DER Composers for Registrant e-Submission of Study Data Summaries

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Vision for PRIA process improvement

- DER Composers have been developed for systematic capture of rat pharmacokinetic and metabolism study data
- Using the same approach, EPA would develop DER Composers to facilitate electronic capture of registrant-submitted toxicity data
- Upon pesticide registration, data would be made available through public databases

Developing DER Composers

Objective:

- improve efficiency in data summary and submission
- maximize electronic data transfer to minimize data errors
- facilitate QA of data
- autopopulate Agency knowledge-bases to improve PRIA workflow;
  - getting data in the hands of the risk assessor more efficiently
  - spend less time compiling data and more time assessing

DER Composers

- Use DER Composers for livestock or rat metabolism data submission as recommended by OECD Working Group on Pesticides, MetaPath Users Group working with OECD Secretariat

- Use DER Composers for EDSP T1S data submission

Computational Tools for Metabolism Research and Risk Assessment

MetaPath

a metabolism pathways database and data evaluation tools

DER Composer

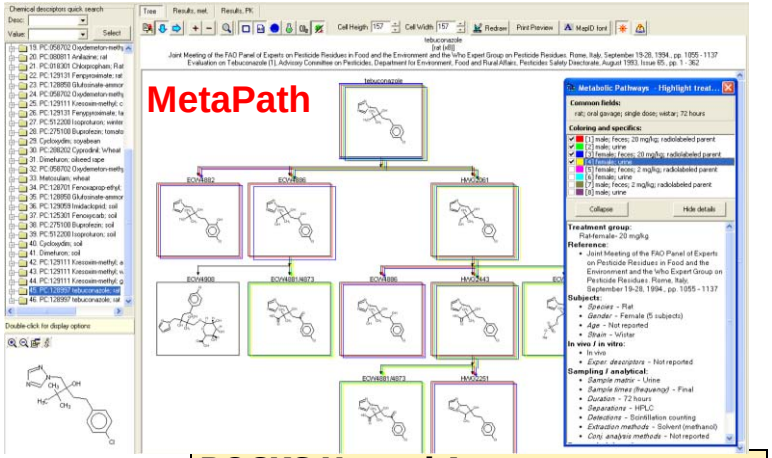
a software template for efficient data entry to facilitate:

- creation of draft Data Evaluation Records (DER) for risk assessor evaluations of OPP metabolism studies
- auto-population of submitted data into MetaPath

Proposed MetaPath/DER Composer use in OPP workflow
Residues Of Concern Knowledgebase Subcommittee (ROCKS)

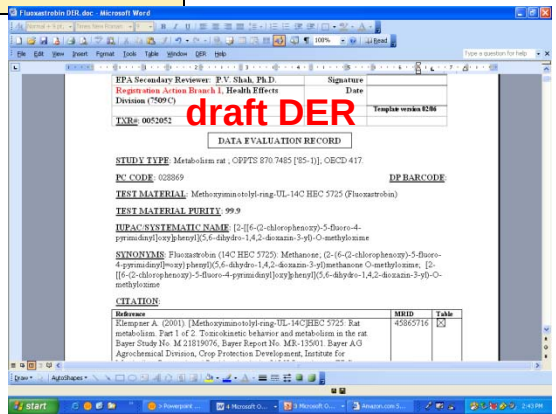
Registrant produces **draft DER** (**doc** file) and **XML** for a 'new' chemical using '**DER Composer**' (rat metabolism, livestock residues, plant residues, environmental degradates)

'new' chemical **xml** (after QA) is added to **MetaPath** database



Assessment Team (Lead Toxicologist and Risk Assessors) review the Toxicology Profile using summary information in **draft DER** and refer to Study File as appropriate

MetaPath tools used to assess common metabolites for Proposed Residue Definitions for inclusion in Risk Assessment and Tolerance Expression recorded in **draft DER**



ROCKS Hazard Assessors pre-meet before full committee meeting to discuss team proposal and consider metabolites of potential hazard concern (using **MetaPath** and/or other (Q)SAR tools for predictions) summarized in **draft DER**

ROCKS Committee Reviews the team's proposal and renders an Expert opinion/ recommendation(s); **draft DER** updated and decision finalized and reported in **final DER**

DER Composer

Developed around Pharmacokinetic & Metabolism, and Nature of the Residue harmonized guidelines:

1) **OPPTS 870.7485 (85-1) Rat Metabolism**
2) **OPPTS 860.1300 Nature of Residues in Animals**

- Data entered in DER Composers can output as:
  - *.xml file for direct data import into MetaPath
  - *.doc file draft Data Evaluation Record to record OPP decisions

- Efficient standardized data entry

- Facilitates electronic data submission and e-population of new data into MetaPath into the future

OECD/OPP Guideline document used as framework for DER Composer development

870.7485 (85-1) Rat Metabolism & PK

EPA Reviewer: _____ **Signature:** _____
[Insert Branch], Health Effects Division (7509C) **Date:** _____
EPA Secondary Reviewer: _____ **Signature:** _____
[Insert Branch], Health Effects Division (7509C) **Date:** _____

Template version 02/06

TXR#:

DATA EVALUATION RECORD

STUDY TYPE: Metabolism - *[species]*; OPPTS 870.7485 [§85-1)]; OECD 417.

PC CODE: **DP BARCODE:**

TEST MATERIAL (PURITY): *[use name of material tested as referred to in the study (common agency chemical name in parenthesis)]*

SYNONYMS: *[other names and code names]*

CITATION: Author *[up to 3, see SOP for exact format]* *(Date)* Title. Laboratory name (location if needed). Laboratory report number, full study completion date. MRID *[no hyphen]*. Unpublished *(OR if published, list Journal name, vol.:pages)*

SPONSOR: *(Name of Study Sponsor - indicate if different from Applicant).*

EXECUTIVE SUMMARY:

In a metabolism study (MRID *[number]*) *[Chemical name (%a.i., batch/lot #), include location of radioactive label]* was administered to *[(# of animals) species, strain]*/sex/dose in *[method of exposure: eg. by gavage]* at dose levels of 0, x, x *[mg/kg or other pertinent units]*.

Be brief (one or two paragraphs) [Describe, as appropriate: recoveries and routes of elimination of radioactivity and time frame as they relate to absorption and excretion of the compound; radioactivity in organs of concern, especially as it relates to bioaccumulation; sex and treatment group differences; and expired air radioactivity; major metabolites; other major factors.]

This metabolism study in the *(species)* is classified *[acceptable, unacceptable (guideline, non-guideline)]* and satisfies *(does not satisfy)* the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in *[species] [If unacceptable, why and is it upgradable. If it does not satisfy the requirement, concisely list only major deficiencies or refer to deficiency section.]*

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were *(not)* provided. *[Discuss deviations from regulatory requirements.]*

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test compound:**

Radiolabelled test material:	*[indicate position of radiolabel, eg., [Phenyl-U-^{14}C] XX]*
Radiochemical purity:	% *[determined by HPLC, GC or TLC]*
Specific activity:	µCi/mg
Lot/batch #:	
Non-Radiolabelled test material:	*[as named in study]*
Description:	(e.g. technical, nature, color, stability)
Lot/batch #:	
Purity:	% a.i. [determined by HPLC, GC or TLC]
Contaminants:	
CAS # of TGAI:	
Structure:	*[Structure, include location of label] Jpeg format or* Not available

2. **Vehicle and/or positive control:** *[when appropriate]*, Lot/Batch #; Purity

3. **Test animals:**

Species:	
Strain:	
Age/weight at study initiation:	
Source:	
Housing:	
Diet:	*(describe) ad libitum*
Water:	*(describe) ad libitum*
Environmental conditions:	
Temperature:	°C
Humidity:	%
Air changes:	/hr
Photoperiod:	hrs dark/ hrs light
Acclimation period:	

4. **Preparation of dosing solutions:**

B. STUDY DESIGN AND METHODS:

1. **Group arrangements**

Animals were assigned *[note how assigned, e.g., random, briefly describe groups as needed]* to the test groups noted in Table 1.

TABLE 1: Dosing groups for pharmacokinetic studies for *(chemical)* *[some form of this data presentation is **RECOMMENDED**. If additional test groups are used (e.g. pilot study,dermal exposure, inhalation exposure or biliary cannulation etc.) include them in the table]*			
Test group	Dose of labeled material (mg/kg)	Number/sex	Remarks: *(eg. time of sacrifice)*
Oral dose			
Treatment 2 [if applicable]			
Treatment 3 [if applicable]			

2. **Dosing and sample collection:** *(briefly describe dosing methods and sample collection)*

   a. **Pharmacokinetic studies:** *[give details of experiments including what was sampled (urine, feces, tissues, cage washes, bile, if appropriate) and when and how often.]*

   b. **Metabolite characterization studies:** *[What was collected for identification, when and from how many animals (samples pooled or not), method type for identification (eg. GC/MS or TLC)].*

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]*

II. RESULTS:

A. PHARMACOKINETIC STUDIES:

1. **Preliminary experiment:** *(if applicable)(Briefly describe results)*

2. **Absorption:** *[Briefly describe absorption, may include an optional table relating excretion of radioactivity (in urine, feces, etc.) to sampling time]*

3. **Tissue distribution** *(include groups that are applicable; describe distribution patterns for each treatment group. Some form of table 2 is recommended, if data are available).*

TABLE 2: Distribution of radioactivity in rat tissues/organs after administration of C^{14}-labeled Compound XX[a].						
Tissue/organ	Percent of radioactive dose administered *(or ppm equivalents)*					
	Oral dose		Treatment 2 (if applicable)		Treatment 3 (if applicable)	
	Male	Female (if applicable)	Male	Female (if applicable)	Male	Female (if applicable)
Organ 1						
Organ 2						

[a] Data obtained from pages *(insert page numbers)* in the study report.

[Write a brief narrative of the contents of Table 2 under the following 4 headings]:

   a. **Oral dose :** As summarized in Table 2.

   b. **Treatment 2:** (If Applicable)

   c. **Treatment 3:**. (If Applicable)

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

TABLE 3: Recovery of radioactivity in tissues and excreta of rats after administration of C^{14}-labeled Compound XX[a].						
	Percent of radioactive dose recovered					
	Oral dose		Treatment 2 (if applicable)		Treatment 3 (if applicable)	
	Male	Female (if applicable)	Male	Female (if applicable)	Male	Female (if applicable)
Expired air						
Tissues						
Carcass						
Cage wash						
Urine[b]						
Feces						
Total						

[a] Data obtained from pages *(insert page #s)* in the study report.
[b] Report at appropriate intervals.

[Write a brief narrative of the contents of Table 3 under the following 4 headings]:

   a. **Oral dose:** As summarized in Table 3

   b. **Treatment 2: (If applicable)**

   c. **Treatment 3: (If applicable)**

B. METABOLITE CHARACTERIZATION STUDIES:

[Give the metabolites identified, include percent of radioactive dose given, where they were identified, when if applicable, how they were identified if applicable, how much parent was present in the excreta. Some form of table 4 is recommended . When available, include summary of metabolic pathways and figures available. Mention which are major vs. minor pathways. Include the registrant's postulated pathway as a figure or attachment, preferably electronic]

TABLE 4. Metabolite profile in excreta of rats dosed with C^{14}-labeled *Compound XX*[a].
[Metabolites must be given as percent of dose. If possible the reviewer should perform the necessary conversions, include Total identified, Total unidentified, Total accounted for, Total lost or unaccounted (see below)]

Dose	Percent of administered dose					
	Oral dose		Treatment 2 (If Applicable)		Treatment 3 (If Applicable)	
Compound	Male	Female (If Applicable)	Male	Female (If Applicable)	Male	Female (If Applicable)
Parent						
Identified metabolite 1						
Identified metabolite 2						
Total identified						
Unidentified metabolite X						
Unidentified metabolite Y						
Undentified at origin or at some band						
Total unidentif.						
Total accounted for [b]						
Lost/unaccounted for [c]						
Total	100	100	100	100	100	100

[a] Data obtained from pages *(insert page #s)* in the study report.
[b] Total accounted for = (Total identified) + (Total unidentified)
[c] 100 - (Total accounted for)

III.DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS:

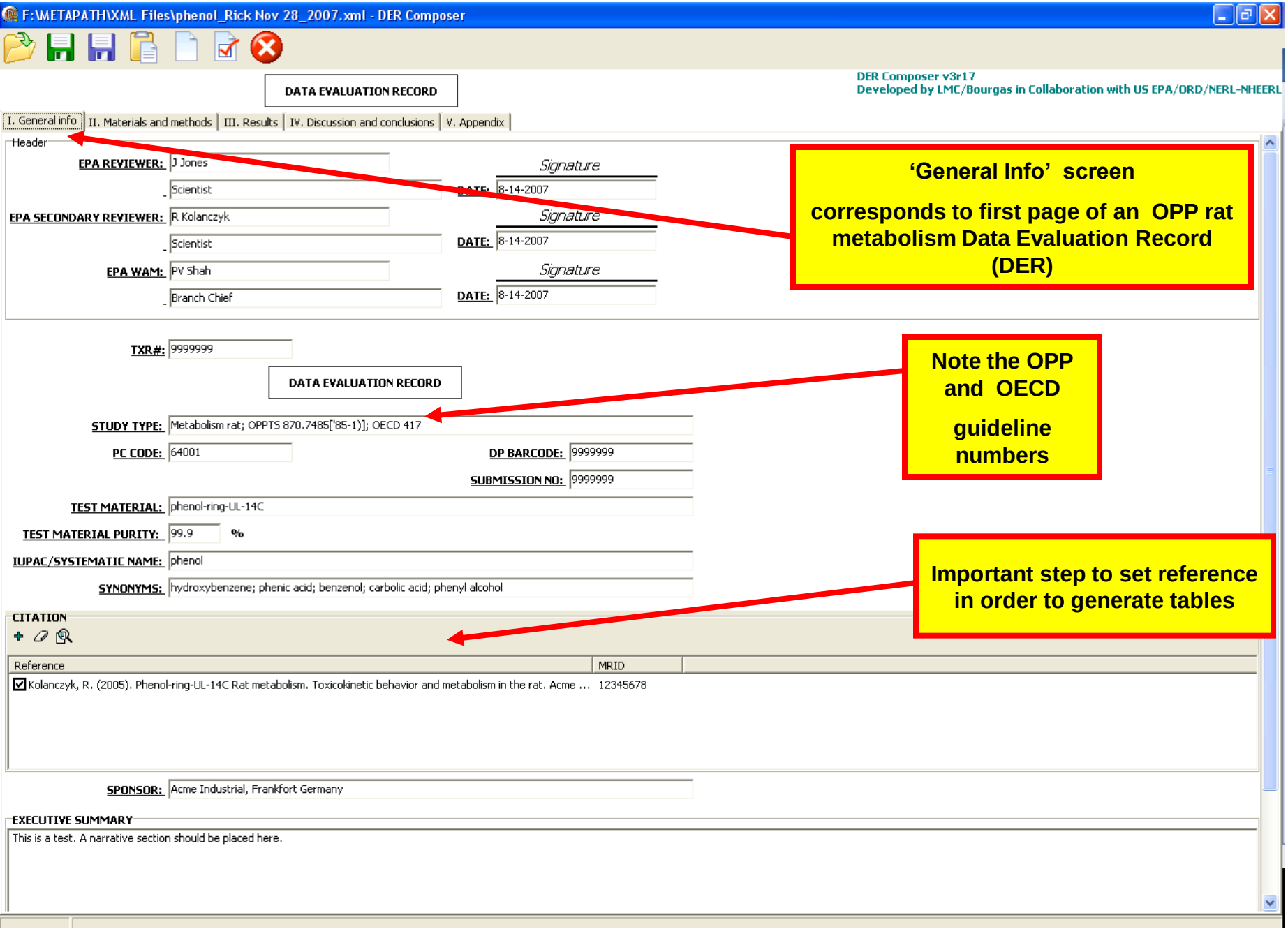
B. REVIEWER COMMENTS:

[Give overall summary tying together all the above data, discussing differences from study author's opinion, deficiencies.]

C. STUDY DEFICIENCIES:

[List each deficiency (distinguishing between major and minor ones) with the data required to resolve the deficiency. If no data can be provided to satisfy the deficiency, indicate impact on the regulatory decision.]

DER Composer – Data Entry Screen for 'General Info'



'General Info' screen

corresponds to first page of an OPP rat metabolism Data Evaluation Record (DER)

Note the OPP and OECD

guideline numbers

Important step to set reference in order to generate tables

OECD/OPP Guideline document used as framework for DER Composer development

870.7485 (85-1) Rat Metabolism & PK

DER Template

NAME OF TECHNICAL/PC Code

Metabolism (*year of study*) / Page 1 of 3
OPPTS 870.7485/ DACO 4.5.9/ OECD 417

EPA Reviewer: _____ **Signature:** _____
[Insert Branch], Health Effects Division (7509C) **Date:** _____
EPA Secondary Reviewer: _____ **Signature:** _____
[Insert Branch], Health Effects Division (7509C) **Date:** _____

Template version 02/06

TXR#:

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SYNONYMS: *[other names and code names]*

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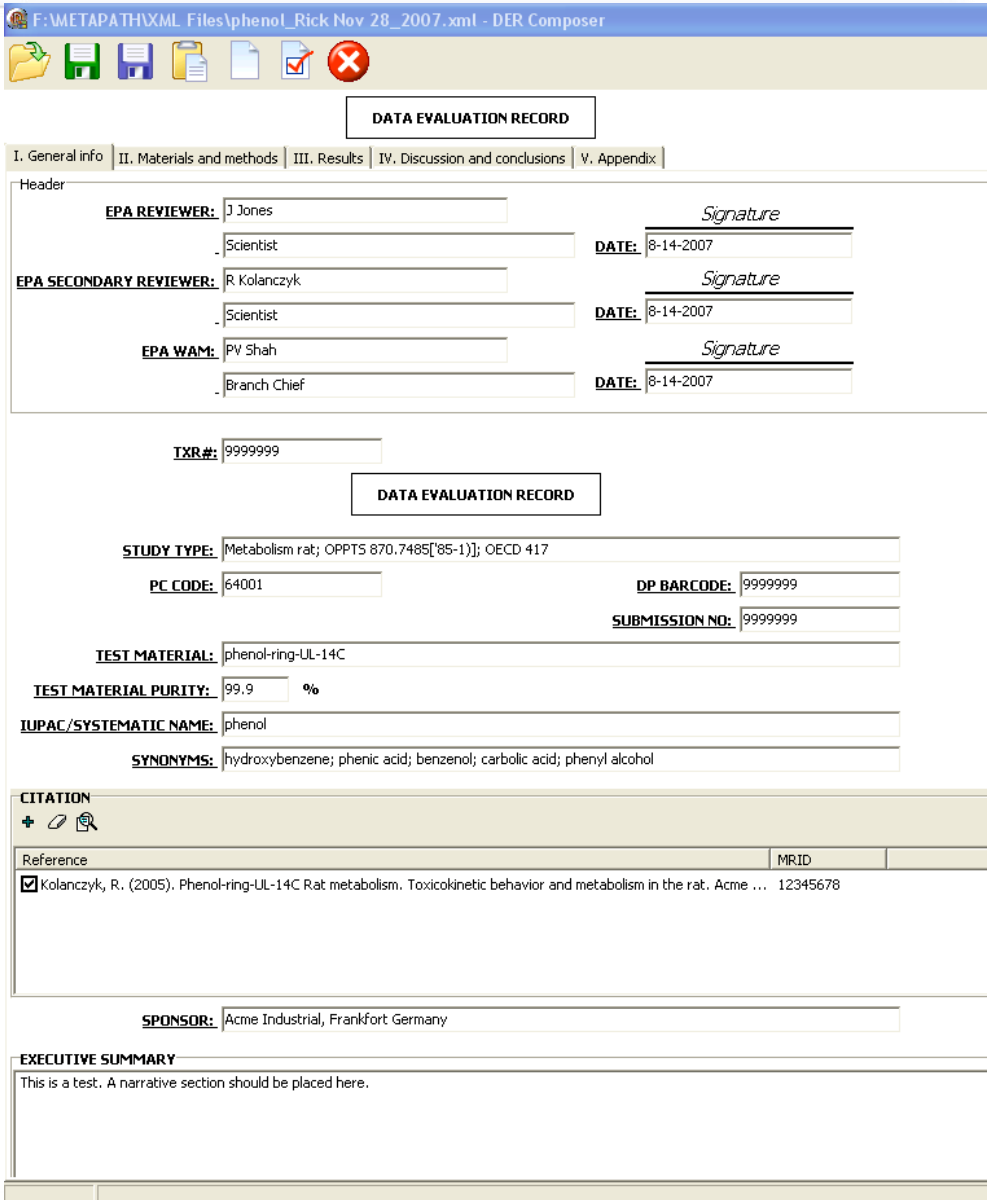
DER Composer entry screen



DER Composer data entry screen

F:\METAPATH\XML Files\phenol_Rick Nov 28_2007.xml - DER Composer

DATA EVALUATION RECORD

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

Header

EPA REVIEWER: J Jones — Signature
Scientist — DATE: 8-14-2007
EPA SECONDARY REVIEWER: R Kolanczyk — Signature
Scientist — DATE: 8-14-2007
EPA WAM: PV Shah — Signature
Branch Chief — DATE: 8-14-2007

TXR#: 9999999

DATA EVALUATION RECORD

STUDY TYPE: Metabolism rat; OPPTS 870.7485['85-1)]; OECD 417
PC CODE: 64001 DP BARCODE: 9999999
SUBMISSION NO: 9999999
TEST MATERIAL: phenol-ring-UL-14C
TEST MATERIAL PURITY: 99.9 %
IUPAC/SYSTEMATIC NAME: phenol
SYNONYMS: hydroxybenzene; phenic acid; benzenol; carbolic acid; phenyl alcohol

CITATION

Reference	MRID
☑ Kolanczyk, R. (2005). Phenol-ring-UL-14C Rat metabolism. Toxicokinetic behavior and metabolism in the rat. Acme ...	12345678

SPONSOR: Acme Industrial, Frankfort Germany

EXECUTIVE SUMMARY

This is a test. A narrative section should be placed here.

DER *.doc file

test3.doc [Compatibility Mode] - Microsoft Word — Table Tools

References | Mailings | Review | View | EndNote X4 | Acrobat | Design | Layout

Ruler | Gridlines | Message Bar | Document Map | Thumbnails | Zoom | 100% | One Page | Two Pages | Page Width | New Window | Arrange All | Split | View Side by Side | Synchronous Scrolling | Reset Window Position | Switch Windows

Show/Hide | Zoom | Window

EPA Reviewer: J Jones — Signature
Scientist — Date 8-14-2007
EPA Secondary Reviewer: R Kolanczyk — Signature
Scientist — Date 8-14-2007
EPA WAM: PV Shah — Signature
Branch Chief — Date 8-14-2007
Template version 02/06

TXR#: 9999999

DATA EVALUATION RECORD

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

PC CODE: 64001

DP BARCODE: 9999999
SUBMISSION NO.: 9999999

TEST MATERIAL: phenol-ring-UL-14C

TEST MATERIAL PURITY: 99.9 %

IUPAC/SYSTEMATIC NAME: phenol

SYNONYMS: hydroxybenzene; phenic acid; benzenol; carbolic acid; phenyl alcohol

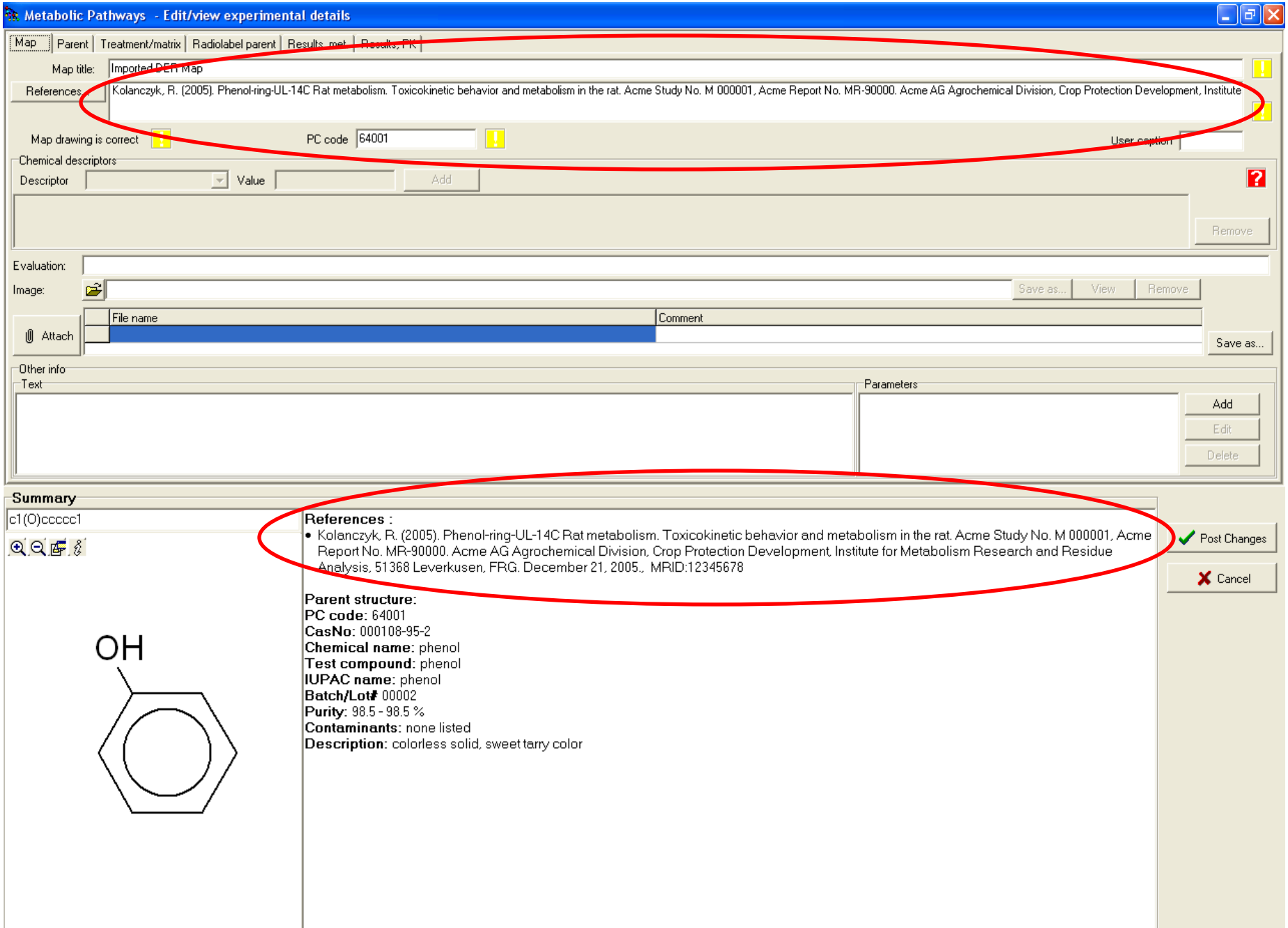
Reference	MRID
Kolanczyk, R. (2005). Phenol-ring-UL-14C Rat metabolism. Toxicokinetic behavior and metabolism in the rat. Acme Study No. M 000001, Acme Report No. MR-90000. Acme AG Agrochemical Division, Crop Protection Development, Institute for Metabolism Research and Residue Analysis, 51368 Leverkusen, FRG. December 21, 2005.	12345678

SPONSOR: Acme Industrial, Frankfort Germany

EXECUTIVE SUMMARY:
This is a test. A narrative section should be placed here.

COMPLIANCE: This is a test. A narrative section should be placed here.

MetaPath – 'General Info'



DER Composer - Materials & Methods

F:\METAPATH\XML Files\phenol_Rick Nov 28_2007.xml - DER Composer

DATA EVALUATION RECORD

DER Composer v3r17
Developed by LMC/Bourgas in Collaboration with US EPA/ORD/NERL-NHEER

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

A. Materials | B. Study design and methods

1. Test Compound

Radiolabelled test material

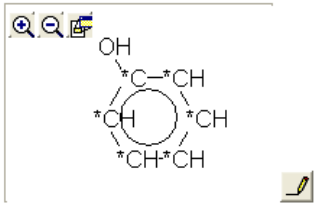
Radiolabelled test material: phenol-ring-UL-14C

Radiolabelled purity: 99.9 %

Specific activity: 100 uCi/mg

Lot/batch #: 20014

Structure:



Non-Radiolabelled test material

Non-Radiolabelled test material: phenol

Description: colorless solid, sweet tarry color

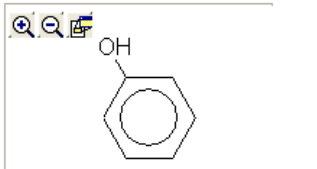
Lot/batch #: 00002

Purity: 98.5 %

Contaminants: none listed

CAS # of TGAI: 108952

Structure:



2. Vehicle and/or positive control

Phenol-ring-UL-14C was suspended in 0.5% Tragacanth solution. No positive controls were utilized in any of the experiments.

3. Test animals

Species: rat

Generate Word Document

'Materials and Methods' Part A: Materials.

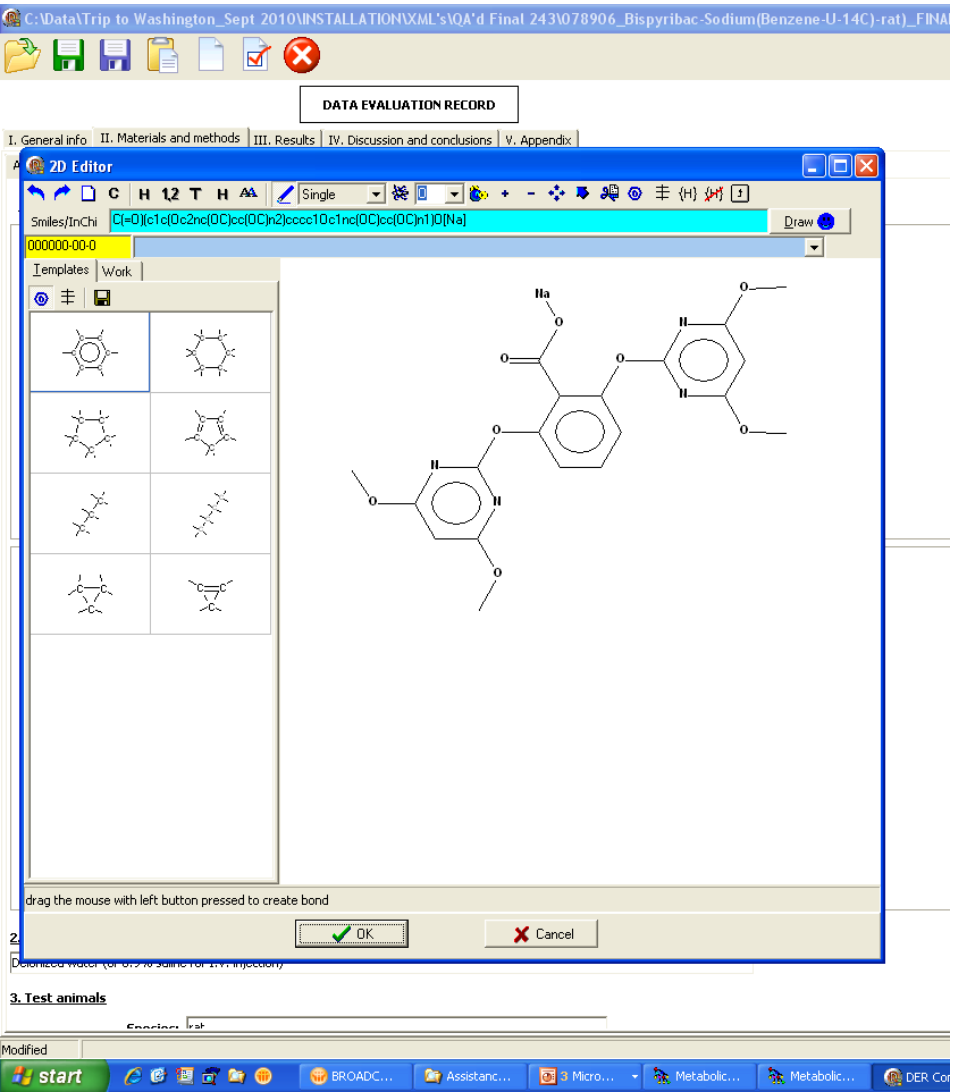
Include radio-label in naming convention

Chemical structure can be drawn with 2D structure drawing package, or from imported SMILES string.

DER Composer - getting chemical structure input

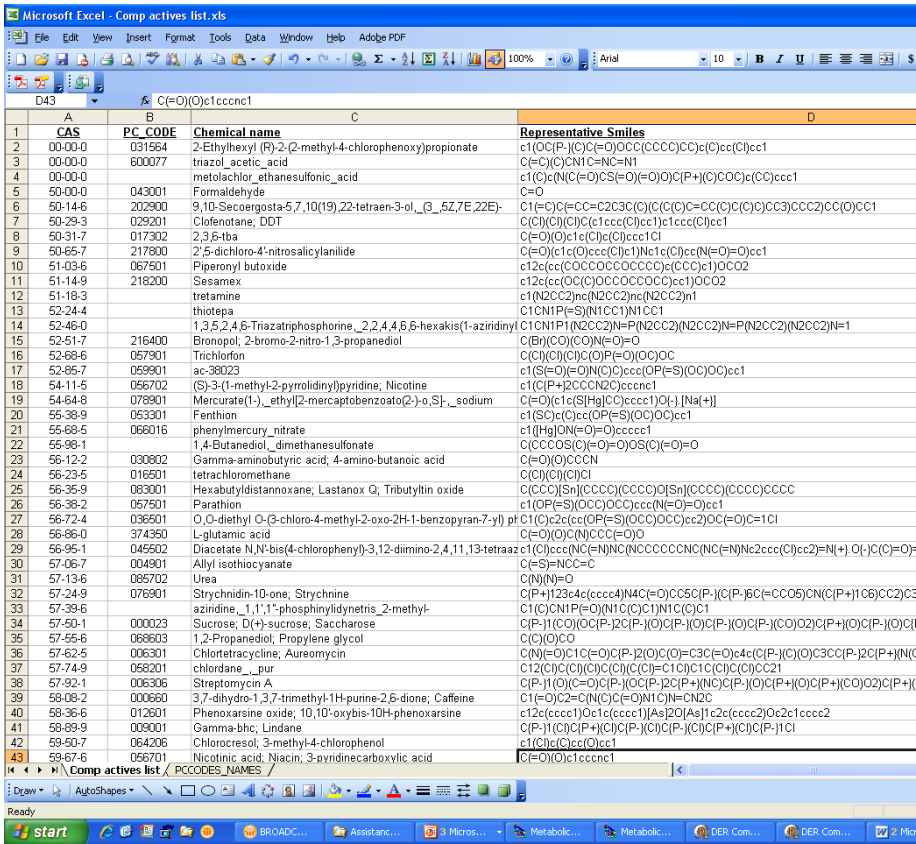
1) Use Drawing Package (re: 2-D Editor Manual provided)

2) Apply SMILES String (e.g., SMILES file for pesticides)



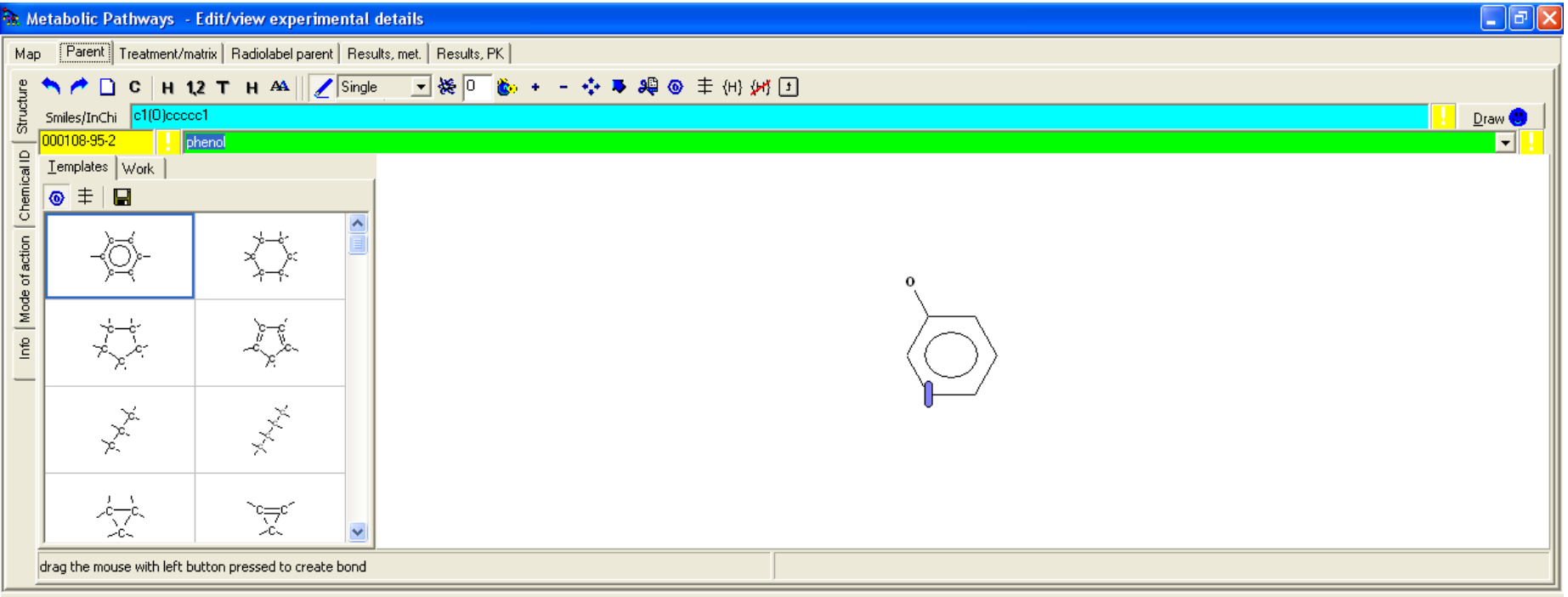
SMILES = simplified molecular input line entry specification

2-D structure described by ASCII string



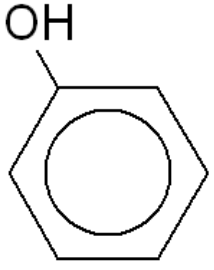
	A	B	C	D
1	CAS	PC_CODE	Chemical name	Representative Smiles
2	00-00-0	031564	2-Ethylhexyl (R)-2-(2-methyl-4-chlorophenoxy)propionate	c1(OC(P-)(C)C(=O)OCC(CCCC)CC)c(C)cc(Cl)cc1
3	00-00-0	600077	triazol_acetic_acid	C(=C)(C)CN1C=NC=N1
4	00-00-0		metolachlor_ethanesulfonic_acid	c1(C)c(N(C(=O)CS(=O)(=O)O)C(P+)(C)COC)c(C)ccc1
5	50-00-0	043001	Formaldehyde	C=O
6	50-14-6	202900	9,10-Secoergosta-5,7,10(19),22-tetraen-3-ol,_(3_,5Z,7E,22E)-	C1(=C)C(=CC=C2C3C(C)(C(C)C)C=CC(C)C(C)CC3)CCC2)CC(O)CC1
7	50-29-3	029201	Clofenotane; DDT	C(Cl)(Cl)(Cl)C(c1ccc(Cl)cc1)c1ccc(Cl)cc1
8	50-31-7	017302	2,3,6-tba	C(=O)(O)c1c(Cl)c(Cl)ccc1Cl
9	50-65-7	217800	2',5-dichloro-4'-nitrosalicylanilide	C(=O)(c1c(O)ccc(Cl)c1)Nc1c(Cl)cc(N(=O)=O)cc1
10	51-03-6	067501	Piperonyl butoxide	c12c(cc(COCCCCCCCCC)c(CCC)c1)OCO2
11	51-14-9	218200	Sesamex	c12c(cc(OC(C)OCCCCCCC)cc1)OCO2
12	51-18-3		tretamine	c1(N2CC2)nc(N2CC2)nc(N2CC2)n1
13	52-24-4		thiotepa	C1CN1P(=S)(N1CC1)N1CC1
14	52-46-0		1,3,5,2,4,6-Triazatriphosphorine,_2,2,4,4,6,6-hexakis(1-aziridinyl	C1CN1P1(N2CC2)N=P(N2CC2)(N2CC2)N=P(N2CC2)(N2CC2)N=1
15	52-51-7	216400	Bronopol; 2-bromo-2-nitro-1,3-propanediol	C(Br)(CO)(CO)N(=O)=O
16	52-68-6	057901	Trichlorfon	C(Cl)(Cl)(Cl)C(O)P(=O)(OC)OC
17	52-85-7	059901	ac-38023	c1(S(=O)(=O)N(C)C)ccc(OP(=S)(OC)OC)cc1
18	54-11-5	056702	(S)-3-(1-methyl-2-pyrrolidinyl)pyridine; Nicotine	c1(C[P+]2CCCN2C)ccccn1
19	54-64-8	078901	Mercurate(1-)_ethyl[2-mercaptobenzoato(2-)-o,S]-,_sodium	C(=O)(c1c(S[Hg]CC)cccc1)O(-).[Na(+)]
20	55-38-9	053301	Fenthion	c1(SC)c(C)cc(OP(=S)(OC)OC)cc1
21	55-68-5	066016	phenylmercury_nitrate	c1([Hg]ON(=O)=O)ccccc1
22	55-98-1		1,4-Butanediol,_dimethanesulfonate	C(CCOS(C)(=O)=O)OS(C)(=O)=O
23	56-12-2	030802	Gamma-aminobutyric acid; 4-amino-butanoic acid	C(=O)(O)CCCN
24	56-23-5	016501	tetrachloromethane	C(Cl)(Cl)(Cl)Cl
25	56-35-9	083001	Hexabutyldistannoxane; Lastanox Q; Tributyltin oxide	C(CCC)[Sn](CCCC)(CCCC)O[Sn](CCCC)(CCCC)CCCC
26	56-38-2	057501	Parathion	c1(OP(=S)(OCC)OCC)ccc(N(=O)=O)cc1
27	56-72-4	036501	O,O-diethyl O-(3-chloro-4-methyl-2-oxo-2H-1-benzopyran-7-yl) ph	C1(C)c2c(cc(OP(=S)(OCC)OCC)cc2)OC(=O)C=1Cl
28	56-86-0	374350	L-glutamic acid	C(=O)(O)C(N)CCC(=O)O
29	56-95-1	045502	Diacetate N,N'-bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraaz	c1(Cl)ccc(NC(=N)NC(NCCCCCCNC(NC(=N)Nc2ccc(Cl)cc2)=N(+).O(-)C(C)=O)=
30	57-06-7	004901	Allyl isothiocyanate	C(=S)=NCC=C
31	57-13-6	085702	Urea	C(N)(N)=O
32	57-24-9	076901	Strychnidin-10-one; Strychnine	C(P+)123c4c(cccc4)N4C(=O)CC5C(P-)(C[P-]6C(=CCO5)CN(C(P+)1C6)CC2)C3
33	57-39-6		aziridine,_1,1',1''-phosphinylidynetris_2-methyl-	C1(C)CN1P(=O)(N1C(C)C1)N1C(C)C1
34	57-50-1	000023	Sucrose; D(+)-sucrose; Saccharose	C[P-]1(CO)(OC[P-]2C[P-](O)C[P-](O)C[P-](O)C[P-](O)C[P-](CO)O2)C[P+](O)C[P-](O)C[
35	57-55-6	068603	1,2-Propanediol; Propylene glycol	C(C)(O)CO
36	57-62-5	006301	Chlortetracycline; Aureomycin	C(N)(=O)C1C(=O)C[P-]2(O)C(O)=C3C(=O)c4c(C[P-](C)(O)C3CC[P-]2C[P+](N(
37	57-74-9	058201	chlordane_,_pur	C12(Cl)C(Cl)(Cl)C(Cl)(C(Cl)=C1Cl)C1C(Cl)C(Cl)CC21
38	57-92-1	006306	Streptomycin A	C[P-]1(O)(C=O)C(P-)(OC[P-]2C[P+](NC)C[P-](O)C[P+](O)C[P+](CO)O2)C[P+](
39	58-08-2	000660	3,7-dihydro-1,3,7-trimethyl-1H-purine-2,6-dione; Caffeine	C1(=O)C2=C(N(C)C(=O)N1C)N=CN2C
40	58-36-6	012601	Phenoxarsine oxide; 10,10'-oxybis-10H-phenoxarsine	c12c(cccc1)Oc1c(cccc1)[As]2O[As]1c2c(cccc2)Oc2c1cccc2
41	58-89-9	009001	Gamma-bhc; Lindane	C[P-]1(Cl)C[P+](Cl)C[P-](Cl)C[P-](Cl)C[P+](Cl)C[P-]1Cl
42	59-50-7	064206	Chlorocresol; 3-methyl-4-chlorophenol	c1(Cl)c(C)ccc(O)cc1
43	59-67-6	056701	Nicotinic acid; Niacin; 3-pyridinecarboxylic acid	C(=O)(O)c1ccccn1

MetaPath - Materials & Methods info for parent chemical



Summary

c1(O)ccccc1



References :

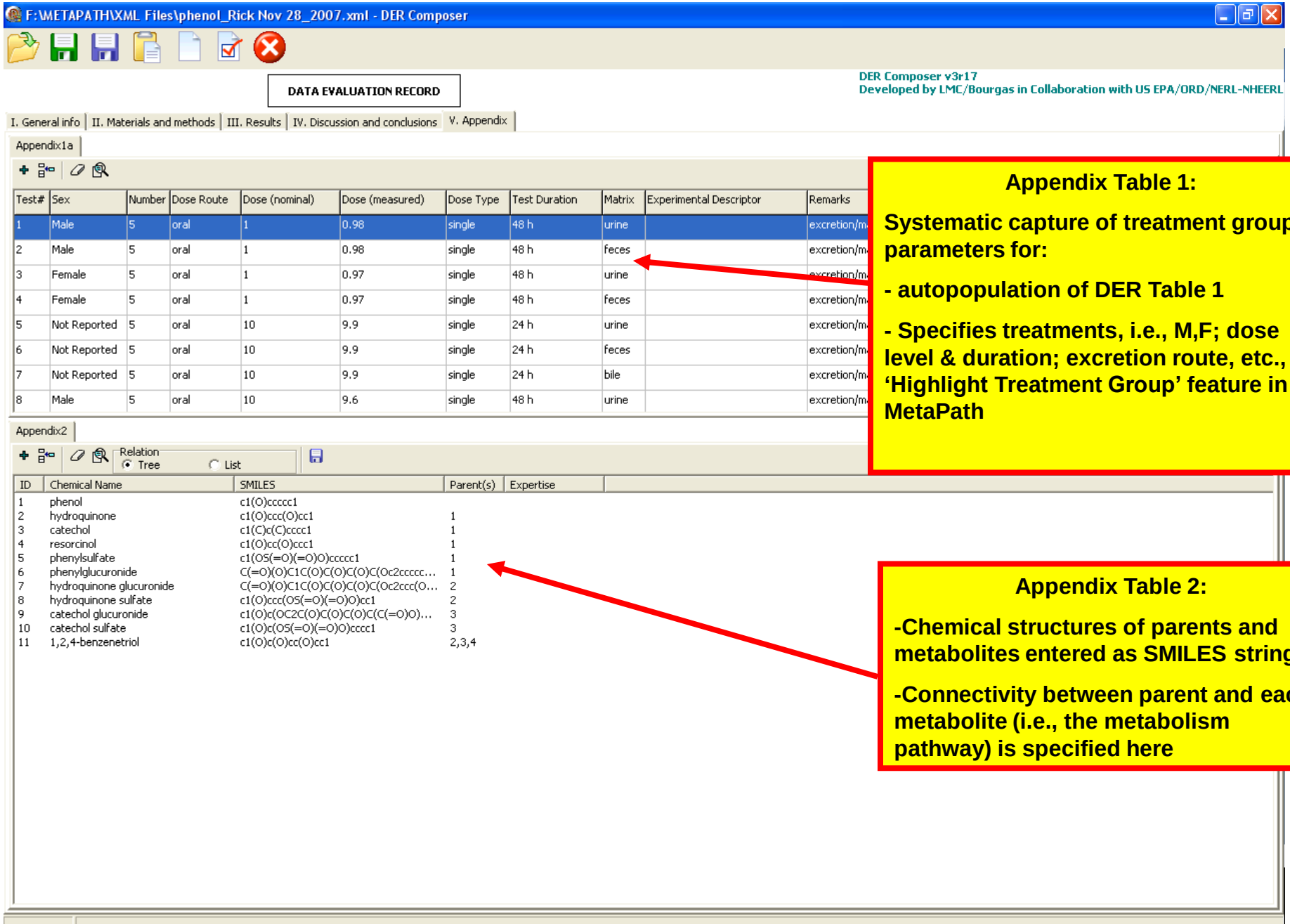
- Kolanczyk, R. (2005). Phenol-ring-UL-14C Rat metabolism. Toxicokinetic behavior and metabolism in the rat. Acme Study No. M 000001, Acme Report No. MR-90000. Acme AG Agrochemical Division, Crop Protection Development, Institute for Metabolism Research and Residue Analysis, 51368 Leverkusen, FRG. December 21, 2005., MRID:12345678

Parent structure:
PC code: 64001
CasNo: 000108-95-2
Chemical name: phenol
Test compound: phenol
IUPAC name: phenol
Batch/Lot# 00002
Purity: 98.5 - 98.5 %
Contaminants: none listed
Description: colorless solid, sweet tarry color

Post Changes

Cancel

DER Composer - Appendix Table 1 & Table 2



Appendix Table 1:

Systematic capture of treatment group parameters for:

- autopopulation of DER Table 1

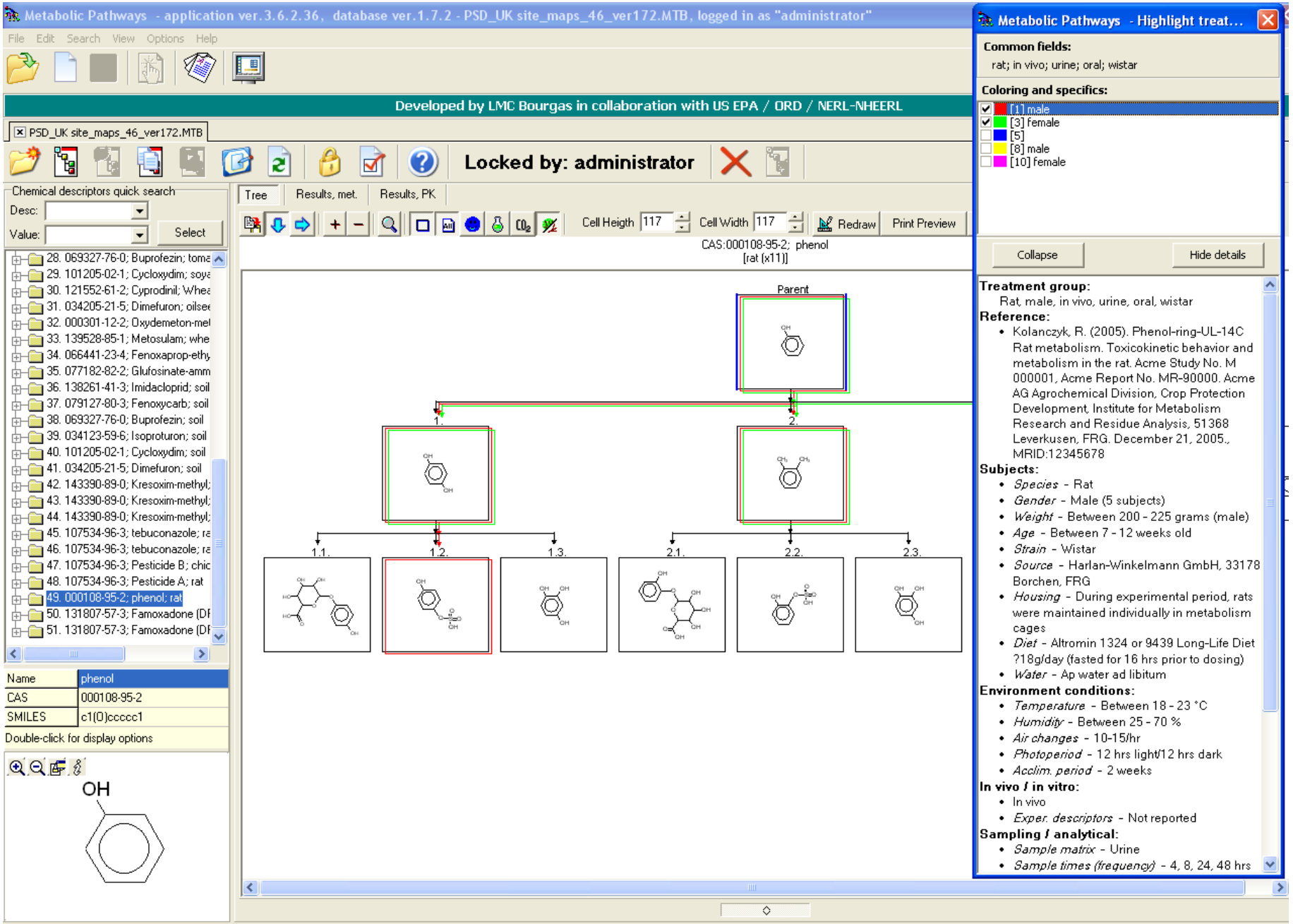
- Specifies treatments, i.e., M,F; dose level & duration; excretion route, etc., as 'Highlight Treatment Group' feature in MetaPath

Appendix Table 2:

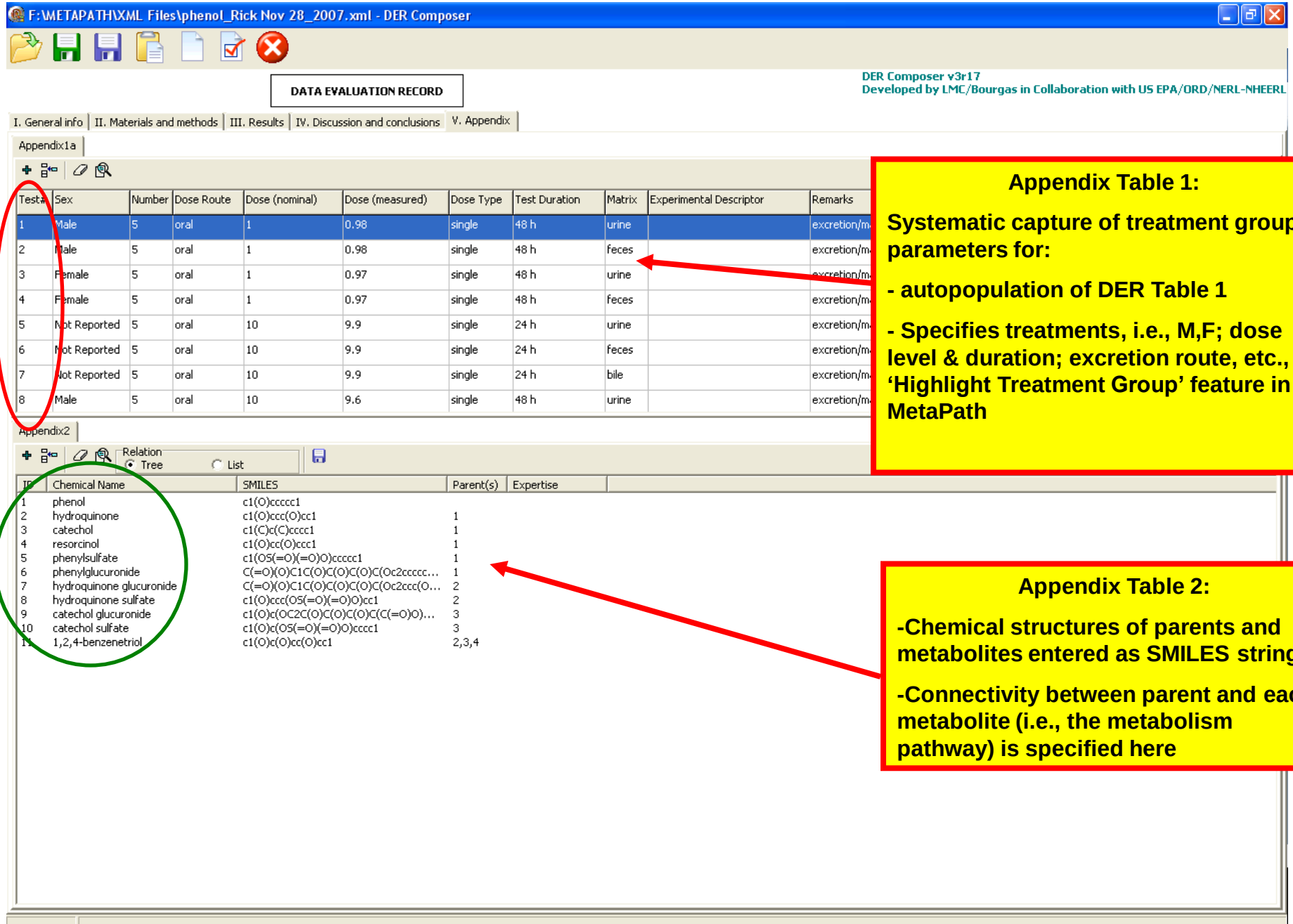
-Chemical structures of parents and metabolites entered as SMILES strings;

-Connectivity between parent and each metabolite (i.e., the metabolism pathway) is specified here

MetaPath - Highlight Treatment Group Feature



DER Composer - Appendix Table 1 & Table 2



Appendix Table 1:

Systematic capture of treatment group parameters for:

- autopopulation of DER Table 1

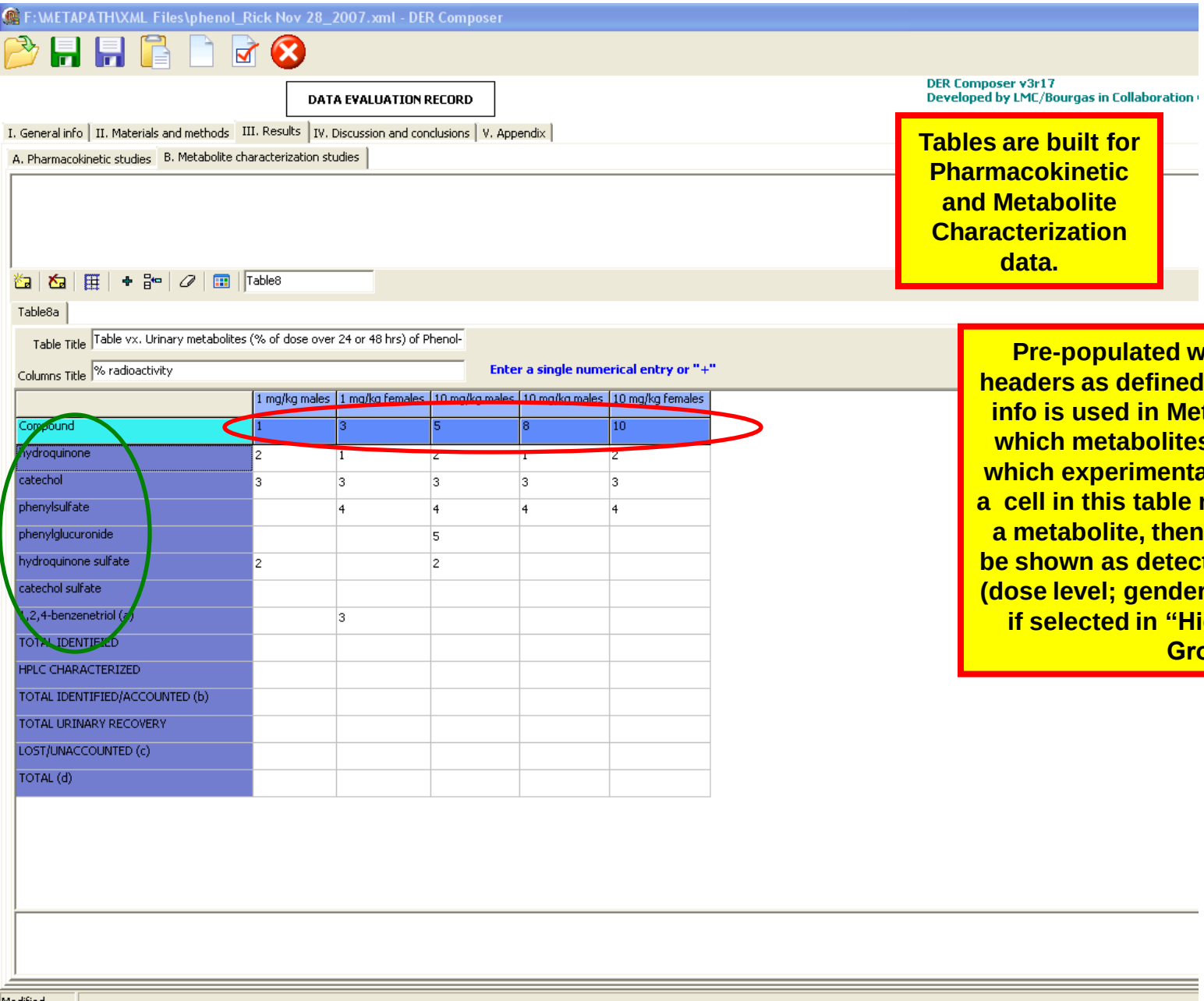
- Specifies treatments, i.e., M,F; dose level & duration; excretion route, etc., as 'Highlight Treatment Group' feature in MetaPath

Appendix Table 2:

-Chemical structures of parents and metabolites entered as SMILES strings;

-Connectivity between parent and each metabolite (i.e., the metabolism pathway) is specified here

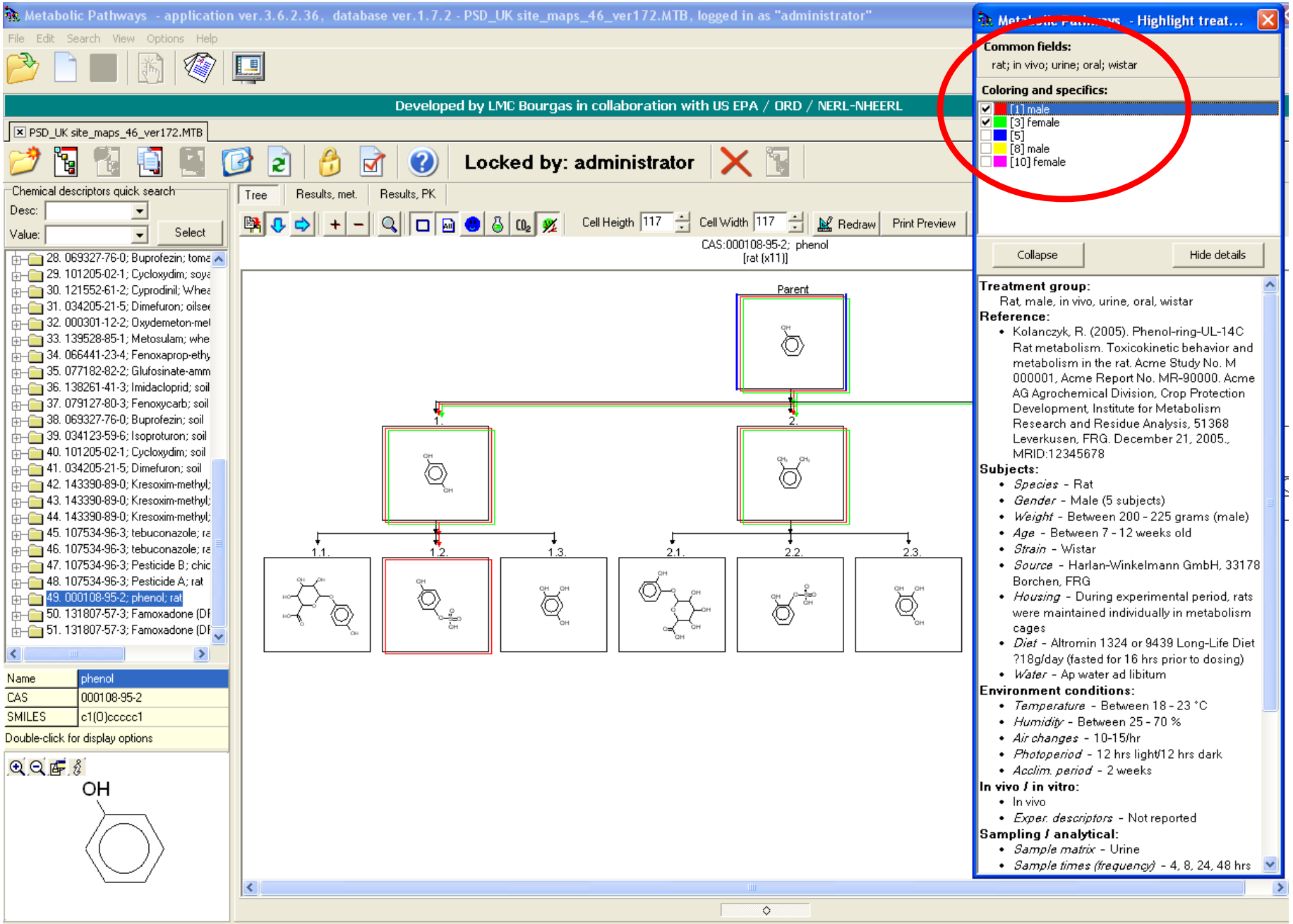
DER Composer - 'Results' – Metabolite Characterization



Tables are built for Pharmacokinetic and Metabolite Characterization data.

Pre-populated with row & column headers as defined in Appendices; this info is used in MetaPath to associate which metabolites were found under which experimental conditions; e.g., if a cell in this table reports a number for a metabolite, then the metabolite will be shown as detected in that treatment (dose level; gender group) in MetaPath if selected in "Highlight Treatment Group"

MetaPath - Highlight Treatment Group Feature



DER Composer – Table (Metabolite Characterization)

F:\METAPATH\XML Files\phenol_Rick Nov 28_2007.xml - DER Composer

DATA EVALUATION RECORD

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

A. Pharmacokinetic studies | B. Metabolite characterization studies

Table8

Table8a

Table Title: Table vx. Urinary metabolites (% of dose over 24 or 48 hrs) of Phenol-

Columns Title: % radioactivity

Enter a single numerical entry or "+"

	1 mg/kg males	1 mg/kg females	10 mg/kg males	10 mg/kg males	10 mg/kg females
Compound	1	3	5	8	10
hydroquinone	2	1	2	1	2
catechol	3	3	3	3	3
phenylsulfate		4	4	4	4
phenylglucuronide			5		
hydroquinone sulfate	2		2		
catechol sulfate					
1,2,4-benzenetriol (a)		3			
TOTAL IDENTIFIED					
HPLC CHARACTERIZED					
TOTAL IDENTIFIED/ACCOUNTED (b)					
TOTAL URINARY RECOVERY					
LOST/UNACCOUNTED (c)					
TOTAL (d)					

MetaPath – Table (Metabolite Characterization)

Metabolic Pathways - application ver.3.6.2.36, database ver.1.7.2 - PSD_UK site_maps_46_ver172.MTB, logged in as "administrator"

File Edit Search View Options Help

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

PSD_UK site_maps_46_ver172.MTB

Locked by: administrator

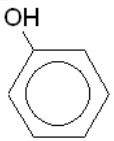
Chemical descriptors quick search

Desc: Value: Select

28. 069327-76-0; Buprofezin; toma
29. 101205-02-1; Cycloxydim; soya
30. 121552-61-2; Cyprodinil; Whea
31. 034205-21-5; Dimefuron; oilsee
32. 000301-12-2; Oxydemeton-mel
33. 139528-85-1; Metosulam; whe
34. 066441-23-4; Fenoxaprop-ethy
35. 077182-82-2; Glufosinate-amm
36. 138261-41-3; Imidacloprid; soil
37. 079127-80-3; Fenoxycarb; soil
38. 069327-76-0; Buprofezin; soil
39. 034123-59-6; Isoproturon; soil
40. 101205-02-1; Cycloxydim; soil
41. 034205-21-5; Dimefuron; soil
42. 143390-89-0; Kresoxim-methyl;
43. 143390-89-0; Kresoxim-methyl;
44. 143390-89-0; Kresoxim-methyl;
45. 107534-96-3; tebuconazole; ra
46. 107534-96-3; tebuconazole; ra
47. 107534-96-3; Pesticide B; chic
48. 107534-96-3; Pesticide A; rat
49. 000108-95-2; phenol; rat
50. 131807-57-3; Famoxadone (DF
51. 131807-57-3; Famoxadone (DF

Name	phenol
CAS	000108-95-2
SMILES	c1(O)ccccc1

Double-click for display options



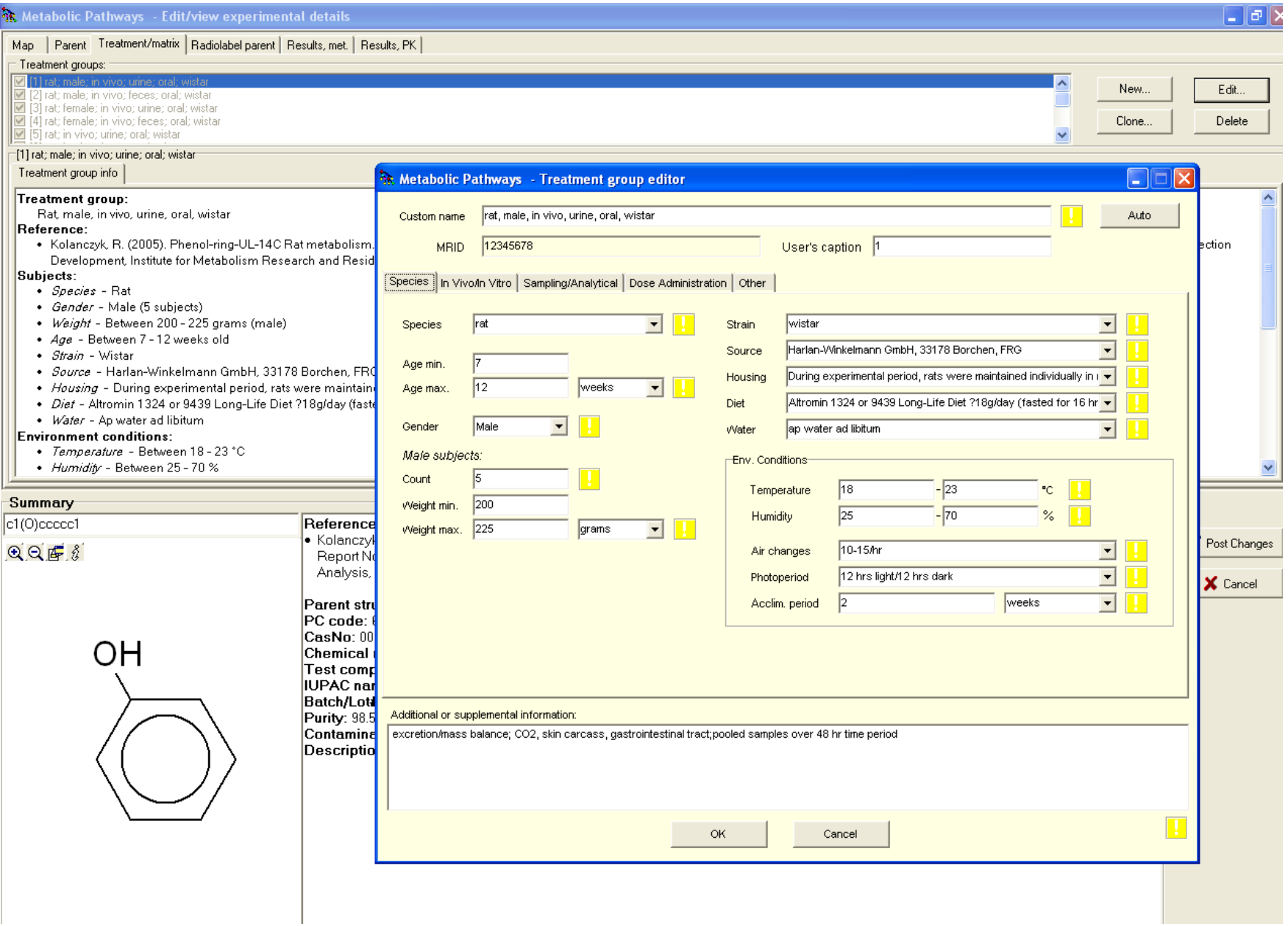
Tree | Results, met. | Results, PK

Table vx. Urinary metabolites (% of dose over 24 or 48 hrs) of Phenol-ring-UL-14C following oral dosing to r

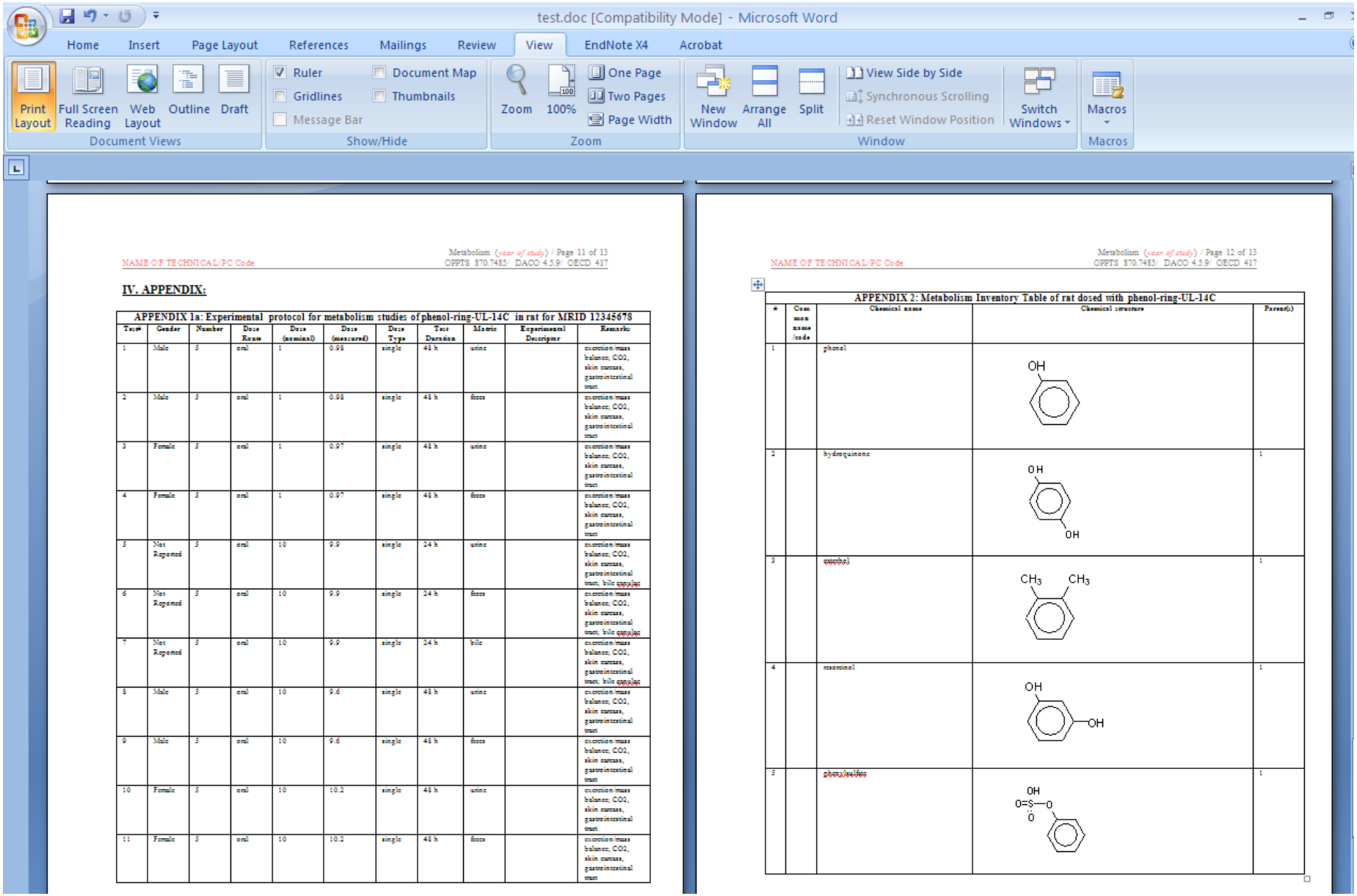
Compound	% radioactivity				
	1 mg/kg		10 mg/kg		
	1	3	5	8	10
hydroquinone	2	1	2	1	2
catechol	3	3	3	3	3
phenylsulfate		4	4	4	4
phenylglucuronide			5		
hydroquinone sulfate	2		2		
catechol sulfate					
1,2,4-benzenetriol (a)		3			
TOTAL IDENTIFIED					
HPLC CHARACTERIZED					
TOTAL IDENTIFIED/ACCOUNTED (b)					
TOTAL URINARY RECOVERY					
LOST/UNACCOUNTED (c)					
TOTAL (d)					

start | Mail - Inbox - IB... | 4 Windows Ex... | 2 Microsoft Of... | DER Composer_... | 3 Micros

MetaPath displays study details for each Treatment Group from Materials & Methods and Appendix 1 of DER Composer



*.doc file output from DER Composer



NAME OF TECHNICAL/PC Code

Metabolism (*year of study*) / Page 11 of 13
OPPTS 870.7485/ DACO 4.5.9/ OECD 417

IV. APPENDIX:

APPENDIX 1a: Experimental protocol for metabolism studies of phenol-ring-UL-14C in rat for MRID 12345678

Test#	Gender	Number	Dose Route	Dose (nominal)	Dose (measured)	Dose Type	Test Duration	Matrix	Experimental Descriptor	Remarks
1	Male	5	oral	1	0.98	single	48 h	urine		excretion/mass balance; CO2, skin excess, gastrointestinal tract
2	Male	5	oral	1	0.98	single	48 h	feces		excretion/mass balance; CO2, skin excess, gastrointestinal tract
3	Female	5	oral	1	0.97	single	48 h	urine		excretion/mass balance; CO2, skin excess, gastrointestinal tract
4	Female	5	oral	1	0.97	single	48 h	feces		excretion/mass balance; CO2, skin excess, gastrointestinal tract
5	Not Reported	5	oral	10	9.9	single	24 h	urine		excretion/mass balance; CO2, skin excess, gastrointestinal tract; bile cannulae
6	Not Reported	5	oral	10	9.9	single	24 h	feces		excretion/mass balance; CO2, skin excess, gastrointestinal tract; bile cannulae
7	Not Reported	5	oral	10	9.9	single	24 h	bile		excretion/mass balance; CO2, skin excess, gastrointestinal tract; bile cannulae
8	Male	5	oral	10	9.6	single	48 h	urine		excretion/mass balance; CO2, skin excess, gastrointestinal tract
9	Male	5	oral	10	9.6	single	48 h	feces		excretion/mass balance; CO2, skin excess, gastrointestinal tract
10	Female	5	oral	10	10.2	single	48 h	urine		excretion/mass balance; CO2, skin excess, gastrointestinal tract
11	Female	5	oral	10	10.2	single	48 h	feces		excretion/mass balance; CO2, skin excess, gastrointestinal tract

NAME OF TECHNICAL/PC Code

Metabolism (*year of study*) / Page 12 of 13
OPPTS 870.7485/ DACO 4.5.9/ OECD 417

APPENDIX 2: Metabolism Inventory Table of rat dosed with phenol-ring-UL-14C

*	Common name /code	Chemical name	Chemical structure	Parent(s)
1		phenol		
2		hydroquinone		1
3		cresol		1
4		resorcinol		1
5		phenylsulfate		1

DATA EVALUATION RECORD

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

A. Materials | B. Study design and methods

'Materials and Methods' tab Part B: Study Design and methods.

Table1a | Table1b

Treatment Group	Dose (nominal)	Dose (measured)	Number	Sex	Remarks
1	1	0.8	4	Male	feces,urine; oral; single; 72
7	1	1.1	4	Male	feces,urine; oral; single; 48
3	1	1.06	4	Female	feces,urine; oral; single; 48
4	100	49	4	Male	feces,urine; oral; single; 48
11	100	99	4	Female	feces,urine; oral; single; 48
10	1	0.94	4	Male	feces,urine; oral; multiple; 48
12	1	0.98	4	Female	feces,urine; oral; multiple; 48
9	1	0.84	6	Male	bile,feces,urine; oral; single; 24

From Appendix 1 - Auto-population of DER Table 1 Group Arrangements

2. Dosing and sample collection

Text box for narrative

Table2a | Table2b

Treatment Group	Matrix	Sampl	Major Method	Conjugate Analysis	Analytical	Analytical Detecti	Remarks
10a,11a,12a,1a,3a,4a,6a,7a,9a	urine	48 hr	none	glucuronidase and sulfatase	HPLC	MS/MS	test 2 samples p
10b,11b,12b,1b,3b,4b,6b,7b,9b	feces	48 hr	ACN/water extraction		HPLC	MS/MS	pooled samples
6c,9c	bile	24 hr	lyophilized/water recon		HPLC	NMR and LC/MS	

Analytical method details can be captured as text, or more systematically in a Table.

C:\Data\Chemicals to be coded\Completed XML's\028869_Fluoxastrobin_mock-up_presentation.xml - DER Composer

DATA EVALUATION RECORD

DER Composer v3r13

. General info | II. Materials and methods | III. Results | IV. Discussion and conclusions | V. Appendix

A. INVESTIGATORS' CONCLUSIONS:

Experiments (MRID 999999999) were conducted to determine the metabolism and distribution of [methoxyimi
100 mg/kg) and multiple (1 mg/kg/day for 14 days) oral doses. Biliary excretion experiments were also conduc
metabolite profiles were assessed for each treatment protocol. An autoradiography study (MRID 888888888)
following a single 3 mg/kg gavage dose. Recovery of administered radioactivity was 91.1-106.6%. The invest
air was inconsequential (0.02%) thereby affirming stability of the molecule. The major route of excretion was
fecal excretion representing 70.4-90.1% of the single low dose, single high dose, and 14-day repeated low d
Excretion was complete (99.3%) within 48 hours following dosing. Tissue/body burdens of radioactivity were
Results of the autoradiography experiments confirmed the rapid absorption and minimal tissue burdens. The s
metabolites in tissue and organs. Slight variations in plasma radioactivity were considered indicative of limited

B. REVIEWER COMMENTS:

Mass balance for administered radioactivity in all experiments was excellent (91-107%). Based on excretion p
0.4-1.4 hrs for the low dose and 5.4-8.0 hrs for the high-dose groups) following single or multiple low (1 mg/k
absorption was somewhat limited as shown by an AUC of 54.10 - 61.30 g/mL hr vs. 1.18 - 1.52 g/mL hr for th
low-dose groups. Plasma elimination was biphasic with an initial phase at 0.7-3.5 hrs for the single and multiple low dose groups and 2.3-4.1 hrs for the high-dose groups. A secondary phase occurred at 10
and 7 hours for the low- and high-dose groups, respectively. Urinary excretion was essentially complete (>90%) at 24 hours postdose and the majority of fecal excretion of radioactivity occurred within 24
hours. Plasma concentration-time plots were suggestive of enterohepatic circulation but this was minimal and still allowed for relatively rapid and complete excretion of administered radioactivity. The major
route of excretion was via the bile and subsequently the feces. In rats without bile cannulae, fecal excretion accounted for 70.4-84.7% of the administered low dose over 48 hours. In high-dose groups, fecal
excretion was slightly higher (86.4-91.1%) with much of the fecal radioactivity (43-54% of administered dose) attributed to parent compound due to saturated absorption. In rats with bile cannulae, biliary
excretion represented 87.4% of the dose and fecal excretion was correspondingly lower (10.6%). Urinary excretion accounted for 16.9-20.2% of the administered low dose and 11.0-14.9% of the high
dose. Repeated dosing did not affect excretion profiles and there was no biologically relevant gender-related variability. Elimination via expired air was inconsequential (0.02%). Tissue/organ/carcass burdens

C. STUDY DEFICIENCIES:

There appears to be an inconsistency in the absorption t1/2 values for Groups 3, 4, and 11 (Table 6 of this Date Evaluation Record) relative to the plasma concentration-time data (Table 3 of this Data Evaluation Record). Specifically, the plasma concentration-time data (Table 3) would appear to suggest absorption half-times of approximately or greater than 0.1, 0.6 and 0.6 hrs for Groups 3 (1 mg/kg), 4 (100 mg/kg), and 11 (100 mg/kg), respectively, rather than the reported values of 0.01, 0.07 and 0.07 hrs. Although this discrepancy does not compromise the validity of the studies, it is a curious anomaly that may be a function of the software generated values for the kinetic parameters or simply a misplaced decimal point. The reviewer would request clarification from the investigators/registrant. There were no other apparent deficiencies in the design, conduct, or reporting of these studies.

Text boxes are included for addition of explanatory information as typically found in DERs

A.) filled in by registrant

B.) & C). Filled in later by OPP to summarize their assessment

This information is captured in DER (*.doc file) but not in MetaPath

DER Composers

- This presentation uses examples from DER Composers for livestock or rat metabolism with the corresponding MetaPath database.

- DER Composers will be used for EDSP T1S data submission with data going to EDSP databases

Designing Computational Tools:

Metabolism Pathways (MetaPath) Expert System for Pesticide Registrant Submitted Health & Ecological Effects Data

Partnership between EPA, Office of Pesticide Programs (OPP) and EPA, ORD, NHEERL & NERL, PMRA Health Canada:

NHEERL, MED - Duluth, MN
P. Schmieder, R. Kolanczyk

NERL, ERD - Athens, GA
J. Jones

Cooperative Agreement with:
Laboratory of Mathematical Chemistry (LMC) , Bourgas University, Bourgas, Bulgaria
O. Mekenyan

OPP, Health Effects Division (HED):
M. Manibusan, C. Olinger, R. Kent

OPP - Residues Of Concern Knowledge-bases Sub-committee (ROCKS)

PMRA, Health Canada:
L. Croteau, M. Gerrits

Ask Tom Steeger
for demonstration of
DER Composer
software

THANKS!