



EPA's National Pesticide Program

Presentation for
Science Advisory Board
Exposure & Human Health Comm.
July 1, 2010

Pesticide Laws

- Administered by EPA's Office of Pesticide Programs (OPP)
- Federal Insecticide, Fungicide, & Rodenticide Act (FIFRA)
 - Pre-market approval (registration) of pesticide products
 - Extensive data required to demonstrate safety
 - Risk / benefit balancing standard
- Federal Food, Drug, & Cosmetic Act (FFDCA)
 - Tolerances for residues in food / feed
 - Risk-only standard – “reasonable certainty of no harm”

Our Programmatic Goal Areas

- Be an Effective Gateway to the Pesticide Market
- Be an Effective Steward of Existing pesticides
- Advance Performance Measures for Human Health & Environmental Outcomes
- Enhance our Science & Policy Framework

Office of the Director

Registration

Pesticide Re-Evaluation

Biopesticides &
Pollution Prevention

Antimicrobials

Health Effects

Environmental Fate
& Effects

Biological &
Economic Analysis

Field & External Affairs

Info Tech Resources
Management

Regulatory

Science

Support

Our Organization
(~790 FTEs; ~\$109 M/yr.)

Partnerships

Regions States Tribes
Other EPA Programs
USDA FDA DOI NOAA
USG NIH CDC

International Partnerships

- Working together on global assessments, international standards, trade & regulatory issues, science methods & guidance
 - North American Free Trade Agreement
 - Organization for Economic, Cooperation & Development
 - World Health Organization, Food & Agricultural Organization
 - European Food Safety Authority, etc

Visit: <http://www.epa.gov/oppfead1/international/>

Advisory Committees

- FIFRA Scientific Advisory Panel
- Human Studies Review Board
- Pesticide Program Dialogue Committee

Regulatory Decisions

- New and amended products
 - 20 new chemicals
 - 339 new uses of existing chemicals
 - 3823 label amendments and new products
- Reregistration / registration review
 - Over 600 pesticide active ingredients were reevaluated for compliance with the FIFRA standard
 - 1,135 active ingredients must be reevaluated by 2022

Significant Policy Initiatives

- Expanding current public participation / transparency processes
 - Public comment on proposed registration actions
 - Inerts disclosure
- Worker Protection Standards
- Web-distributed labeling

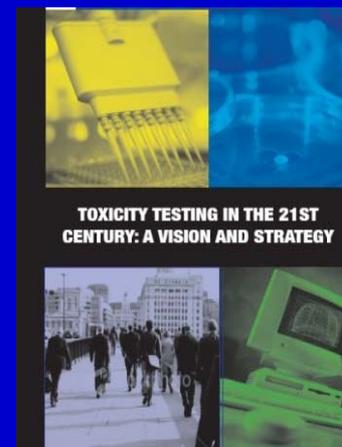
New Science Initiatives

- Expanded Risk Assessment paradigm
 - Workers
 - Children
- Endocrine Disruptor Screening Program
- Nanotechnology
- 21st Century Computational Toxicology

21st Century Computational Toxicology

NRC 2007 “Toxicity Testing in the 21st Century: A Vision & Strategy”

- Transformative paradigm shift using *in vitro* & computer systems.
 - broader coverage of chemicals, end points, life stages.
 - mechanistic & dose information for risk assessment.
 - reduce cost & time of testing, increase efficiency & flexibility.
 - use fewer animals.
- Based on toxicity pathways.



Goal: Managing Chemical Risks

Increase effectiveness, reliability, and focus of risk management decisions for human health and the environment

- Prioritize & screen data-poor chemicals faster, & close information gaps credibly & effectively
 - determine which specific effects data, groups of chemicals, and exposures are essential
- Enhance interpretation of information used in risk assessment, e.g.,
 - Low dose effects
 - Cross-species extrapolation
 - Life stage and susceptibility effects

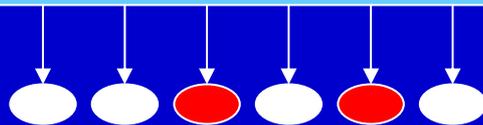
Different Testing Schemes

Integrated Testing & Assessment

Use Existing Knowledge of Exposure & Effects

Examine a chemical or a group of chemicals with shared properties

- Physical Chemical Properties
- Structure-based extrapolation
- Biological activity-based extrapolation
- Other relevant information

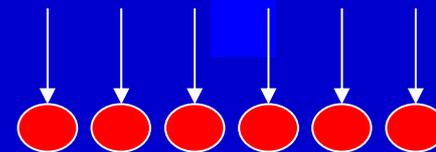
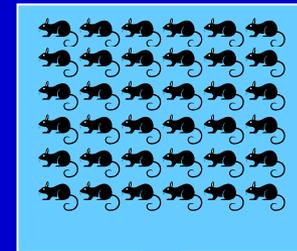


ImmunoTox
NeuroTox
DevTox
ReproTox
Cancer

Determine Information needs and follow up actions

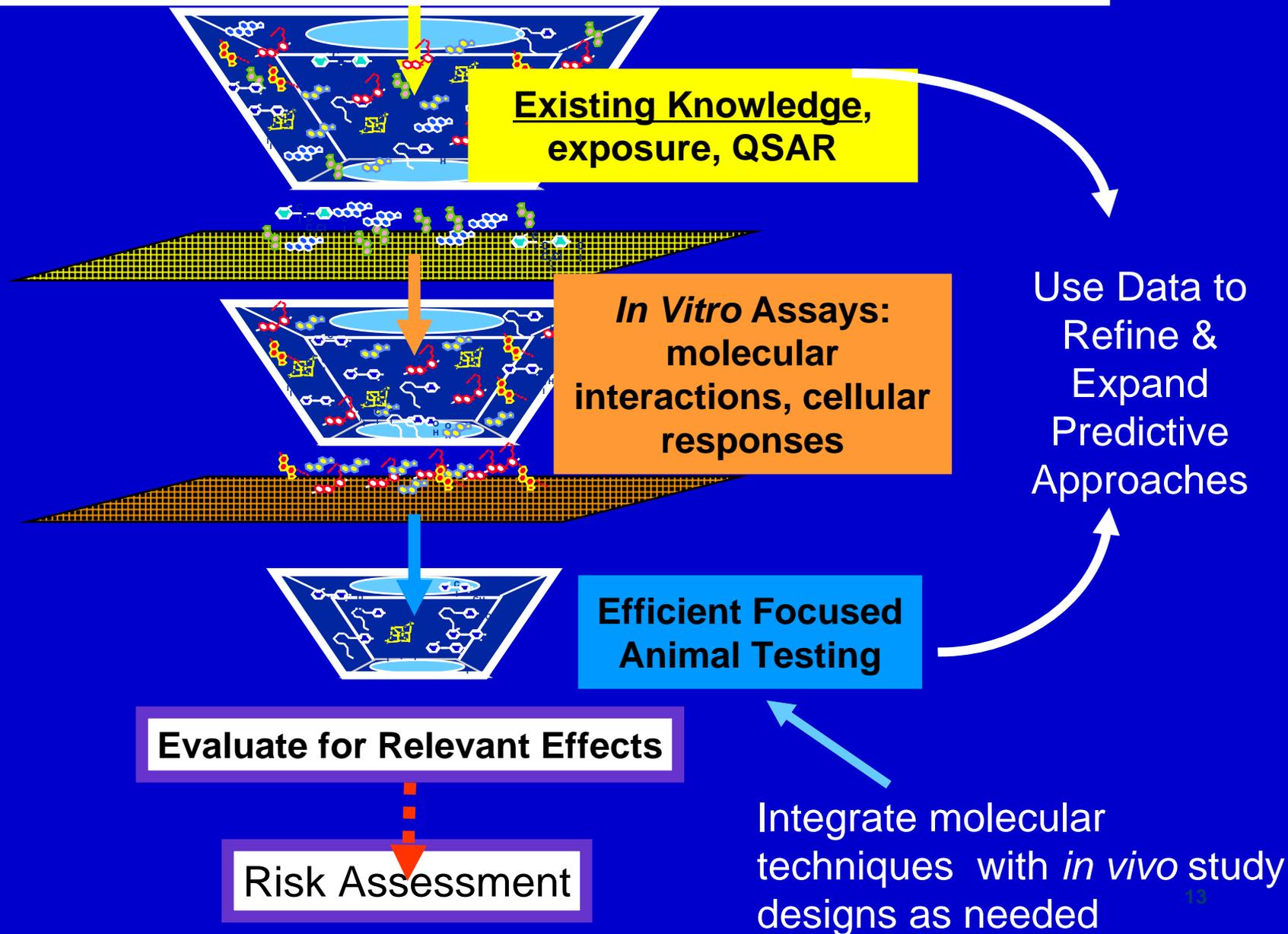
Testing Battery

Chemical by chemical testing for all potential outcomes



ImmunoTox
NeuroTox
DevTox
ReproTox
Cancer

Enhance Integrated Testing & Assessment with New Technologies & Toxicity Pathway Knowledge



Strategic Direction

Increasing Effectiveness, Reliability, and Rate of Assessments



Today

Heavy Reliance on
Extensive Animal Testing

Generate information
For All possible Outcomes

Empirical approach

Paradigm Shift

Increasing Reliance on
in silico & *in vitro* Predictions

Tailor *In vivo* Testing
(intelligent testing)

Mechanism-Based Approach

Transition new *in silico* & *in vitro* methods into Integrated Approaches for Testing & Assessment (IATA)

Near Term Goal: present to 2012-13

Strengthen priority setting / screening for data-limited chemicals to focus on *in vivo* testing

Use new technologies to enhance interpretation in existing risk assessment paradigm for all chemicals (data poor and rich)

Transition away from chemical-by-chemical approaches using IATA: leverage knowledge based on groups of chemicals with shared properties

Enhance Integrated Approaches to Testing & Assessment (IATA)

Benefits:

- Allow use of new methods in real-time and in real situations within current risk assessment paradigm
- Provide an improved means to credibly predict risks and focus information needs and follow up actions
- Focus societal resources on chemicals of greatest concern
- Supports responsible use of animals

More Efficient Animal Studies

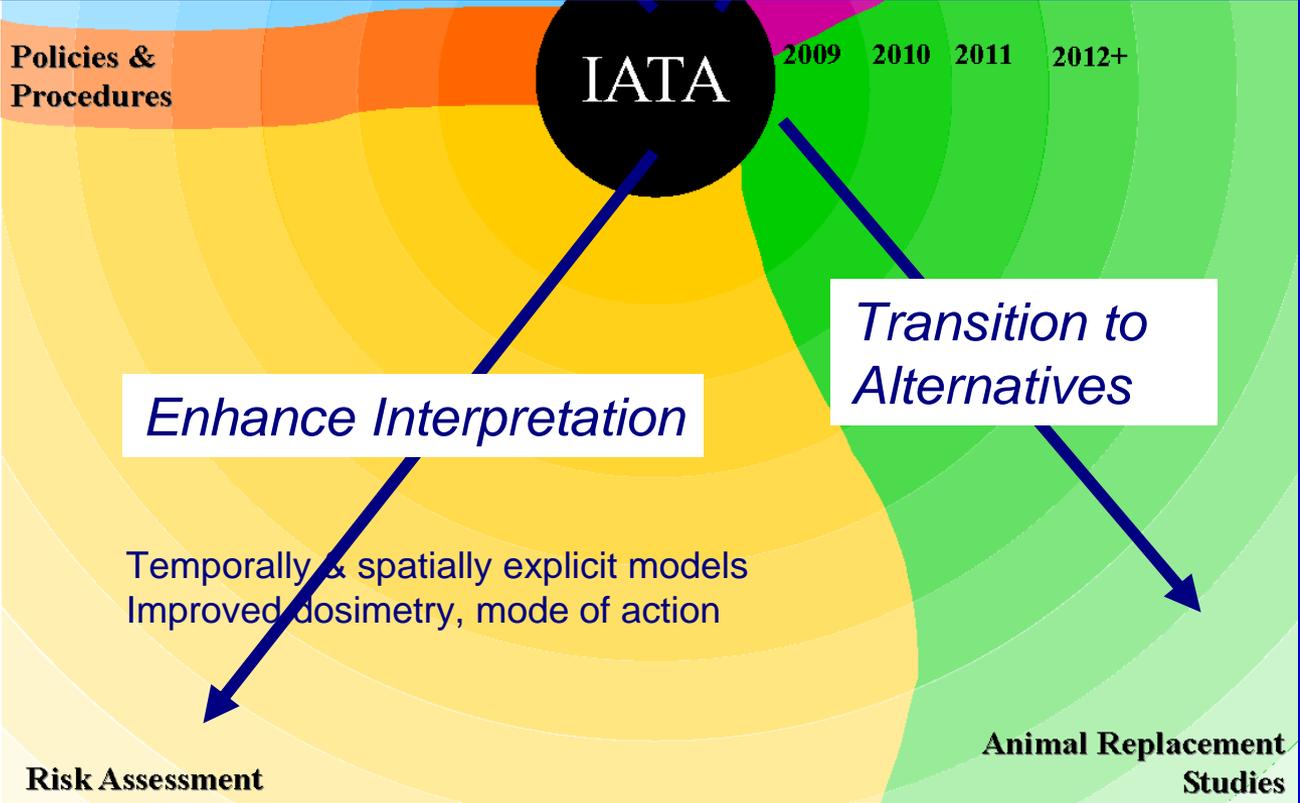
Chemical Priority & Screening Tools

Project Plans

Expand Tool Box

Design Intelligent Testing

Evolution to a new paradigm will depend on success of technological developments and acceptance.



A Paradigm Shift Based on Incremental Steps

Near-term Steps:

- Compile & integrate information for easy access
- Collaborate on research via national and international partnerships
- Develop risk assessment and management approaches via collaboration of regulatory programs and research community
- Engage external scientific peer review and all stakeholders early to ensure transparency and input with new approaches as they progress

International Partnerships



- Information Sharing
- Common Application Tool Boxes
- Mutually Accepted Test Guidelines
- Harmonize Frameworks & Guidance
- Global Acceptance

Organization for Economic Cooperation & Development
North American Free Trade Agreement
International Program for Chemical Safety
European Food Safety Authority, etc.

Stakeholder Engagement



- Why are changes needed?
- What are the expected improvements in health and environmental protection?
- How will new paradigm change risk-based decisions?
- What is the expected timeline for transition to new tools?
- How will we recognize successes and failures?


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Pesticide Program Dialogue Committee 21st Century Toxicology/New Integrated Testing Strategies Workgroup

August 2008

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 For more information contact [Vera Au](mailto:au.vera@epa.gov) (au.vera@epa.gov).

Meeting dates scheduled for the remainder of 2009.

- November 18, 2009, 2:00 - 4:00 pm ET, One Potomac Yard South, Room N-4830
- December 9, 2009, 2:00 - 4:00 pm ET, One Potomac Yard South, Room N-4830

- [Previous Meetings](#)
- [Objectives](#)
- [Workgroup Members](#)
- [EPA Workgroup Members](#)

Previous Meetings

- October 13, 2009
 - [Agenda](#)
 - **New!** [Medical Management of Pesticide Poisoning: Why We Need Diagnostic Tools \(PDF\)](#) (30 pp, 177.24K) by, James R. Roberts, MD, MPH
 - **New!** [Why Do We Need Diagnostic Tests and Biomarkers for Pesticides? \(PDF\)](#) (27 pp, 486.69K) by, Matthew Keifer MD, MPH
- September 9, 2009
 - [Agenda](#)
 - [Executive Summary \(PDF\)](#) (1 p, 27.28K)
- July 8, 2009
 - [Agenda](#)
 - [Metabolic Simulator presentation \(PDF\)](#) (22 pp, 749K) by
 - [Executive Summary \(PDF\)](#) (1 p, 21.71K)
- June 10, 2009
 - [Agenda](#)
 - [Executive Summary\(PDF\)](#) (1 p, 23.27K)
- May 20, 2009

Related Links

- [Symposium on Toxicity Pathway-Based Risk Assessment](#) [\[EXIT Disclaimer\]](#)
- [Transforming Environmental Health Protection \(PDF\)](#) by Francis Collins, George Gray, and John Bucher in Science
- [OPPT models & methods developed to screen chemicals for potential hazards or risks](#)
- [Use of Structure-Activity Relationship Information and Quantitative SAR Modeling for Fulfilling Data Requirements for Antimicrobial Pesticide Chemicals and Informing EPA's Risk Management Process - EPA-HQ-OPP-2008-0110-0045](#)

November 16, 2010
FACA Workshop to
Broaden the Dialogue

In Summary

- **In the near-term (present to 2-3 years):**
 - Accelerated and enhanced priority setting / screening to focus animal testing
 - Enhance interpretation of current information
- **In the long-term (~10 years):**
 - Greater reliance on *in silico*, *in vitro*, and highly targeted animal studies only as needed
 - Mechanism-based assessments is the standard

Achievable with strong scientific & stakeholder support through a transparent process

Example

MetaPath (metabolism pathways)

- Collaborative Regulatory Program & Office of Research Development Project
 - OPP & ORD
 - National Health and Environmental Effects Research Laboratory (NHEERL), Mid-Continent Ecology Division (MED), Duluth, MN
 - National Exposure Research Laboratory (NERL), Ecosystems Research Division (ERD), Athens, GA
- Databases & Information Sharing, Common Application Tool Box, International Partnerships (Global Acceptance), Stakeholder Engagement

MetaPath (metabolism pathways)

- Database that stores information on pesticide metabolism
 - Lab animals, livestock, plants, and environmental transformation products
 - Allows for visualization of parent chemicals & metabolites displayed as a pathway or map
 - Enables efficient and systematic comparisons of metabolites across chemicals, species, and environmental media to identify metabolites of potential risk concern

Key Benefits of MetaPath

- Provides a 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.
- Systematic compilation of metabolism information will facilitate development of a metabolism simulator

Building a Scientific Database to Use Metabolism information in Real Time

MetaPath

Metabolic Simulator 2013

**Lab animal
(mostly rat)**

Livestock

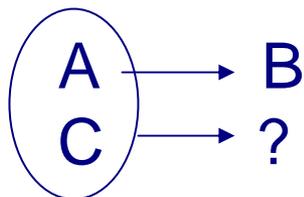
**Plant & Env
Degradates**

Predict

Easy information retrieval & searching

- >Are there similar metabolites
from different parent compounds
- >Are there sex & species differences

Read Across



The main MetaPath display screen

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

List of pesticides in the database:

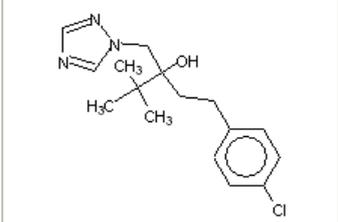
Search by Common name, ChemName, CAS, Agency Code, etc

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

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

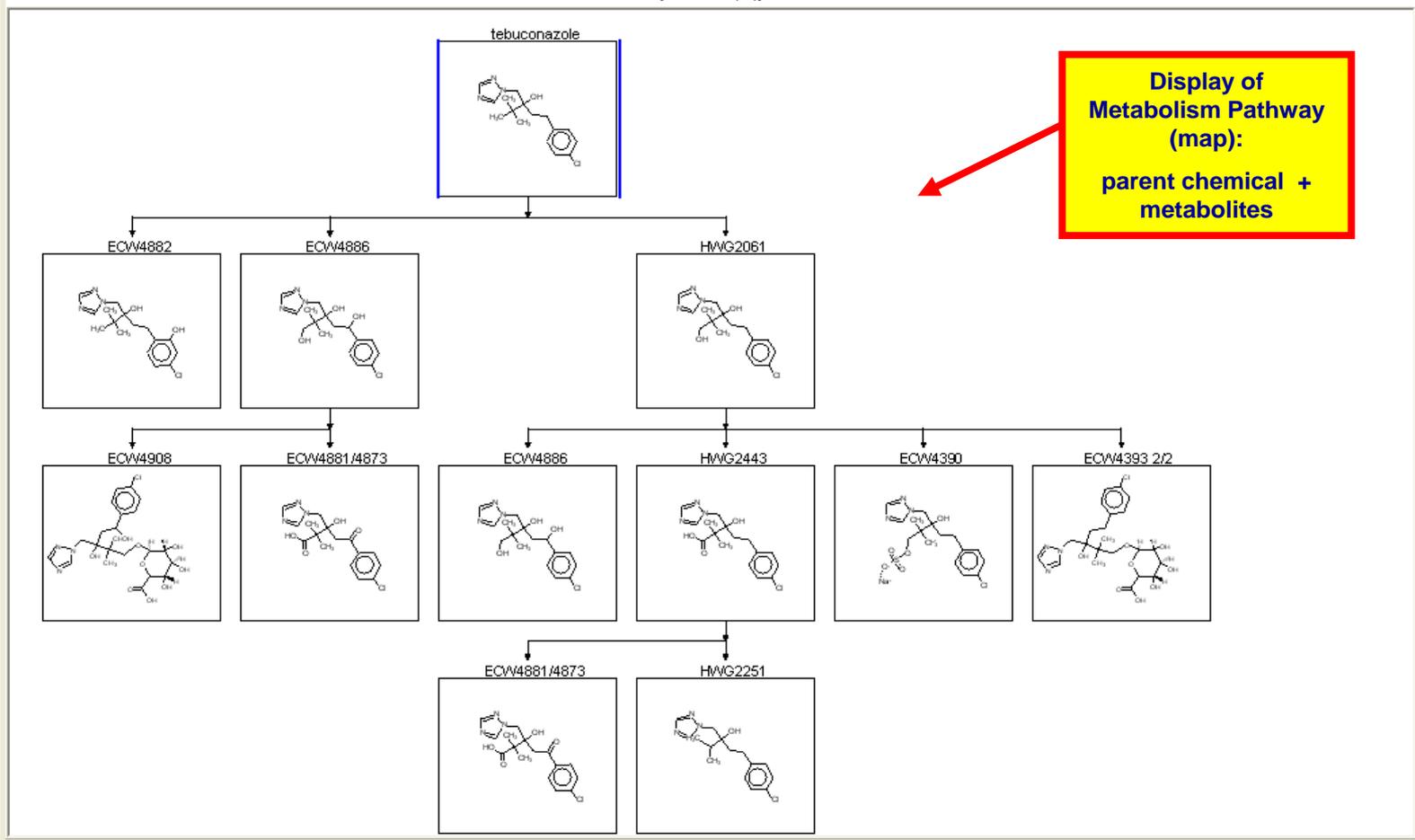
Double-click for display options



Tree Results, met. Results, PK

Cell Height 146 Cell Width 146 Redraw Print Preview MapD font

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

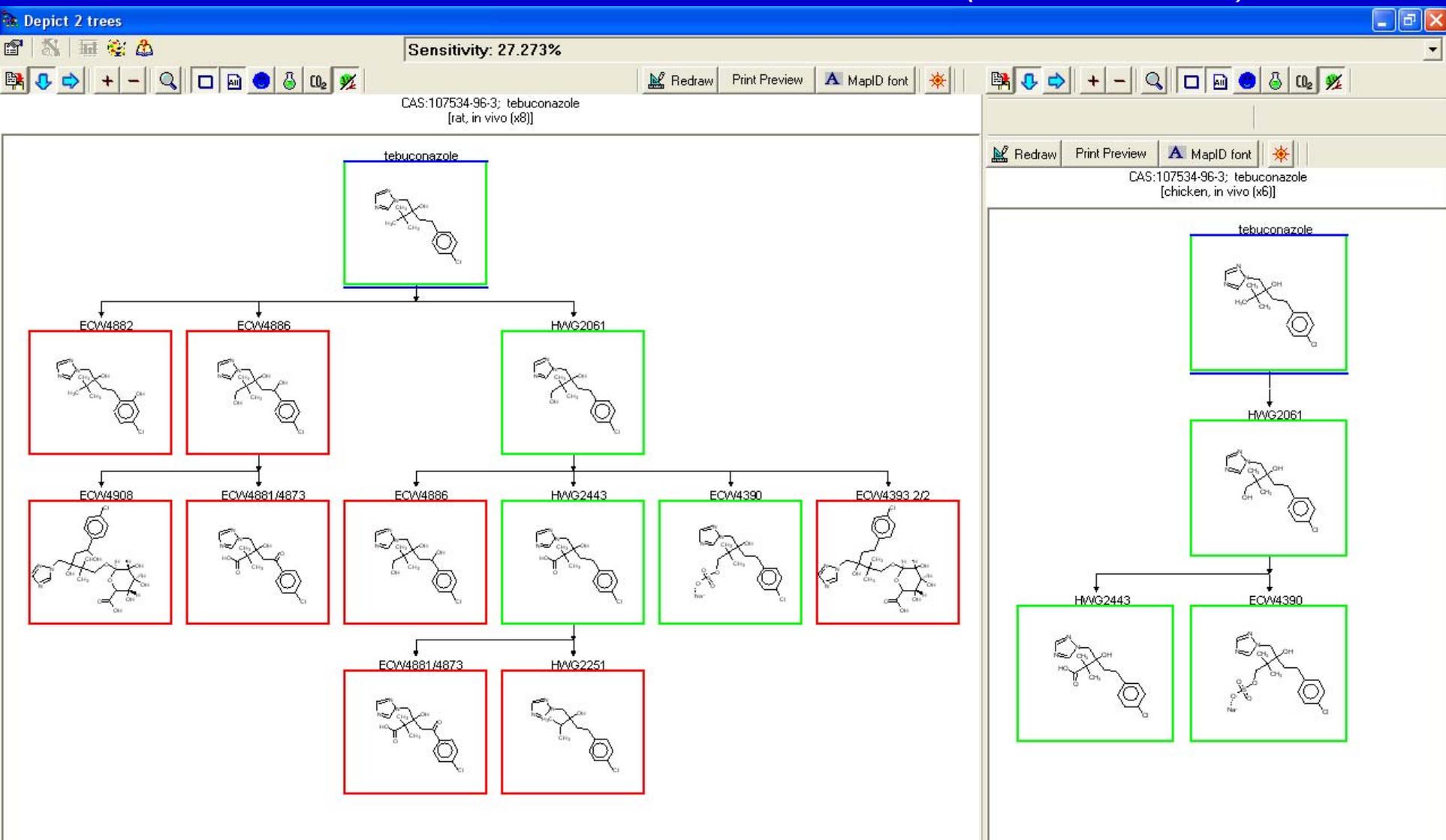


Display of Metabolism Pathway (map):

parent chemical + metabolites

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

Example: All 3 metabolites found in laying hens exposed to tebuconazole (*right screen - green boxes*) are found in rats (*left screen - green boxes*), however, 8 additional metabolites are found in the rat that were not observed as residues in hens (*left screen – red boxes*).



A MetaPath data evaluation tool that shows which metabolites were found in which Treatment Group (e.g. Matrix)

Highlight Treatment Group icon:
Indicates which metabolites were observed under what experimental condition; the "Highlight treatment group" pop-up box allows User to select the treatment(s) and observe which metabolites were formed (indicated in map by colored boxes).

In this example the metabolites found at 20 mg/kg dose in M & F in green & yellow boxes were only seen in urine and not in feces; the metabolite still only in a black box was not found in rats at the high dose.

Coloring and specifics:

<input checked="" type="checkbox"/>	[1] male; feces; 20 mg/kg; radiolabeled parent
<input checked="" type="checkbox"/>	[2] male; urine
<input checked="" type="checkbox"/>	[3] female; feces; 20 mg/kg; radiolabeled parent
<input checked="" type="checkbox"/>	[4] female; urine
<input type="checkbox"/>	[5] female; feces; 2 mg/kg; radiolabeled parent
<input type="checkbox"/>	[6] female; urine
<input type="checkbox"/>	[7] male; feces; 2 mg/kg; radiolabeled parent
<input type="checkbox"/>	[8] male; urine

Treatment group:
Rat-female- 20 mg/kg

Reference:

- Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the Who Expert Group on Pesticide Residues. Rome, Italy, September 19-28, 1994., pp. 1055 - 1137

Subjects:

- Species - Rat
- Gender - Female (5 subjects)
- Age - Not reported
- Strain - Wistar

In vivo / in vitro:

- In vivo
- Exper. descriptors - Not reported

Sampling / analytical:

- Sample matrix - Urine
- Sample times (frequency) - Final
- Duration - 72 hours
- Separations - HPLC
- Detections - Scintillation counting
- Extraction methods - Solvent (methanol)
- Conj. analysis methods - Not reported

Draft DER created using the Livestock DER Composer (p.1 of txt file for editing by risk assessor is shown)

Metabolism (year of study) / Page 1 of 17
 OPPTS 870.7485/ DACO 4.59/ OECD 417

NAME OF TECHNICAL/PC Code	
EP A Reviewer:	Signature
[Insert Branch], Health Effects Division (7509C)	Date 1/28/2010
EP A Secondary Reviewer:	Signature
[Insert Branch], Health Effects Division (7509C)	Date 1/28/2010
EP A WAM:	Signature
[Insert Branch], Health Effects Division (7509C)	Date 1/28/2010
TXR#:	Template version: 02.06

DATA EVALUATION RECORD

STUDY TYPE: Nature of the Residues in Animals - Lactating goat; DACO 6.2 / OPPTS 860.1300/OECD II6.2.2, 6.2.3 & IIIA 8.2, 8.4.1, 8.4.2

AGENCY CODE(S): (US EPA PC CODE) 111111, (PMRA NUMBER) 2222222, (EFSA NUMBER) 3333333, (AUSTRALIAN CODE) 4444444

DP BARCODE: D287253

SUBMISSION NO.: 1999-1713/1714

TEST MATERIAL COMMON NAME: Famoxadone (XXXX-XXX)

TEST MATERIAL PURITY: 99.9 %

IUPAC NAME: 3-anilino-5-methyl-5-(4-phenoxyphenyl)-1,3-oxazolidine-2,4-dione

CAS NAME: 5-methyl-5-(4-phenoxyphenyl)-3-(phenylamino)-2,4-oxazolidinedione

SYNONYMS: XXXX-XXX; Famoxadone

Reference	MFID
Das, J. Smith, Bruce M III 2010 Metabolism of [14C] Famoxadone in Lactating Goat. <i>Academy Company, Wilmington, USA. Research C-4-3</i> ; 100 pp.	88888888
Toner, J 1999 [14C] XXXX-XXX Absorption, distribution, metabolism and excretion following oral administration to the dairy goat for three consecutive days. <i>Academy Company, Wilmington, USA. AMR 1831-93</i>	88888888
Black J 2004 [14C] XXXX-XXX Absorption, distribution, metabolism and excretion following oral administration to the dairy goat for three consecutive days. <i>E.I. duPont & Nemours and Company, Wilmington, USA. AMR 1831-93 Supplement No. 1</i>	88888888

SPONSOR:

EXECUTIVE SUMMARY:
 Famoxadone, radiolabelled either in the [14C]phenoxyphenyl [14C-POP] or [14C]phenylamino [14C-PA] moiety, was administered orally (gelatin capsules) to three lactating goats (Alpine & Toggenburg strain) at approximately 10 mg/kg relative to food intake per day (58-62 µCi/mg; 22-23mCi/mole) for seven consecutive days. Tissue and milk samples were homogenized, combusted and radioassayed by liquid scintillation counting (LSC). Identification and characterization of 14C-residues was achieved by high-performance chromatography (HPLC) with a diode array detector/radiodetector. Mass spectrometry (MS) was used to confirm the identity of the parent compound and metabolites.

International Collaborations



- OECD Working Group on Pesticides
- European Food Safety Authority and the Pesticide Steering Committee
- Canada's Pesticide Management Regulatory Authority
- Australia's Pesticides & Veterinary Medicines Authority and Office of Chemical Safety & Environmental Health