Environmental Assessment for Pharmaceuticals

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Agency's Roles and Priorities

Primary Federal agency for regulating pharmaceuticals and personal care products.

- Foods
- **Human Drugs**
- **Animal Drugs**
- Cosmetics
- Medical Devices

Statutes & Regulations

Statutory authorities:

- Food, Drug, & Cosmetic Act of 1938
- Public Health Service Act of 1944
- National Environmental Policy Act of 1969

Regulatory responsibilities:

- Title 21 Code of Federal Regulations

FDA Implementation of NEPA

Council on Enviromental Quality

40 CFR, Part 1500 - 1508

1) Categorical Exclusions
2) Environmental Assessments
3) Environmental Impact Statements

FDA Regulations

NEPA regs -- 21 CFR Part 25

Categorical Exclusion

Classes of actions that individually or cumulatively do not significantly affect the quality of the human environment are ordinarily excluded from the requirement to prepare an EA or EIS

Categorical Exclusions

- Action on original and abbreviated new human and animal drugs and biologics if there is no increase in use of the active moiety
- Approvals of original and abbreviated human drugs entry into aquatic environment < 1 PPB
- Action on a drugs and biologics for a naturally occurring substance if no significant change
- Investigations on new human and animal drug

Categorical Exclusions

Veterinary approvals for:

- non-food animals
- individually given anesthetics
- topicals & ophthalmics
- Rx drugs for terrestrial species

Extraordinary circumstances trump a claim of categorical exclusion.

Extraordinary circumstances

- At the expected level of exposure there is the potential for serious harm to the environment
- Adverse effect on species or the critical habitat of an endangered or threatened species

FDA Actions that may* need Environmental Assessment

Approval of:

- New Drug Application (NDA),
- Biologics License Application (BLA),
- New Animal Drug Application (NADA)
- Device Pre-Market Approval (PMA)

Action on:

- Investigational New Drug Application (IND)
- Investigational New Animal Drug Application (INAD)
- Investigational Device Exemption (IDE)

*** Unless Excluded by 21 CFR 25.31**

Agency's Roles and Priorities

- Review categorically exclusions
- Review the EA submitted by the sponsor.
- Determine appropriate action:
  - Finding of No significant Impact (FONSI)
  - Environmental Impact Statement (EIS)

FDA Environmental Assessment

- Concise public document
- Sufficient evidence and analysis
  - environmental impact statement or
  - a finding of no significant impact.
- Aids an agency's compliance with NEPA
- Facilitates preparation of EIS
- Includes:
  - need for the proposal
  - alternatives
  - list of agencies and persons
- Identifies potential mitigations

Availability

Most actions are categorically excluded

- **published in the Federal Register**

Many actions have environmental assessments

- **published in the Federal Register**
- **public display in our Document Management**
- **113 Environmental Assessment for new animal drugs and feed additives**

on line at:

(http://www.fda.gov/cvm/efoi/ea/ea.htm)

Current and Future Environmental Assessments

Risk = exposure to a chance of loss (or of losing something we value)

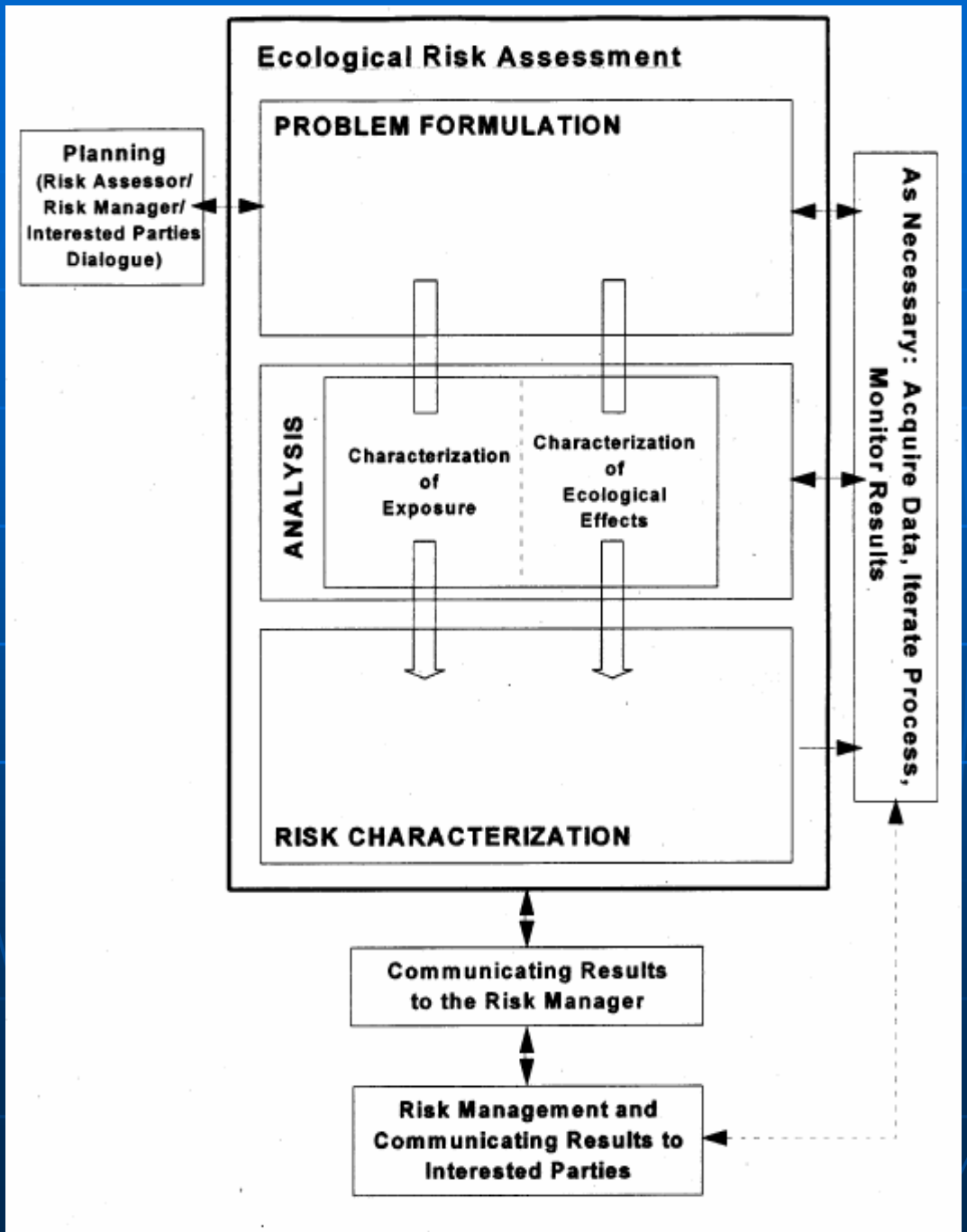
Risk = Hazard x Exposure

NAS Risk Assessment Paradigm (1983)

Risk Assessment

- Hazard Identification
- Dose-Response (effects) Assessment
- Exposure Assessment
- Risk Characterization

Risk Management


Ecological Risk Assessment
PROBLEM FORMULATION
Planning
(Risk Assessor/
Risk Manager/
Interested Parties
Dialogue)
ANALYSIS
Characterization
of
Exposure
Characterization
of
Ecological
Effects
RISK CHARACTERIZATION
As Necessary: Acquire Data, Iterate Process,
Monitor Results
Communicating Results
to the Risk Manager
Risk Management and
Communicating Results to
Interested Parties

EA Focus

- Ecosystem protection
- Laboratory studies on invertebrates, fish, plants at different trophic levels
- Measurement endpoints: mortality, immobilization, reproduction, growth, functional responses
- Biogeochemical cycling (nitrogen, carbon transformation)

Guidance

CDER guidance

Environmental Assessment of Human Drug and Biologics Applications (July 1998)
http://www.fda.gov/cder/ guidance/index.htm

CVM guidance

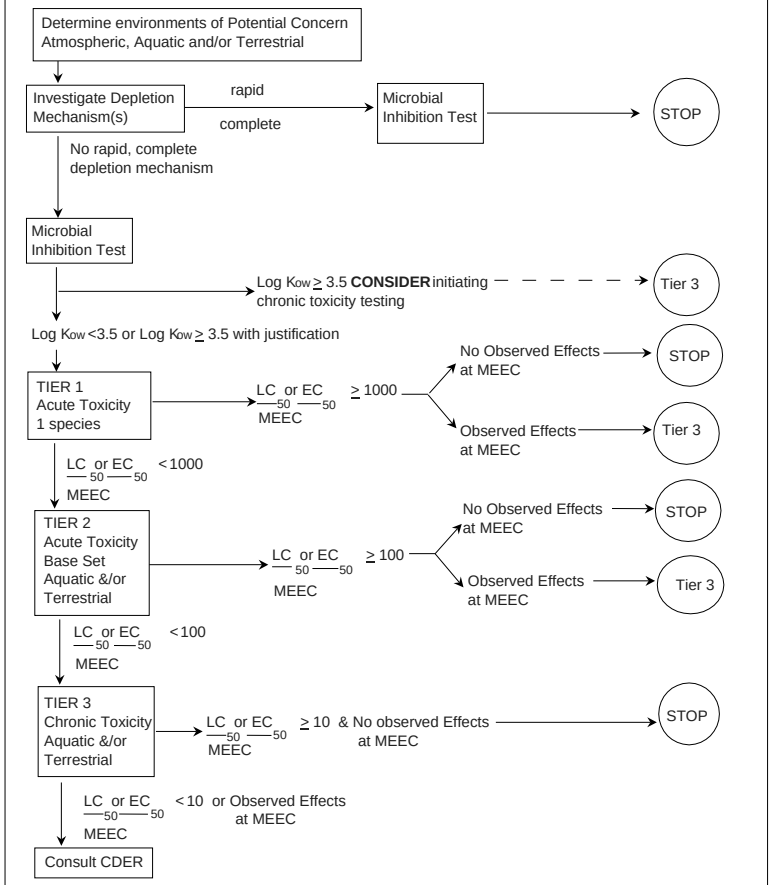
Environmental Impact Assessment for Veterinary Medicinal Products

Phase I (Sept. 1998)
(http://www.fda.gov/cvm/guidance/guide89.PDF)
VICH Veterinary Drug

Phase II (pending final FDA adoption)
http://vich.eudra.org/pdf/10_2004/GL38_st7.pdf

Human Tiered Approach

Figure 1
Tiered Approach to Fate and Effects Testing



Note: MEEC = EEC or EIC whichever is greater

Veterinary Phase I Guidance

- legal and exposure criteria
- exempt from full risk analysis
- extensive *in vivo* metabolism
- aquatic introduction concentration
  < 1 μg/L
- terrestrial introduction concentration
  < 100 μg/Kg

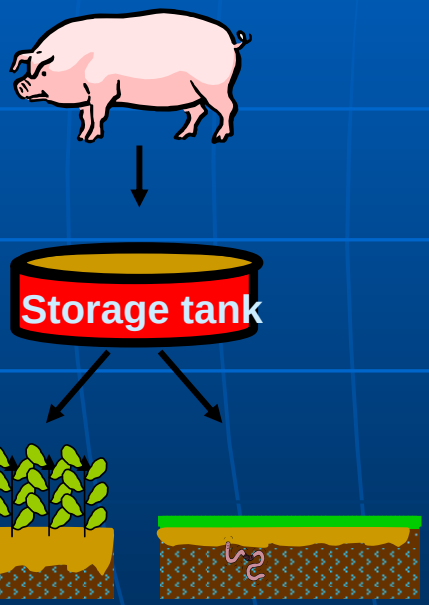
Veterinary Phase II

Risk-quotient method = PEC : PNEC.

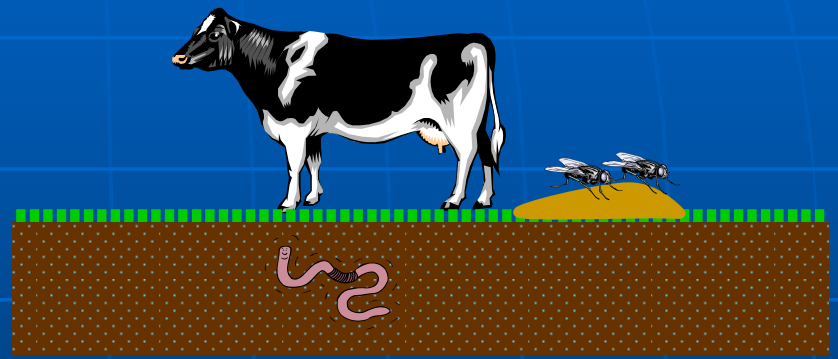
- Predicted environmental concentration (PEC)
- Predicted no effect concentration (PNEC)
- Assessment Factor (AF)
- Three Tiers (A,B,C) as needed

Veterinary Scenarios Phase II Guideline

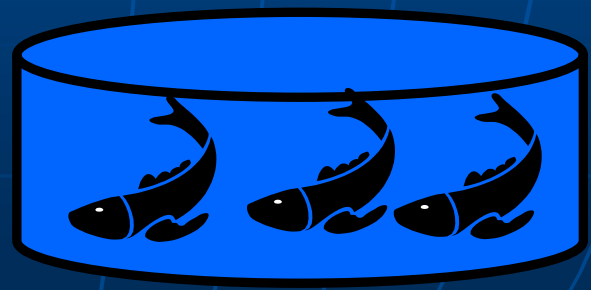
Intensively reared animals



pasture animals



aquaculture



Assessment Factors

- Numerical factor that is applied to the endpoint value of an effects study to derive a predicted no-effect concentration (PNEC)

Interspecies	X10
Laboratory to Field	X10
Acute to Chronic	X10

Base Set Data Requirements

Physical-chemical studies

- **Water Solubility**
- **Dissociation Constant**
- **UV-Visible Absorption Spectrum**
- **Melting Temperature**
- **Vapour Pressure**
- **Octanol / Water Partition**

Environmental fate studies

- **Soil adsorption / desorption**
- **Degradation in soil**
- **Degradation in aquatic systems**
- **Photolysis (optional)**
- **hydrolysis (optional)**

Aquatic effect studies

- **Algae**
- **Daphnia**
- **Fish**

Terrestrial effect studies

- **Micro-organisms**
- **Terrestrial plants**
- **Earthworm**

TIER A Assessment

Surface water	Endpoint	AF
• algae (96 h)	EC50	100
• invertebrate (48 h)	EC50	1000
• fish (96 h)	LC50	1000
Soil		
• earthworm (chronic)	NOEC	10
• higher plants (3 species)	EC50	100
• micro-organisms (28 days)	< 25% of control	
Dung (pasture animals)		
• dung fly	EC50	100
• dung beetle	EC50	100

TIER B Assessment

Surface water	Endpoint	AF
• algae (96 h)	NOEC	10
• invertebrate (21 d)	NOEC	10
• fish (28 d)	NOEC	10
• sediment species (varies)	NOEC	10

Soil		
• earthworm	no recommendation	
• higher plants (more species)	NOEC	10
• micro-organisms (100 days)	< 25% of control	

Bioaccumulation

- BCF > 1000 l/kg ⇨ investigate secondary poisoning

TIER C Assessment

Refined Risk Analysis

- Specialized environmental fate modeling
- Probabilistic exposure analyses

Specialized Laboratory and/or Field Testing

- Pulsed exposure studies
- Microcosm and mesocosm studies
- In-stream studies

Risk Management

- Use restrictions
- Mandatory treatment requirements
- Effluent discharge limits

On-going Activities

On-going collaborations:

- With the Office of Clean Water/EPA on animal drugs in effluents from aquaculture facilities
- With the Joint Subcommittee on Aquaculture on environmental impact of animal drugs used in aquaculture
- With USGS Toxic program and EPA Field offices on pharmaceuticals in the environment

On-going Activities

- Veterinary International Conference on Harmonisation
- Conferring with pharmaceutical manufacturers on improved methods to estimate environmental exposure levels
- Monitoring literature reports associated with PPCPs in the environment

Planned Activities

- Organizing workshop with Society of Environmental Toxicology & Chemistry on veterinary drugs in the environment
- Assess the value of providing guidance on disposal of unused drugs

Science Needs

- Data on background levels from natural sources (including humans)
- Data on levels of mimics from industrial sources
- Data on minimum effect levels
  - Pharmaceuticals
- Comparison of predicted and actual levels of pharmaceuticals

Science Needs

Specific questions:

- Effects of ‘sunscreens’ on aquatic environment
- Effects of triclosan on aquatic environment

Thank You

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