Pesticides and Animal Health

- Adverse Effects and Drug/Chemical Residues

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Veterinary Approvals

FDA Approved: Spot-On and Pour-On Formulations
EPA Registered: Spot-On and Pour-On Formulations

US FDA
Ivermectin (Ivomec®)
Selamectin (Revolution®)
Firponil (Frontline®, TopSpot®)

US EPA
Permethrin
Imidaclorpid (Advantage)
Outline of Presentation

- Dermal Absorption Basics
  - How are these drugs/insecticides absorbed? Spp Diff?

- Once absorbed, what are the adverse effects of insecticides in veterinary species?

- Can there be Residues in meat and milk if livestock species are treated with these drugs?

- FARAD Cases and their resolution

- Summary and Challenges
Possible Routes of Absorption

- **A.** - intercellular
- **B.** - transcellular
- **C.** - intrafollicular
- **D.** - via sweat ducts
What is the objective of your drug/insecticide therapy?

Does it require systemic absorption?

Does it require local skin distribution?
Differences in Drug Distribution
Avermectins vs. Neonicotinoids vs. Fipronil vs Pyrethroids

Avermectins (e.g., Selamectin)
The PK of avermectins (ivermectin, selamectin, etc) is route specific.
Selamectin

Pharmacokinetics Results – Cats

Concentration (ng/mL)

Time (hours)

0.05 mg/kg IV
0.1 mg/kg IV
0.2 mg/kg IV
24 mg/kg Topical
24 mg/kg Oral
What is the Ideal Animal Model for Human Skin?

Many dermal absorption studies utilize porcine skin because of demonstrated similarities in:

- Structure
- Function
- Lipid composition
Species Differences in In Vivo Dermal Absorption

(from Principles And Methods of Toxicology)

Which species is predictive of human dermal absorption????
- Dermal Absorption Basics
  - How are these drugs absorbed?

- Once absorbed, what are the adverse effects of insecticides in veterinary species?

- Can there be Residues in meat and milk if livestock species are treated with these drugs?

- FARAD Cases and their resolution

- Future and Challenges
Adverse Effects of Ectoparasiticides

- Occasional to rare in companion animals
  - Idiosyncratic reactions or not reading/following the label

- Rare in food animals

- Reason: These drugs target receptors in the insect and are more selective for these receptors in insects than vet. spp and humans
## Adverse Effects of Ectoparasiticides

<table>
<thead>
<tr>
<th>Active Ingredients</th>
<th>Comparative Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organochlorines</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Organophosphates</strong></td>
<td>Very Toxic !!!</td>
</tr>
<tr>
<td>Pyrethrins</td>
<td>Yes</td>
</tr>
<tr>
<td>Neonicotinoids</td>
<td>No</td>
</tr>
<tr>
<td>Fipronil</td>
<td>No</td>
</tr>
<tr>
<td>Macrolide Endectocides,</td>
<td>No (except some breeds)</td>
</tr>
<tr>
<td>Growth inhibitors</td>
<td>Harmless</td>
</tr>
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</table>
Adverse Reactions to OPs

• Animals vary in response to insecticides
  – age (young vs. adult), health, stress, species (cats are sensitive)

• Toxicity
  – muscarinic and nicotinic effects
  – some OPs cause OPIDN (clinical signs delayed 7 - 21 days)
  – highly toxic to birds, fish, aquatic invertebrates, and honeybees.
  – Brahman cattle, greyhounds, and cats are sensitive to OPs
  – being lipophilic, may get residues in meat and milk
    • famphur & fenthion = 35 & 45 days meat WDT (No dairy approval)
    • But coumaphos (Co-Ral) has no meat or milk WDT
Adverse Reactions to OPs

All related to Overstimulation of ACh Receptors

**Muscarinic acetylcholine receptors** symptoms of:
- Visual disturbances (miosis),
- Bronchoconstriction, increased bronchial secretions,
- Increased salivation, lacrimation, sweating, peristalsis, and urination

**Nicotinic acetylcholine receptors** in the central nervous system:
- Anxiety, headache, convulsions, ataxia, depression of respiration and circulation, tremor, general weakness, and potentially coma.

At the neuromuscular junction:
- Muscle weakness, fatigue, muscle cramps, and paralysis
Adverse Reactions to Pyrethrins

- more selective for insects, and safer than OPs & Carbamates

- most common way cats can be poisoned by pyrethrins is by inappropriate application of dog flea and tick medications in cat

- clinical signs include nerve and muscular disorders
  - Type I compounds (permethrin) → rapid onset of hyperactivity (as DDT)
  - Type II compounds (fenvalerate) → serious side effects at low doses
Adverse Reactions to Pyrethroids

Onset of clinical signs is usually within a few hours of exposure but may be delayed up to 24 hours

- Profuse drooling
  - Vomiting
  - Tremors
- Hyperexcitability
  - Agitation
  - Seizures
- Weakness
- Difficulty breathing
- Dermal Absorption Basics
  - How are these drugs absorbed?

- Once absorbed, what are the adverse effects of insecticides in veterinary species?

- Can there be Residues in meat and milk if livestock species are treated with these drugs?

- FARAD Cases and their resolution

- Future and Challenges
Why should I care about residues?

- **Lost milk product** ($6000 to $80,000)
- **Lost cull price** ($500)
- **Danger to consumer**
- **Regulatory problems**

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**CONSENT DECENTR SIGNED IN DRUG RESIDUE CASE**

On July 5, 1995, a Consent Decree of Permanent Injunction was signed by David L. Hogan, owner of Hogan's Misty Meadow Dairy, Tillamook, Oregon. The dairy is primarily a producer of fluid milk, with a producing herd of 700 cows. In addition, the farm produces bull calves which are sold for slaughter or for further raising, and then slaughtered for human food. The injunction action against Mr. Hogan was based on 16 residue incidents involving viola of CCAFP March 1990 through June 1994. The illegal drug residues involved included streptomycin, neomycin, gentamicin, penicillin, and oxytetracycline. The Consent Decree permanently restrained and enjoined Mr. Hogan from introducing or maintaining any cattle intended for commerce with any cattle.
Can people really get sick from residues?

• Yes!

• In one 6 month period in 1993 more than 1,200 hospitalizations and 3 deaths in France and Spain were reported to have resulted from eating beef livers contaminated with the illegal growth promotant clenbuterol.

• 6/38 animals tested + at OK state fair in 1995.

• Vet: 8 months & $80,000 for smuggling it into US in 1999.
Why should I care?

Perceptions and not science are often the drivers evidenced by growth of the organic food industry

“dose makes the poison” is ignored
Potential Sources of Residues

• Not following the label WDT

• Extra-label use without using an appropriate WDT

• Environmental contamination

• Contamination of feed

• Emergency treatment of wounded and sick animals

• Slaughter of unidentified animals
Relevant FARAD Cases

Can these Ectoparasiticide drugs be used in an extralabel manner?

Yes, for FDA approved drugs

NO, for EPA Registered products
Real Case: Cydectin

• **Background**
  – A goat farmer found that oral Ivomec was not reducing parasitism in his goat herd, and he decided to dose the goats orally with Cydectin.
  
  – He also treated with 4 X the approved cattle dose.

• **Questions:**
  – Is this approved or extra-label use of this drug?
  
  – Can we use the approved meat WDT for cattle of Zero days if we treat goats topically or orally?
Real Case: Cydectin

• **Answer**
  - Cydectin is approved for topical use in cattle NOT goats.
  - There is no approval for ORAL use in cattle, but if it was, there will be a significant WDT for cattle destined for slaughter. i.e.,

  NOT ZERO DAYS  !!!

Therefore, expect to with-hold meat goats for at least several weeks before slaughter if goats are treated orally with this drug.
Real Case: Heptachlor

Two incidents of mass contamination of livestock.

Case confined to Hawaii in 1982:

- EPA granted an emergency exemption to pineapple growers to use heptachlor.
- Dairy cattle fed contaminated pineapple green-chop byproducts.
- Widespread contamination of the Hawaiian milk supply and losses estimated at millions dollars.

Ethanol plant in SW Missouri routinely purchased surplus seed grain that had been treated with insecticides and fungicides.

- Spent distiller’s grains were used in the manufacture of animal feeds.
- Heptachlor residues were detected in milk samples from > 50 dairies.
- Several beef and swine herds also were quarantined.
- Losses undoubtedly would have totaled several million dollars if FARAD had not provided withdrawal time information.
What about practical approaches for managing a chemical contaminant exposure in livestock?

- Melamine
- PCBs
- Petrochemicals
- Other POPs
- Solvents
- etc
Melamine Exposure in swine: Use of PBPK Modeling

<table>
<thead>
<tr>
<th>T_{1/2}</th>
<th>Cl</th>
<th>V_{ss}</th>
<th>AUC</th>
<th>Kel</th>
<th>MRT</th>
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</thead>
<tbody>
<tr>
<td>(hr)</td>
<td>(L/hr/kg)</td>
<td>(L/kg)</td>
<td>hr*µg/ml</td>
<td>l/hr</td>
<td>(hr)</td>
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<tr>
<td>Mean</td>
<td>4.07</td>
<td>0.11</td>
<td>0.61</td>
<td>59.26</td>
<td>0.18</td>
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<tr>
<td>SE</td>
<td>0.39</td>
<td>0.01</td>
<td>0.04</td>
<td>5.89</td>
<td>0.02</td>
</tr>
</tbody>
</table>
When is it safe to use the milk or meat from dairy animals exposed to melamine?
Summary & Challenges

- These drugs/insecticides can be absorbed across skin to work locally or systemically. 
  » (Formulation Dependent !!!)
- Once absorbed, any adverse effects are usually associated with very few drug classes (OPs and Pyrethroids).
- Veterinarian, Client, and Patient can be affected
- Drug/Insecticide Residues in meat and milk can occur in livestock treated with these drugs if used Extralabel !!
- The FARAD National Program uses its PK database and novel Pharmacometrics methods in risk management of challenges associated with drug and pesticide exposure
The End