Environmental Assessment for Veterinary Pharmaceuticals

U.S. EPA Workshop on Fate and Effects of Hormones in Waste from
Concentrated Animal Feeding Operations
Chicago, IL
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- Background
- Regulations
- Environmental Review
- Recent Development

FDA'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

Federal Food, Drug and Cosmetic Act

Target Animal Safety

Target Animal Efficacy

Human Food Safety

Manufacturing

Other Public Health

National Environmental Policy Act (NEPA, 1969)

- NEPA requires Federal Agencies consider environment
- Basic national charter for the protection of the environment
- Accurate scientific analysis, expert comment and public scrutiny are essential

FDA Implementation of NEPA

Council on Enviromental Quality

40 CFR, Part 1500 - 1508

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

FDA Regulations

NEPA regs -- 21 CFR Part 25

FDA Role

- CVM Action
  - Approval of New and abbreviated animal drug applications (NADA, ANADA)
  - Feed additive petitions (FAP)
  - NADA, ANADA and FAP supplements
  - Allow investigations

- Environmental Review of Use and Disposal
  - Administration
  - Excretion
  - Disposal

Agency's Roles and Priorities

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

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

Extraordinary circumstance –

- Information indicates that a normally excluded specific action may significantly affect the human environment

- provision to require an Environmental Assessment for actions that are normally categorically excluded

Categorical Exclusions

Veterinary approvals for:

- no increase
- non-food animals
- anesthetics, topical & ophthalmic
- minor use / minor species
- Rx drugs for terrestrial species
- INADs

Extraordinary circumstances trump a claim of categorical exclusion.

Environmental Assessment

Concise, objective, well-balanced public document

- Information on drug, use and disposal
- Analysis and risk characterization
- Descriptions of potential mitigations

Provides sufficient evidence and analysis

- Finding of No Significant Impact (FONSI)
- Environmental Impact Statement (EIS)

Public display

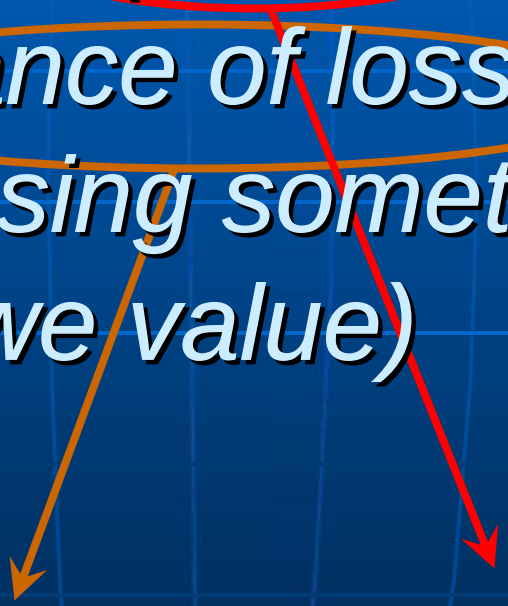
- http://www.fda.gov/cvm/efoi/ea/ea.htm

EA Focus

- Ecosystem protection
- Laboratory studies on chemistry, fate, and effects on invertebrates, fish, plants
- Measurement endpoints: mortality, immobilization, reproduction, growth
- Biogeochemical cycling (nitrogen, carbon transformation)

Current and Future Environmental Assessments

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



Risk = Hazard x Exposure

Courtesy H.C. Claycamp, CVM

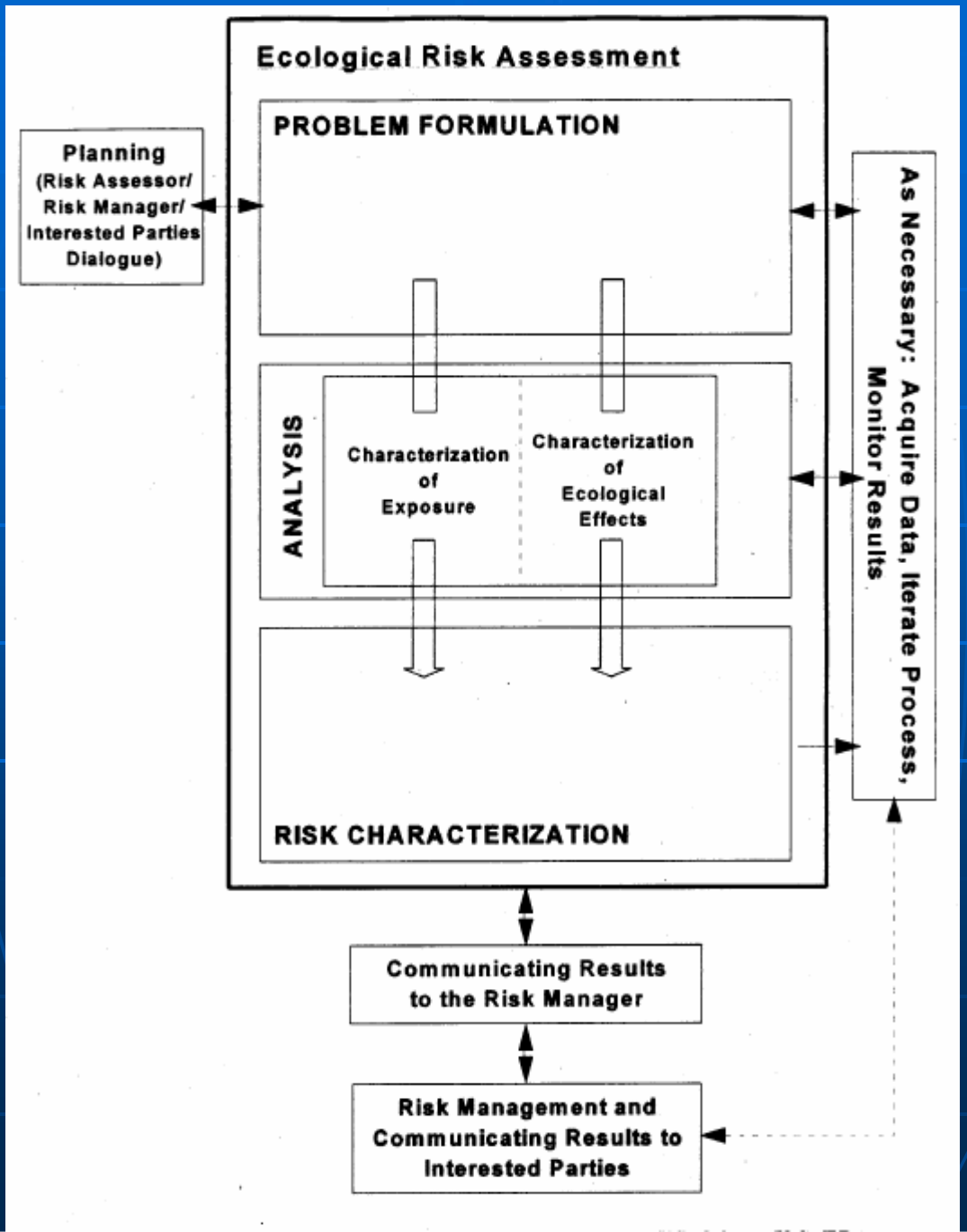
NAS Risk Assessment Paradigm (1983)

Risk Assessment

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

Risk Management

Courtesy H.C. Claycamp, CVM


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

Guidance

CVM guidance

Environmental Impact Assessment for Veterinary Medicinal Products

Phase I (March 7, 2001) (http://www.fda.gov/cvm/guidance/guide89.PDF) VICH Veterinary Drug

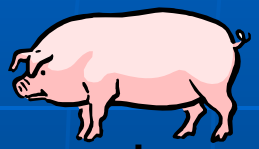
Phase II (January 9, 2006) http://www.fda.gov/cvm/Guidance/guide166.pdf

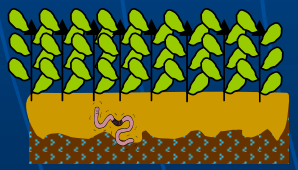
Veterinary Phase I Guidance

- 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

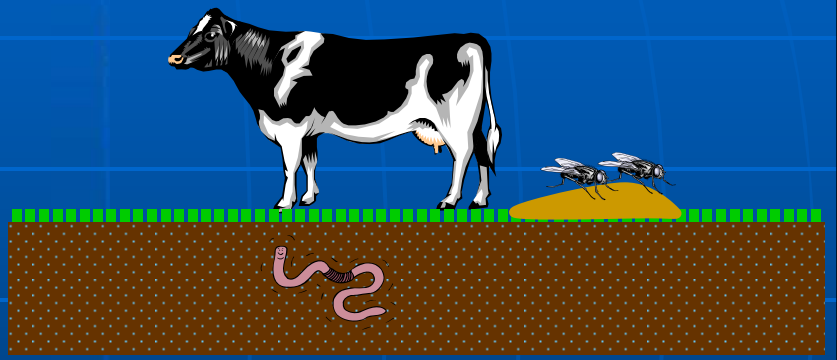
Veterinary Scenarios Phase II Guideline

Intensively reared animals

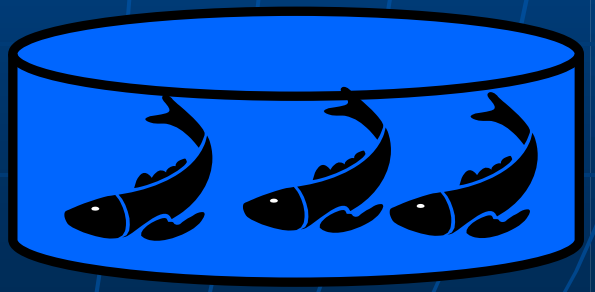




pasture animals



aquaculture



Courtesy J.A. de Knecht, RIVM

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

Terrestrial PEC

- Currently
  - Soil PEC
    - Relying in historical algorithms
    - concentration drug in excreta
    - application rate to soil
    - soil incorporation
  - Feedlot/Field Runoff
    - Rough estimate
    - 2 inches rain on an area
    - Mass of drug
    - EPA model – GENEEC

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

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)

On-going Activities

- Office Science and Technology Policy
- With USGS Toxic program
- EPA Field offices on pharmaceuticals in the environment
- Improved guidance methods to predicting environmental exposure levels
- Share analytical methods

On-going Activities

May 30, 2007, Meeting EPA Office of Water

- FDA holds that NEPA gives it authority to review and in some cases label to mitigate
- NEPA does not convey any environmental enforcement authority to FDA
- FDA must approve drugs that have been shown safe and effective under the FFDCA even with significant environmental impacts
- EPA must take an enforcement lead in helping to mitigate impacts
- Natural hormones must also be considered in any activity
- Explore methods for data sharing

Planned Activities

- Closer scrutiny of hormonally active products
- Continue interactions EPA, USDA
- Begin work with pharmaceutical and livestock industries
- Possible activities:
  - Livestock and Poultry Environmental Learning Center
  - Develop new and improve conservation and best management practices (C and BMP) for CAFO, pasture and manure handling
  - Induce and lead users (cattle, swine and poultry) to implement C and BMP

    e.g., labeling, other

Science Needs

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

Thank You

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Questions / Discussion