Designing Computational Tools for OPPTS: Metabolite Database and Information Support System for Pesticide Registrant Submitted Health & Ecological Effects Data

Partnership between EPA Office of Pesticide Programs (OPP) and
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OPP, Environmental Fate and Effects Division (EFED):
M. Shamim

OPP - Residues Of Concern Knowledgebased Sub-committee (ROCKS)

MetaPath
Internationally Harmonized Platform

"MetaPath …. has been identified as the harmonized platform that can be used in an OPP-**EFSA (European Food Safety Agency)** project to workshare data encoding efforts and future development of (metabolism) decision-support systems."

Steve Bradbury
OPP Deputy Director of Programs

Health Canada – Pest Management Regulatory Agency (PMRA)

Invitation:

MetaPath seminar
hands-on training session on it's capabilities

Computational Tools for Metabolism Research and Risk Assessment

MetaPath

a metabolism pathways expert system

DER Composer

a software template for efficient data entry to create:

- OPP metabolism studies Data Evaluation Records (DER) and
- auto-population of MetaPath

Metabolism Simulator

use observed metabolite occurrence data from MetaPath and knowledge of biotransformation reaction types to simulate metabolism pathways

Metabolism Computational Tools
MetaPath addresses OPP needs in 3 ways:

1) Repository of data:
   rat *in vivo* metabolism (pathways and metadata)
   residues in plants and livestock
   environmental degradates in water, soil, air

2) Answers Risk Assessment questions:
   OPP - Residues Of Concern Knowledgebased Sub-committee (ROCKS)
   Are any of the metabolites (direct formation), residues (in food), and/or degradates (in drinking water) formed of toxicological concern?

3) Provides knowledge-base for predictions:
   systematic data for building metabolism simulator –

MetaPath - Data Repository

[Guideline 870.7485; OECD 417]

- Metabolic maps (pathways) from rats, plants, livestock, and environmental degradates
- Chemical structures of parents and metabolites.
- Associated (metadata) coded to:
  - Assign metabolites formed to treatment groups (gender; dose level; exposure route; exposure time)
  - species (e.g., rat vs. chicken vs. corn vs. wheat)
  - analytical methods used for metabolite id (e.g., first generation analytical techniques (TLC) vs. more sophisticated separation and detection (HPLC-MS detection)
- 'Residues' definitions, lists metabolites included in the tolerance
- Tabulates metabolite, residue amounts and other parameters of interest

MetaPath - OPP Risk Assessment Questions

- Have we seen this metabolite before? Where? How often? Under what test conditions?
  - Structure searches for types of compounds: (e.g. all conazoles)
- Have we seen this toxicophore before? Where? How often?
  - Substructure search
- How many pesticides of X chemical class have we assessed? Are there common metabolites of concern?
- What species, gender, dose differences do we see (e.g. metabolites found in rat but not chicken; peanut but not wheat; M but not F; low dose but not high dose, etc)?
- Based on data from similar parent chemicals, was an expected metabolite not found (e.g., potentially due to different test conditions, or analytical method used for isolation, separation, identification, etc)?
- What concerns have we noted in the past for similar chemicals? Are we using consistent rationale for decision making? Is there new evidence? (potentially can help retain institutional memory)

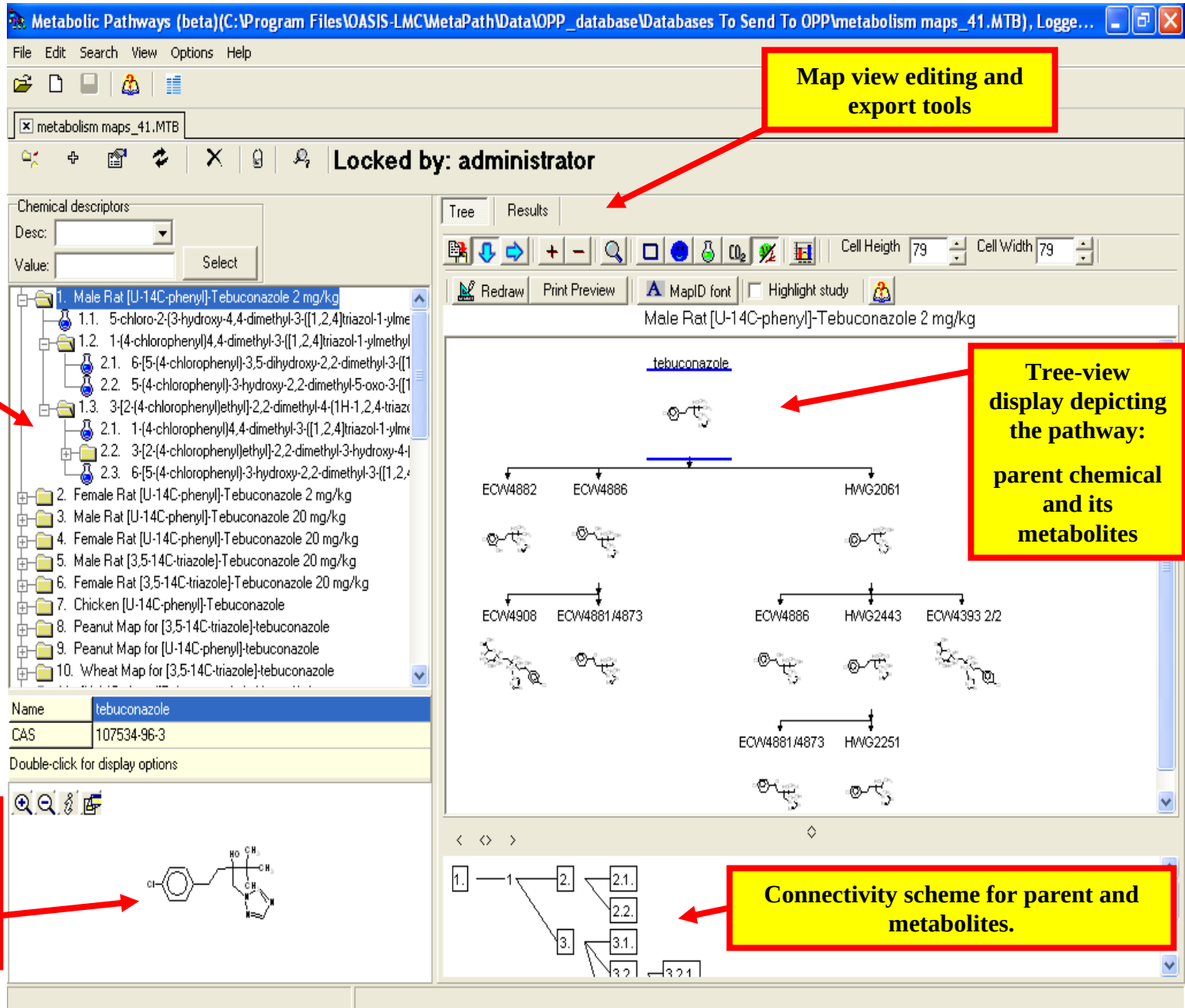
MetaPath - Knowledge-base for Predictions for Risk Assessment and Research

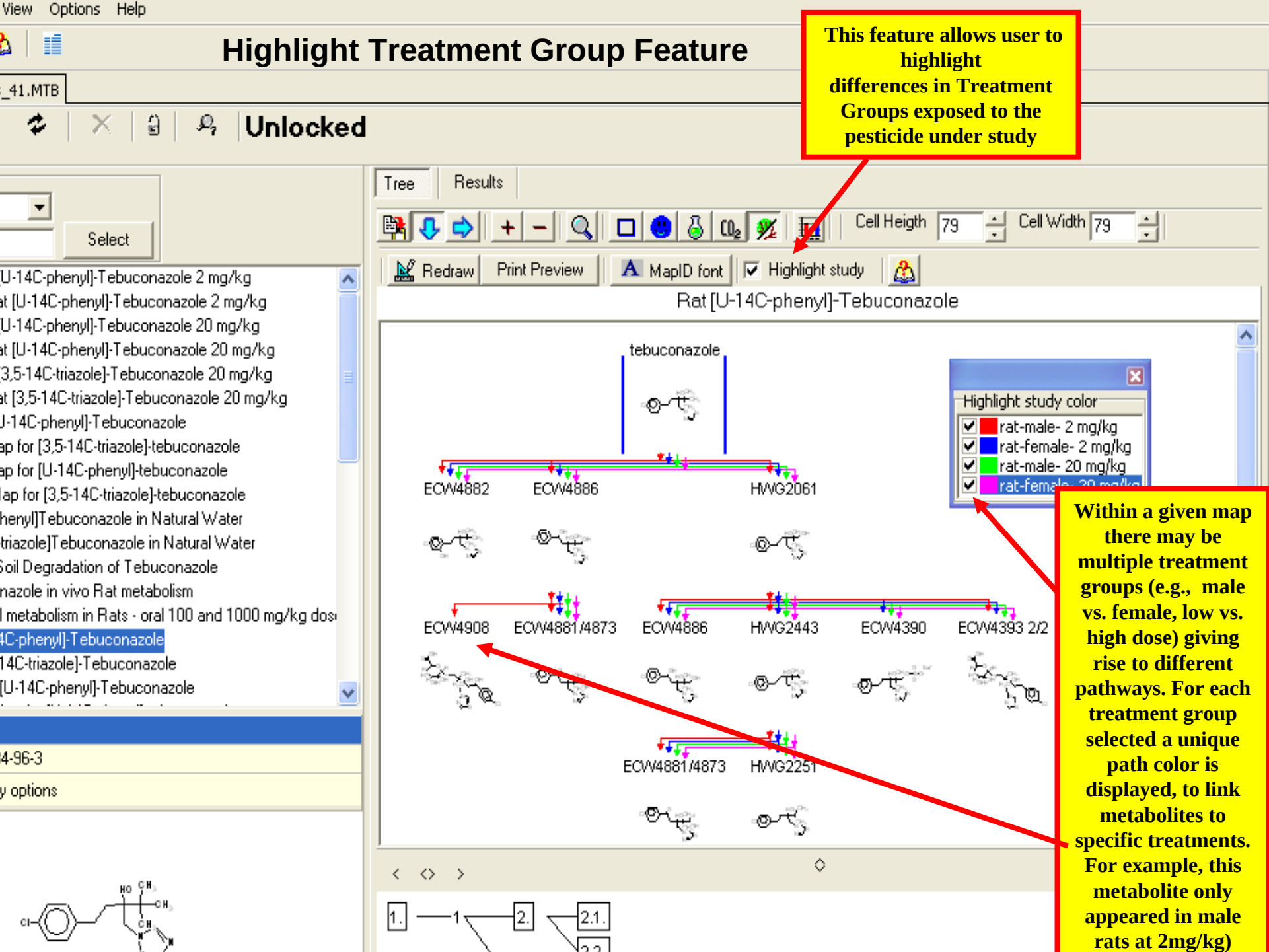
- Provides database of experimentally-determined metabolic pathways, all collected under the same guidelines, to be used for metabolism research and development of a metabolism simulator

- Are there metabolites of concern that might not have been measured – due to radiolabel used, analytical method, experimental condition, etc?

- How likely is it that transient toxic intermediates were formed? What are they?

General METAPATH Display Overview.




View Options Help
Highlight Treatment Group Feature
This feature allows user to highlight differences in Treatment Groups exposed to the pesticide under study
_41.MTB
Unlocked
Select
U-14C-phenyl]-Tebuconazole 2 mg/kg
t [U-14C-phenyl]-Tebuconazole 2 mg/kg
U-14C-phenyl]-Tebuconazole 20 mg/kg
t [U-14C-phenyl]-Tebuconazole 20 mg/kg
3,5-14C-triazole]-Tebuconazole 20 mg/kg
t [3,5-14C-triazole]-Tebuconazole 20 mg/kg
J-14C-phenyl]-Tebuconazole
ap for [3,5-14C-triazole]-tebuconazole
ap for [U-14C-phenyl]-tebuconazole
lap for [3,5-14C-triazole]-tebuconazole
henyl]Tebuconazole in Natural Water
triazole]Tebuconazole in Natural Water
Soil Degradation of Tebuconazole
nazole in vivo Rat metabolism
l metabolism in Rats - oral 100 and 1000 mg/kg dos
4C-phenyl]-Tebuconazole
14C-triazole]-Tebuconazole
[U-14C-phenyl]-Tebuconazole
4-96-3
y options
Tree
Results
Cell Heigth 79
Cell Width 79
Redraw
Print Preview
MapID font
Highlight study
Rat [U-14C-phenyl]-Tebuconazole
tebuconazole
ECW4882
ECW4886
HWG2061
ECW4908
ECW4881/4873
ECW4886
HWG2443
ECW4390
ECW4393 2/2
ECW4881/4873
HWG2251
Highlight study color
rat-male- 2 mg/kg
rat-female- 2 mg/kg
rat-male- 20 mg/kg
Within a given map there may be multiple treatment groups (e.g., male vs. female, low vs. high dose) giving rise to different pathways. For each treatment group selected a unique path color is displayed, to link metabolites to specific treatments. For example, this metabolite only appeared in male rats at 2mg/kg)
1.
1
2.
2.1.

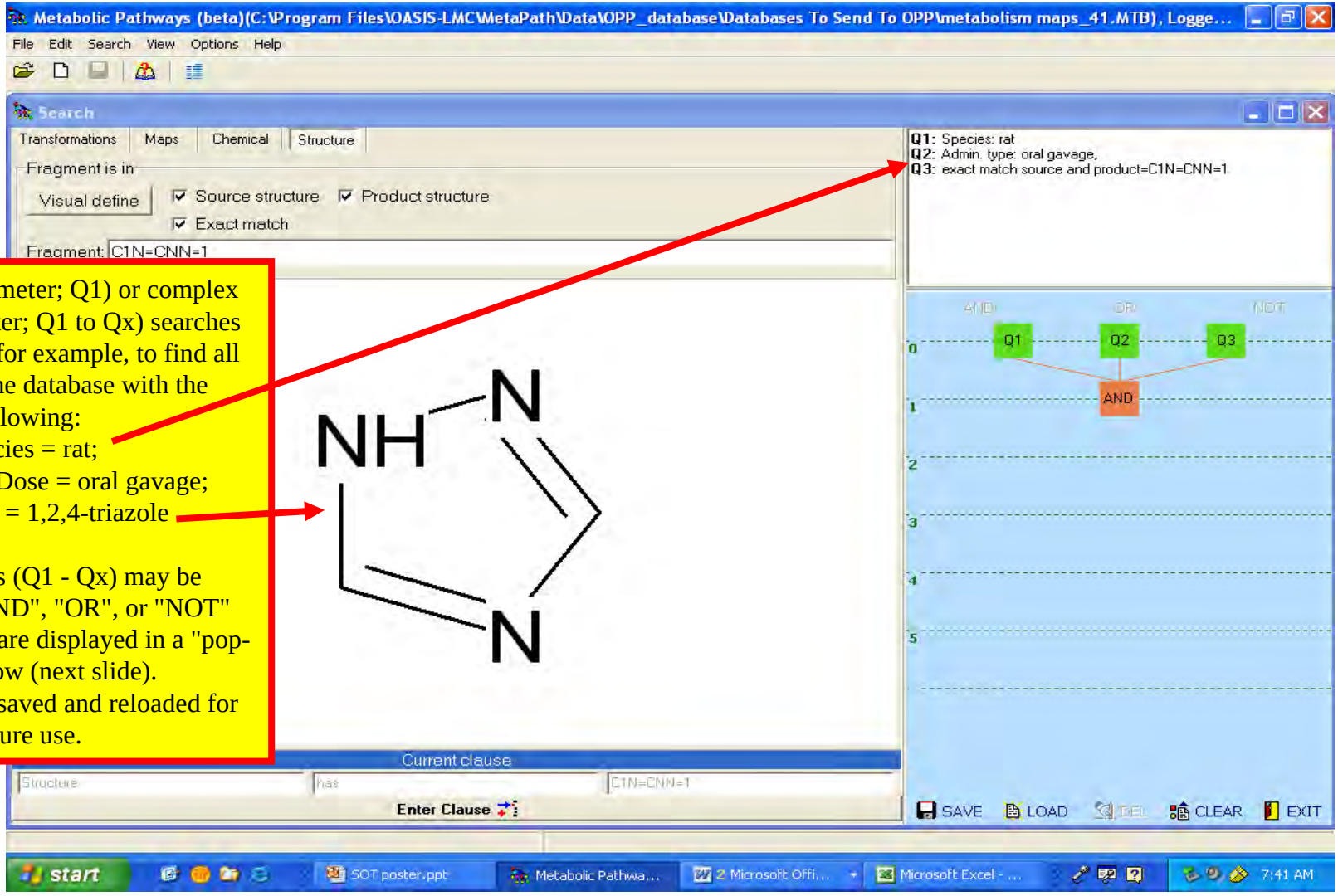
Similarity Searching: Setting up a Query (Q)

The database can be searched by building Queries (Q)

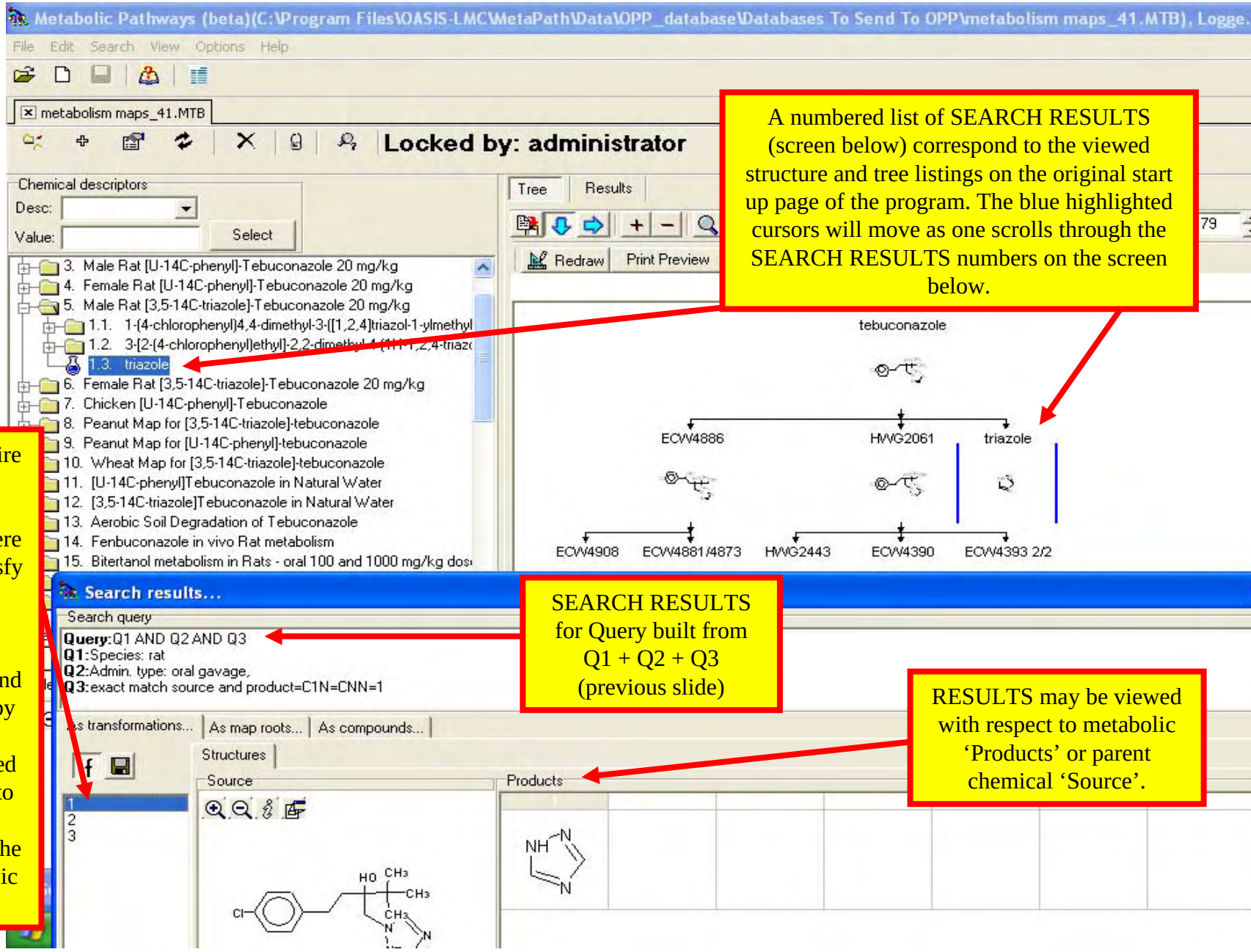
by structure or sub-structure, species, dose administration, etc.

Simple (one parameter; Q1) or complex (multiple parameter; Q1 to Qx) searches can be designed, for example, to find all chemicals in the database with the following:
Species = rat;
Administered Dose = oral gavage;
Metabolite = 1,2,4-triazole

Search clauses (Q1 - Qx) may be combined as "AND", "OR", or "NOT" and search results are displayed in a "pop-up" window (next slide).
Searches can be saved and reloaded for future use.



Similarity Searching: Display of SEARCH RESULTS



A numbered list of SEARCH RESULTS (screen below) correspond to the viewed structure and tree listings on the original start up page of the program. The blue highlighted cursors will move as one scrolls through the SEARCH RESULTS numbers on the screen below.

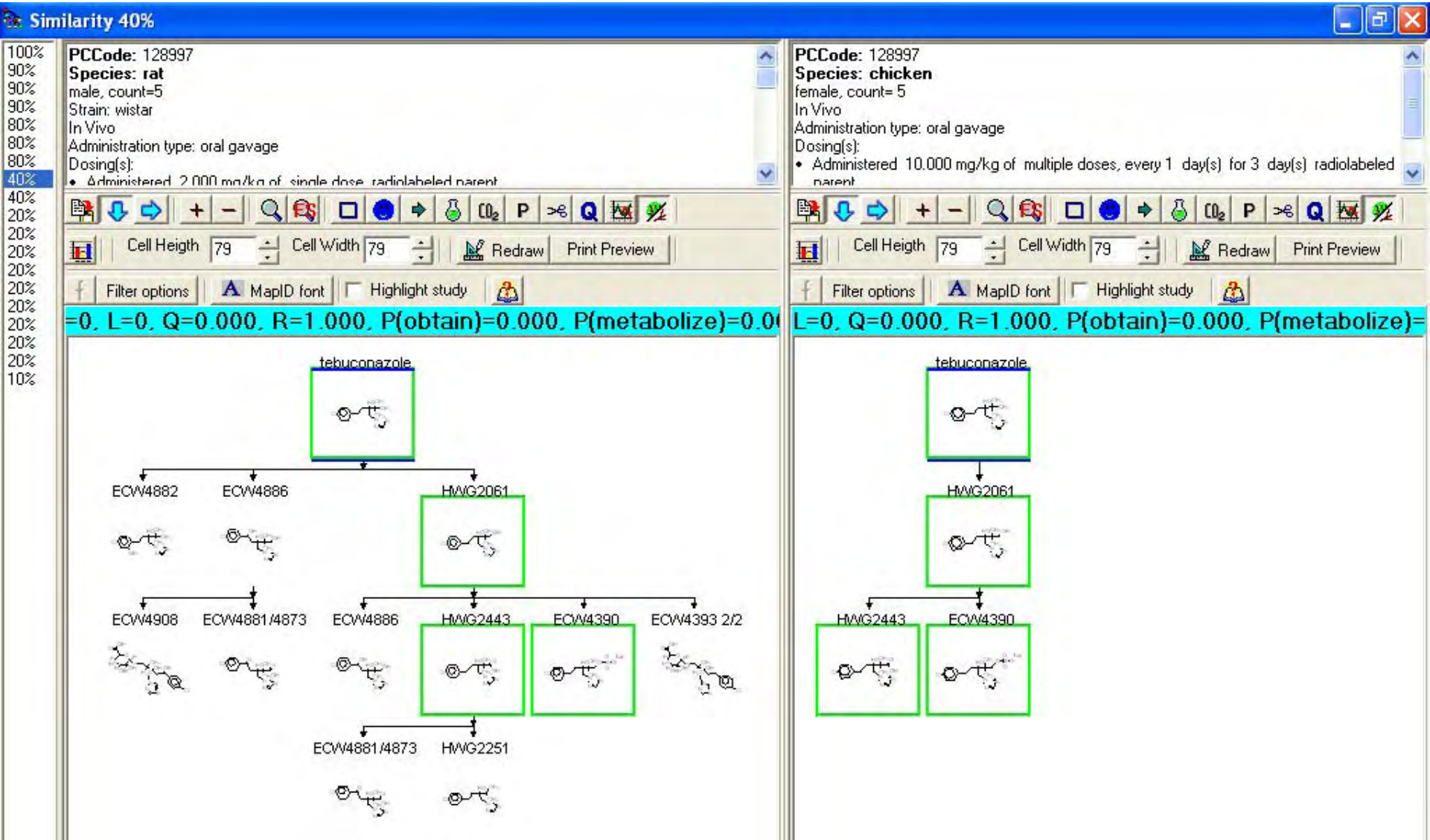
Within the entire database of maps, 3 metabolites were found that satisfy the search criteria, i.e., a triazole metabolite found in rats dosed by oral gavage. Info is provided to trace back to the parent chemical and the entire metabolic pathway.

SEARCH RESULTS for Query built from Q1 + Q2 + Q3 (previous slide)

RESULTS may be viewed with respect to metabolic 'Products' or parent chemical 'Source'.

Map Comparisons – One selected map is compared to another, or to all others within a database.

Example: All 3 metabolites found in chickens exposed to tebuconazole (right screen – green boxes) are found in rats (left screen- green boxes), however, many more metabolites are found in the rat that do not occur in chicken (left screen – no boxes).



Bioassay information associated with the study for a given chemical/map may be displayed as RESULTS tables for user interpretation, or selected for export and printing.

etabolic Pathways (beta)(C:\Program Files\OASIS-LMC\MetaPath\Data\OPP_database\Databases To Send To OPP\metabolism maps_41.MTB), Logge...

Edit Search View Options Help

metabolism maps_41.MTB

Unlocked

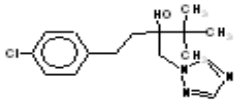
mical descriptors

Select

1. Male Rat [U-14C-phenyl]-Tebuconazole 2 mg/kg
2. Female Rat [U-14C-phenyl]-Tebuconazole 2 mg/kg
3. Male Rat [U-14C-phenyl]-Tebuconazole 20 mg/kg
4. Female Rat [U-14C-phenyl]-Tebuconazole 20 mg/kg
5. Male Rat [3,5-14C-triazole]-Tebuconazole 20 mg/kg
6. Female Rat [3,5-14C-triazole]-Tebuconazole 20 mg/kg
7. Chicken [U-14C-phenyl]-Tebuconazole
8. Peanut Map for [3,5-14C-triazole]-tebuconazole
9. Peanut Map for [U-14C-phenyl]-tebuconazole
10. Wheat Map for [3,5-14C-triazole]-tebuconazole
11. [U-14C-phenyl]Tebuconazole in Natural Water
12. [3,5-14C-triazole]Tebuconazole in Natural Water
13. Aerobic Soil Degradation of Tebuconazole
14. Fenbuconazole in vivo Rat metabolism
15. Bitertanol metabolism in Rats - oral 100 and 1000 mg/kg dos
16. Rat [U-14C-phenyl]-Tebuconazole
17. Rat [3,5-14C-triazole]-Tebuconazole
18. Chicken [U-14C-phenyl]-Tebuconazole

107534-96-3

e-click for display options



Tree | Results

Table 2: Distribution of metabolites in excretia of female rats following a single dose of 2 mg/kg [U-14C-phenyl]-Tebucona
72 hours

[U-14C-phenyl]-Tebuconazole (2 MG/KG) Female Rat Metabolism (%)

	Urine - Female 2 mg/kg	Feces - Female 2 mg/kg	Total Excretia - Female 2
HWG 2443	13.20	25.00	38.20
ECW 4393 2/2	5.10	No data	5.10
ECW 4390	2.10	No data	2.10
HWG 2061	0.30	19.60	19.90
ECW 4873	1.10	0.10	1.20
ECW 4908	0.00	No data	0.00
triazole	No data	No data	No data
ECW 4886	No data	0.50	0.50
ECW 4882	No data	3.30	3.30
HWG 2251	No data	0.70	0.70
tebuconazole	No data	0.60	0.60
not identified	13.60	10.30	23.90

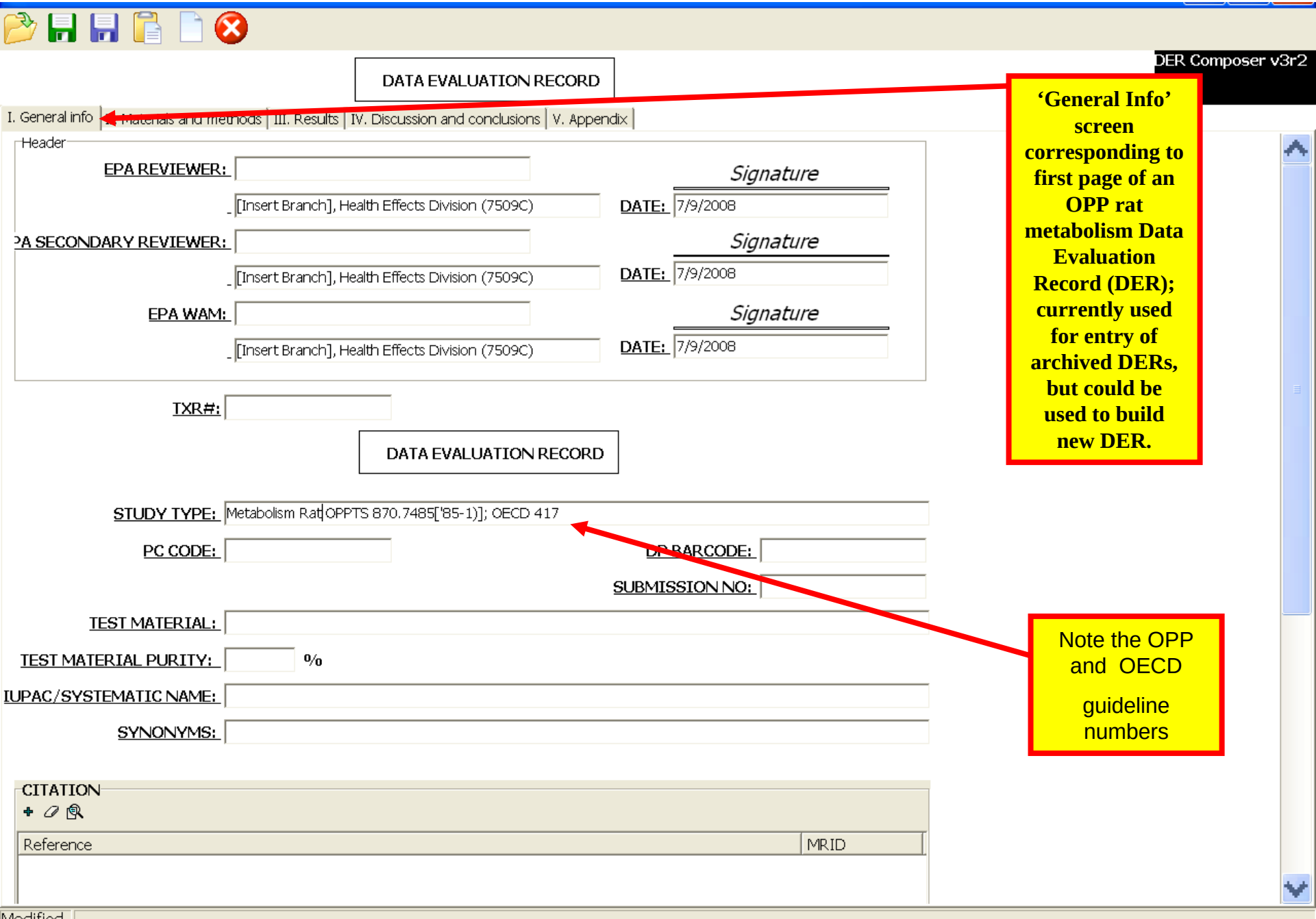
Table 3: Administered radioactivity from [U-14C-phenyl]-tebuconazole in excretia [%]
Total Radio-label Recovered in Rat Excretia After 72 Hours(%)

	Males	Females
Urine	16.00	29.00
Feces	79.00	65.00
Total Excretia	95.00	94.00

DER Composer :
System for Auto-population of **MetaPath**

- Data is captured in DER Composer and saved as both:
  - XML file for automatic population of METAPATH
  - *.doc file for submission of draft DER to OPP
- Efficient standardized data entry
  - QA protocols and checklists
- Allows easy updating of MetaPath into the future

screen shots from ‘DER Composer’ software



‘General Info’ screen corresponding to first page of an OPP rat metabolism Data Evaluation Record (DER); currently used for entry of archived DERs, but could be used to build new DER.

Note the OPP and OECD guideline numbers

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

DATA EVALUATION RECORD

DER Composer v3r13

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

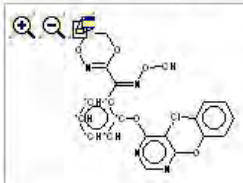
Radiolabelled test material: [methoxyiminotolyl-ring-UL-14C] Fluoxastrobin

Radiolabelled purity: 98 %

Specific activity: 153 uCi/mmole

Lot/batch #: 11675/1 (test 1; MRID 999

Structure:



Non-Radiolabelled test material

Non-Radiolabelled test material: Fluoxastrobin, E-isomer

Description: colorless crystals

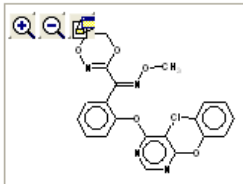
Lot/batch #: M00358 (MRID 99999999; M

Purity: 98.8 %

Contaminants: none noted for either test article

CAS # of TGAI: 193740-76-0

Structure:



2. Vehicle and/or positive control

Methoxyiminotolyl-ring-UL-14C] Fluoxastrobin was suspended in 0.5% Tragacanth solution. No positive controls were utilized in any of t

3. Test animals

Species: rat

Strain: Wistar Hsd/Cob:Wu

'Materials and Methods' tab, Part A: Materials.

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

C:\Program Files\OASIS-LMC\MetaPath\DER XML templates_viewer\fluoxastrobin...

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

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

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

This information is captured in table format similar to what is found in the DER.

2. Dosing and sample collection

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

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.

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DATA EVALUATION RECORD

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

A. Pharmacokinetic studies | B. Metabolite characterization studies

1. Urine: Following enzymatic cleavage, seven urinary metabolites were identified (one tentatively). The quantitation of these components from eight of the test groups is summarized in Table 7. None of the metabolites represented more than -5.2% of the administered dose. For most of the treatment groups, Metabolite 14 was the most prevalent metabolite accounting for greater than 4% of the administered dose in all groups except the single high-dose males (Test 4), and the bile cannulated rats (Test 9). The urinary metabolites were primarily the result of cleavage between the second and third rings of the parent compound (Metabolite 18) and between the first and second rings (Metabolite 13). The urinary metabolite profiles of the various test groups did not appear to exhibit significant quantitative or qualitative. differences. Similarly, there was no notable gender-related variability.

Table8

Table8a | Table8b | Table8c

Table Title: TABLE.8. Fecal metabolites (%of dose over 24-48 hrs) of [methoxyimir

Columns Title: Fecal metabolites

Enter a single numerical entry or "+"

	Male 1 mg/kg	Male 1 mg/kg	FeMale 1 mg/kg	Male 1000 mg/kg	Female 1000 mg/kg	Male 1 mg/kg multiple	Female 1 mg/kg multiple
Fecal metabolite	1b	7b	3b	4b	11b	10b	12b
Parent	6.3	1.7	2.5	53.1	43.0	7.1	7.5
Metabolite 1	11.5	9.6	10.7	5.4	6.7	6.7	8.8
Metabolite 2	0.8		0.3		0.3	0.3	0.2
Metabolite 7	1.8	0.7	0.4	0.4	0.1	0.7	0.7
Metabolite 10	12.9	6.5	6.3	4.7	2.4	5.3	4.7
Metabolite 13	2.1	1.2	1.2	0.9	0.3	0.8	0.8
Metabolite 14 (isomer 1)	0.6	3.2	1.3	0.6	1.7	2.6	2.6
Metabolite 14 (isomer 2)	5.4	12.7	11.7	5.4	12.1	8.8	13.0
Metabolite 15 (isomer 1)	0.2	3.6	0.8	0.7	5.1	8.1	2.0
Metabolite 15 (isomer 2)	2.2	12.1	8.3	0.6	1.7	2.6	10.7
Metabolite17	1.3	0.6	0.6	1.0	0.2	0.8	0.4
Metabolite 18	3.5	2.8	3.0	1.6	3.7	2.3	4.5
Metabolite 19	1.1	0.9	0.8	0.5	0.7	0.6	0.9
Metabolite 22	1.1	0.7	0.95	0.4	0.4	0.65	0.65
Metabolite 23	1.0	0.4	0.3	0.3	0.1	1.3	1.3
Total identified	58.2	60.3	53.1	81.9	78.6	52.6	60.5
HPLC characterized	15.2	14.2	12.1	2.1	5.6	12.3	13.5
Exhaustive extraction	2.1	2.4	1.6	1.6	1.2	2.8	2.3
Solids							

Tables are built for Pharmacokinetic and Metabolite Characterization data.

(3) Lost/Unaccounted = Total urinary recovery -Total Identified/Accounted
(4) Total = % of total urinary radioactivity (Total identified/accounted + Total urinary radioactivity recovery)
(5) 50% Metabolite 1/50% Metabolite 2 - both were listed together in DER table (ADW)

Modified

DATA EVALUATION RECORD

DER Composer v3r13

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

TORS' CONCLUSIONS:

RID 999999999) were conducted to determine the metabolism and distribution of [methoxyiminotolyl-ring-UL-14C] Fluoxastrobin in male and female rats following single (1 mg/kg and multiple (1 mg/kg/day for 14 days) oral doses. Biliary excretion experiments were also conducted at the low dose. Excretion/distribution profiles, kinetic parameters, mass balance, and es were assessed for each treatment protocol. An autoradiography study (MRID 888888888) examined absorption time course distribution pattern in male and female rats over 48 hours e 3 mg/kg gavage dose. Recovery of administered radioactivity was 91.1-106.6%. The investigator concluded that Fluoxastrobin was rapidly and nearly completely absorbed. Excretion via expired quential (0.02%) thereby affirming stability of the molecule. The major route of excretion was in the feces via the bile with biliary excretion accounting for 87.4% of a single low dose, and epresenting 70.4-90.1% of the single low dose, single high dose, and 14-day repeated low dose. Urinary excretion accounted for 11-20% of the dose (4.8% in bile-cannulated rats). omplete (99.3%) within 48 hours following dosing. Tissue/body burdens of radioactivity were low (0.3-0.7% of administered dose) at the time of termination regardless of dose regimen. utoradiography experiments confirmed the rapid absorption and minimal tissue burdens. The study author concluded that there was no evidence for accumulation of the test article or its ssue and organs. Slight variations in plasma radioactivity were considered indicative of limited enterohepatic circulation. Metabolism of [methoxyiminotolyl-ring-UL-14C] Fluoxastrobin was rapid and

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

COMMENTS:

r administered radioactivity in all experiments was excellent (91-107%). Based on excretion profiles and plasma concentration data, Fluoxastrobin was rapidly and thoroughly absorbed (tmax of he low dose and 5.4-8.0 hrs for the high-dose groups) following single or multiple low (1 mg/kg) doses but appeared to be saturated at the 100 mg/kg dose. At the high dose (100 mg/kg), somewhat limited as shown by an AUC of 54.10 - 61.30 g/mL hr vs. 1.18 - 1.52 g/mL hr for the low and multiple-dose groups, and Cmax values that were only 14 - 33 fold greater than the s. 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 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 oncentration-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 on 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 ightly 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 sented 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 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

CIENCIES:

o 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 rd). 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 d 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 unction 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 nt deficiencies in the design, conduct, or reporting of these studies.

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DATA EVALUATION RECORD

DER Composer v3r13

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Appendix1a

Test#	Sex	Number	Dose Route	Dose (nominal)	Dose (measured)	Dose Type	Test Duration	Matrix	Experimental Descriptor	Remarks
1a	Male	4	oral	1 mg/kg	0.8 mg/kg	single	72 h	urine		
1b	Male	4	oral	1 mg/kg	0.8 mg/kg	single	72 h	feces		
7a	Male	4	oral	1 mg/kg	1.1 mg/kg	single	48 h	urine		
7b	Male	4	oral	1 mg/kg	1.1 mg/kg	single	48 h	feces		
3a	Female	4	oral	1 mg/kg	1.06 mg/kg	single	48 h	urine		
3b	Female	4	oral	1 mg/kg	1.06 mg/kg	single	48 h	feces		
4a	Male	4	oral	100 mg/kg	49 mg/kg	single	48 h	urine		
4b	Male	4	oral	100 mg/kg	49 mg/kg	single	48 h	feces		
11a	Female	4	oral	100 mg/kg	99 mg/kg	single	48 h	urine		
11b	Female	4	oral	100 mg/kg	99 mg/kg	single	48 h	feces		
10a	Male	4	oral	1 mg/kg	0.94 mg/kg	multiple	48 h	urine		

Appendix Table 1:

Systematic capture of treatment group parameters for:

-Autopopulation of DER Table 1

-Specifying metabolite differences

due to treatments, gender, matrix

Appendix2

Relation: (•) Tree ( ) List

ID	Chemical Name	SMILES	Parent(s)	Expertise
1	Parent	N(=C(C1=NOCCO1)c1c(cccc1)Oc1c(c(...		
2	Metabolite 1	N1=C(OCCO1)C(=NOC)c1c(cccc1)Oc1...	1	
3	Metabolite 2	NC(=O)C(=NOC)c1c(cccc1)Oc1ncnc(c...	1	
4	Metabolite 3	O([C@@H]1O[C@H]([C@@H]([C@H](...	1	
5	Metabolite 4 (isomer 1)	NC(C(=O)O)CSc1cc(c(cc1)Oc1ncnc(c1...	1	Expert ADW: s...
6	Metabolite 4 (isomer 2)	NC(C(=O)O)CSc1cc(c(cc1)Cl)Oc1ncnc(...	1	Expert ADW: s...
7	Metabolite 5	O(c1cc(c(cc1OC)Cl)Oc1ncnc(c1F)Oc1c...	1	Expert JJ: gluc...
8	Metabolite 6	C1(C(c2c(Oc3c(F)c(Oc4c(Cl)cc(O)c(OC...	1,7	Expert ADW: gl...
9	Metabolite 7	O(c1cc(c(cc1O[C@H]1[C@@H](O)[C...	1,8	Expert ADW: gl...
10	Metabolite 8	O(c1cc(c(cc1O)Cl)Oc1ncnc(c1F)Oc1c(c...	1	Expert ADW: gl...
11	Metabolite 9	O(c1cc(c(cc1)Cl)Oc1ncnc(c1F)Oc1c(cc...	1	Expert ADW: gl...
12	Metabolite 10	N1=C(OC(CO1)O)C(=NOC)c1c(cccc1)...	1	Expert JJ: hydr...
13	Metabolite 11	C1(C(c2c(Oc3c(F)c(O)ncn3)cccc2)=N...	2	Expert ADW: O...
14	Metabolite 12	N1=C(OCCO1)C(=NOC)c1c(cccc1)O	2	
15	Metabolite 13	O1C(=NOCC1)C(=O)c1c(cccc1)Oc1c(c...	2	
16	Metabolite 14 (isomer 1)	Oc1cc(c(cc1O)Cl)Oc1ncnc(c1F)Oc1c(c...	8,9	Expert ADW: is...
17	Metabolite 14 (isomer 2)	N1=C(OCCO1)C(=NOC)c1c(cccc1)Oc1...	8,9	Expert ADW: is...
18	Metabolite 15 (isomer 1)	Oc1cc(c(cc1O)Oc1ncnc(c1F)Oc1c(cccc...	7,8	Expert ADW: O...
19	Metabolite 15 (isomer 2)	Oc1c(c(c(cc1)Oc1ncnc(c1F)Oc1c(cccc1...	7,8	Expert ADW: O...
20	Metabolite 16	N1=C(OCCO1)C(=NOC)c1c(cccc1)Oc1...	11	
21	Metabolite 17	N1=C(OCCO1)C(=NOC)c1c(cccc1)Oc1...	11	
22	Metabolite 18	C1(C(c2c(Oc3c(F)c(Oc4c(Cl)ccc(O)c4)...	11	
23	Metabolite 19	C1(C(c2c(Oc3c(F)c(Oc4c(Cl)ccc(OC{P-...	11	Expert ADW: gl...
24	Metabolite 20	C(=O)(C(c1c(Oc2c(F)c(O)ncn2)cccc1)...	13	
25	Metabolite 21	O=C(N)C(=NOC)c1c(cccc1)Oc1ncnc(c...	24	
26	Metabolite 22	N#Cc1c(cccc1)O	25	

Appendix Table 2:

Chemical structures of parents and metabolites entered as SMILES strings;

Connectivity between parent and each metabolite (i.e., the metabolism pathway).

Summay - USES OF METAPATH

• Allows a systematic compilation of experimental information on observed metabolites, biotransformation reaction types, and relative biotransformation rates into a structure-searchable database.

• Provides structure-based accessibility for identifying metabolites and transformations observed under specific testing environment.

• Identifies differences in metabolic maps traceable to gender, exposure dose, species, analytical extraction and detection methods used for metabolite id, etc.

• Identifies similar metabolites (e.g., with common toxicophores) arising from different parent chemicals.

•Identifies metabolites appearing as residues in plants, livestock (food sources) and environmental degradates (drinking water sources) that contain a potentially toxic moiety, to evaluate residues of concern

•Assists in the preparation of documents and reports.

• Provides databases of experimentally-determined metabolic pathways, all collected under the same guidelines, to be used for metabolism research and development of a metabolism simulator

Next Steps: **MetaPath** & **DER Composer**

- Current focus:
  - Locating and coding remaining rat *in vivo* metabolism pathways from OPP files for registered pesticides
  - Fully implement use of DER composer in OPP by contractors producing draft metabolism DERs
  - Working with ROCKS to optimize use of MetaPath in RA
- Near Term:
  - Build 'DER Composers' for additional study types:
    - Residues in plants, livestock (OPP/HED; ROCKS)
      - OPP, ORD, EU_EFSA discussing collaboration especially on collection of plant and livestock residue data;
    - Environmental degradates (OPP/EFED; ROCKS)
    - Exploring further EFSA and Health Canada PMRA interests
- Longer Term:
  - As knowledge-base continues to build, shift emphasis more to metabolism simulators (highly complex computational challenge)
  - In-lab testing of hypotheses generated using these computational tools