



# MetaPath, an international database on pesticide metabolism

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Residues and Food Safety Unit  
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"What does the future hold for harmonised human health risk assessment of plant protection products?"  
Berlin 23-24 November 2017

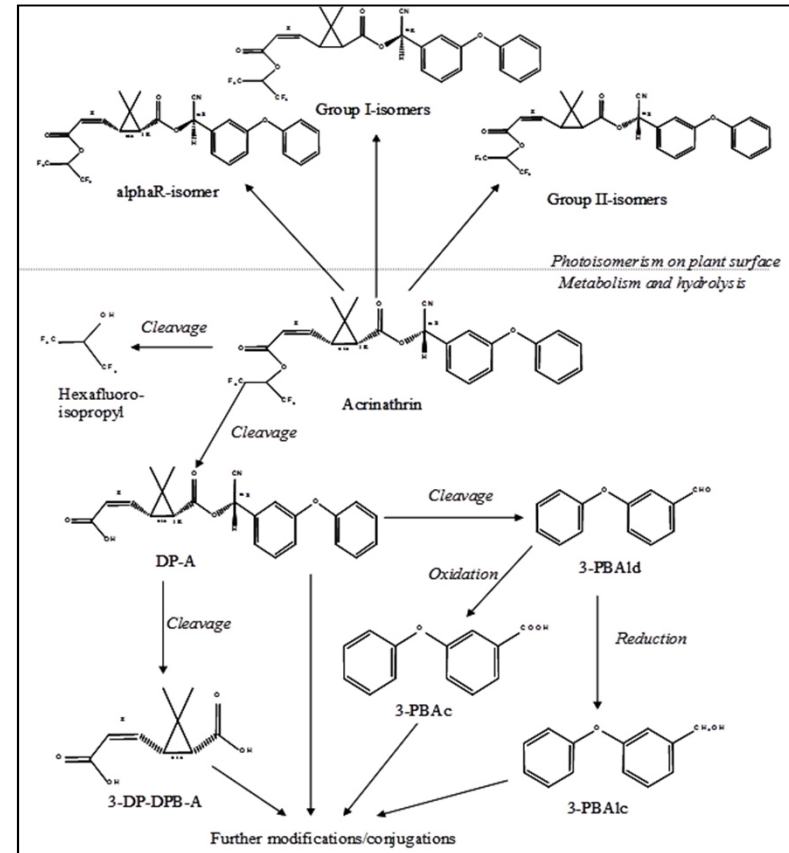
# Evaluation of phytopharmaceutical active substances

- **Regulatory Requirement world wide**

- Toxicology:
  - Rat (ADME)
- Consumer Safety:
  - Plants
  - Livestock
  - Processed commodities
- Environment:
  - Soil
  - Water

- **Metabolism Studies**

- Fate of radiolabelled active substances
- Identification of relevant metabolites
  - Toxicological properties
  - Distribution in different organs /compartments
- Residue Definition in food and environment compartments



# Metabolite management

- 494 Active Substances approved in Europe (1359 in total)
- > 3000 studies available (approved AS)
- Identify easily metabolites that are common to several pesticides.
- No tool available



# MetaPath Project


➤ **Metabolism Pathways** database is a computation tool for reviewing metabolism data.

Aim: “to Improve Efficiency In Pesticide Risk Assessments”

➤ Robust summaries of metabolism studies for use in regulatory peer review process:

- Data evaluation tool;
- Metabolic profiles;
- Search and comparison;

➤ Project lead by US-EPA



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Regulatory Toxicology and Pharmacology

journal homepage: [www.elsevier.com/locate/yrtph](http://www.elsevier.com/locate/yrtph)

MetaPath: An electronic knowledge base for collating, exchanging and analyzing case studies of xenobiotic metabolism

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# MetaPath User Group

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- **OECD Project Proposal: MetaPath, a Pesticide Metabolite Database with Data Evaluation Tools** [ENV/JM/PEST(2010)12],
- **MetaPath User Group:** *45 experts from AUS, AUT, BEL, CAN, DEU, FRA, SVK, UK, USA, EU (ECHA, EFSA), Industry (BIAC), OECD (Secretariat + LMC Bulgaria as Software developer)*



# Metabolism Computational Tools

## ➤ **Metabolism Study Summary (MSS) Composers:**

*data entry software (ready to be used by applicants)*

- Generate robust summary reports to be included in the Draft Assessment Reports (rat, livestock, plants, rotational crops)
- Based on OECD Harmonised Templates (all OHT elements are included).
- Generate e-submissions of summaries of metabolism studies by applicants to be included in MetaPath for use in regulatory peer review process (XML for data upload in MetaPath)

## ➤ **METAbolism PATHways (METAPATH):**

*database and data evaluation tools*

- Database of metabolism pathways and metadata
- Tool for structure search, map comparisons, identifying common residues, etc

# « MSS 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

**1. Test Compound**

Radio-labeled test material

ADD DEL **Radio-labeled test material:** [14C-phenoxy]cypermethrin

Radio-labeled #1

**Radio-labeled purity:** 99.0 %

**Specific activity:** 22.5 µCi/mg

**Lot/batch #:** sample number 430

Structure:

Non-Radio-labeled test material

**Non-radio-labeled test material:** cypermethrin

**Description:**

**Lot/batch #:**

**Purity:** %

**Contaminants:** No relevant impurities

**CAS # of TGAI:** 52315-07-8

Structure:

**Physicochemical Properties**

Parameter	Note	Value	Reference
-----------	------	-------	-----------

Livestock

Organism

Materials et methods  
A : materials

Chemical  
-internal drawing tool  
-Import smiles codes

# « MSS composer »

DER Composer (Livestock) v3r22  
Developed by LMC/Bourgas in Collaboration with US

**DATA EVALUATION RECORD**

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

Appendix1a

Test#	Sex	Number	Dose Route	Dose (nominal)	Dose (measured)	Dose Type	Test Duration	Matrix
1a	Female	1	oral	1 mg/kg	1 mg/kg	multiple	7 days	urine
1b	Female	1	oral	1 mg/kg	1 mg/kg	multiple	7 days	faeces
1c	Female	1	oral	1 mg/kg	1 mg/kg	multiple	7 days	milk
1d	Female	1	oral	1 mg/kg	1 mg/kg	multiple	7 days	liver
1e	Female	1	oral	1 mg/kg	1 mg/kg	multiple	7 days	kidney
1f	Female	1	oral	1 mg/kg	1 mg/kg	multiple	7 days	muscle
1g	Female	1	oral	1 mg/kg	1 mg/kg	multiple	7 days	fat
2a	Female	1	oral	10 mg/kg	8.6 mg/kg	multiple	7 days	urine

Appendix2

Relation: Tree | List

ID	Common Name / Code	Chemical Name	SMILES	Parent(s)	Expe
1	Acetamidrid	(1E)-N-[(6-chloro-3-pyridinyl)meth...	c1(Cl)ccc(CN(C)C(C)=NC#N)cn1		
2	IM-2-1/N-desmethyl...	N1-[(6-chloro-3-pyridyl)methyl]-N...	c1(Cl)ccc(CNC(C)=NC#N)cn1	1	
3	IC-0	6-chloronicotinic acid	C(=O)(O)c1ccc(Cl)nc1	1,2	
4	IM-2-3	N-[(6-chloro-3-pyridyl)methyl]acet...	c1(Cl)ccc(CNC(C)=O)cn1	2	
5	IM-2-4	(6-chloro-3-pyridyl)methylamine	c1(Cl)ccc(CN)cn1	4,6	
6	IM-2-2/IM-2-1-amide	(E)-N2-carbamoyl-N1-[(6-chloro-3-...	c1(Cl)ccc(CNC(C)=NC(N)=O)cn1	2	

Appendix2 Editor

Common Name / Code: IM-2-3

Chemical Name: N-[(6-chloro-3-pyridyl)methyl]acetamide

Chemical Structure: c1(Cl)ccc(CNC(C)=O)cn1

Parent(s):

- 1: (1E)-N-[(6-chloro-3-pyridinyl)methyl]-N'-cyano-N-methylethani
- 2: N1-[(6-chloro-3-pyridyl)methyl]-N2-cyano-acetamidine (c1(Cl)ccc(CNC(C)=NC#N)cn1)
- 3: 6-chloronicotinic acid (C(=O)(O)c1ccc(Cl)nc1)
- 5: (6-chloro-3-pyridyl)methylamine (c1(Cl)ccc(CN)cn1)
- 6: (E)-N2-carbamoyl-N1-[(6-chloro-3-pyridyl)methyl]-N1-acetamidine (c1(Cl)ccc(CNC(C)=NC(N)=O)cn1)

Expertise:

None  Assumed by author(s)  Expertly specified

Expert:

Decision:

Submit Cancel



# MetaPath database

Metabolic Pathways - application ver.5.1.0.39, database ver.3.1.0 - RegulatoryDB\_708\_Mar2017.MTB, logged in as "administrator"

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

Locked by: administrator

Chemical descriptors quick search  
tree: [dropdown]  
value: [input] [Select]

1. 220899-03-6; Metrafenone [Bromophenyl-6-14]  
2. 220899-03-6; Metrafenone [Trimethoxyphenyl]  
3. 149877-41-8; Bifenazate [14C-phenyl] (D234;  
4. 28057-48-9; d-Trans-Allethrin [Cyclopropyl-1-1  
5. 28057-48-9; d-Trans-Allethrin [14C-alcohol]; F  
6. 150114-71-9; Aminopyralid [per-2,6-14C] (XD  
7. 57960-19-7; Acequinolyl [dodecyl-C-14] (AKD  
8. 57960-19-7; Acequinolyl [phenyl-U-C-14] (AK  
9. 741-58-2; Bensulide [phenyl ring-C-14]; Rat  
10. 335104-84-2; Tembotrione [14C-cyclohexyl]  
11. 335104-84-2; Tembotrione [14C-phenyl] (AE  
12. 420-04-2; Cyanamide [C14]; Rat  
13. 8018-01-7; Mancozeb [14C-ethylene]; Rat  
14. 239110-15-7; Fluopicolide [14C-2,6-pyridyl] (I  
15. 239110-15-7; Fluopicolide [phenyl-U-C-14] (I  
16. 272451-65-7; Flubendiamide [phthalic ring-U-  
17. 272451-65-7; Flubendiamide [aniline ring-U-  
18. 272451-65-7; Flubendiamide [phthalic ring-U-  
19. 99485-76-4; Cumyluron [phenyl ring-C-14] (C  
20. 99485-76-4; Cumyluron [chlorophenyl ring-C  
21. 193740-76-0; Fluoxastrobin [methoxyiminotc  
22. 193740-76-0; Fluoxastrobin [chlorophenyl-UL  
23. 94-75-7; 2,4-D [Phenyl-U-14C]; Dog  
24. 94-75-7; 2,4-D [Phenyl-U-14C]; Rat  
25. 1929-73-3; 2,4-D BEE [2-butoxyethyl(1,2-14  
26. 129630-19-9; Pyraflufen-ethyl [phenyl-14C]  
27. 129630-19-9; Pyraflufen-ethyl [pyrazole-5-1  
28. 94-74-6; MCPA [phenyl ring-C-14]; Dog  
29. 94-74-6; MCPA [14C-UL-Phenyl]; Rat  
30. 2039-46-5; MCPA-DMA [Phenyl-U-14C]; Rat  
31. 29450-45-1; MCPA-EHE [Phenyl-U-14C]; Rat  
32. 99-30-9; Dicloran [phenyl-UL-14C]; Rat  
33. 70-38-2; Dimethrin [14C] (2,4-dimethylbenzy  
34. 60-51-5; Dimethoate [O-methyl-C-14]; Rat  
35. 1113-02-6; Omethoate [Methylene-14C]; Ra  
36. 330-54-1; Diuron [14-C]; Rat  
37. 374726-62-2; Mandipropamide [chlorophenyl  
38. 374726-62-2; Mandipropamide [methoxyphen  
39. 122-39-4; Diphenylamine [phenyl ring-U-C-14

Tree Results, met. Results, PK  
CAS:220899-03-6  
Rat, in vivo (x8)  
1 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., MRID:46415747

Metrafenone [Bromophenyl-6-14C] (BAS 560F)

CL 3000402 CL 376991 CL 434223 CL 377160 1Xinterm to CL1500700

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

CL 1500702 CL 1500697

name: Metrafenone [Bromophenyl-6-14C] (BAS 560F)  
double-click for display options

# MetaPath database

Metabolic Pathways - application ver.4.1.0.12, database ver.2.1.0 - OPP\_406\_FEB\_24\_2012\_VER2.1.0+neonicotinoides.MTB, logged in as "administrator"

File Edit Search View Options Help

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

OPP\_406\_FEB\_24\_2012\_VER2.1.0+neonicotinoides.MTB

Unlocked

Chemical descriptors quick search

Desc: Value: Select

- 389. Chlorimuron-ethyl [14C-U-phe
- 390. Chlorimuron-ethyl [14C-2-pyrin
- 391. MRID:40449723 Ethofenpro
- 392. MRID:40449723 Ethofenpro
- 393. MRID:415349-01 Cyprocona
- 394. MRID:429914-16 Triflusulfurc
- 395. MRID:429914-16 Triflusulfurc
- 396. MRID:419317-11 Flumetsular
- 397. MRID:433454-10 Sulfentrazo
- 398. MRID:433454-10 Sulfentrazo
- 399. MRID:422563-54, 422563-5E
- 400. MRID:422563-57 Imidaclopric
- 401. MRID:422563-54 Imidaclopric
- 402. MRID:432589-01 Pyridaben [
- 403. MRID:432589-01 Pyridaben [
- 404. MRID:429186-55 Fipronil [U-
- 405. MRID:46030306 Kasuganyc
- 406. Benoxacor [14C-phenyl]; c12
- 407. Acetamiprid (NI-25); c1(Cl)cc
- 408. Acetamiprid (NI-25); c1(Cl)cc
- 409. Flonicamid (IKI-220); C(F)(F)(F
- 410. Flonicamid (IKI-220); C(F)(F)(F
- 411. Imidacloprid (NTN-33893); c1
- 412. Imidacloprid (NTN-33893); c1
- 413. Imidacloprid (NTN-33893); c1
- 414. Imidacloprid (NTN-33893); c1
- 415. Thiacloprid (YRC2894); c1(Cl)
- 416. Thiacloprid (YRC2894); c1(Cl)

Tree Results, met. Results, PK

Cell Height 142 Cell Width 142 Redraw Print Preview MapID font

CAS:135410-20-7; Acetamiprid (NI-25)  
[Laying hens, in vivo (x18)]  
Burri, R., IIA. 7.2/02 (1997): 14C-NI-25 (Acetamiprid): Absorption, Distribution, Metabolism and Excretion after Repeated Oral Administration to Laying Hens

Parent

Common fields:  
Laying hens; female; in vivo; oral; 10 mg/kg diet; white leghorn hybrids

Coloring and specifics:

- [2a] excreta
- [2b] egg white
- [2c] egg yolk
- [2d] liver
- [2e] muscle
- [2] skin (+fat)

Collapse Hide details

Treatment group:  
Laying hens, female, in vivo, egg white, oral, 10 mg/kg diet, single dose (radiolabeled), white leghorn hybrids

Reference:  
• Burri, R., IIA. 7.2/02 (1997): 14C-NI-25 (Acetamiprid): Absorption, Distribution, Metabolism and Excretion after Repeated Oral Administration to Laying Hens

Subjects:

- Species - Laying hens
- Gender - Female (5 subjects)
- Weight - Between 1.7 - 2 kg (female)
- Age - 8 months old
- Strain - White leghorn hybrids
- Source - Geflügelzucht Rüegg, CH-8330 Pfäffikon/Switzerland
- Housing - Metabolism units allowing the collection of excreta and eggs
- Diet - Powdered hen feed ad libitum
- Water - Tap water ad libitum

Double-click for display options

CN(C)Cc1ccc(Cl)nc1

# Identification of Common Metabolites

## Comparison of 2 metabolic maps

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

OPP\_406\_FEB\_24\_2012\_VER2.1.0+neonicotinoides.MTB

Unlocked

Chemical descriptors quick search

Tree Results, met. Results, PK

Desc: Value:

Depict 2 trees

Sensitivity: 33.333%

Redraw Print Preview MapID font

CAS:135410-20-7: Acetamiprid (NI-25)  
[Lactating goat, in vivo (x14)]  
Burri, R., IIA, 7.2/01 (1997): 14C-NI-25 (Acetamiprid). Absorption, Distribution, Metabolism and Excretion after Repeated Oral Administration to Lactating Goats

CAS:138261-41-3: Imidacloprid (NTN-33893)  
[Laying hens, in vivo (x8)]  
Klein, O. and Brauner, A. (1992): [Methylen-14C]-imidacloprid: Absorption, distribution, excretion and metabolism in laying hens

Parent

Parent

Parent

2 3 4

2.1 2.2 3.1 4.1

2.1.1 3.1.1 4.1.1 4.1.2

2.1.1.1 2.1.1.2 3.1.1.1 3.1.1.2 4.1.1.1 4.1.2.1

2.1.1.1.1 2.1.1.1.2 3.1.1.1.1 3.1.1.2.1 4.1.1.1.1

Double-click for display options

anses

# Identification of Common Metabolites

Identify identical or similar molecule: (Search → Chemicals)

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

Metabolic Pathways - Compose a search query

Maps | Chemical | Structure

Fragment is in: Structure drawing...  
Exact match  
Fragment: c1cc(Oc2cccc(C(=O)=O)c2)ccc1

Q1: exact match structure=c1cc(Oc2cccc(C(=O)=O)c2)ccc1

AND OR NOT

Metabolic Pathways - Search results

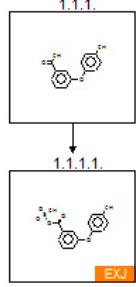
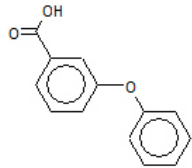
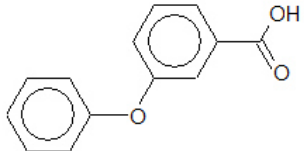
Search query  
Query: Q1  
Q1: exact match structure=c1cc(Oc2cccc(C(=O)=O)c2)ccc1

As map parents | As compounds

No.	Chemical name	M...
1	3-Phenoxybenzoic acid	67
2	3-phenoxybenzoic acid	68
3	3-Phenoxybenzoic acid (m...	97
4	3-Phenoxybenzoic acid (m...	98
5	PBA	134
6	3-Phenoxybenzoic acid (m...	157
7	Structure 9	186
8	(IUPAC) 3-phenoxybenzoic...	324
9	(IUPAC) 3-phenoxybenzoic...	325
10	PBacid	378
11	PBacid	378
12	PBacid	379
13	PBacid	380

Structure info

CAS: 0  
Name: 3-phenoxybenzoic acid  
Synonyms:  
Mode of action class:



# Projet Advancement

- Studies in the base :
  - 376 active substances
  - 715 metabolic profiles
    - 65% Rat
    - 19% Livestock
    - 9% Plants
    - 7% Rotational crops
  - 80% quality assessment

QA Checklist for Review of Generated XMLs: Assessment of Coding of OPP Rat Metabolism DER's

<enter xml file name in this cell>	
1. Are there entries and are they correct for: ?	
a. TRX#	
b. PC Code	
c. DP Barcode	
d. Submission No.	
e. MRID	
2. Radiolabelled Test Material	
a. Is chem name correct including radiolabel (C-14) position ?	
b. Is structure correct?	
3. Non-Radiolabelled Test Material	
a. Is chem name correct	
b. Is structure correct	
c. Is CAS number correct ?	
4. Animals	
a. species	
b. strain	
c. age	
d. weight	
5. Analytical info.	
a. major method (direct analysis; methanol extraction)	
b. conjugate analysis (glucuronidase; sulfatase)	
c. analytical separation (TLC; HPLC; GC)	
d. analytical detection (liquid scintillation count;UV; MS)	
6. Appendix 1	
a. check treatment groups	
b. confirm those entered in Table 7	
7. Check Table 7	
a. Are all treatment groups identified for metabolites identified ?	
b. Are metabolite fields correctly entered	
8. Appendix 2	
a. check "expert decision" rationale for all metabolites	
Check in MetaPath, following import of XML:	
9. Does the .xml and map import into MetaPath without error?	
10. Check metabolism table(s) under RESULTS tab in MetaPath	
11. Check imported map (in MetaPath) versus the original map in the DER. Are all structures correctly drawn as well as connectivity of metabolites. This will also check whether Appendix 2 in the XML was done correctly.	
12. Check the "Highlight Treatment Group" function within MetaPath; compare to the DER metabolite results and Table(s) 7 in the XML to ensure correspondence between metabolite formation and treatment group.	

# OECD QSAR ToolBox new version

## QSAR TOOLBOX

Software for grouping chemicals into categories and filling gaps in (eco)toxicity data needed for assessing the hazards of chemicals

### HOME

The category approach used in the Toolbox:

- Focuses on intrinsic properties of chemicals (mechanism or mode of action, (eco-) toxicological effects).
- Allows for entire categories of chemicals to be assessed when only a few members are tested, saving costs and the need for testing on animals.
- Enables robust hazard assessment through mechanistic comparisons without testing.

The QSAR Toolbox is a software intended to be used by governments, the chemical industry and other stakeholders to fill gaps in (eco-)toxicity data needed for assessing the hazards of chemicals. The Toolbox incorporates information and tools from various sources into a logical workflow. Grouping chemicals into chemical categories is crucial to this workflow.

### NEWS

#### April 2017

QSAR Toolbox 4.0 now available for [free download](#). The new version represent a major update of the software, focused on making the Toolbox more user friendly. For more details consult the release notes

# MetaPath in the OECD QSAR ToolBox

QSAR Toolbox 2.1.2.865 [Document\_1]

QSAR TOOLBOX

Input Profiling Endpoint Category Definition Data Gap Filling Report

Apply New Scheme Show Boundaries Delete Scheme Profiling Profiling Schemes

The OECD QSAR Toolbox for Grouping Chemicals into Categories

Developed by LMC, Bulgaria

Filter endpoint tree...

	1	2
Structure	<chem>Oc1ccccc1O</chem>	<chem>Oc1ccccc1O</chem>
<input checked="" type="checkbox"/> Substance Identity		
<input checked="" type="checkbox"/> Physical Chemical Properties		
<input checked="" type="checkbox"/> Environmental Fate and Transport		
<input checked="" type="checkbox"/> Ecotoxicological Information		
<input checked="" type="checkbox"/> Human Health Hazards		
<input checked="" type="checkbox"/> Profile		

Metabolism

Documented

- Observed Liver metabolism
- Observed Microbial metabolism

Simulated

- Dissociation simulation
- Liver metabolism simulation
- Microbial metabolism simulation
- Skin metabolism simulation

About Options Select all Unselect all Show metabolite database Show metabolite tree

# MetaPath in the OECD QSAR ToolBox

Metabolite tree viewer

**[94.001.Liver] 134-62-3; N,N-Diethyl-m-toluamide; Rat**  
 Yeung, J. M., W. G. Taylor, Drug Metab. Dispos., 16(4), (1988). (in vitro), (p. 600 - 604)

**Treatment group 1 Rat, male, in vitro, Microsomes, liver, incubation media, in vitro incubation, 1000 nmol, single dose (non-radiolabeled), Wistar**

Study: Rat, male, in vitro, Microsomes, liver, incubation media, in vitro incubation, 1000 nmol, single dose (non-radiolabeled), Wistar  
 Citations: Yeung, J. M., W. G. Taylor, Drug Metab. Dispos., 16(4), (1988). (in vitro), (p. 600 - 604)  
 Subjects: Species - Rat  
 Gender - Male (5 subjects)  
 Weight - Between 275 - 300 g (male)  
 Age - 12 weeks old  
 Strain - Wistar  
 Source - Charles River (St. Constant, Quebec, Canada)  
 Housing - Polycarbonate metabolism cages  
 Diet - Ad libitum (Purina lab. chow)  
 Water - Ad libitum

Environmental co...: Env. temperature - Between 18 - 22 °C  
 Humidity - Between 50 - 60 %  
 Photoperiod - 12-h light/dark cycle  
 Acclim. period - 4 days

In vivo / in vitro: In vitro  
 Phase I enzymes - Detected (looked for and found)  
 Phase II enzymes - Not determined (not looked for)  
 Experimental system - Microsomes  
 Organ / Tissue - Liver  
 In vitro temperature - 37 °C  
 Exper. descriptors - Not reported

Sampling / anal...: Sample matrix - Incubation media  
 Sample times (frequency) - Minutely  
 Duration - 120 minutes  
 Amount - 500 microl.  
 Separations - High-performance liquid chromatography (HPLC)  
 Detections - Ultraviolet spectroscopy (UV)  
 Extraction methods - Solvent (acetonitrile)  
 Conj. analysis methods - Not reported

Dose administra...: Administration type - In vitro incubation  
 Dosing (non-radiolabeled parent) - 1000 nmol, single dose

Additional infor...: Microsomes from male rats metabolized DEET much faster than did those from females.

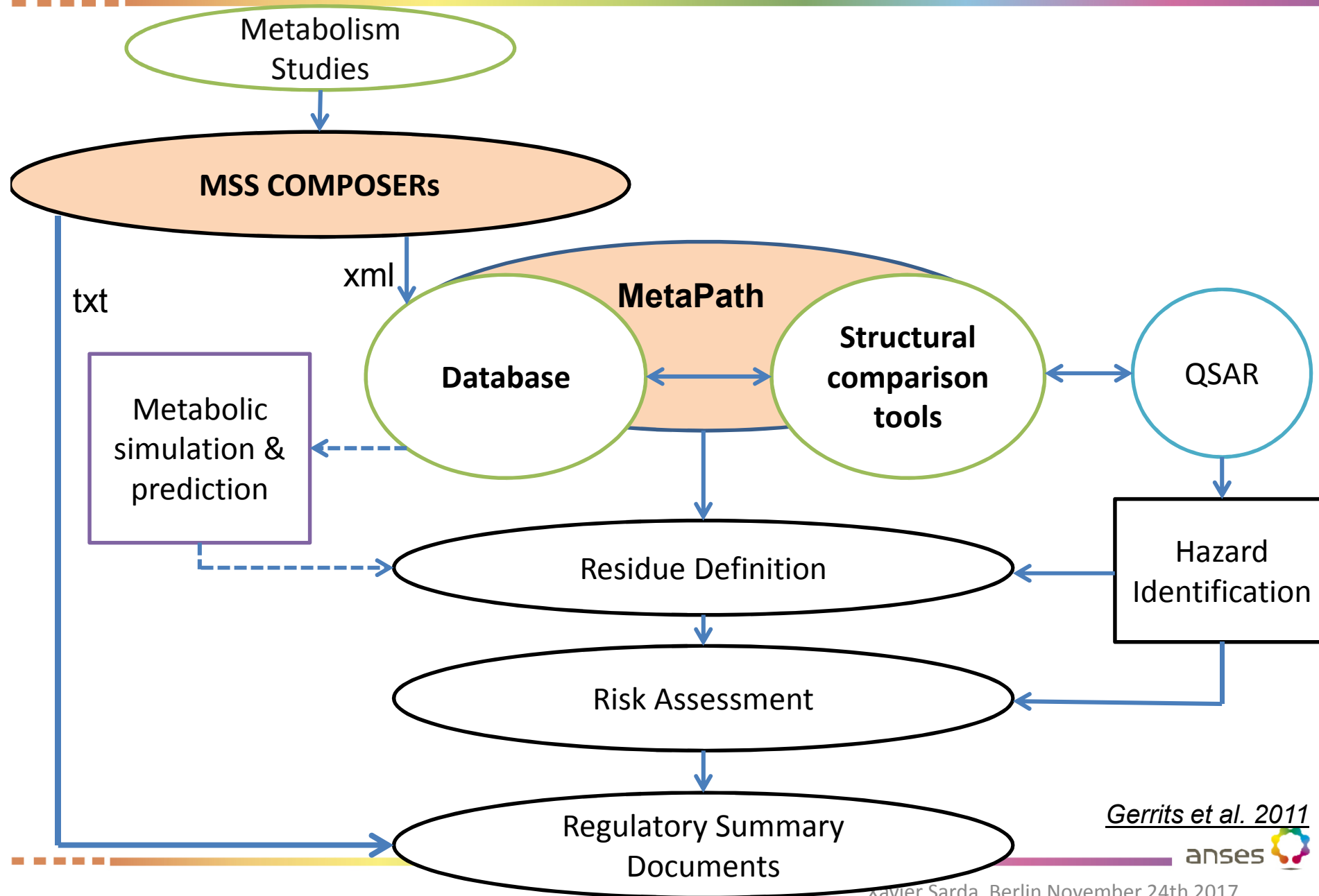
**Treatment group 2 Rat, female, in vitro, Microsomes, liver, incubation media, in vitro incubation, 1000 nmol, single dose (non-radiolabeled), Wistar**

**Quantity of metabolite as function of time**

Time, min	5.00	10.0	15.0	20.0	30.0	40.0	60.0	90.0	120
Quantity, nmol	35.0	47.0	59.0	71.0	82.0	82.0	82.0	82.0	82.0



# Use of MetaPath in pesticide evaluation



# Conclusion

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- Identification of common metabolites
  - Chemical Structure
  - Similarity
- Facilitate risk assessment
  - Residue definition
  - Aggregate RA
- Improve hazard identification (QSAR complementarity)
- Reduce animal testing
- Mutualize between regulatory agencies
- Streamline information flow between industry and regulators

# MetaPath User Group Perspectives

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## Future:

- Increased participation in the **MetaPath Users Group**
- Populate the database
- Electronic data submission by registrants using **MSS Composers**
- Continue integration with OECD QSAR Toolbox for public release of metabolism maps
- Develop **MSS Composers** for all environmental fate studies  
Soil/Water/Air (*as resources become available*)

Thank You

