PC
3D Objects
Desktop
Documents
Downloads
Music
Pictures
Videos
OSDisk (C:)
DATA (D:)
Name
Date modified
Type
Size
20_April_2021_Training 4/13/2021 8:17 AM File folder
ANSES MSS Composer Guidance 4/10/2021 7:07 PM File folder
EFSA_2020_March_ver5.2.2_MSS_ver1.8 4/10/2021 7:08 PM File folder
New folder 2/25/2021 12:52 PM File folder
Mesotrione.xml 3/4/2021 10:14 AM XML Document 39
Mesotrione_Rat.xml 4/13/2021 10:24 AM XML Document 54
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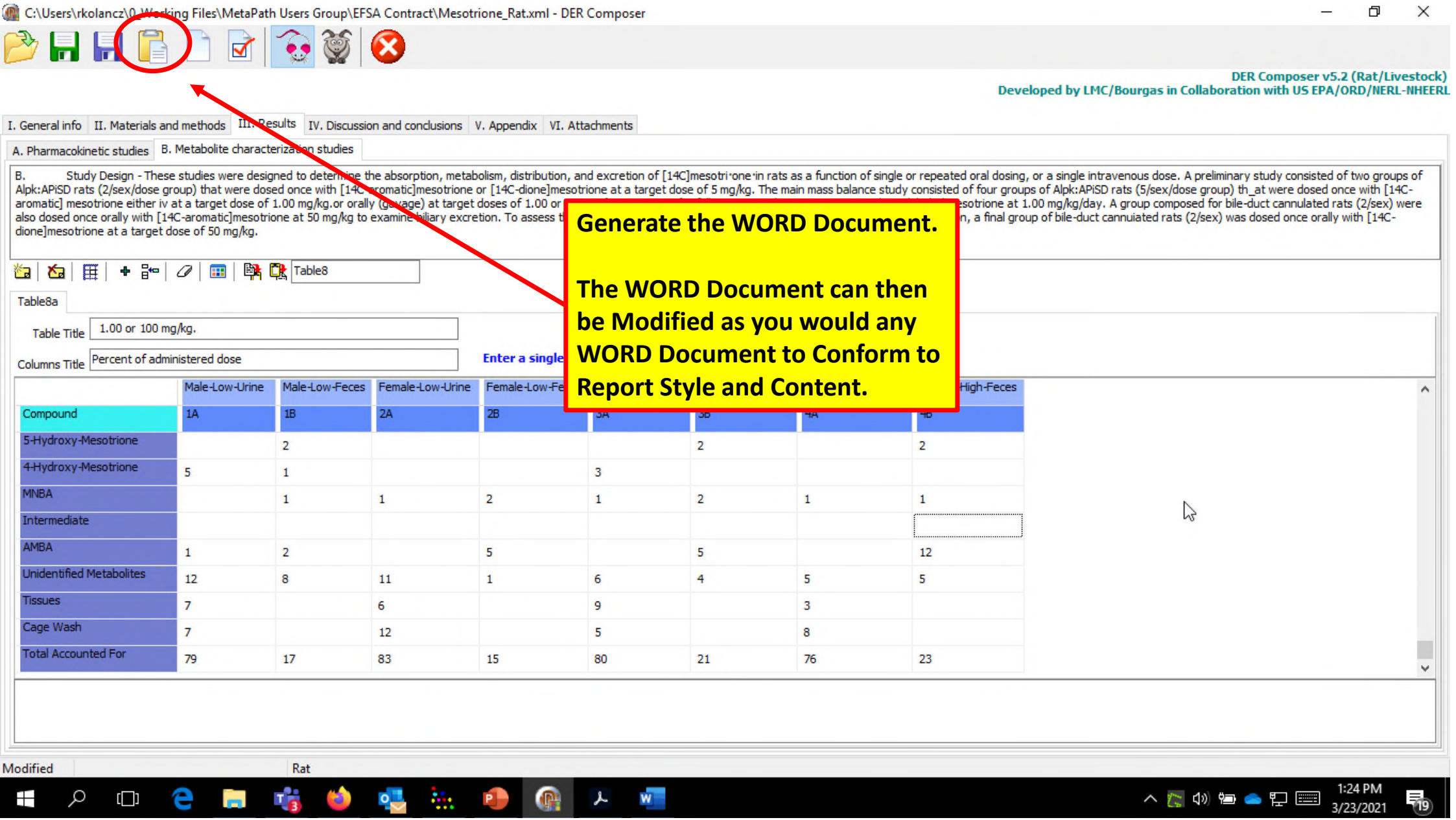
Save as type: XML File (*.xml)
Hide Folders
Save
Cancel
Rat
11:16 AM
4/13/2021



	Male-Low-Urine	Male-Low-Feces	Female-Low-Urine	Female-Low-Fe				High-Feces
Compound	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

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 %

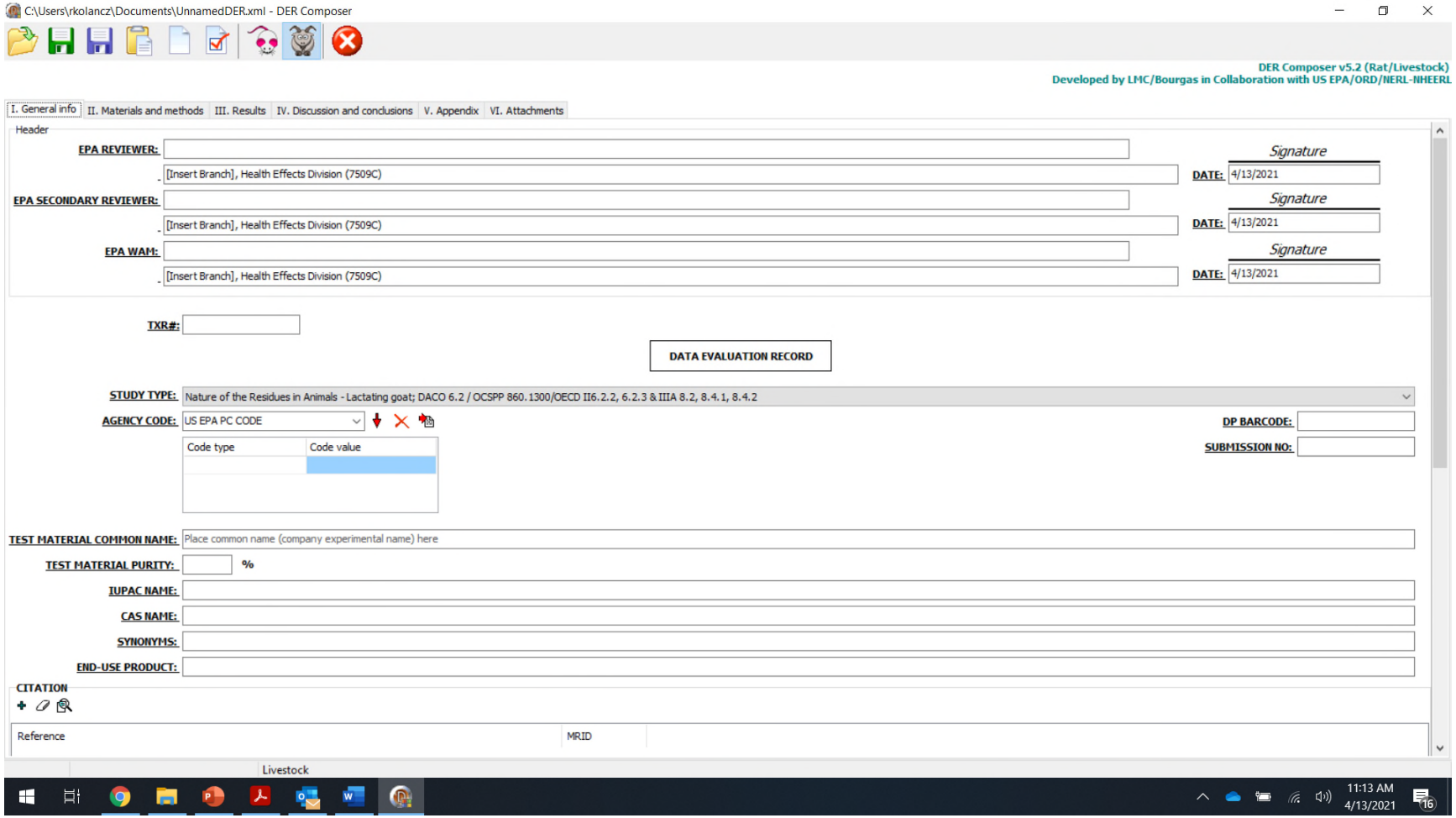
IUPAC NAME: 2-[4-(Methylsulfonyl)-2-nitrobenzoyl]cyclohexane-1,3-dione

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/PR0990, 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: Biotransfonnation 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/UR0522, May 29, 1996. Unpublished.	44505105
(1996) ZA.1296: 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/UR0525. May 24. 1996. Unpublished.	44505106

Go To Live Demo

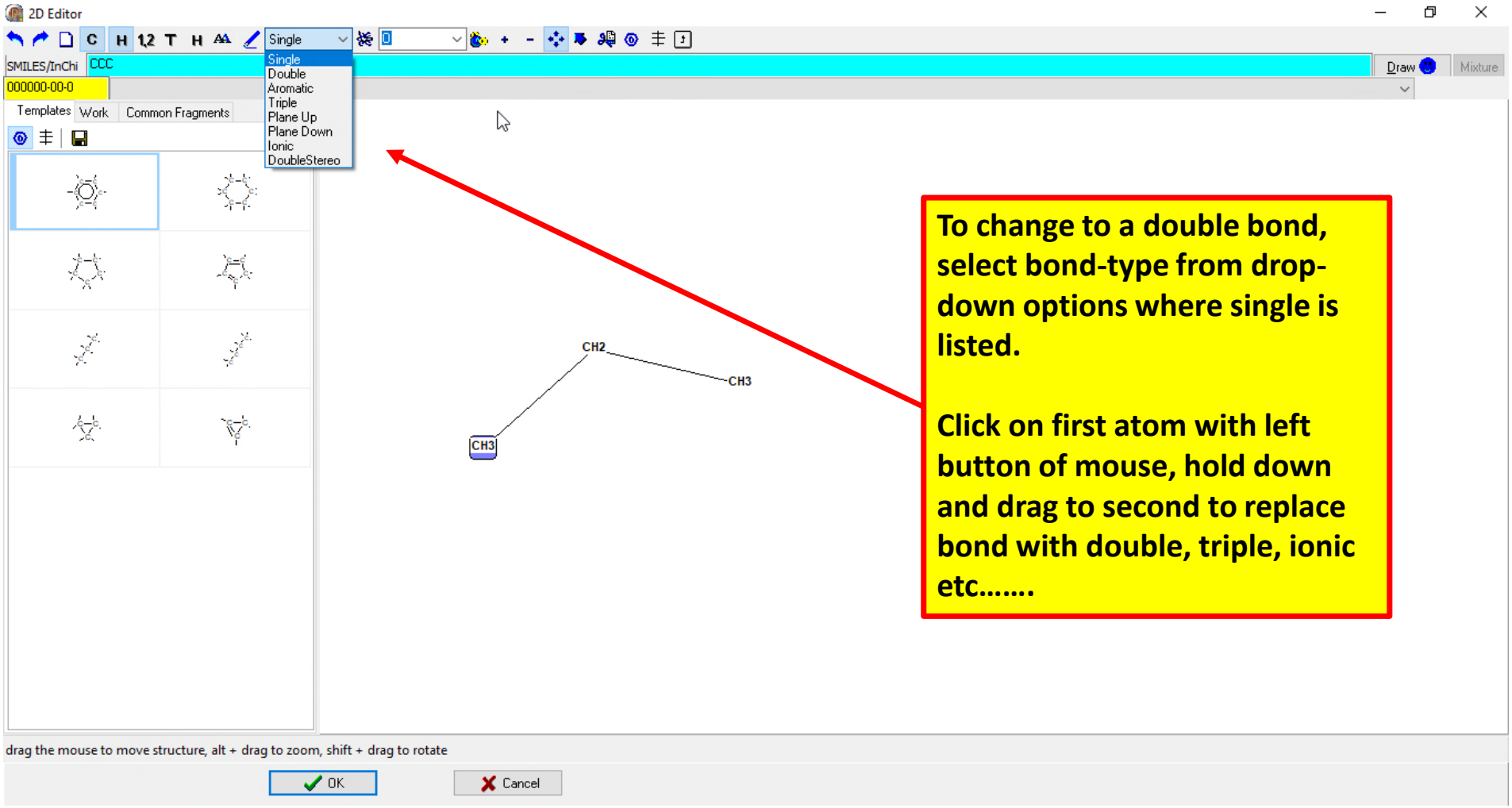


Transition Back to Juan to finish

- **Drawing Tools**
- **Structure Editor**

STRUCTURE EDITING

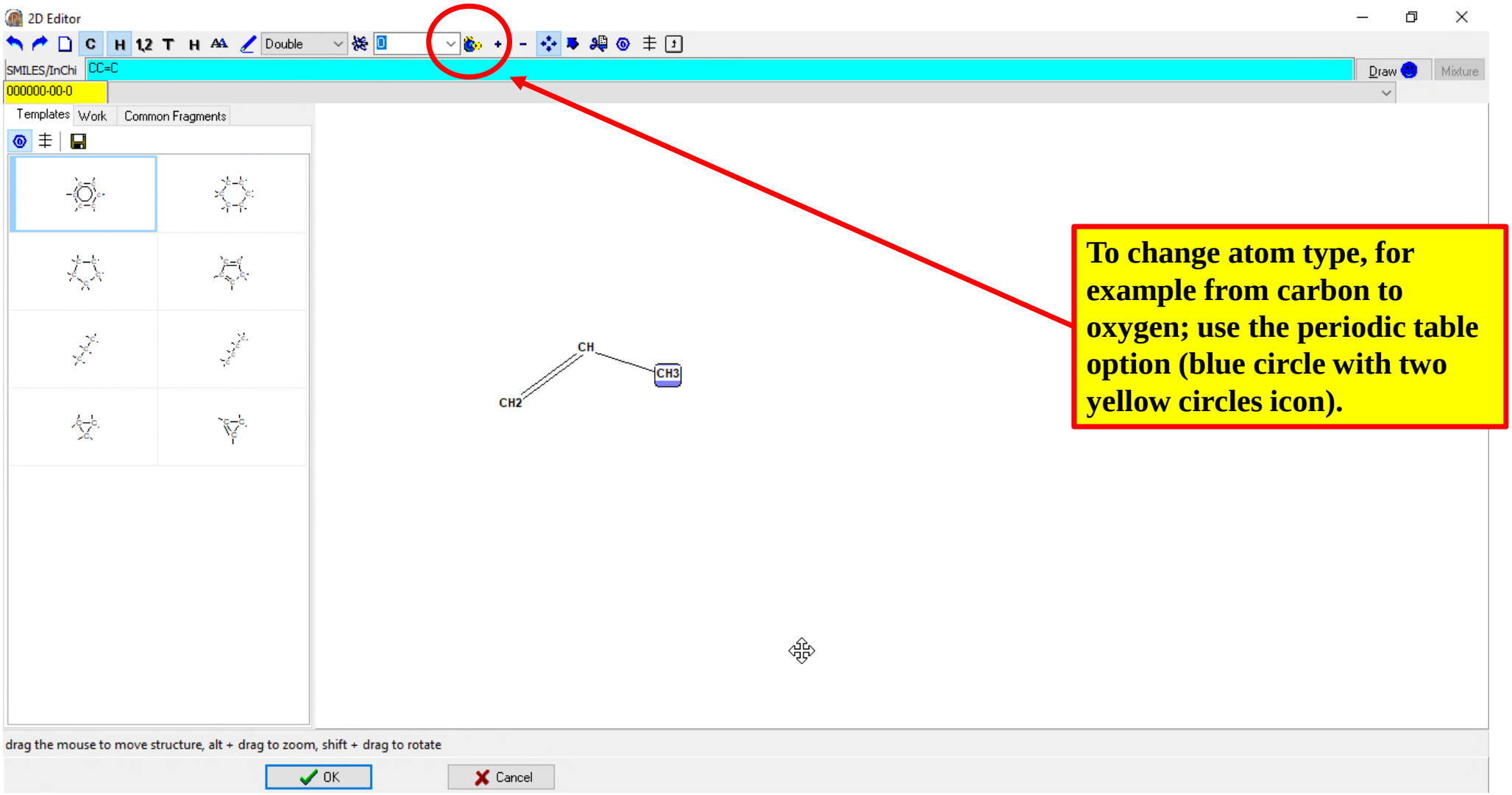
The following screen-shots illustrate some other functions of the STRUCTURE DRAWING package that may be used to modify/edit/draw 2-D structures of parent/metabolites.



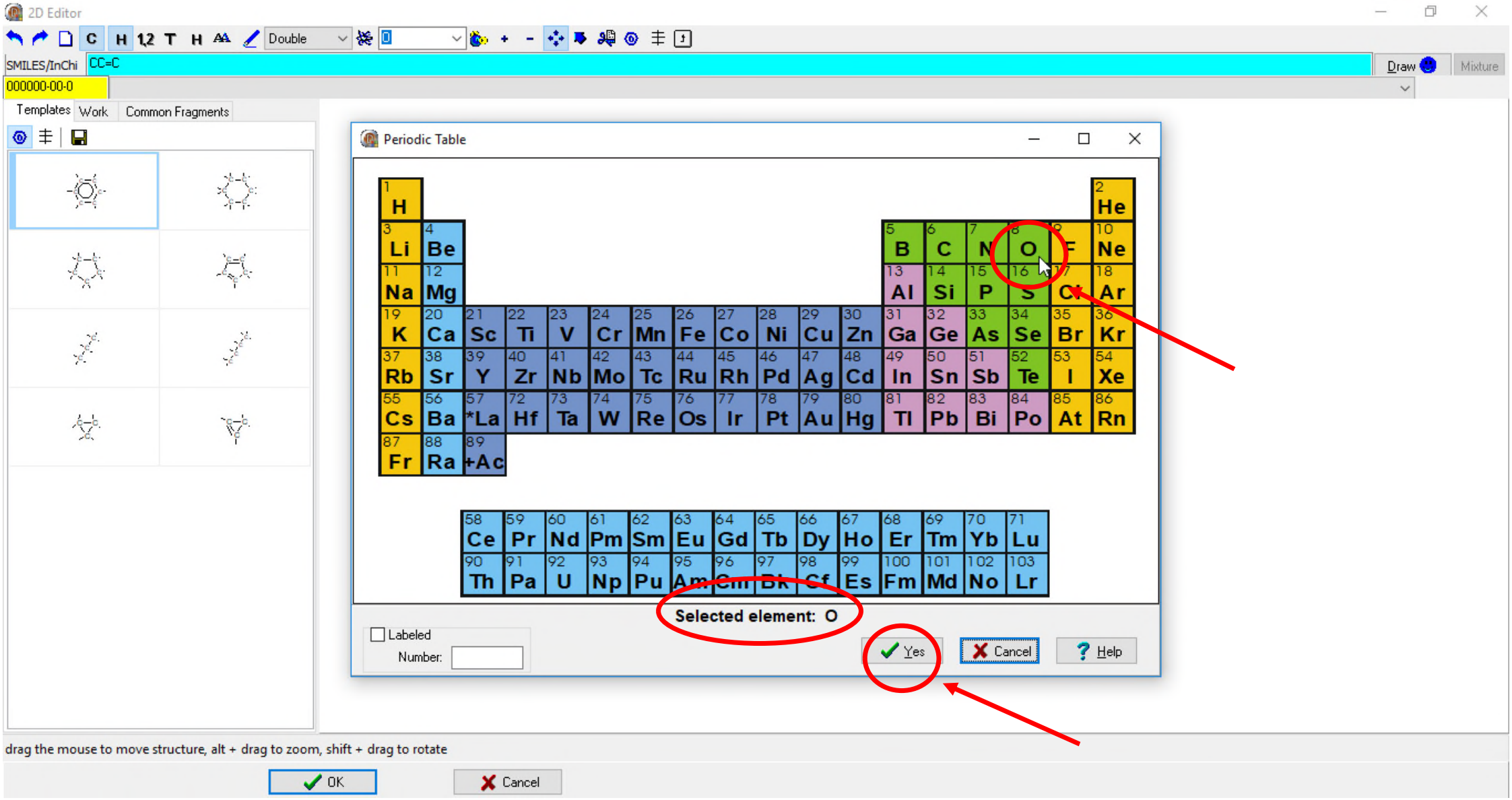
To change to a double bond, select bond-type from drop-down options where single is listed.

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

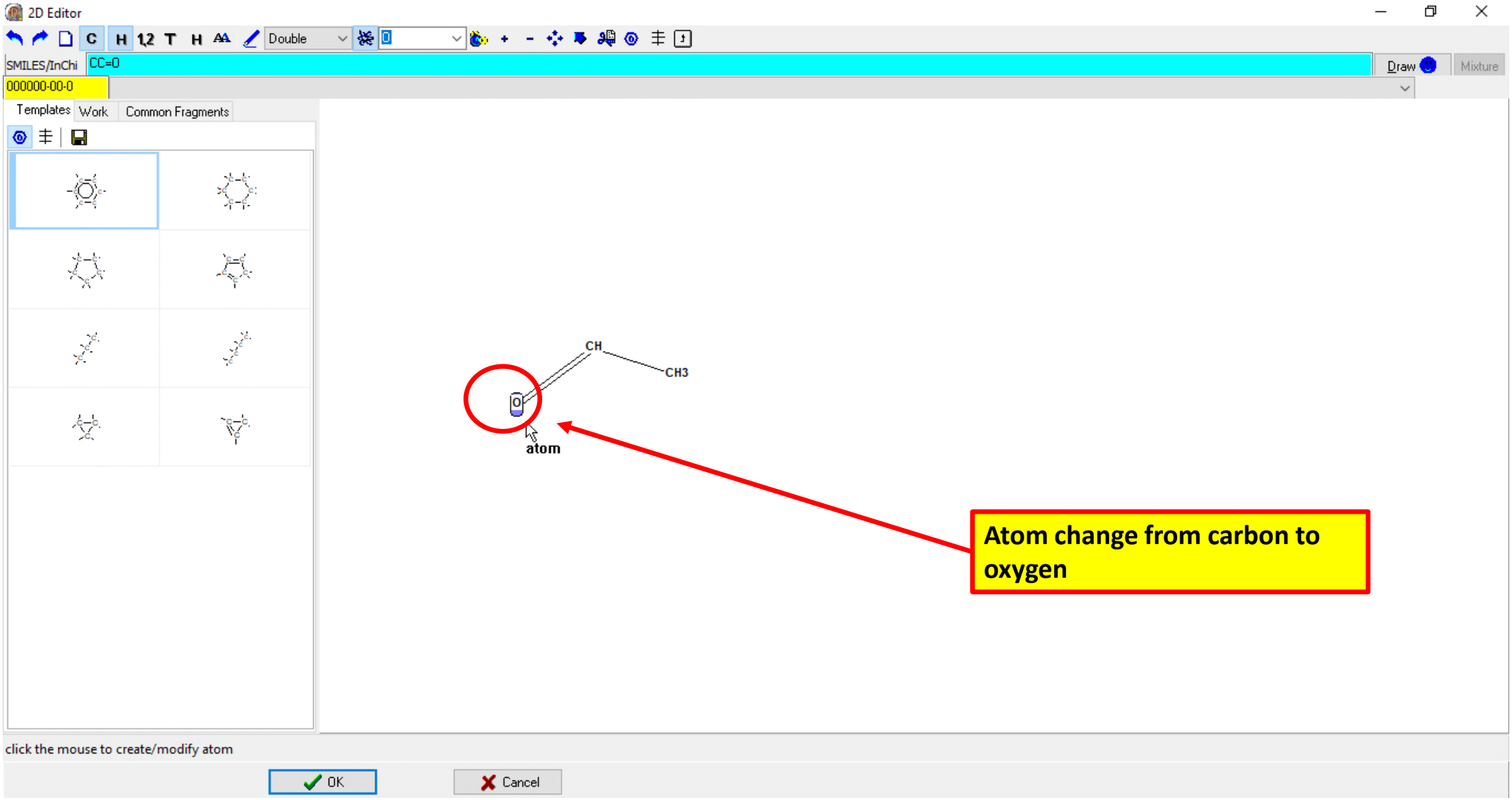
To change atom type, for example from carbon to oxygen; use the periodic table option (blue circle with two yellow circles icon).

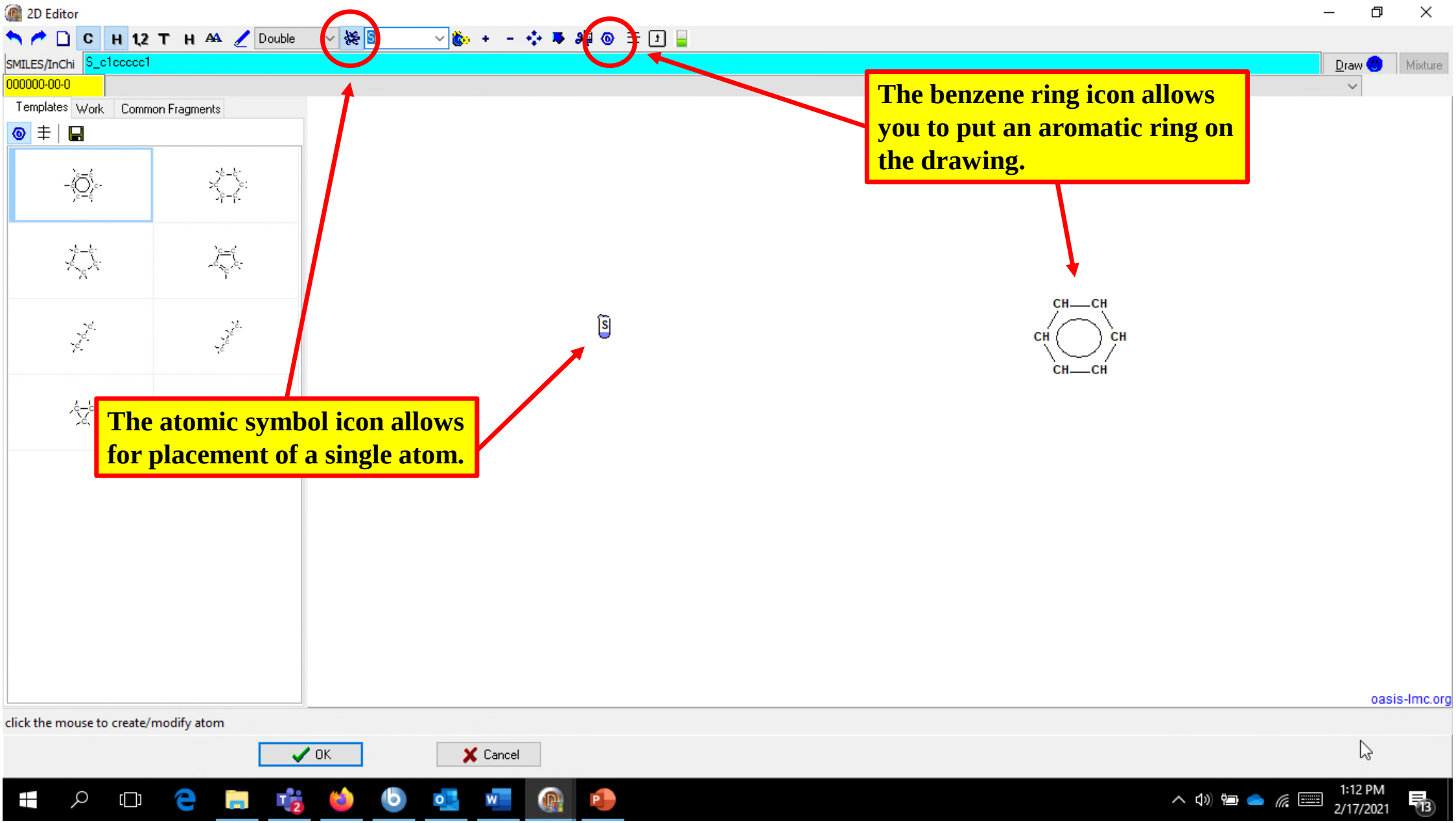


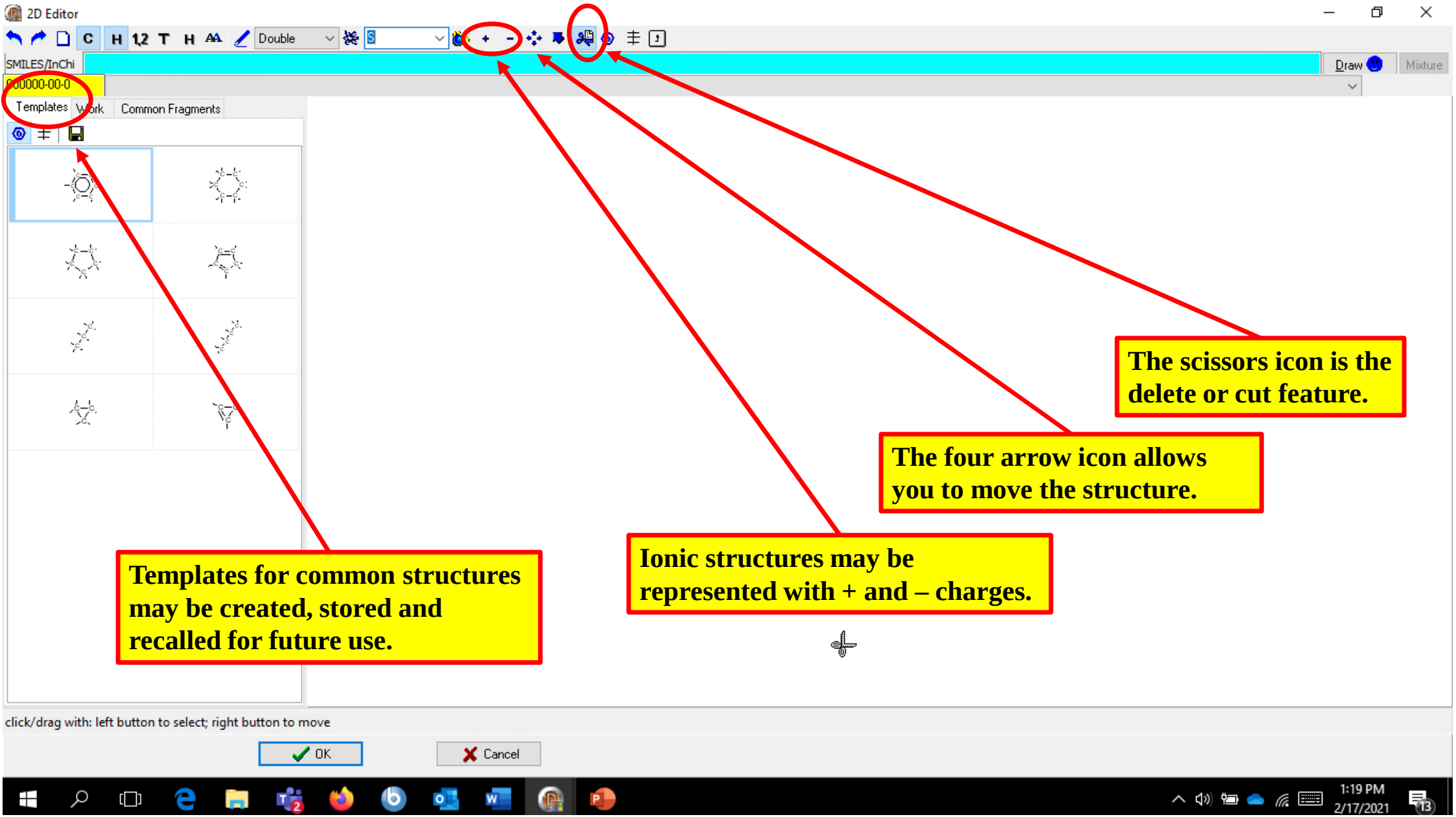
The table opens, click on atom choice, click yes to accept choice and the table goes away.



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




2D Editor
Double
SMILES/InChi
S_c1ccccc1
Draw
Mixture
000000-00-0
Templates
Work
Common Fragments
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.
CH
CH
CH
CH
CH
CH
oasis-lmc.org
click the mouse to create/modify atom
OK
Cancel
1:12 PM
2/17/2021


2D Editor
Double
SMILES/InChi
Draw
Mixture
000000-00-0
Templates
Work
Common Fragments
The scissors icon is the delete or cut feature.
The four arrow icon allows you to move the structure.
Ionic structures may be represented with + and – charges.
Templates for common structures may be created, stored and recalled for future use.
click/drag with: left button to select; right button to move
OK
Cancel
1:19 PM
2/17/2021

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