Pesticide Risk Assessment

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ENVIRONMENTAL and MOLECULAR TOXICOLOGY

Hazard v. Risk

- A **hazard** is any source of **potential** damage, harm or adverse effects on something or someone.
- A chemical hazard is the potential for harm or an adverse effect at **any** chemical dose.
- Hazard identification: testing for all plausible adverse effects.

Hazard v. Risk

- **Risk** is the chance or probability that a person or wildlife will be harmed or experience an adverse effect if exposed to a hazard.

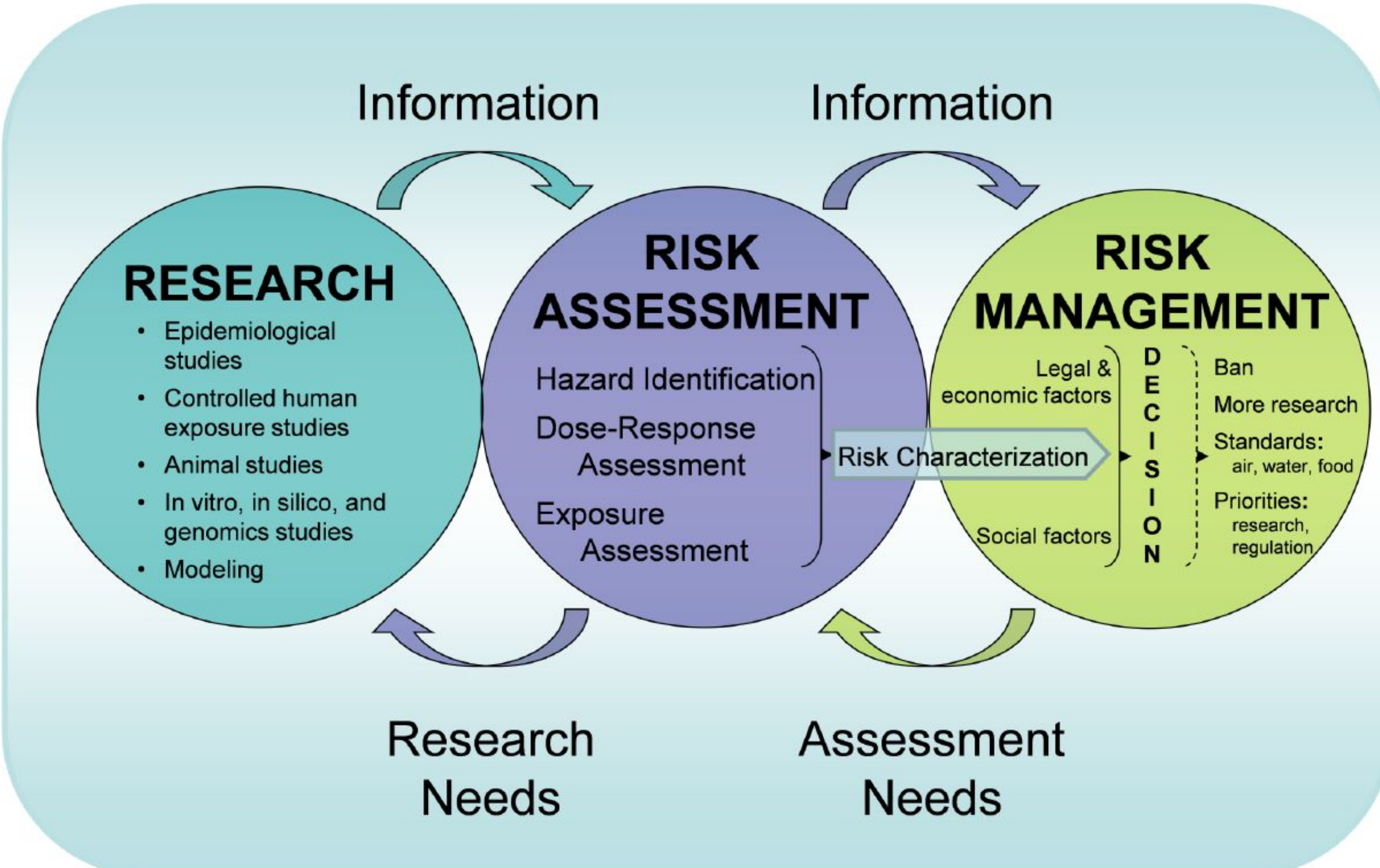
Hazard: possibility of harm

Risk: probability of harm

What is a Risk Assessment?

- Identify hazards and risk factors that have the potential to cause harm (hazard identification).
- Analyze and evaluate the risk associated with that hazard (risk analysis, and risk evaluation).
- Determine appropriate ways to eliminate the hazard or control the risk when the hazard cannot be eliminated (risk management).

Risk Analysis Paradigm



Federal Pesticide Laws

Food Quality Protection Act
(FQPA)

Pesticide Registration
Improvement Act
(PRIA)

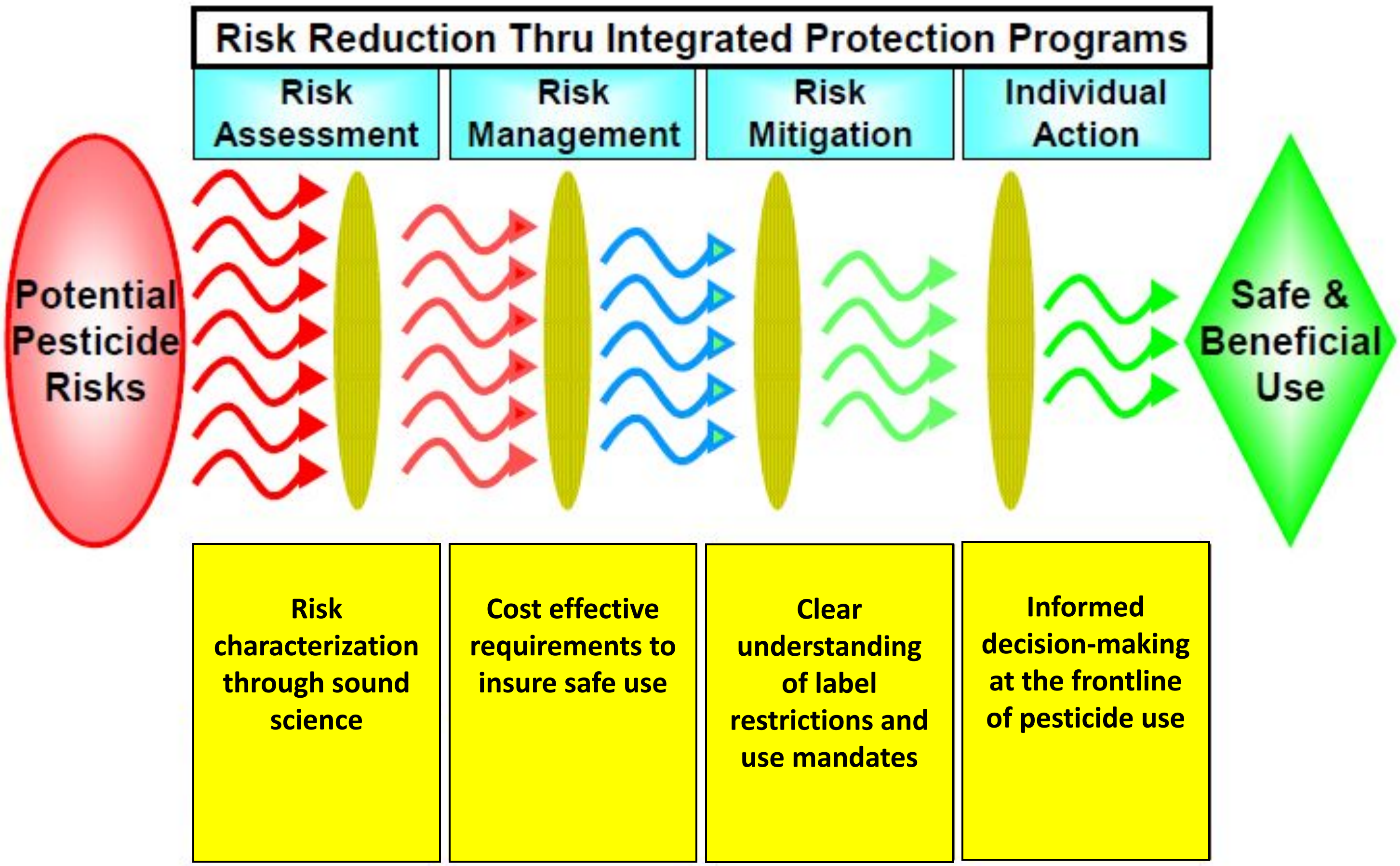
Federal Food Drug
And Cosmetic Act
(FFDCA)

Federal Insecticide Fungicide
And Rodenticide Act
(FIFRA)

MRLs (Tolerance) Established
*Maximum Residue Level

Product Registered

Pesticide Risk Assessment and Management Continuum



Pesticide Regulation Under FIFRA/FQPA

- Administered by EPA’s Office of Pesticide Programs
- Extensive testing prior to approval, register if:
  - **Use will not result in “unreasonable adverse effects on human health or the environment”**
  - **Consumption of food from crops treated with pesticides will result in “a reasonable certainty of no harm.”**

Pesticide Registration Application

- Chemistry for each pesticide product.
  - Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)
  - Federal Food, Drug, and Cosmetic Act (FFDCA)
  - Food Quality Protection Act (FQPA)
  - 40CFR parts 158.320 to 158.355
  - OPPT Test Guidelines Series 830 Product Properties

Types of Pesticide Products (Food or non-Food Use)

- Technical Grade Active Ingredient (TGAI) or Manufacturing Use Product (MUP)

- End-use or formulated products

- For food uses, Tolerance/Maximum Residue Level (MRL) must be established for each active ingredient (A.I.)

TGAI/MUP[1] Co-products

- If impurity is of toxicological concern, it must be reported to the Agency at any level present.
- Some breakdown or conversion products of the active ingredient
- Most from unintentional reactions occurring during pesticide synthesis
- TGAI used in testing for Ecological Risk Assessment

[1]Technical Grade Active Ingredient (TGAI)/Manufacturing Use Product (MUP)

Organophosphate insecticide Malathion

- At least 11 co-products, in addition to the active ingredient, are routinely detected in malathion technical mixtures.

- Malathion technical mixtures stored for extended periods under warm, humid conditions may contain isomalathion at concentrations as high as 7%.

- Typically the total co-product concentration in a malathion technical mixture is less than 5%.

Malathion Co-products

1.	isomalathion	0.20%
2.	malaoxon	0.10%
3.	diethyl fumarate	0.90%
4.	O,S,S-trimethyl phosphorodithioate [OSS(O)]	0.003%
5.	O,O,S-trimethyl phosphorothioate [OOS(O)]	0.04%
6.	O,O,S-trimethyl phosphorodithionate [OOS(S)]	1.2%
7.	O,O,O-trimethyl phosphorothionate [OOO(S)]	0.45%
8.	diethyl hydroxysuccinate	0.05%
9.	ethyl nitrite	0.03%
10.	diethyl mercaptosuccinate	0.15%
11.	diethyl methylthiosuccinate	1.0%

Which are of toxicological concern?

Malathion Co-products of Toxicological Concern

- Potent neurotoxins, acetylcholinesterase (AChE) inhibitors
  - isomalathion and malaoxon
- Inhibit carboxyesterase /synergize AChE inhibition
  - isomalathion
  - O,S,S-trimethyl phosphorodithioate
  - O,O,S-trimethyl phosphorothioate
  - O,O,S-trimethyl phosphorodithionate
  - O,O,O-trimethyl phosphorothionate

Pesticide registration under FIFRA (as amended by FQPA)

- 40 CFR 158 Rulemaking; data requirements
- Harmonized Test Guidelines; EPA Office of Pesticide Programs, EPA Office of Chemical Safety and Pollution Prevention, and OECD[1] Countries
- Continuous review; frequently updated

[1]Organisation for Economic Co-operation and Development: does not require member countries to make the same regulatory decisions; facilitates pesticide registration by minimizing duplication of testing requirements.

Pesticide Reevaluation

- The 1988 amendments to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) authorized EPA to conduct the pesticide reregistration program.
  - review supporting scientific studies
  - update human health and ecological risk assessments using current science
  - cancel or re-register uses
  - develop risk mitigation measures (new label language)
- Determination summarized in a Reregistration Eligibility Decision (RED)
- Reregister a pesticide if it can be used "without unreasonable adverse effects on human health or the environment."

Data for EPA Pesticide Registration and Reevaluation

- Studies accepted by U.S. EPA for pesticide registration or reassessment purposes must comply with Good Laboratory Practices (GLPs).
- GLPs are federal regulations; 21 CFR Part 58 (U.S. Food and Drug Administration) and 40 CFR Part 160 (U.S. EPA)
- GLP regulations describe the minimal standards for conducting laboratory and field studies that support or are intended to support pesticide registration or reregistration.
- U.S. EPA also considers information in the open literature as a part of the registration or reregistration process; greater weight is given to those studies that were specifically designed to be used for risk assessment purposes, and those conducted under GLPs.

Pesticide registration or Reevaluation

- Registrants submit new data or in response to a EPA data call in.
- Data comes from studies that they follow a relatively uniform set of guidelines or study protocols.
- These guidelines are harmonized with the EU/other developed countries.
- The Office of Chemical Safety and Pollution Prevention (OCSPP) harmonized guidelines are organized in the following 11 series:
  - 810 - Product Performance Test Guidelines
  - 830 - Product Properties Test Guidelines
  - 835 - Fate, Transport and Transformation Test Guidelines
  - 840 - Spray Drift Test Guidelines
  - 850 - Ecological Effects Test Guidelines
  - 860 - Residue Chemistry Test Guidelines
  - 870 - Health Effects Test Guidelines
  - 875 - Occupational and Residential Exposure Test Guidelines
  - 880 - Biochemicals Test Guidelines
  - 885 - Microbial Pesticide Test Guidelines
  - 890 - Endocrine Disruptor Screening Program Test Guidelines

Series 830 - Product Properties Test Guidelines[1]

Group A — Product Identity, Composition, and Analysis Test Guidelines

830.1000 - Background for Product Properties Test Guidelines (March 1998)
830.1550 - Product Identity and Composition (August 1996)
830.1600 - Description of Materials Used to Produce the Product (August 1996)
830.1620 - Description of Production Process (August 1996)
830.1650 - Description of Formulation Process (August 1996)
830.1670 - Discussion of Formation of Impurities (August 1996)
830.1700 - Preliminary Analysis (August 1996)
830.1750 - Certified Limits (August 1996)
830.1800 - Enforcement Analytical Method (August 1996)
830.1900 - Submittal of Samples (November 2008)

[1]The final Product Properties Test Guidelines are generally intended to meet testing requirements for physical and chemical properties of pesticide products under FIFRA and toxic substances under TSCA.

Series 830 - Product Properties Test Guidelines

Group B — Physical/Chemical Properties Test Guidelines

830.6302 - Color (August 1996)
830.6303 - Physical State (August 1996)
830.6304 - Odor (August 1996)
830.6313 - Stability to Normal and Elevated Temperatures, Metals, and Metal Ions (August 1996)
830.6314 - Oxidation/Reduction Chemical Incompatability (August 1996)
830.6315 - Flammability (August 1996)
830.6316 - Explodability (August 1996)
830.6317 - Storage Stability (June 2002)
830.6319 - Miscibility (August 1996)
830.6320 - Corrosion Characteristics (August 1996)
830.6321 - Dielectric Breakdown Voltage (August 1996)
830.7000 - pH (August 1996)
830.7050 - UV/Visible Absorption (August 1996)
830.7100 - Viscosity (August 1996)
830.7200 - Melting Point/Melting Range (March 1998)
830.7220 - Boiling Point/Boiling Range (August 1996)
830.7300 - Density/Relative Density/Bulk Density (June 2002)
830.7370 - Dissociation Constants in Water (August 1996)
830.7520 - Particle Size, Fiber Length, and Diameter Distribution (August 1996)
830.7550 - Partition Coefficient (n-octanol/water), Shake Flask Method (August 1996)
830.7560 - Partition Coefficient (n-octanol/water), Generator Column Method (August 1996)
830.7570 - Partition Coefficient (n-octanol/water), Estimation by Liquid Chromatography (August 1996)
830.7840 - Water Solubility: Column Elution Method; Shake Flask Method (March 1998)
830.7860 - Water Solubility, Generator Column Method (March 1998)
830.7950 - Vapor Pressure (August 1996)

Commonly used in Ecological Risk

- Dissociation Constants in Water
- Partition Coefficient (n-octanol/water)
- Water Solubility
- Vapor Pressure

835 - Fate, Transport and Transformation Test Guidelines

Group A — Laboratory Transport Test Guidelines

835.0001 - Principles and Strategies Related to Biodegradation Testing of Organic Chemicals under the Toxic Substances Control Act (TSCA) (November 2008)

835.1110 - Activated Sludge Sorption Isotherm (January 1998)

835.1210 - Soil Thin Layer Chromatography (January 1998)

835.1220 - Sediment and Soil Adsorption/Desorption Isotherm (January 1998)

835.1230 - Adsorption/Desorption (Batch Equilibrium) (November 2008)

835.1240 - Leaching Studies (November 2008)

835.1410 - Laboratory Volatility (November 2008)

Group B — Laboratory Abiotic Transformation Test Guidelines

835.2120 - Hydrolysis (November 2008)

835.2130 - Hydrolysis as a Function of pH and Temperature (January 1998)

835.2210 - Direct Photolysis Rate in Water by Sunlight (January 1998))

835.2240 - Photodegradation in Water (November 2008)

835.2310 - Maximum Direct Photolysis Rate in Air from UV/Visible Spectroscopy (January 1998)

835.2370 - Photodegradation in Air (November 2008)

835.2410 - Photodegradation in Soil (November 2008)

835 - Fate, Transport and Transformation Test Guidelines

Group C — Laboratory Biological Transformation Test Guidelines

835.3100 - Aerobic Aquatic Biodegradation (January 1998)
835.3110 - Ready Biodegradability (January 1998)
835.3140 - Ready Biodegradability – CO2 in Sealed Vessels (Headspace Test) (November 2008)
835.3160 - Biodegradability in Sea Water (January 1998)
835.3170 - Shake Flask Die-Away Test (January 1998)
835.3180 - Sediment/Water Microcosm Biogradation Test (January 1998)
835.3190 - Aerobic Mineralization in Surface Water – Simulation Biodegradation Test (October 2008)
835.3200 - Zahn-Wellens/EMPA Test (January 1998)
835.3210 - Modified SCAS Test (January 1998)
835.3215 - Inherent Biodegradability – Concawe Test (October 2008)
835.3220 - Porous Pot Test (January 1998)
835.3240 - Simulation Test – Aerobic Sewage Treatment: A. Activated Sludge Units (October 2008)
835.3260 - Simulation Test – Aerobic Sewage Treatment: B. Biofilms (October 2008)
835.3280 – Simulation Tests to Assess the Primary and Ultimate Biodegradability of Chemicals Discharged to Wastewater (October 2008)
835.3300 - Soil Biodegradation (January 1998)
835.3400 - Anaerobic Biodegradability of Organic Chemicals (January 1998)
835.3420 - Anaerobic Biodegradability of Organic Compounds in Digested Sludge: By Measurement of Gas Production (October 2008)

835 - Fate, Transport and Transformation Test Guidelines

Group D —Transformation in Water and Soil Test Guidelines

835.4100 - Aerobic Soil Metabolism / 835.4200 – Anaerobic Soil Metabolism (October 2008)
835.4300 - Aerobic Aquatic Metabolism / 835.4400 – Anaerobic Aquatic Metabolism (October 2008)

Group E — Transformation Chemical-Specific Test Guidelines

835.5045 - Modified SCAS Test for Insoluble and Volatile Chemicals (January 1998)
835.5154 - Anaerobic Biodegradation in the Subsurface (January 1998)
835.5270 - Indirect Photolysis Screening Test: Sunlight Photolysis in Waters Containing Dissolved Humic Substances (January 1998)

Group F — Field Dissipation Test Guidelines

835.6100 - Terrestrial Field Dissipation (October 2008)
835.6200 - Aquatic (Sediment) Field Dissipation (October 2008)
835.6300 - Forestry Dissipation (October 2008)
835.6400 - Combination and Tank Mixes Field Dissipation (October 2008)

Group G — Ground Water Monitoring Test Guidelines

835.7100 - Guidance for Prospective Ground-Water Monitoring Studies

Group H — Volatility from Soil Test Guidelines

835.8100 - Field Volatility (November 2008)

Series 850 - Ecological Effects Test Guidelines

Group A - Aquatic and Sediment-dwelling Fauna and Aquatic Microcosms

850.1000 - Aquatic and Sediment-Dwelling Fauna and Aquatic Microcosms (December 2016)
850.1010 - Aquatic Invertebrate Acute Toxicity Test, Freshwater Daphnids (December 2016)
850.1020 - Gammarid Amphipod Acute Toxicity Test (December 2016)
850.1025 - Oyster Acute Toxicity Test (Shell Deposition) (December 2016)
850.1035 - Mysid Acute Toxicity Test (December 2016)
850.1045 - Penaeid Acute Toxicity Test (December 2016)
850.1055 - Bivalve Acute Toxicity Test (Embryo-Larval) (December 2016)
850.1075 - Freshwater and Saltwater Fish Acute Toxicity Test (December 2016)
850.1300 - Daphnid Chronic Toxicity Test (December 2016)
850.1400 - Fish Early Life Stage Toxicity Test (December 2016)
850.1710 - Oyster Bioconcentration Factor (BCF) (December 2016)
850.1730 - Fish Bioconcentration Factor (BCF) (December 2016)
850.1735 - Spiked Whole Sediment 10-Day Toxicity Test , Freshwater Invertebrates (December 2016)
850.1740 - Spiked Whole Sediment 10-Day Toxicity Test, Saltwater Invertebrates (December 2016)

Group B - Terrestrial Wildlife

850.2000 - Background and Special Considerations- Tests with Terrestrial Wildlife (June 2012)
850.2100 - Avian Acute Oral Toxicity Test (June 2012)
850.2200 - Avian Dietary Toxicity Test (June 2012)
850.2300 - Avian Reproduction Test (June 2012)
850.2400 - Wild Mammal Toxicity Testing (June 2012)
850.2500 - Field Testing for Terrestrial Wildlife (June 2012)

Series 850 - Ecological Effects Test Guidelines

Group C - Terrestrial Beneficial Insects, Invertebrates, and Soil and Wastewater Microorganisms

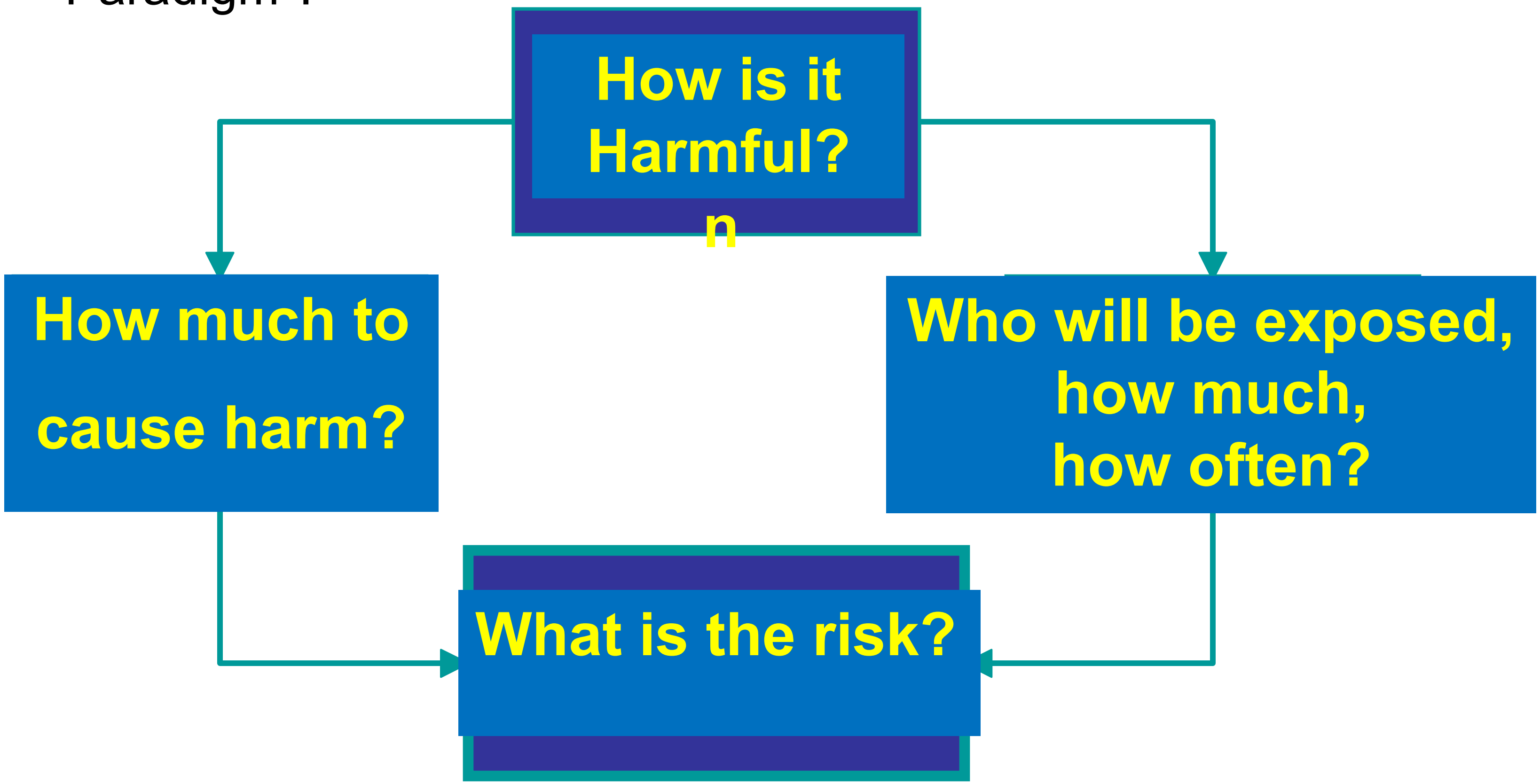
850.3000 - Terrestrial Beneficial Insects, Invertebrates and Microorganisms (June 2012)
850.3020 - Honey Bee Acute Contact Toxicity Test (June 2012)
850.3030 - Honey Bee Toxicity of Residues on Foliage (June 2012)
850.3040 - Field Testing for Pollinators (June 2012)
850.3100 - Earthworm Subchronic Toxicity Test (June 2012)
850.3200 - Soil Microbial Community Toxicity Test (June 2012)
850.3300 - Modified Activated Sludge, Respiration Inhibition Test (June 2012)

Group D - Terrestrial and Aquatic Plants, Cyanobacteria, and Terrestrial Soil Core Microcosm

850.4000 - Terrestrial and Aquatic Plants, Cyanobacteria, and Terrestrial Soil-Core Microcosms (June 2012)
850.4100 - Seedling Emergence and Seedling Growth (June 2012)
850.4150 - Vegetative Vigor (June 2012)
850.4230 - Early Seedling Growth Toxicity Test (June 2012)
850.4300 - Terrestrial Plants Field Study (June 2012)
850.4400 - Aquatic Plant Toxicity Test Using Lemna spp. (June 2012)
850.4450 - Aquatic Plants Field Study (June 2012)
850.4500 - Algal Toxicity (June 2012)
850.4550 - Cyanobacteria (Anabaena flos-aquae) Toxicity (June 2012)
850.4600 - Rhizobium-Legume Toxicity (June 2012)
850.4800 - Plant Uptake and Translocation Test (June 2012)
850.4900 - Terrestrial Soil-Core Microcosm Test (June 2012)

How Does the US Environmental Protection Agency (EPA) Assess Risk?

National Academy of Sciences (NAS) 4-step risk assessment Paradigm*:



* From the National Research Council's *Risk Assessment in the Federal Government: Managing the Process*, 1983.

Pesticide Ecological Risk Assessment

Hazard Identification

- Have all plausible toxicological outcomes that effect receptor fitness and survival been considered?

Dose-Response Assessment

- At what dose level do the effects occur; what is the critical effect; what is the NOAEL, LOAEL, MATC, benchmark dose (BMD), POD?

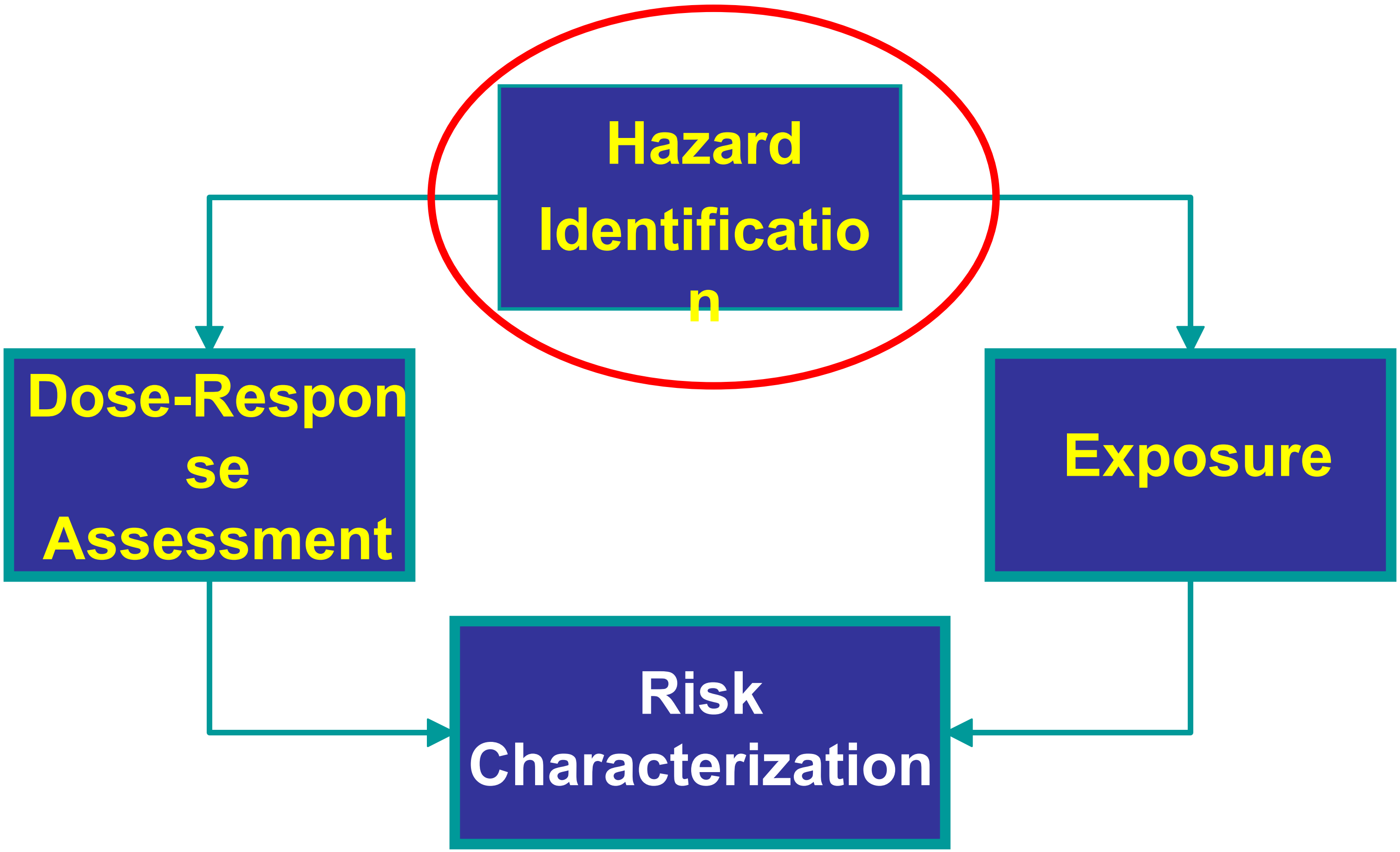
Exposure Assessment

- What is the estimated environmental concentration (EEC), route and pattern of receptor exposure?

Risk Characterization

- Combine hazard, dose-response, and exposure; compare EECs to receptor levels of concern (LOCs)?

National Academy of Sciences
4-step risk assessment Paradigm*



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Hazard Identification

Important toxicological effects observed that are adverse to fitness and survival

Any critical exposure periods and routes

Metabolism and potential for bioaccumulation

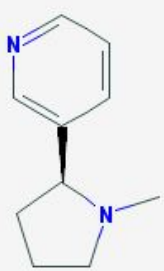
Quality of the data and uncertainties

Studies which provide conflicting results, and why a particular study might be deemed to be the most appropriate

Transparent, clear, consistent, and reasonable characterization is necessary for effective regulation of pesticides

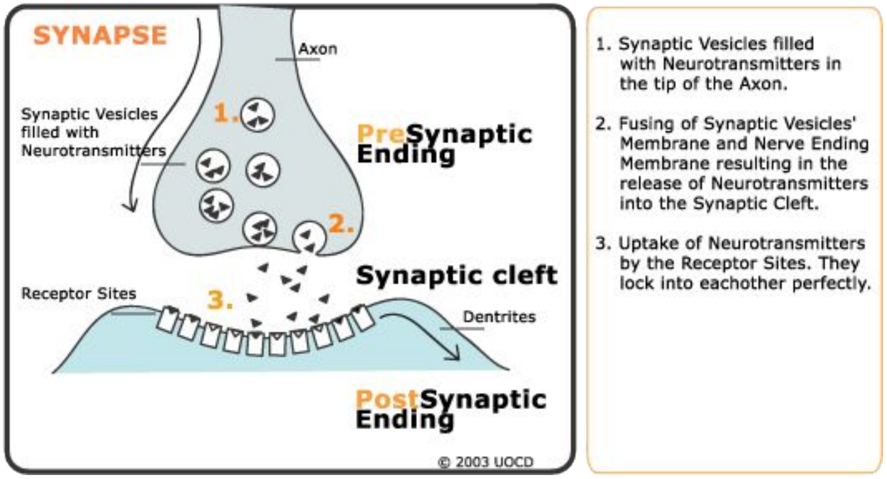
Neonicotinoids Mode of action

- Derivatives of nicotine (first insecticide use - France 1690)
- Mode of action - disrupt the nervous system by binding to postsynaptic nicotinic acetylcholine receptors.
- Toxic effects: modified feeding behavior, paralysis, and subsequent death.
- At low doses – neurobehavioral effects?

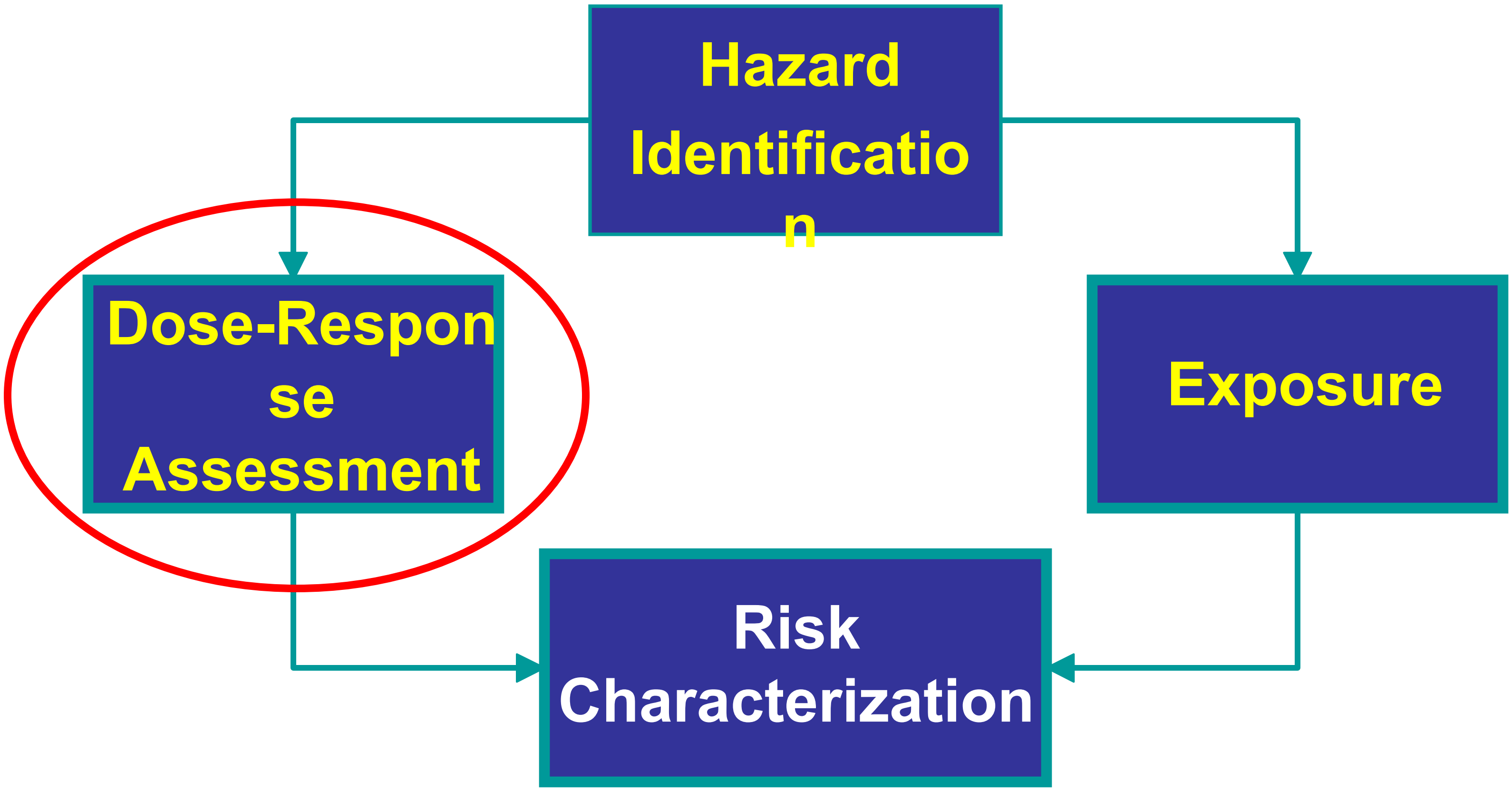


nicotine

Imidacloprid



National Academy of Sciences 4-step risk assessment Paradigm*



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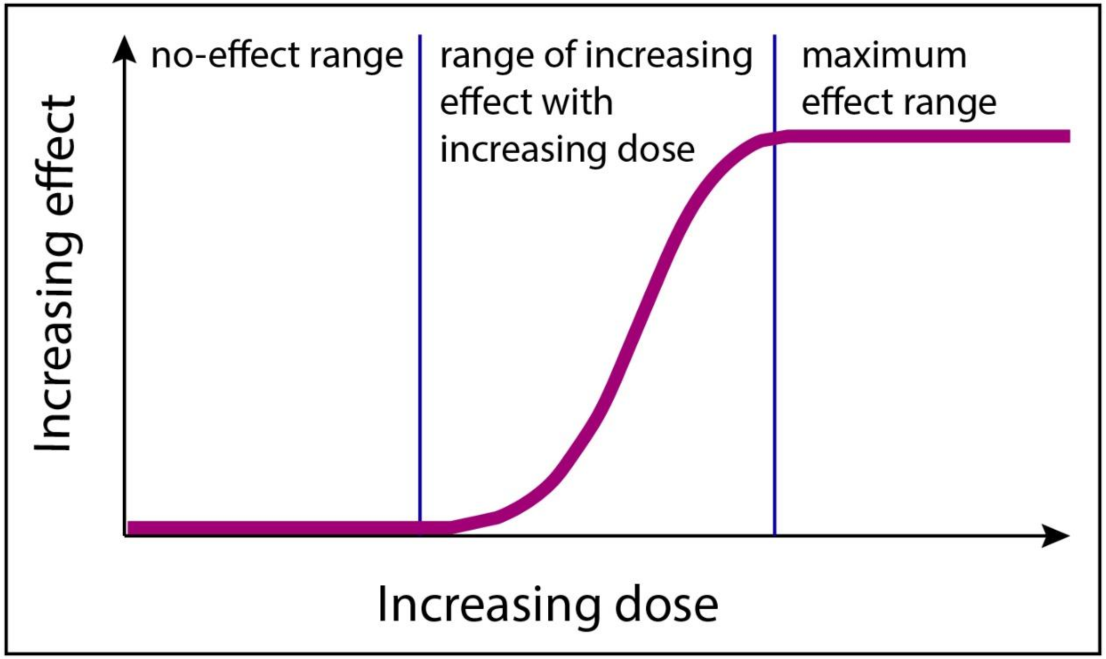
Dose response curves



How Is Dose-Response Assessed?

- Depends on:
  - Duration of exposure (acute, chronic)
  - Route of exposure (absorption, diet)

Dose-Response Assessment and Endpoint Selection

Provides a quantitative description of the hazard potential which can be used to assess the level of concern (LOC) for adverse effects to individuals who may be exposed.

Dose-response Assessment and Endpoint Selection: Definitions

Endpoint: Toxic Effect upon which the risk assessment is based

Lowest Observed Adverse Effect Level (LOAEL): Lowest dose from a study at which adverse toxic effects were observed

No Observed Adverse Effects Level (NOAEL): The dose below the LOAEL at which no adverse toxic effects are observed

Benchmark dose (BMD): a statistical estimate of a dose or concentration that produces a predetermined change in the response rate (i.e., the "benchmark") of an adverse effect.

Point of Departure (POD): Any dose level used to quantify risk (generic)

Components of a quantitative risk assessment

- Select data set
- Select response
- Scale dose from test species to receptors
- Fit dose-response model
- Make other appropriate adjustments

Questions when evaluating test species studies

- Dose levels
- Sample size
- Duration of exposure
- Duration of experiment
- Endpoints evaluated - relevance to fitness and survival

Preferences for selecting a response

- Prefer
  - Test species responding most like receptors of interest
  - Most sensitive test species
  - Same route as environmental exposure
  - Another route of environmental exposure

Characteristics of a good data set

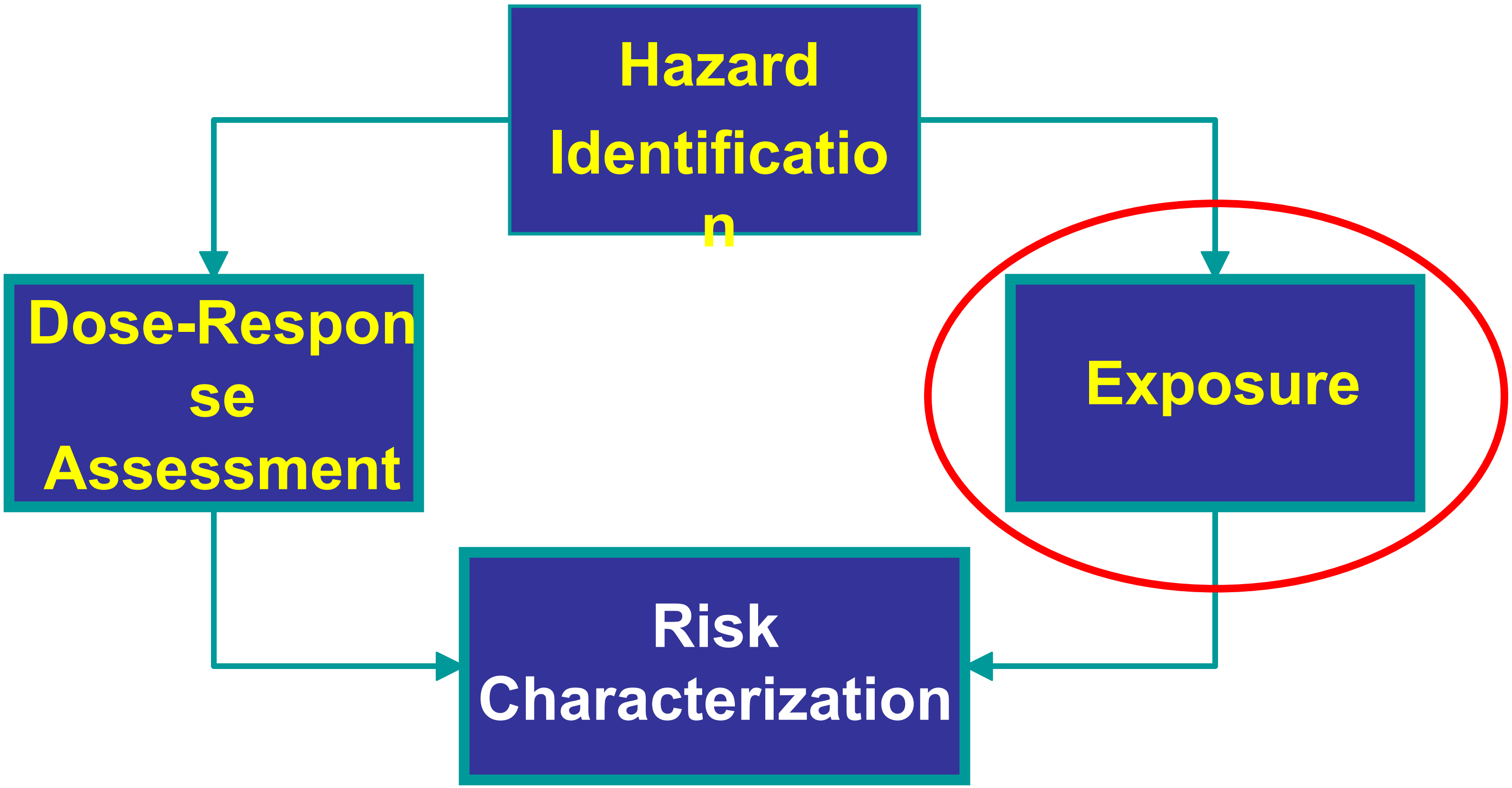
- Similar route of exposure
- Similar pharmacokinetics and mechanism of action
- Dosing is both acute and chronic, preferably lifetime
- Large number of dose groups
- Large number of animals
- Proper controls
- Good survival
- Dose-response relationship evident

Scaling dose from test species to receptors of interest

- Use toxicokinetic data to inform cross-species dose scaling if appropriate and if adequate data are available.

- Otherwise, use default - scale single dose (acute studies) or daily applied dose (chronic studies) in proportion to body weight (mg/kg)

National Academy of Sciences 4-step risk assessment Paradigm*



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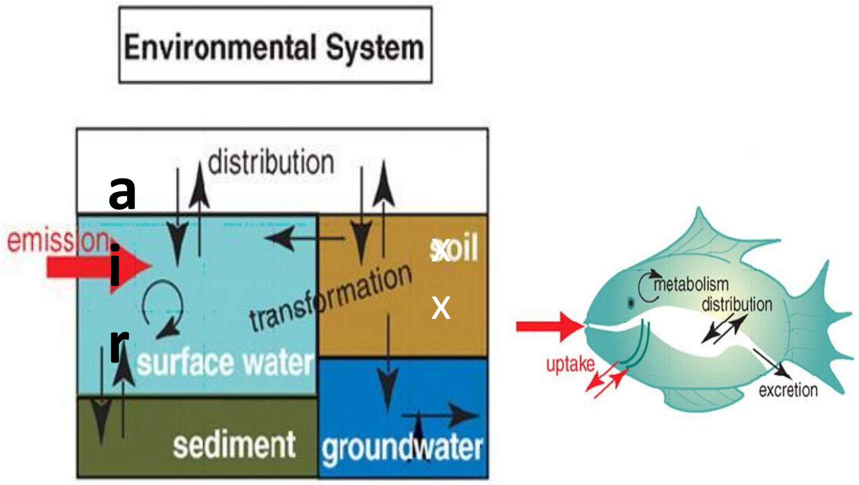
Exposure Assessment

- Exposure assessment is the step in the risk assessment process that quantifies the uptake of an agent resulting from contact with various environmental media

- Exposure assessments can address past, current, or future anticipated exposures



Concepts of Exposure, Intake, Uptake, and Dose

The process of a chemical entering the organism can be described in two steps—contact (exposure), followed by actual entry (crossing the boundary).

Absorption (crossing the boundary) leads to the availability of an amount of chemical to biologically significant sites within the body (target tissue dose).

Risk: Conceptual Framework