Initial Steps (1-3 yrs) Case Study

Using Searchable Databases and Predictive Systems: MetaPath

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Case Study Overview:

- Metabolism Pathway Database (MetaPath) is a computational tool that can be used now in the current risk assessment paradigm
- Leverages all existing metabolism knowledge and allows for the potential to reduce animal testing by focusing testing requirements on data needed to support risk assessment
- Streamlines the current risk assessment process by enhancing the efficiency and effectiveness of identifying common and relevant metabolites for inclusion in the risk assessment

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Pesticide Risk Assessment

- Pesticide risk assessments must consider exposure to active ingredient (parent compound) and exposure to major metabolites or environmental degradates that have toxic potential.
  - Metabolism data plays a critical role in pesticide risk assessments, particularly in defining residues of concern in plants, livestock, and drinking water.
- The determination of which metabolites/degradates to include in the risk assessment and tolerance expression must be made for every pesticide active ingredient.
- To expedite the systematic review of pesticide metabolism data, the USEPA initiated the development of MetaPath, a relational and searchable database.

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MetaPath and DER Composer

- Database stores information on pesticide metabolism
  - Stores pathway and summary information on pesticide metabolism in lab animals, livestock, plants, and environmental transformation products
  - Allows visualization of parent chemicals & metabolites displayed as a pathway
  - Enables efficient and systematic metabolite comparisons across chemicals, species, and environmental media of potential risk concerns
- Data Evaluation Record (DER) Composer
  - Captures data efficiently for output in a Word document
  - Enables the continuous autopopulation of MetaPath.

Com

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MetaPath Benefits

- Provides a common platform for global joint reviews/work share efforts
- Provides structure-based searching and identification of structurally similar or unique metabolites
- Identifies common metabolites as residues in plants and livestock.
- Compiles metabolism information systematically to facilitate the development of the metabolism simulator (predictive software,.

Build scientific database to use existing metabolism information in real time & situations

Predictive Model 2013

MetaPath → **Metabolic Simulator**

Lab animal (mostly rat)

Livestock

Plant & Env Degradates

Predict

Easy Information Retrieval & Searching

- Similar metabolites from different parent compounds?
- Sex & species differences?
- Common metabolites formed across rat, livestock, plants, and in the environment?
- Differences in metabolism in a single dose vs. repeat dose study?

Main MetaPath Display

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-NHEERL

List of pesticides in database:

Search by Common name, ChemName, CAS, Agency Code, etc

Clickable 'Tabs' to view supporting information, e.g., Results tables of summary metabolite quantities as compiled from Registrant studies and reported in DER/DARs.

Locked by

Tree | Results, met. | Results, PK

Cell Heigth 146 Cell Width 146 Redraw Print Preview MapID font

28. [28] Buprofezin; c1(N2C(=O)N
29. [29] Cycloxydim; C(C1C(=O)CC
30. [30] Cyprodinil; c1(C2CC2)cc(
31. [31] Dimefuron; C1(C(C)(C)C)=
32. [32] Oxydemeton-methyl; C(CS
33. [33] Metosulam; c1(Cl)c(NS(=
34. [34] Fenoxaprop-ethyl; c12c(c
35. [35] Glufosinate-ammonium; C
36. [36] Imidacloprid; c1(Cl)ccc(Cl
37. [37] Fenoxycarb; c1(OCCNC(=
38. [38] Buprofezin; c1(N2C(=O)N
39. [39] Isoproturon; c1(C(C)C)ccc
40. [40] Cycloxydim; C(C1C(=O)CC
41. [41] Dimefuron; C1(C(C)(C)C)=
42. [42] Kresoxim-methyl; C(=O)(C
43. [43] Kresoxim-methyl; C(=O)(C
44. [44] Kresoxim-methyl; C(=O)(C
45. [45] tebuconazole; C(C)(C)(C)(
46. [46] tebuconazole; C(C)(C)(C)(

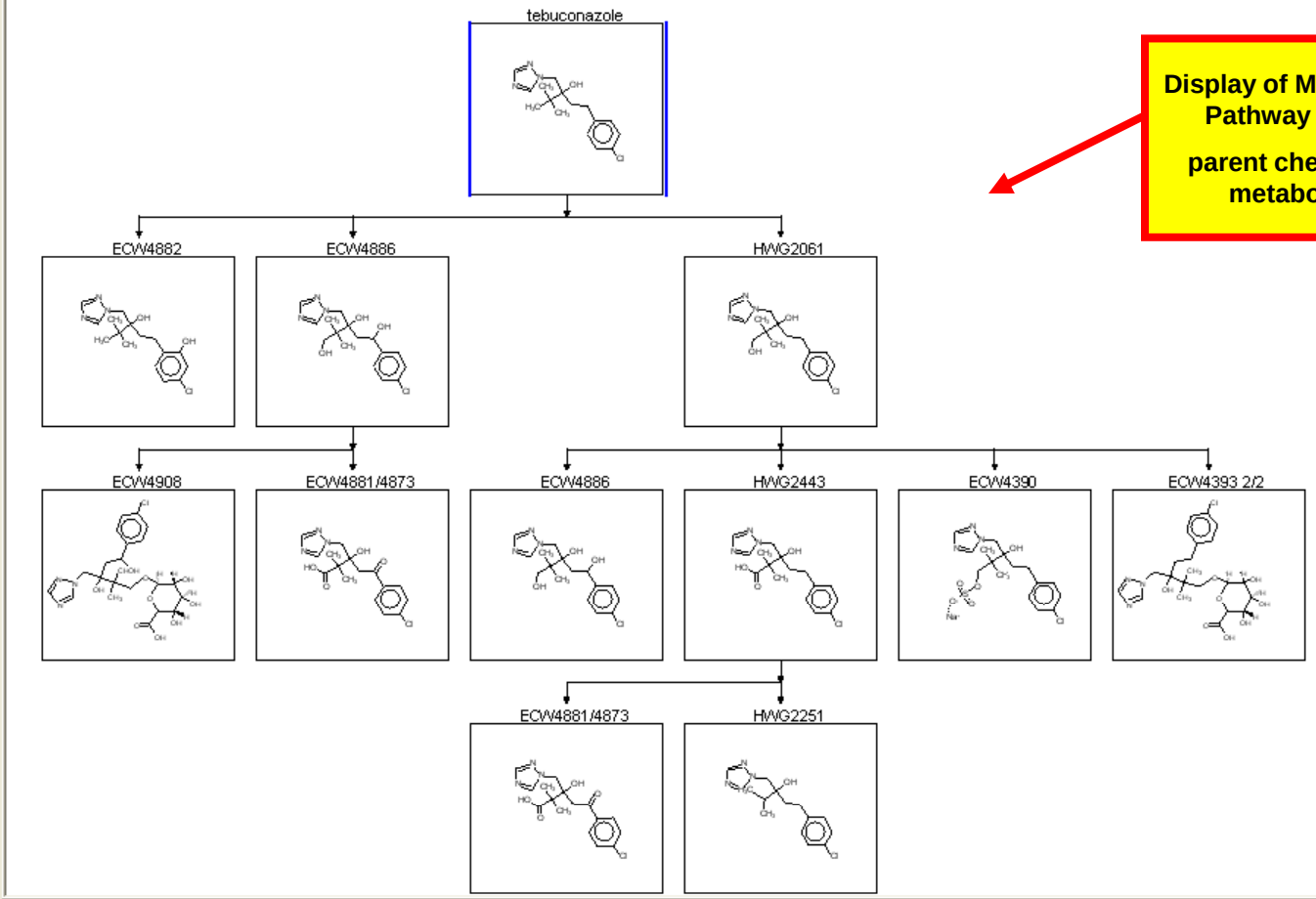
Name	tebuconazole
CAS	107534-96-3
SMILES	C(C)(C)(C)C(O)(CCc1ccc(Cl)cc1

Double-click for display options

CAS:107534-96-3; tebuconazole
[rat, in vivo (x8)]

Display of Metabolism Pathway (map):

parent chemical + metabolites



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Example 1: Reduction in Animal Testing

- An older pesticide “A” is undergoing re-evaluation
  - The rat metabolism study identified three specific metabolites of toxicity concern
  - Question: Will these same three metabolites be found in poultry metabolism map?
    - We have no poultry metabolism data on pesticide “A”
    - Search MetaPath for structural analogs with poultry metabolism data to determine whether same/similar metabolites are formed.

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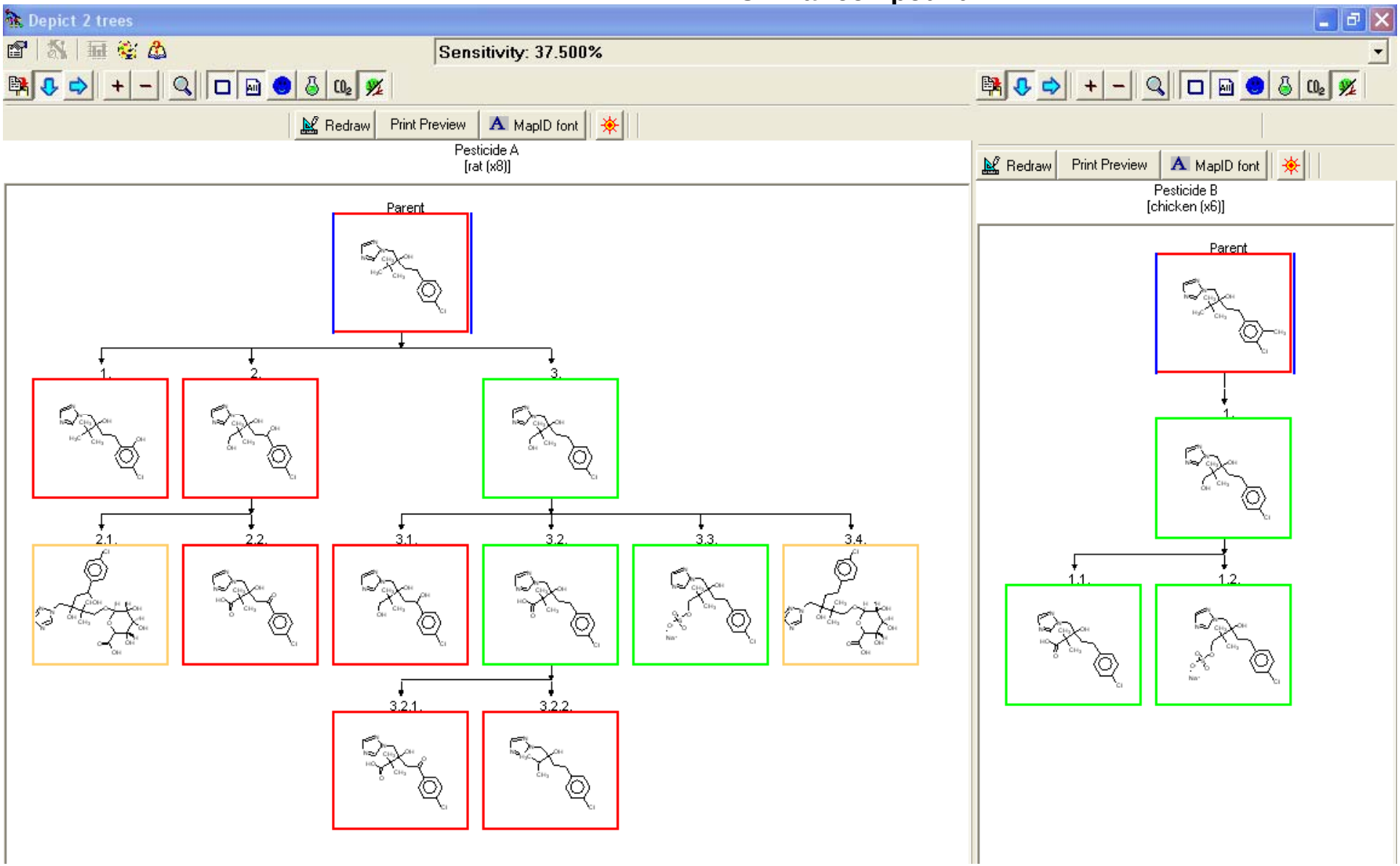
Map Comparisons – One selected map can be compared to another structurally similar compound



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Results:

- Poultry metabolism data from a structurally similar compound confirmed all three metabolites are formed and should be accounted for in the exposure assessment
- No additional poultry metabolism study needed on Pesticide “A” because the data from Pesticide “B” adequately addressed the metabolites of concern so there is an immediate reduction of animal testing

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Example 2: Increased Effectiveness/Efficiency of Risk Assessment

- New Pesticide “C” is a Sulfonylurea
  - Question: Are there any other registered pesticide active ingredients that are structurally related to Pesticide “C”?
    - If so, what are the common metabolites of toxicity concern?
    - Structural sub-fragment search in MetaPath for sulfonylurea pesticides and compare metabolic maps

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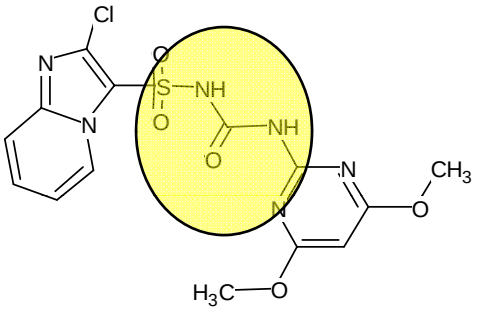
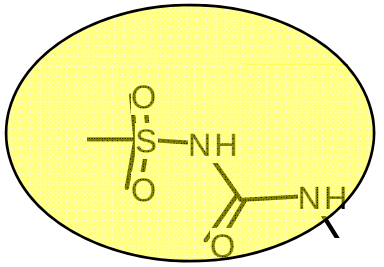
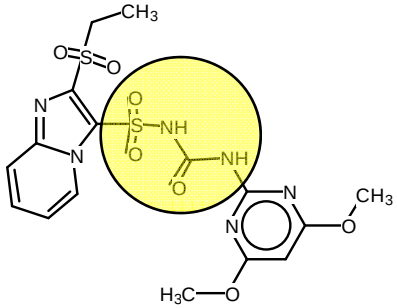
Search MetaPath for structural analogs to Parent



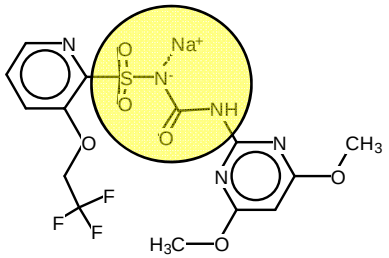
Pesticide C



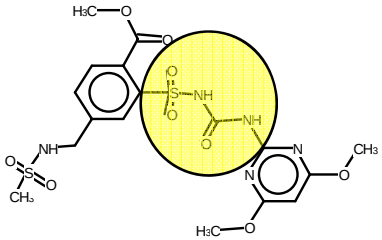
Structural sub-fragment search



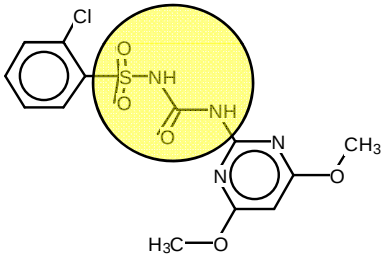
Pesticide W



Pesticide X



Pesticide Y



Pesticide Z

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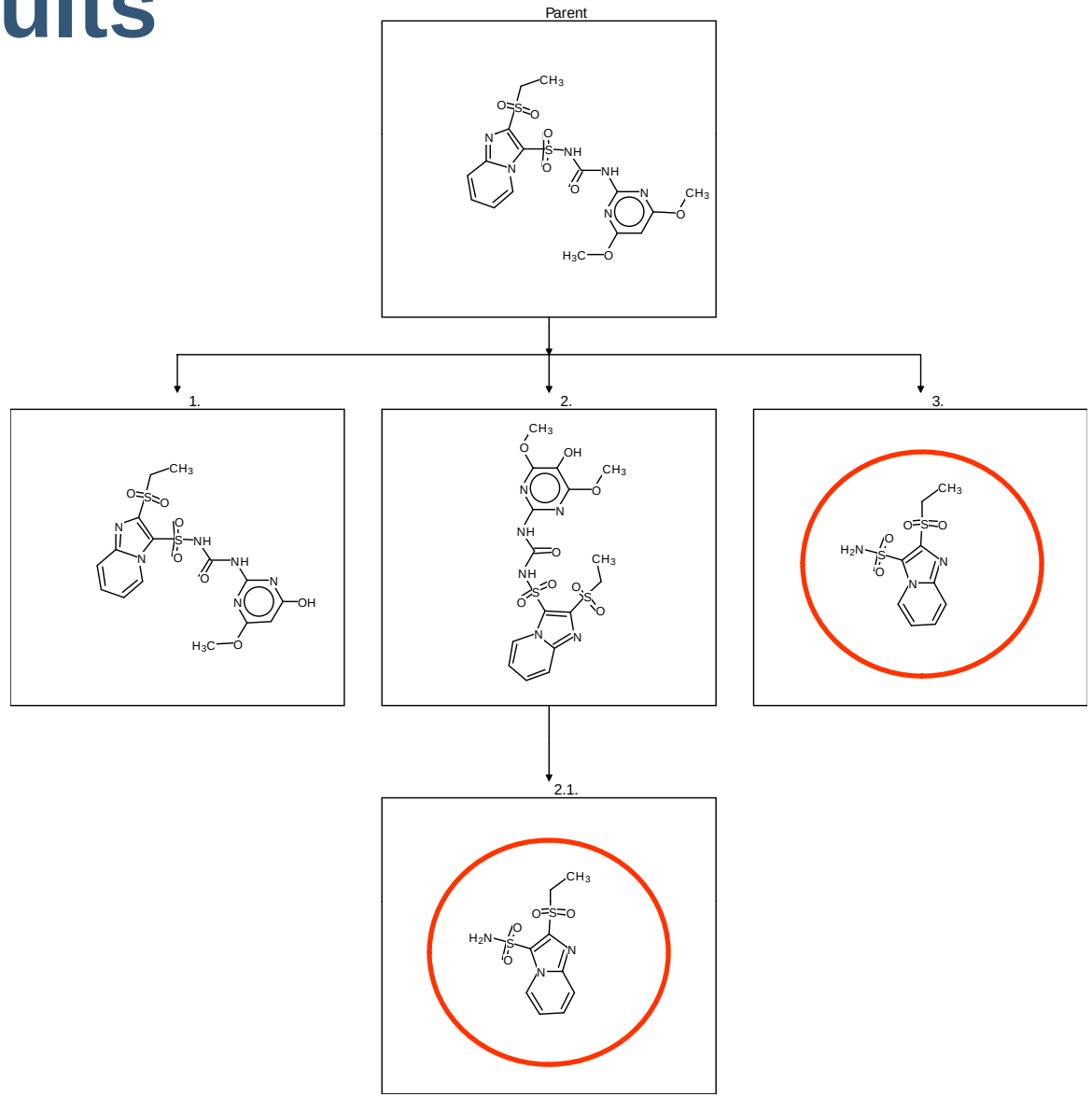
Results

Metabolism maps for each pesticide related to “C” are examined. For instance, map for Pesticide “W” has metabolites of concern



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Results:

- Four additional sulfonylurea pesticides with submitted rat metabolism maps
- Efficient comparison across maps to identify major, common metabolites with potential toxicity concerns to include in the risk assessment
- Enhances the effectiveness of the risk assessment by allowing reviewers to compare metabolism maps to identify similarity and differences in metabolic profiles

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International Collaborations

- **Goal:** Common international platform for populating & evaluating metabolism information
  - International MetaPath User Group established under OECD (Working Group on Pesticides)
  - Collaborators include:
    - Health Canada
    - European Food Safety Authority
    - Australia's Pesticides & Veterinary Medicines Authority and Office of Chemical Safety & Environmental Health
    - Germany's Federal Institute for Risk Assessment
    - France's French Agency for Food, Environment and Occupational Health and Safety

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