MetaPath, an international database on pesticide metabolism

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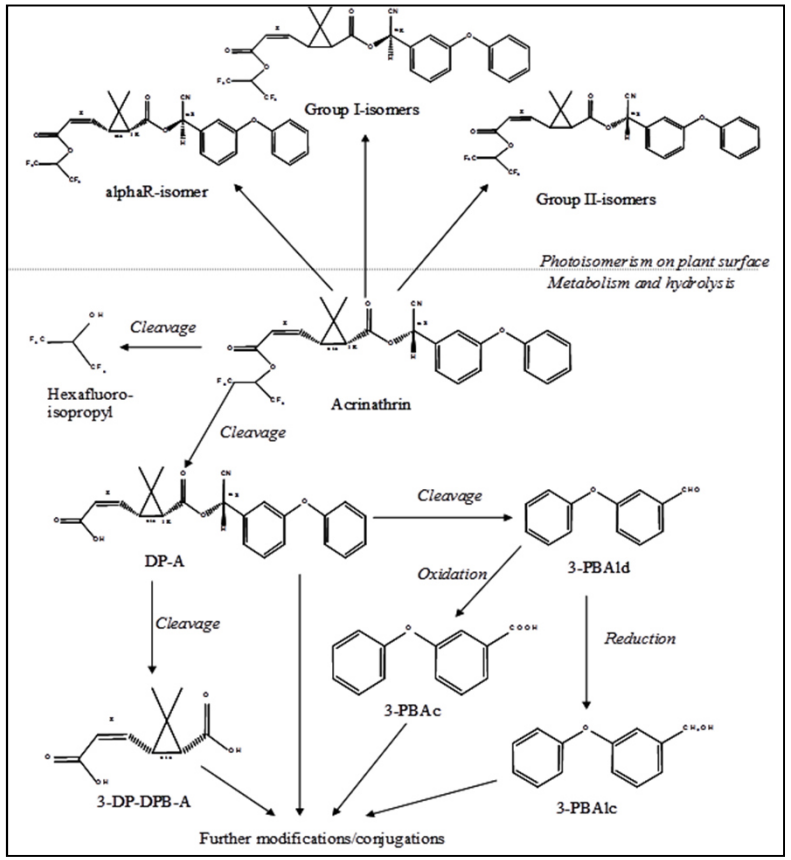
"What does the future hold for harmonised human health risk assessment of plant protection products?“
Berlin 23-24 November 2017

Evaluation of phytopharmaceutical active substances

- **Regulatory Requirement world wilde**
  - 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

- ***Meta***bolism ***Path***ways 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

Regulatory Toxicology and Pharmacology 63 (2012) 84–96

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Regulatory Toxicology and Pharmacology

journal homepage: 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

- **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 Sofware developer)*

Metabolism Computational Tools

- **M**etabolism **S**tudy **S**ummary **(MSS)** Composers:

data entry software (ready to be used by applicants)

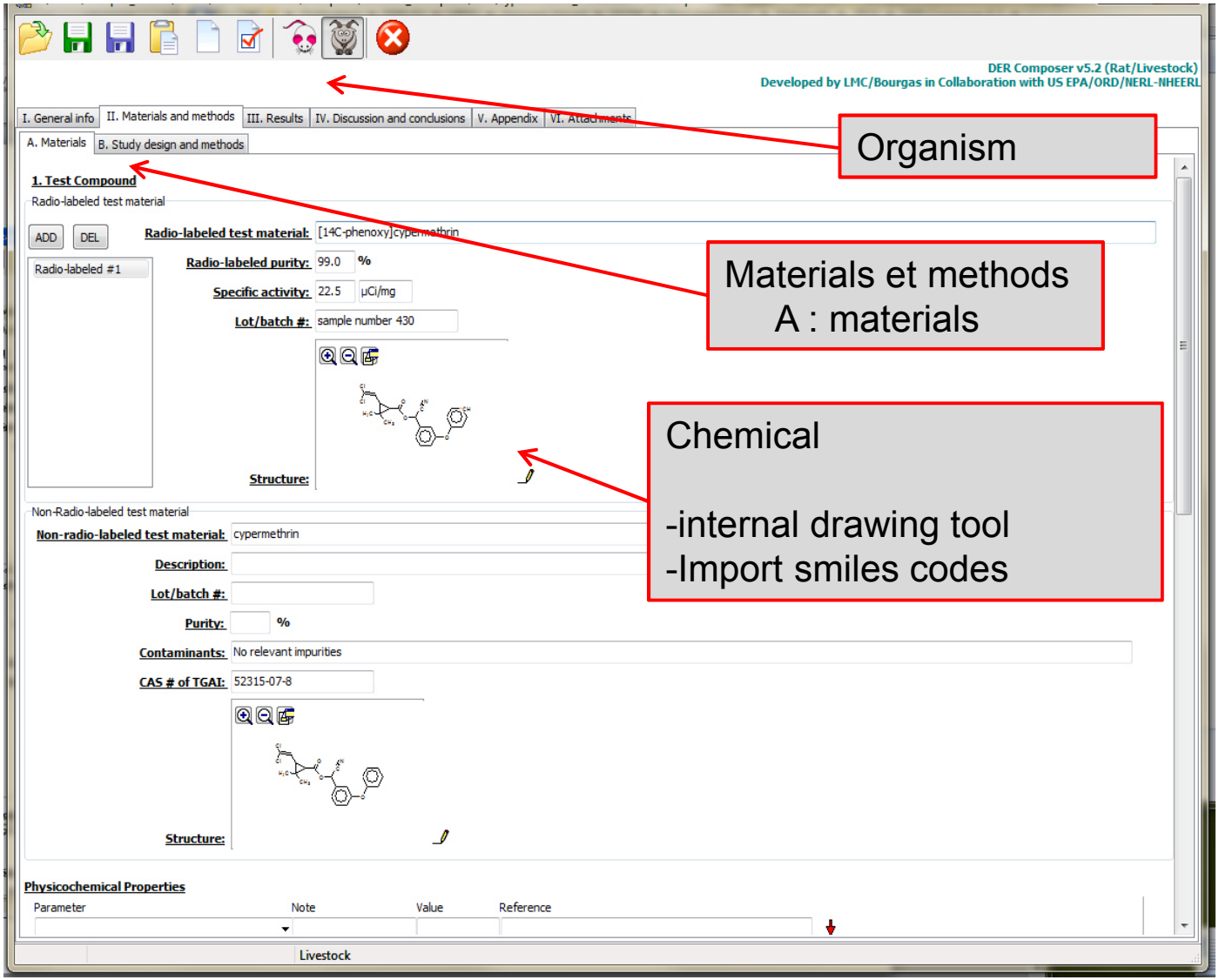
  - Generate robust summary reports to be included in the Draft Assessment Reports (rat, livestock, plants, rotational crops)
  - Based on OECD Harmonised Templates (all OHT elements are included).
  - Generate e-submissions of summaries of metabolism studies by applicants to be included in MetaPath for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

- **META**bolism **PATH**ways **(METAPATH):**

database and data evaluation tools

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

« MSS Composer »



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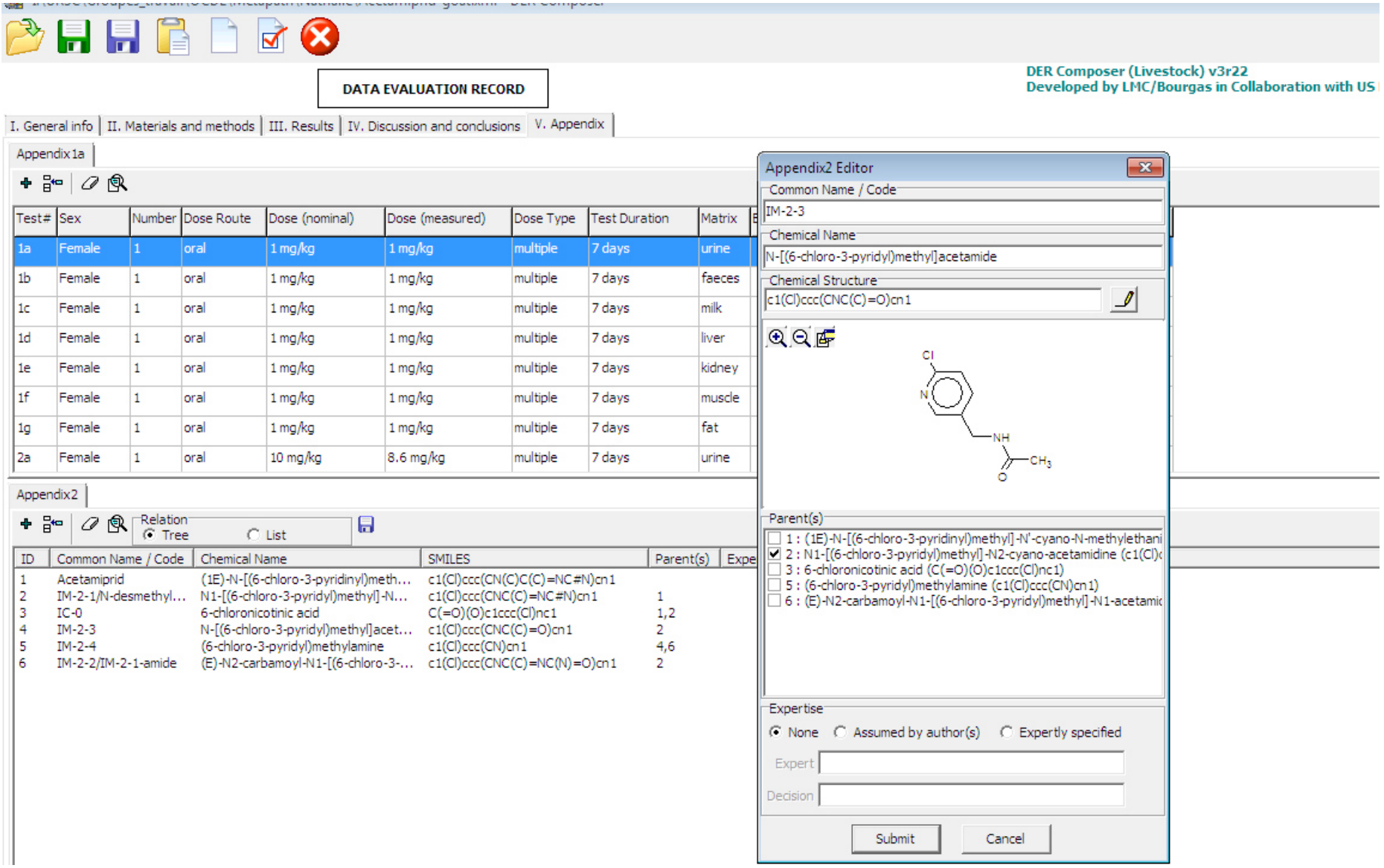
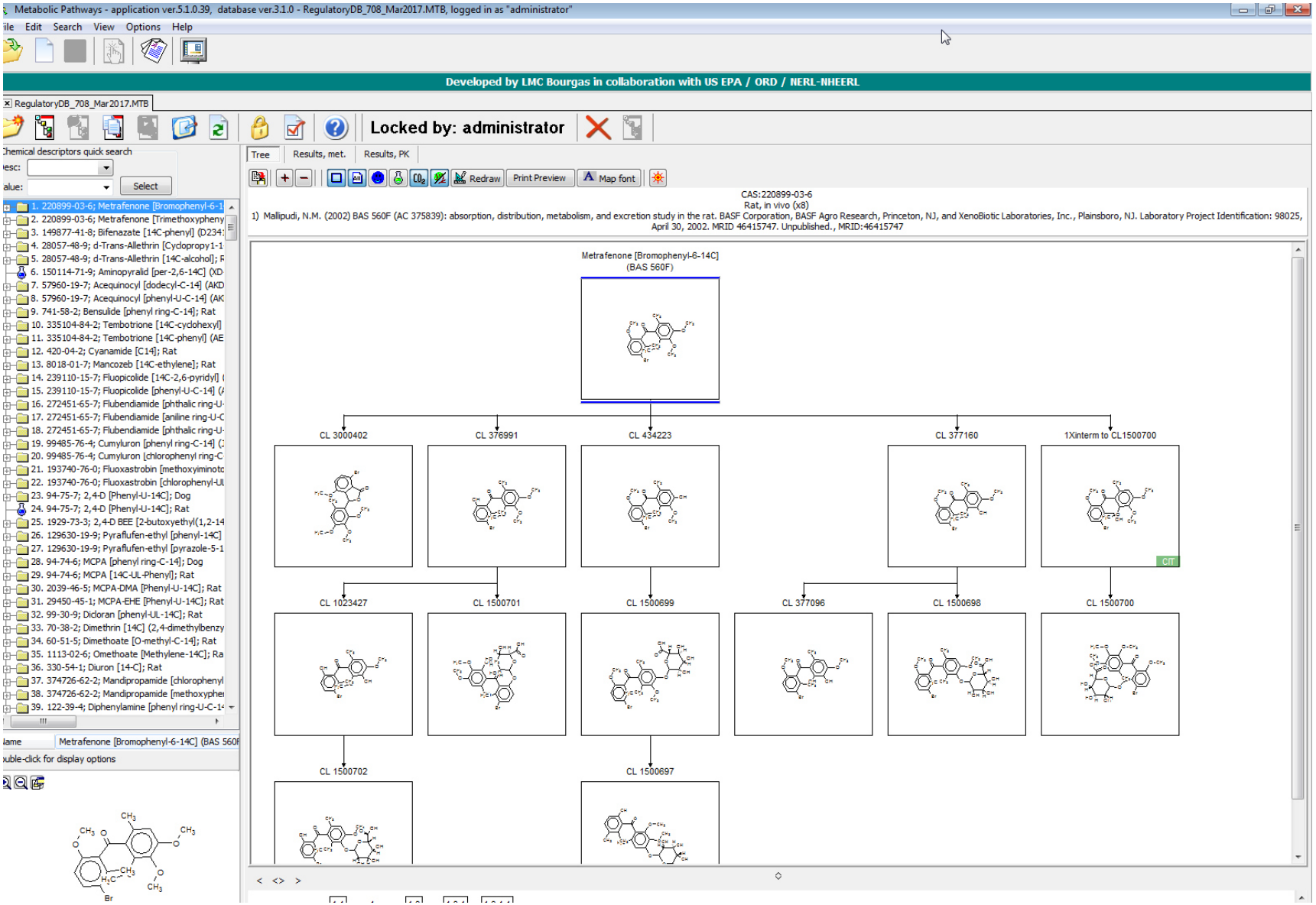
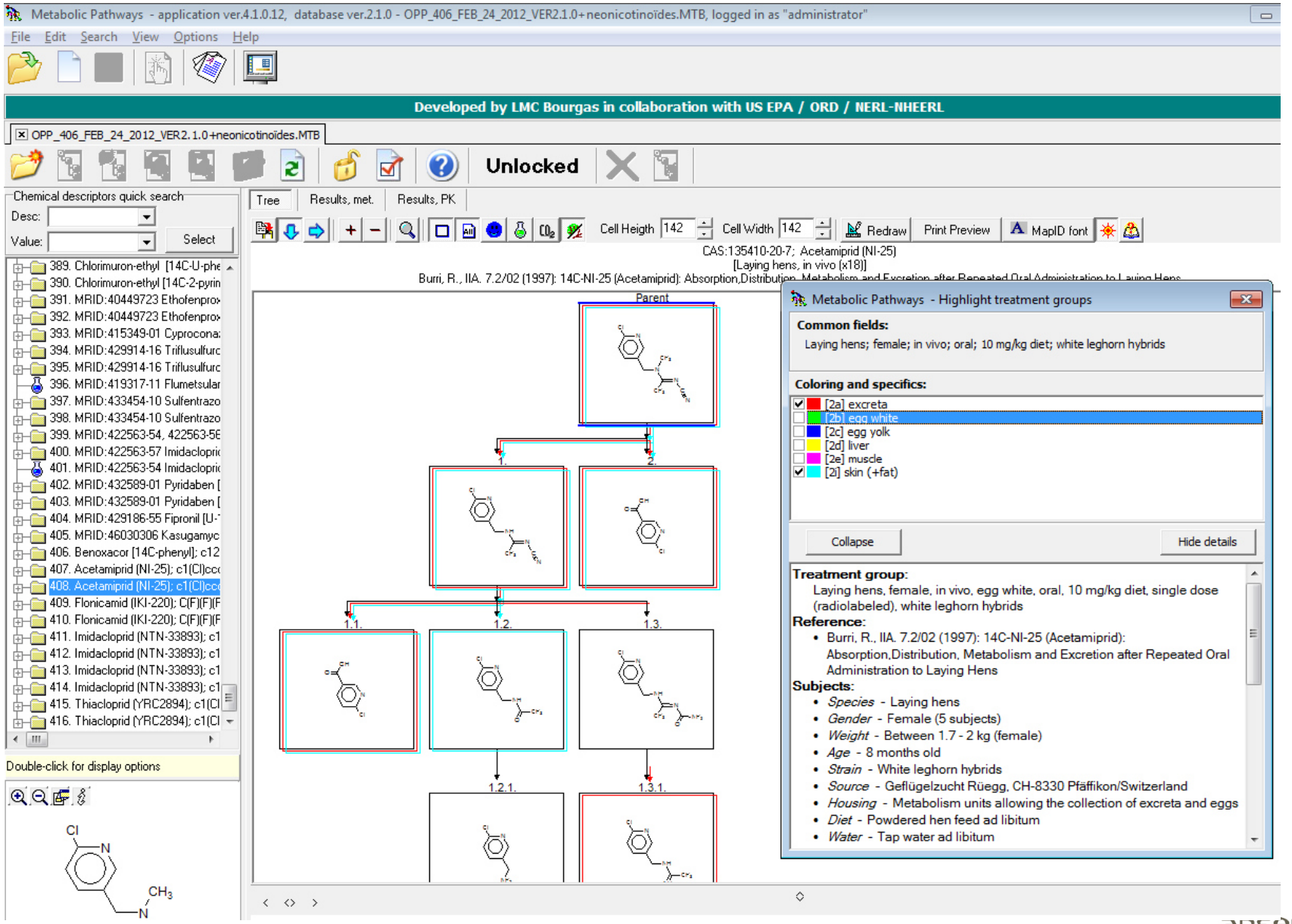


MetaPath database

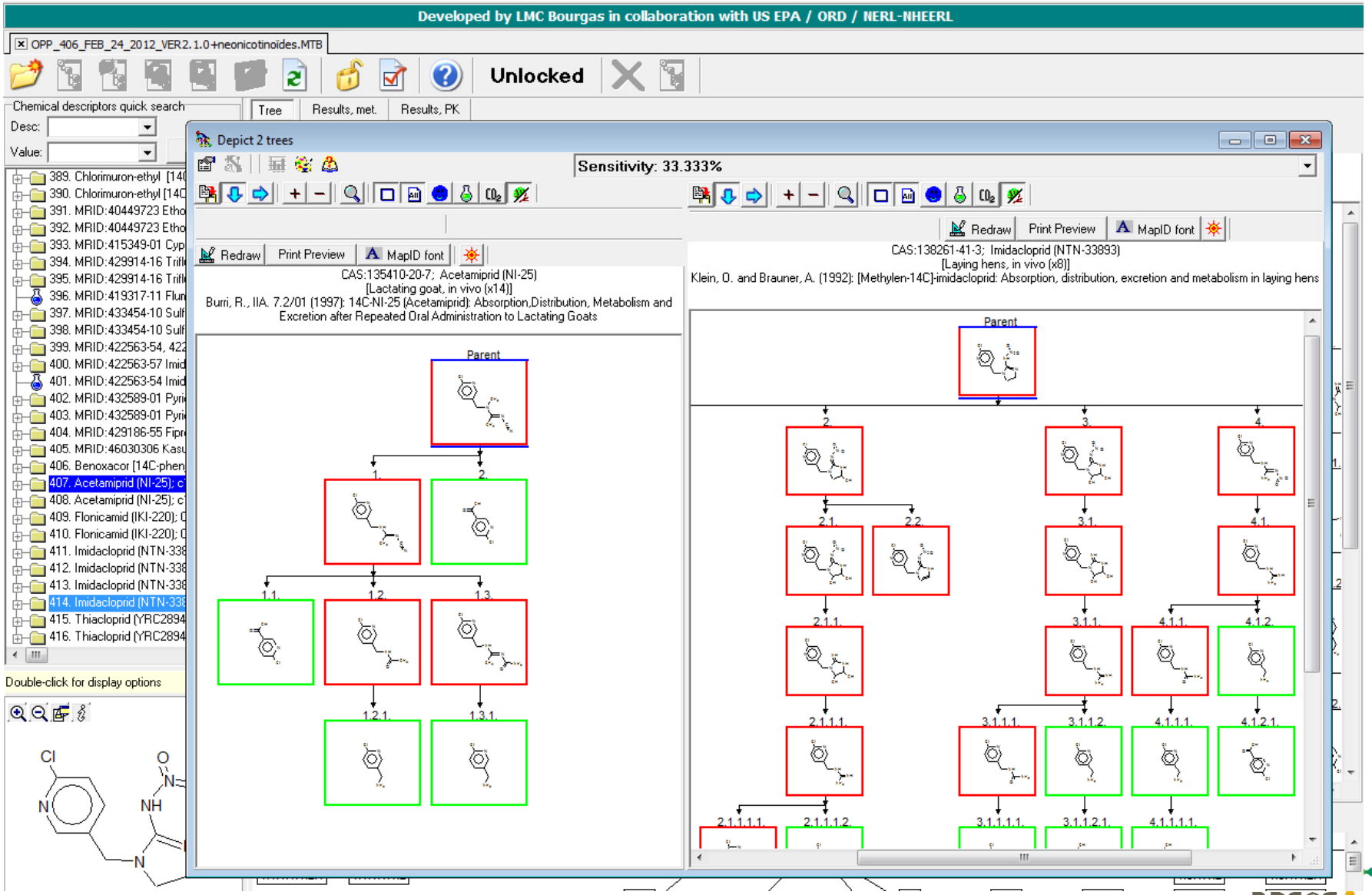


MetaPath database



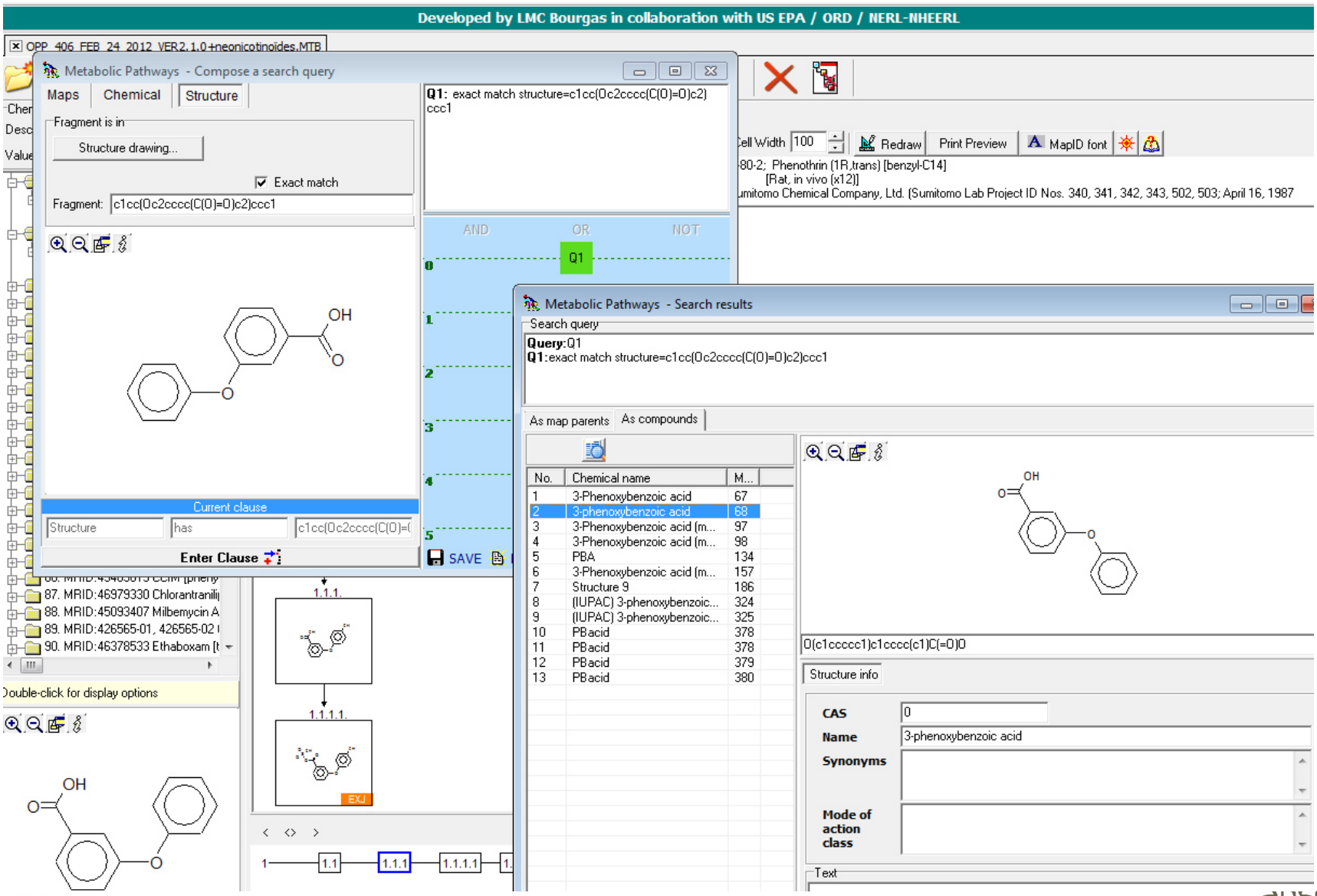
Identification of Common Metabolites

Comparison of 2 metabolic maps



Identification of Common Metabolites

Identify identical or similar molecule: *(Search→Chemicals)*



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

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.

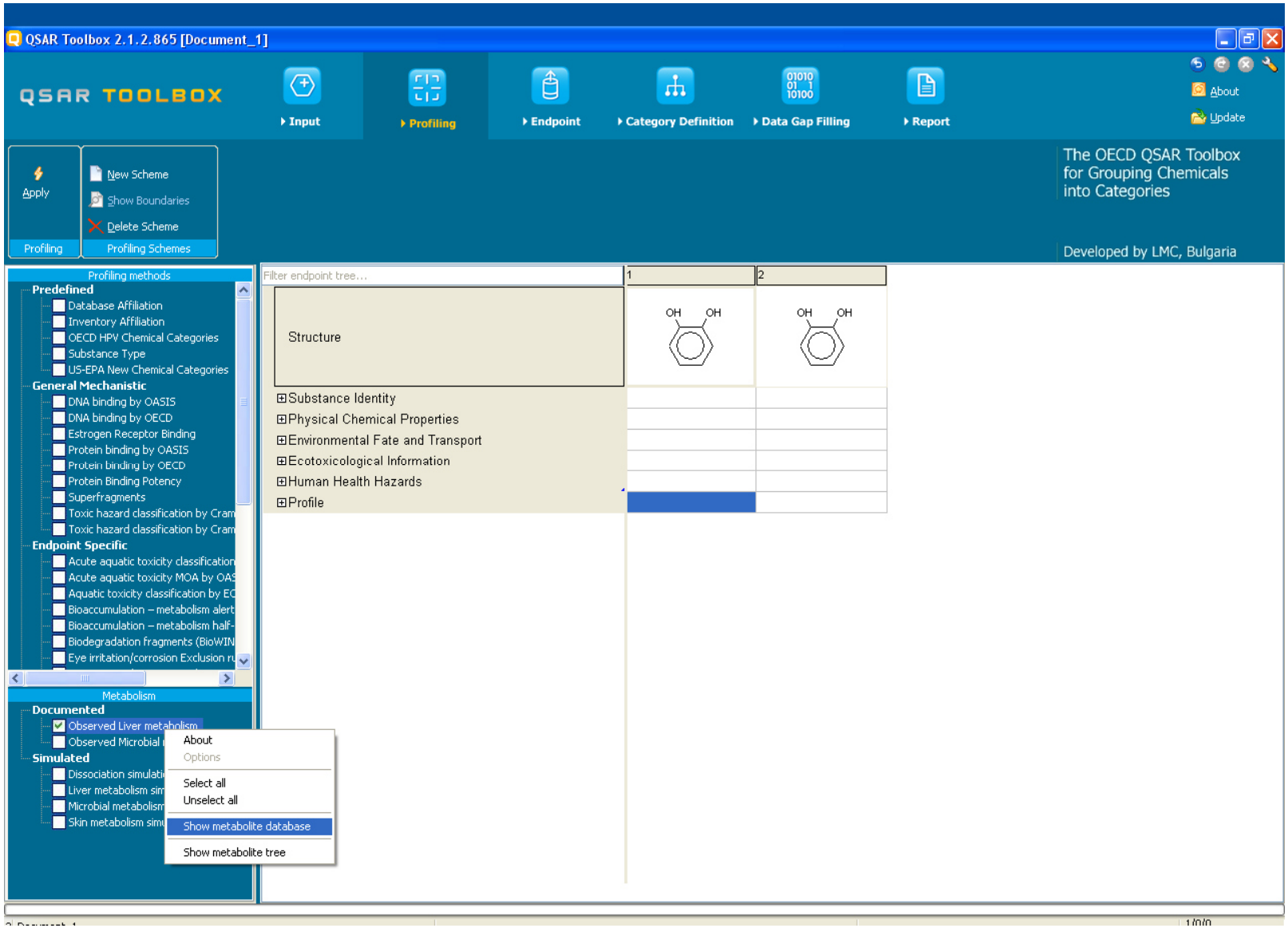
The QSAR Toolbox is a software intended to be used by governments, the chemical industry and other stakeholders to fill gaps in (eco-)toxicity data needed for assessing the hazards of chemicals. The Toolbox incorporates information and tools from various sources into a logical workflow. Grouping chemicals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

NEWS

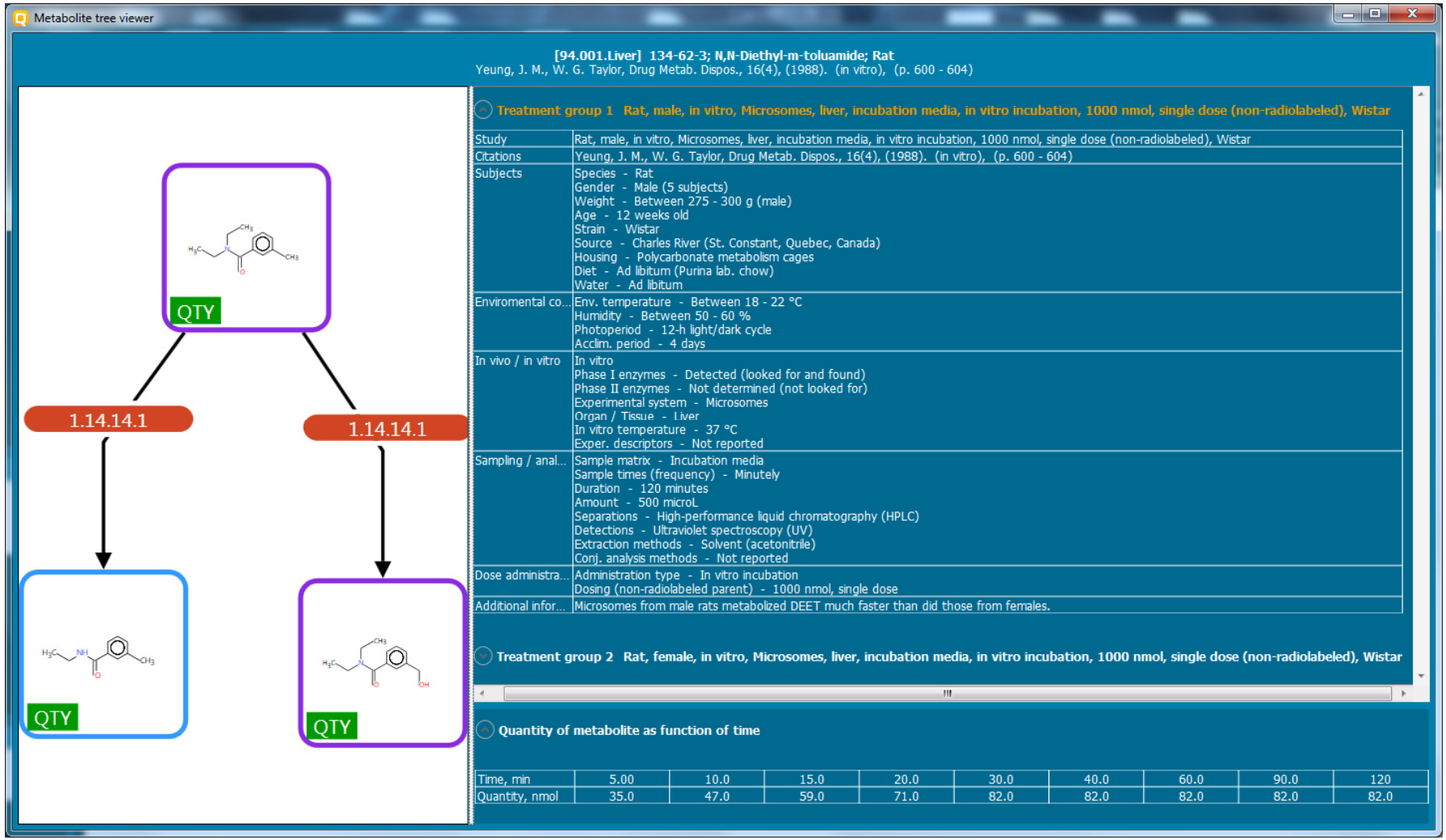
April 2017

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

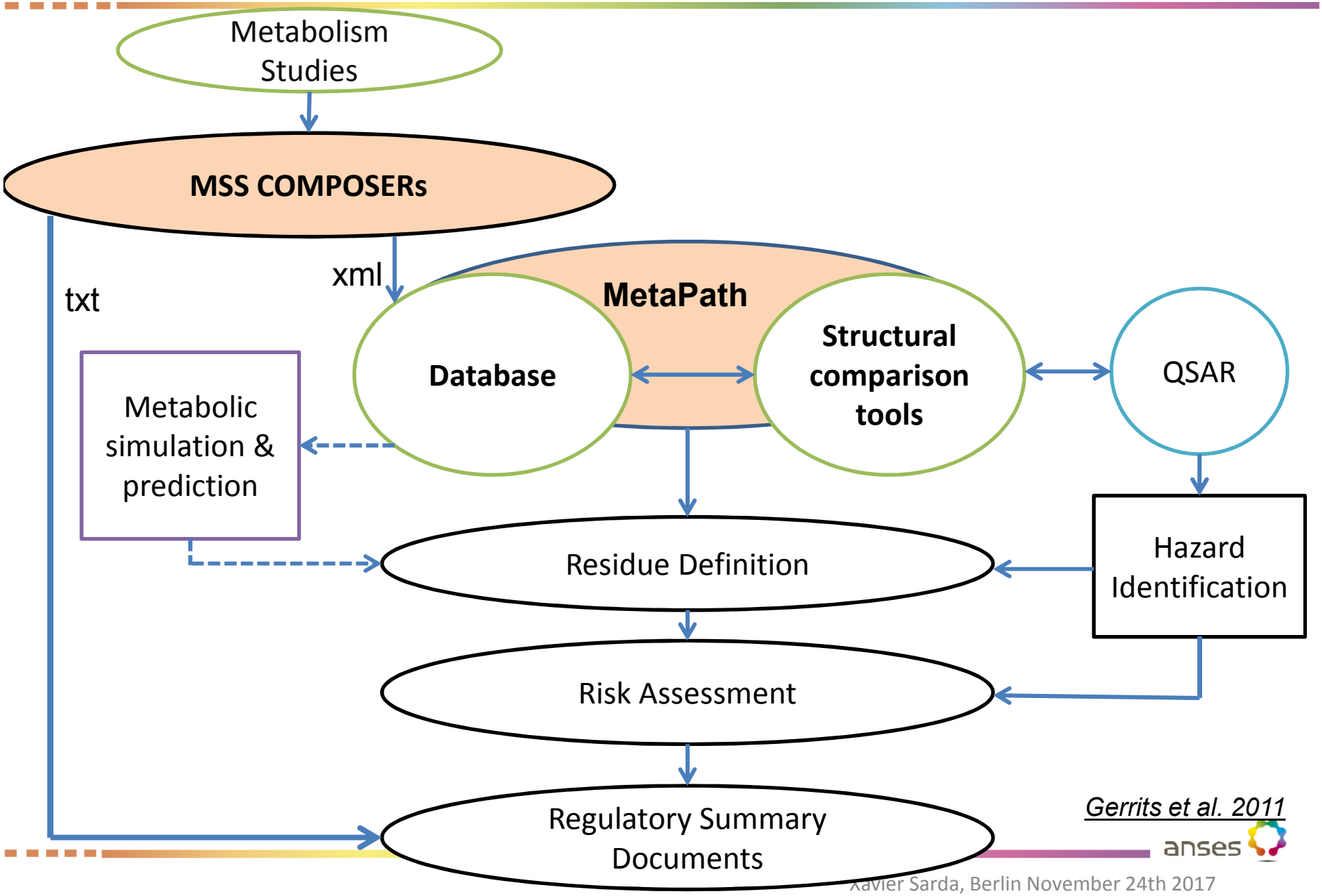
MetaPath in the OECD QSAR ToolBox



MetaPath in the OECD QSAR ToolBox



Use of MetaPath in pesticide evaluation



Gerrits et al. 2011

Conclusion

- 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

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