Activities to facilitate the application of the EFSA PPR guidance document on residue definition.

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LIST OF QUESTIONS AND COMMENTS

1. Only parent as source chemical for read-across?
2. Which specific QSAR and read-across methodology should be used?
3. Is the metabolite common to another substance?
4. Increased workload.
5. I am not a computational toxicologist…

1. ONLY PARENT AS SOURCE CHEMICAL FOR READ-ACROSS?

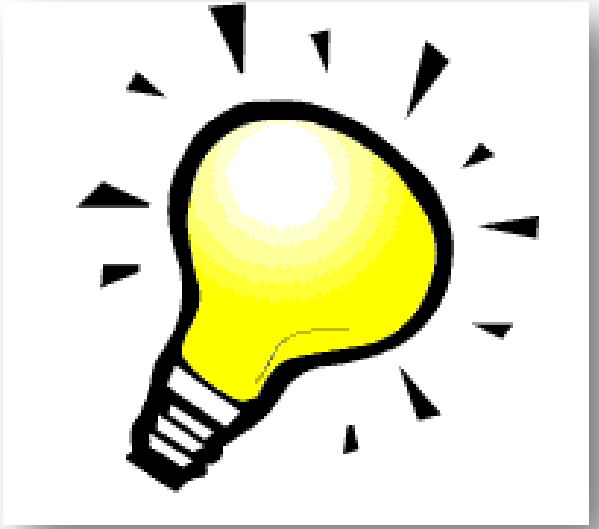
The guidance says:

- *"The first intention is to use the active substance and (if available) its metabolites that have been tested for genotoxicity as source chemical(s)".*

GENOTOXICITY DATABASE

EU peer reviewed genotoxicity studies (≈5000)

- Ongoing EFSA Grant
- ✓ Source: Draft assessment reports.
- ✓ Active substances (n>370)
- ✓ Metabolites (n>500)
- ✓ XML database
- ✓ Excel file (OECD QSAR toolbox).
- Ready by end of 2016



2. ANY SPECIFIC QSAR AND READ-ACROSS?

The guidance says:

- *"to maximise the sensitivity and specificity of the prediction, at least two independent (Q)SAR models, where possible"*

EVALUATION OF EXISTING QSARS AND READ-ACROSS FOR GENOTOXICITY OF PESTICIDES

- EFSA procurement launched 08/2016.
- ✓ Follow up of JRC Report (2010).
- ✓ Genotoxicity Database.
- ✓ Commercial and freely available.
- 19 months.

JRC (2010). Applicability of QSAR analysis to the evaluation of the toxicological relevance of metabolites and degradates of pesticide active substances for dietary risk assessment. http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2010.EN-50/abstract

3. IS THE METABOLITE COMMON TO ANOTHER SUBSTANCE ?

The guidance says:

- *"if a metabolite is not characterised by the toxicity studies conducted with the parent compound, but found to be common to another active substance and covered in terms of toxicity studies of this active substance"*

ONLINE PESTICIDES OUTPUTS DATABASE

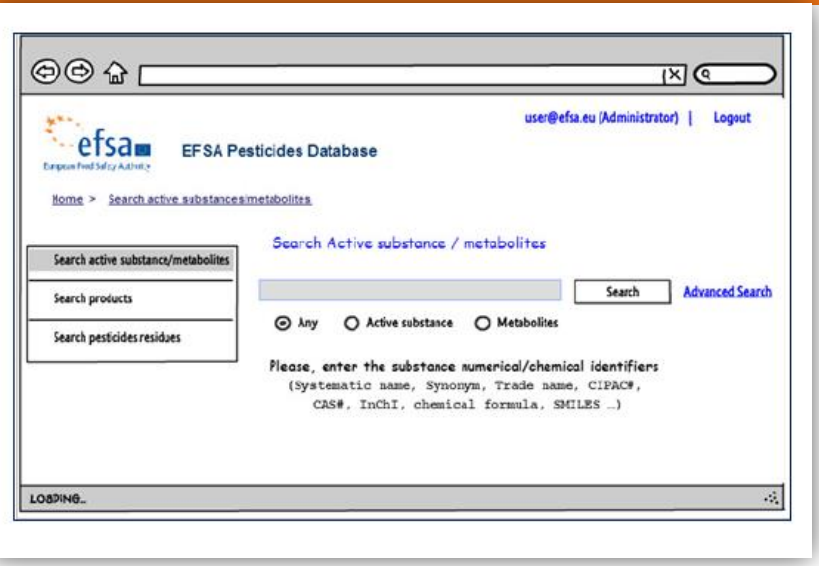
Appendix A – List of end points for the active substance and the representative formulation

Identity, Physical and Chemical Properties, Details of Uses, Further Information (Regulation (EU) N° 283/2013, Annex Part A, points 1.3 and 3.2)

Active substance (ISO Common Name)	Linuron
Function (*e.g.* fungicide)	Herbicide
Rapporteur Member State	Italy
Co-rapporteur Member State	Germany

Identity (Regulation (EU) N° 283/2013, Annex Part A, point 1)

Chemical name (IUPAC)	3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea
Chemical name (CA)	*N*-(3,4-dichlorophenyl)-*N*-methoxy-*N*-methylurea
CIPAC No	76
CAS No	330-55-2
EC No (EINECS or ELINCS)	006-021-00-01
FAO Specification (including year of publication)	AGP: CP/93



- Ongoing EFSA procurement (end of 2017): from pdf to web-based.
- ✓ End points in the EFSA conclusions (physico-chemical, toxicology, residues, ecotoxicology an fate and behaviour).
- ✓ Article 10 and 12 MRL opinions (PROFile).

4. INCREASED WORKLOAD

- All residues/metabolites for genotoxicity assessment.
- Triggers in metabolism studies for toxicity assessment.
- Common metabolites.
- (Complex) exposure estimates.
- Need for good quality of summaries reports.

…Smiles, drawing structures, tabular forms, calculations, QSARs, read-across, comparative assessment…

OECD METAPATH USERS GROUP

- Started in 2009 as a pilot project between USEPA and PMRA.
- Ongoing OECD project (USEPA lead).
- In Europe:
  - BfR, AGES, ANSES.
  - ECHA
  - EFSA (joined in August 2016)
- Need for Applicant/Industry engagement.

OECD METAPATH USERS GROUP

Aim: "Promote the use of Computational Tools to Improve Efficiency In Pesticide Risk Assessments"

- ✓ improve efficiency in data summary and submission.
- ✓ maximize electronic data transfer to minimize data errors.
- ✓ facilitate "quality assurance" (QA) of data.
- ✓ get data in the hands of the risk assessor more efficiently.
- ✓ spend less time compiling data and more time assessing.

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The computational tools:

- **M**etabolism **S**tudy **S**ummary (MSS) Composers: data entry software (ready to be used by applicants).
  - Generate robust summaries reports to be included the Draft Assessment Reports (rat, livestock, plants, rotational crops).
  - Based on OECD harmonised templates (all elements are included).
  - Generate e-submission of summaries of metabolism studies by applicants to be included in MetaPath for use in regulatory peer review process.
- **META**bolism **PATH**way (MetaPath): database and data evaluation tools.

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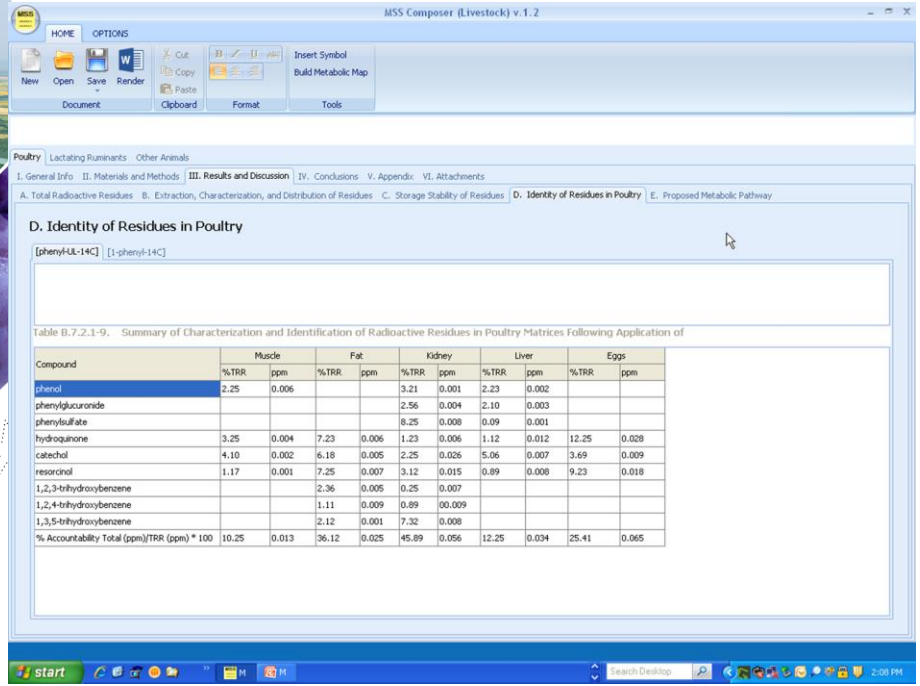
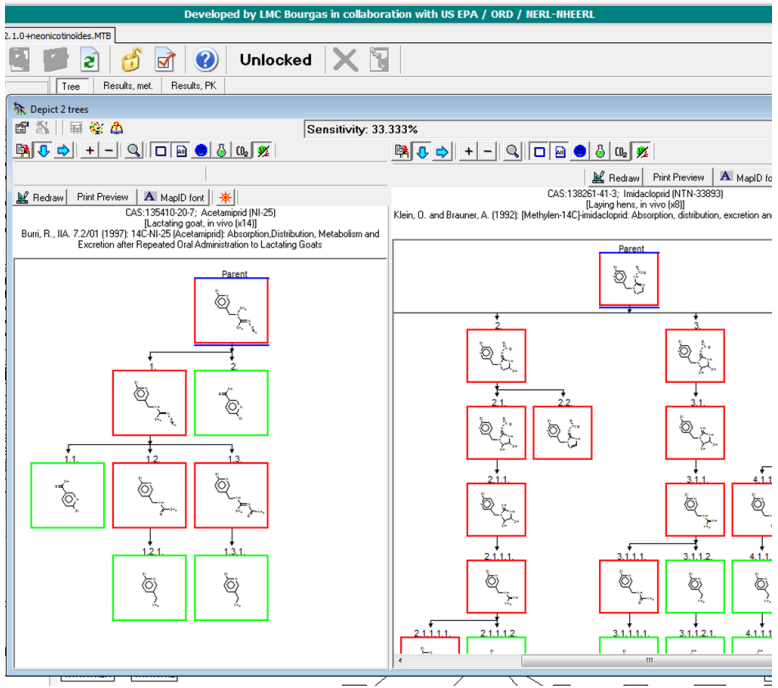
MSS Composers and MetaPath





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Other benefits:

- Industry: product development: earlier identification/resolution of potential residue-related regulatory concerns – to better anticipate concerns and reduce product registration delays; identification and selection of products with more favourable regulatory characteristics; tool for decision-making.
- Codex MRLs: common system/data used across regulatory authorities to efficiently reach consensus on assessments, maximum residue limits (MRLs)/tolerances.
- Metabolism simulator/predictive tool to further facilitate risk assessment.

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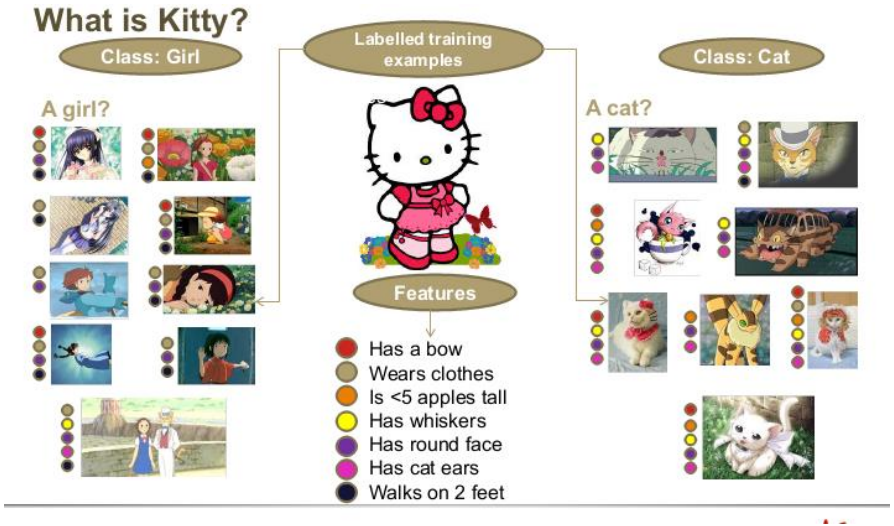
5. I AM NOT A COMPUTATIONAL TOXICOLOGIST

...Similarity...



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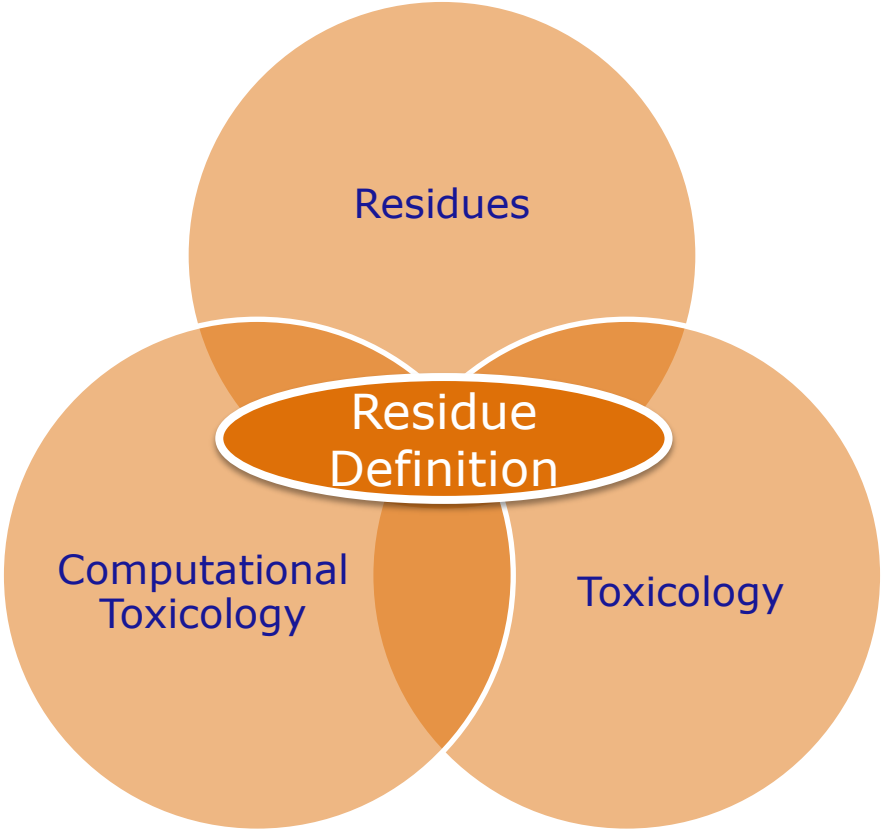
Training is needed.

CONCLUDING REMARK:



LIST OF SOLUTIONS

1. Compilation of a database, specific for the pesticide active substance and their metabolites, comprising the main genotoxicity endpoints. GP/EFSA/PRAS/2014/01.
2. Evaluation of the applicability of existing (Q)SAR models for predicting the genotoxicity of pesticides and similarity analysis related with genotoxicity of pesticides for facilitating of grouping and read across. OC/EFSA/PRAS/2016/01.
3. Development of a consolidated database covering EFSA pesticide outputs on active substances. OC/EFSA/PRAS/2015/02.
4. OECD MetaPath Users Group.
5. Training to be organized.

THANK YOU

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