ROAD MAP FOR IMPLEMENTING THE USEPA ENDOCRINE DISRUPTOR SCREENING PROGRAM

Karen Whitby, Ph.D.
Email: whitby.karen@epa.gov
Office of Pesticide Programs
U.S. Environmental Protection Agency

December 6, 2005

Introduction and Overview

- Regulatory Context
- Data Requirements
- Risk Assessment
- New Testing Strategies
- Path Forward

Regulatory Context

The Pesticide Program

- **Governed by Two Statues**:
  - **The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)—1947**
    - Licensing of pesticides
    - Data requirements
  - **The Federal Food Drug and Cosmetic Act (FFDCA)—1906**
    - Tolerances
    - Reasonable certainty of no harm standard

FQPA Amendments to Section 408 of FFDCA

When establishing tolerances the Agency must consider available information…

- "concerning the special susceptibility of infants and children to the pesticide chemical residues…" [FFDCA 408(b)(2)C]

- "cumulative effects of such residues and other substances that have a common mechanism of toxicity…" [FFDCA 408(b)(2)D(v)]

FQPA Amendments to Section 408 of FFDCA

When establishing a tolerance the Agency must consider available information…

- "concerning aggregate exposure from dietary and non-occupational sources… [FFDCA 408(b)(2)D(vi)]
- "whether the pesticide…may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen or other endocrine effects" [FFDCA 408(b)(2)D(viii)]

Data Requirements

Pesticide Data Requirements Are Mandated by FIFRA

- Exposure and Hazard Guideline Data Requirements
  - Listed in 40 CFR 158

http://www.epa.gov/pesticides/science/guidelines.htm

- Other data as needed
  - Data Call-In (DCI) under FIFRA 3(c)(2)(b)

Ecological Effects Data

Freshwater Aquatic

Fish acute toxicity test (bluegill sunfish and rainbow trout)

Aquatic invertebrate toxicity test (Daphnia magna)

Mysid acute toxicity test

Fish chronic exposure (fathead minnow)

•Early life stage

•Full life cycle

Chronic invertebrate toxicity test (Daphnia magna)

Estuarine Marine

Fish acute toxicity test (sheepshead minnow)

Acute invertebrate toxicity test (oyster)

Fish chronic exposure (sheepshead minnow)

•Early life stage

•Full life cycle

Chronic invertebrate exposure (oyster)

Ecological Effects Data

Birds

Acute oral toxicity test (mallard duck or bobwhite quail)

Subacute dietary toxicity test (mallard duck and bobwhite quail)

Chronic toxicity test (mallard duck and bobwhite quail)

Small Mammals*

Studies not required on wild mammals

HH hazard data are used:

- Acute oral toxicity – rats
- Subchronic dietary toxicity test – rodents
- Developmental toxicity – rats
- 2 Generation reproductive toxicity - rats
- Chronic exposure toxicity - rodents

*Wild mammal testing may be requested on a case-by-case basis. Other endpoints may be considered on a case-by-case basis.

Current HH Requirements for a Conventional Food-Use Pesticide

Acute	Subchronic
Oral toxicity—rat	90-day feeding—rodent and non-rodent
Dermal toxicity	21- or 28-day dermal
Acute inhalation—rat	Dermal Penetration
Primary eye irritation—rabbit	90-day dermal*
Primary dermal irritation	90-day inhalation—rat*
Dermal sensitization	90-day neurotoxicity—rat*
Delayed neurotoxicity—hen*	
Acute neurotoxicity—rat*	

**conditionally-required*

Current HH Requirements for a Conventional Food-Use Pesticide

Chronic

Chronic feeding—rodent and nonrodent

Carcinogenicity—rat and mouse

Developmental and Reproductive Toxicity

Prenatal Developmental Toxicity—rat and rabbit

2-Generation Reproduction

Mutagenicity

Bacterial reverse mutation assay

In vitro Mammalian gene mutation

In vivo cytogenetics

Metabolism

Rat metabolism

Examples of Special Studies

Special Studies
(triggered, case-by-case)

Pharmacokinetics

Immunotoxicity

Developmental Neurotoxicity

Companion Animal Safety

Scheduled Controlled Operant Behavior

Peripheral Nerve Function

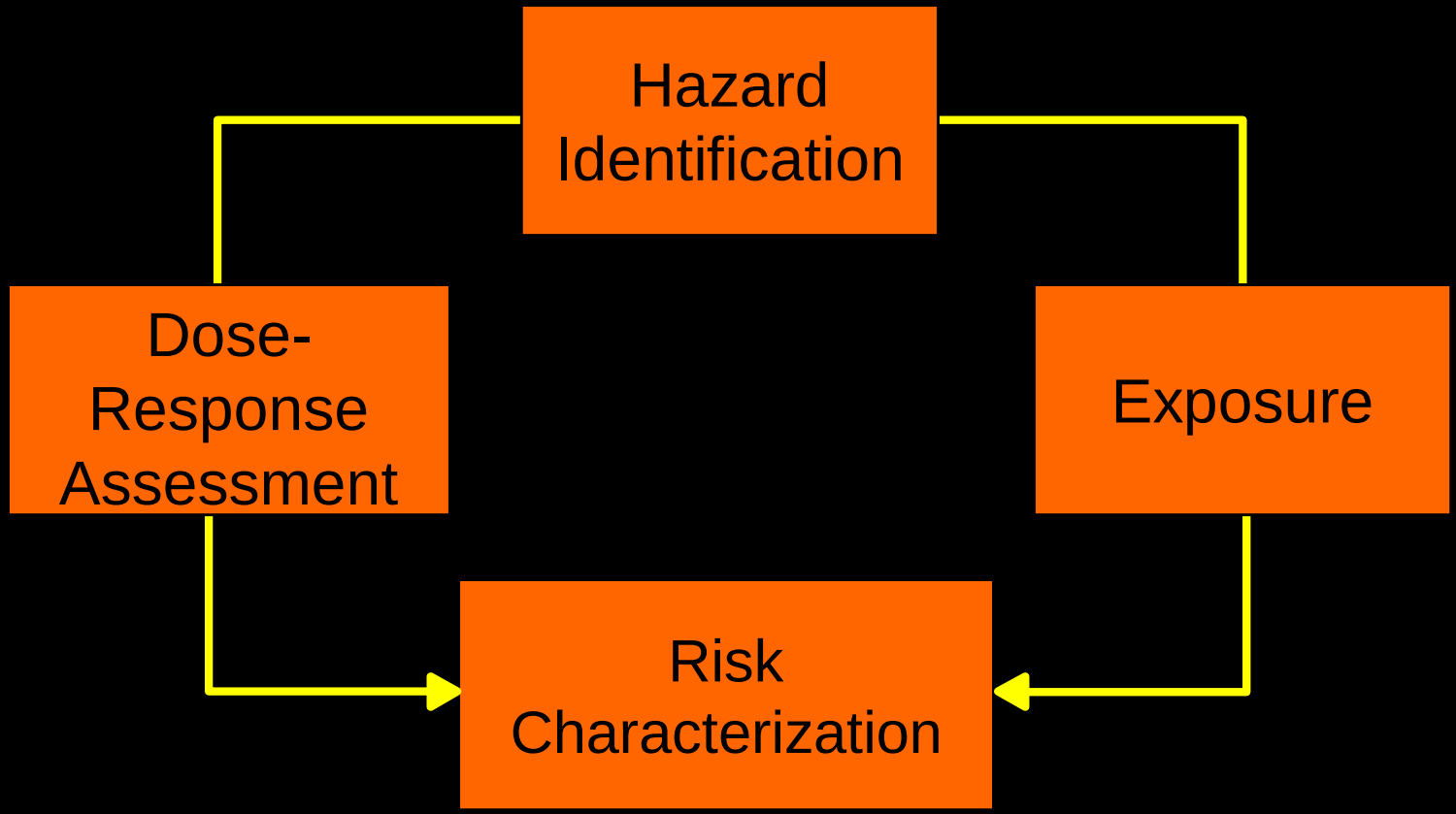
Neurophysiology: sensory evoked potentials

Mechanistic studies provided by the registrant

Risk Assessment

How Do We Assess Risk?

Risk = f (toxicity, exposure)



Risk Assessment

- Risk = NOAEL (from hazard data)/ Estimated Exposure

- EPA Risk Assessment Guidelines

http://www.epa.gov/ncea/raf/rafguid.htm

Hazard Identification

- Hazard ID qualitatively characterizes the inherent toxicity of a chemical.

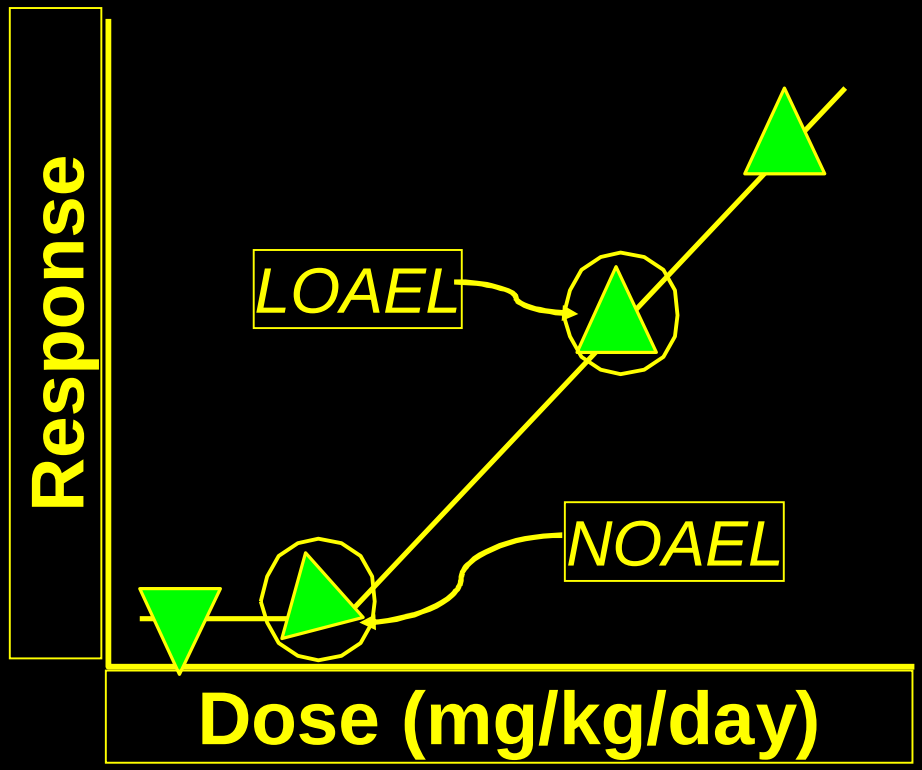
- Hazard ID should be based on a thorough review of all data that may provide information that is relevant to evaluating hazard, i.e., multiple species, *in vitro* tests, Structure Activity Relationships (SAR) and epidemiological studies.

Hazard Identification

- Characterization of the nature of effect: target organ toxicity, birth defects, repro effects, neurotoxicity, immunotoxicity, genotoxicity or cancer.
- Characterization of time to effect: acute, subchronic, and chronic effects.
- Characterization of the causative agent i.e., parent or metabolite.
- Relevance of effects observed in animals to humans and their biological significance.

The Dose Makes the Poison

The Dose-Response Curve



Eco Exposure

Aquatic Exposure

- EECs calculated by computer models
- GENEEC2 and PRZM-3 and EXAMS II to evaluate runoff and drift
- Water monitoring data may also be used, if available

Terrestrial Exposure

Spray applications – model estimates ingestion of residues on food items (vegetative matter and insects).

Granular, bait, and treated seed applications- Quantify multiple routes of exposure through estimates of loading of pesticide per unit area

Eco Risk Quotients

Acute Exposure RQ:

- Initial tier

  Peak level on short grass = RQ

  most sensitive bird LC50

  Granular formulation a.i./ft^2 = RQ

  most sensitive bird LD50

- More comprehensive tiers

  Peak on each food item = RQ

  most sensitive bird LC50

Chronic Exposure RQ

- Initial tier

Peak level each food item = RQ

most sensitive bird reproduction NOEC

- More comprehensive assessment

  time weighted average concentration food item = RQ

  most sensitive bird reproduction NOEC

LOCs for Eco RQs

Aquatic Organisms

High Acute Risk:

EEC/LC50 or EC50 $\geq$ 0.5

Acute Risk Restricted Use:
EEC/LC50 or EC50 $\geq$ 0.1

Acute Risk Endangered Species Concerns:

EEC/LC50 or E LC50 $\geq$ 0.05

Chronic Risks: EEC/NOEC $\geq$ 1

Terrestrial Organisms

High Acute Risk:

EEC/LC50 or LD50/ft^2 $\geq$ 0.5

Acute Risk Restricted Use:

EEC/LC50 or LD50/ft^2 $\geq$ 0.2

Acute Risk Endangered Species Concerns:

EEC/LC50 or ED50/ft^2 $\geq$ 0.1

Chronic Risks: EEC/NOEC $\geq$ 1

A Few Words on HH Exposure

Exposure Assessment	Data Source
Occupational	Pesticide Handler's Exposure Database (PHED) - model based on real data - ORETF - ARETF
Residential	Residential Standard Operating Procedures (SOP's)
Dietary (food)	Residue data are required under 40 CFR 158 USDA food consumption data

HH Risk Assessments Conducted

Dietary Exposure

Acute

Chronic

Non-Dietary Exposure

Incidental Oral } *short- and intermediate-term*

Dermal } *short-, intermediate-, and long-term*

Inhalation }

Acute Dietary Risk

- **Objective:** Identify hazard (dose and endpoint) after an acute exposure

- Two risk assessments may be conducted:

1) General Population (including infants and children)
2) Females 13+

Dietary

Acute Dietary Risk

- **General Population**
  - Used to assess potential hazard after single day of exposure

- **Relevant Studies**:

  Acute Neurotoxicity Study

  Developmental Toxicity Study

  Subchronic or Chronic Studies

If effects seen after 1-2 days of dosing

Dietary

Acute Dietary Risk

- Females 13+ Population
  - Used when concern for prenatal exposure is identified
  - Relevant Studies:

•Prenatal Developmental Study–Rodents or Non-rodents (use developmental endpoint)

•Developmental Neurotoxicity Study (DNT)

•Multigeneration Reproduction Toxicity Study

Dietary

Chronic Dietary Risk

- General Population
- Relevant Studies:

•Combined Chronic/Oncogenicity Study--RAT

•Carcinogenicity Study--MOUSE

•Chronic Oral Toxicity Study–DOG

•Multigeneration Reproduction Toxicity Study--RAT

•Subchronic Oral Toxicity Studies

Dietary

Non-dietary Risk Assessment Overview

- **Incidental Oral Exposure**
  - Short- and intermediate-term
- **Dermal Exposure**
  - Short-, intermediate-, and long-term
- **Inhalation Exposure**
  - Short-, intermediate-, and long-term

Non-Dietary

Short- or Intermediate- Term Incidental Oral Exposure

- Relevant Studies:
  - •Prenatal Developmental Toxicity Studies (maternal endpoints only)
  - •Multigeneration Reproduction Toxicity Study
  - •Acute or Developmental Neurotoxicity Study
  - •Subchronic Oral Toxicity Studies
  - •Chronic Oral Toxicity Studies

Non-Dietary

Dermal Exposure

- Relevant Studies:
  - •21/28-day Dermal Toxicity Study
  - •90-day Dermal Toxicity Study
  - •Oral Toxicity Studies:
    - -Prenatal Developmental Toxicity Study
    - -Developmental Neurotoxicity Study
    - -Multigeneration Reproduction Toxicity Study
    - -Subchronic Oral Toxicity Studies
    - -Chronic Oral Toxicity Studies (if interim evaluations are available)

If primary endpoint of concern in the database is not evaluated in the Dermal Toxicity Studies

Non-Dietary

Inhalation Exposure

- Relevant Studies:
  - •28-day Inhalation Toxicity Study
  - •90-day Inhalation Toxicity Study
  - •Oral Toxicity Studies:
    - -Prenatal Developmental Toxicity Study
    - -Multigeneration Reproduction Toxicity Study
    - -Acute or Developmental Neurotoxicity Study
    - -Subchronic Oral Toxicity Studies
    - -Chronic Oral Toxicity Studies (if interim measures are available)

If primary endpoint of concern in the database has not been evaluated in Inhalation Toxicity Studies

Non-Dietary

Application of Uncertainty/Safety Factors

General	Chemical-Specific
Intraspecies Uncertainty Factor	LOAEL to NOAEL
Interspecies Uncertainty Factor	Subchronic to Chronic
FQPA Safety Factor	Database problems (e.g., lack of similar species, strain, etc.)

HH Risk Estimates

Dietary Exposure

$$\text{RfD} = \frac{\text{NOAEL}}{\text{UF}}$$

$$\textit{\% RfD} = \frac{\textit{Dietary Exposure (mg/kg BW/day)}}{\textit{RfD (mg/kg BW/day)}} \textit{ X 100}$$

Occupational and Residential Exposure

$$\textit{MOE} = \frac{\textit{NOAEL (mg/kg BW day)}}{\textit{Exposure (mg/kg BW day)}}$$

New Testing Strategies

Lessons Learned from Risk Assessments

- FQPA and advances in science and technology are driving the need for new testing techniques.
- Existing guideline studies do not adequately address regulatory mandates.
- Risk assessment needs should drive study design.
- EPA is moving toward a hypothesis driven risk assessment paradigm.
- There is a need for more efficient and effective process to assess hazard by different durations & routes of interest.
- There is a need for studies that facilitate risk assessment for relevant life stages.
- Conduct retrospective analyses of utility of various hazard studies in pesticide database.