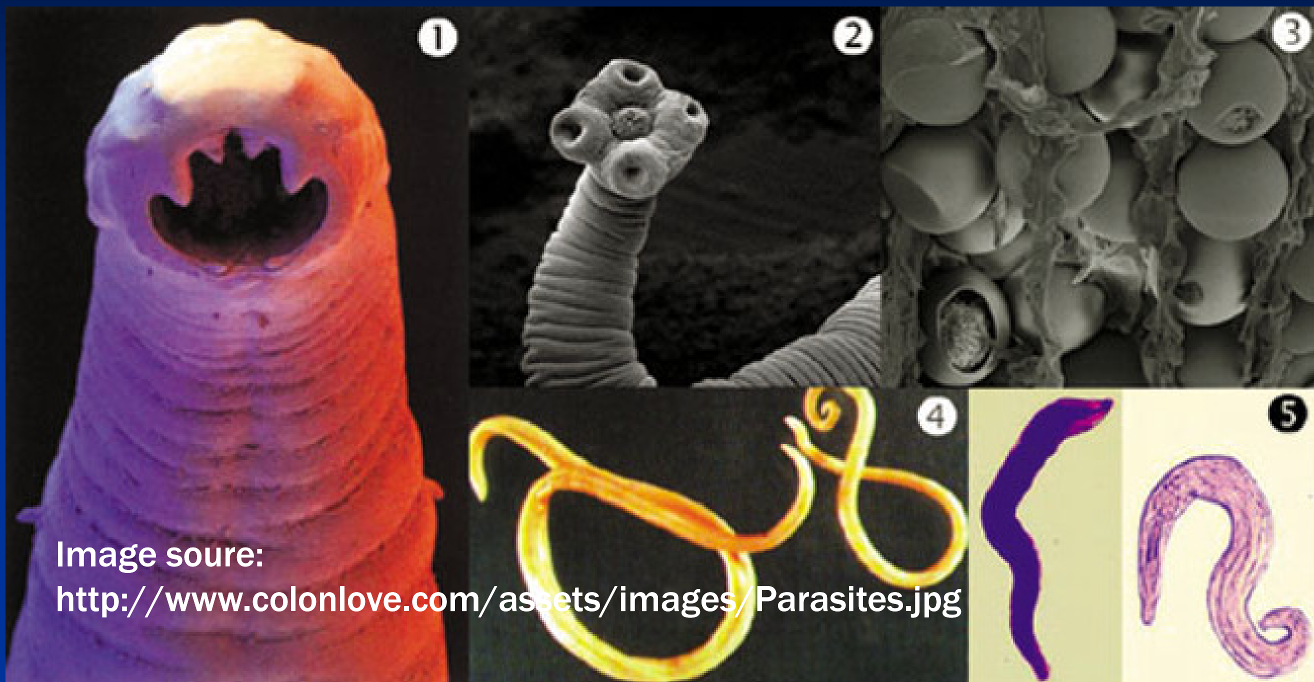


Image soure:
http://www.colonlove.com/assets/images/Parasites.jpg

C.8.
C.9.
/S.II

Cursuri Romeo T. Cristina®

Antiparasitic medication

Introduction

- the antiparasitic therapy is based on a large number of substances, the majority of them are synthetic.
- Most antiparasitic drugs affect the neuromuscular system of the parasite by *blocking the neuromuscular junctions,* with the final result of: paralysis, death and disposal.
- it is known that helminths have also a reversible paralysis, so that if they are not eliminated in due time, they will recover.

- The substances of the organophosphorus group are known for their effectiveness on both helminths and ectoparasites are grafted in their use by relative high toxicity.
- Their mechanism is based on *blocking the acetylcholinesterase enzyme,* which is the enzyme necessary for the hydrolysis of acetylcholine.
- By blocking this enzyme, the mediator can no longer be released, the stimulus remains open resulting the exhaustion and death of the parasite.

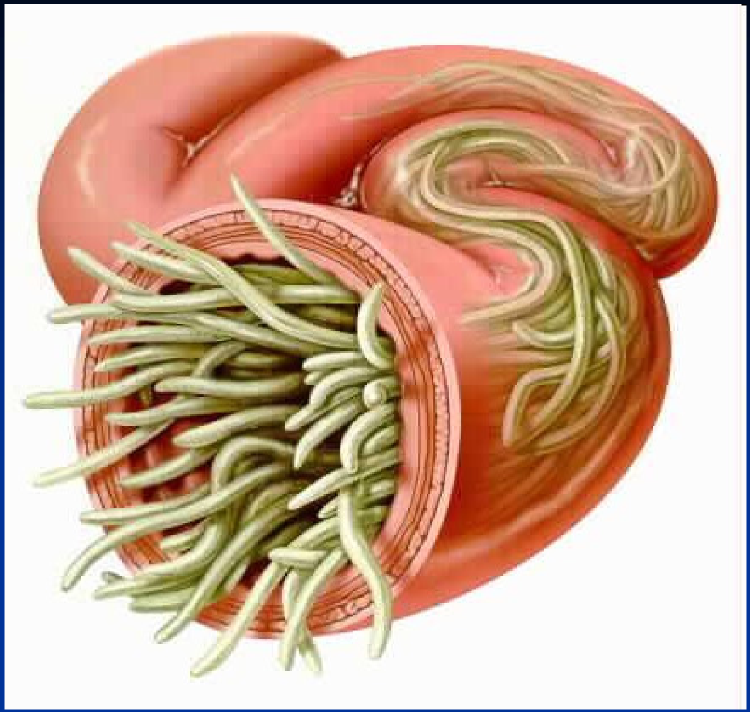
- Other substances *interfere* with the processes *of ATP phosphorylation.*
- dichlorophenol, niclosamide, benzimidazoles block the incorporation of phosphorus into ATP molecule and interferes succinate and fumarate reductase enzymatic systems .
- The inhibitory effect occurs on mitochondria.
- Other action: *ovigere inhibition function* (benzimidazoles, phenothiazines).

- Currently there are few substances (avermectins) that act selectively on the parasites located in the CNS, serouses and muscles.
- External antiparasitic also benefit from uptake of vegetable or synthetic contact insecticides,
- Carbamates and organophosphates are the most important.
- The advisable mode of removing helminths is to treat pregnant animals, at calving and then 2-3 times/year the young animals.

A complete anthelmintic:

- ☞ high therapeutic index;
- ☞ broad spectrum anthelmintic, on adult forms and especially on young ones;
- ☞ absence of side effects and low toxicity;
- ☞ short residual time;
- ☞ high retention time;

Drugs from the last generation (Ivomec, Abamectin, Closantel) have a a quite long persistence, that's why two or three treatments are sufficient.



http://3.bp.blogspot.com/_bBqysXGhPys/TVLcNzxDIFI/AAAAAAAACT4/NcJYzxRtYjo/s1600/intestin%252BiIld%252Bwith%252Bround%252Bworms.JPG

Modality of action of the anthelmintic substances

So far, *there are known four* main *mechanisms* of action:

1. Affect neurophysiology

- at the interneuronal and neuromuscular synapses level:
- *acetylcholinesterase* (O.P.): neguvon and cumaphos, couples to cholinesterase inhibiting *the degradation of acetylcholine in choline and acetate.*

Acetylcholine acts on the postsynaptic receptors causing *spastic paralysis* of the nematodes that in this case stays no longer attached, being expulsed.

Cholinomimetics

- imidazothiazoles and tetrahydropyrimidines are fixed also on the postsynaptic receptors:

- It produces *intense depolarization,* but reversible, of the muscular fiber.

Anticholinergics

(eg piperazines group) in helminths and invertebrates affects acetylcholine and gamma amino butyric acid inhibitor (GABA) neuro-transmitters causing reversible flaccid paralysis.

2. That decouple the oxidative phosphorylation

Salicylanilides and substituents of nitrophenols,

Act on the mitocondrial wall and decouples the oxidative phosphorylation after succinate synthesis which accumulates in cells, with the production of ATP.

3. Affect cell integrity

Some anthelmintic components prevent the polymerization of tubulin from which result microtubules (formations with constitutive role in cytoskeleton, present in cytoplasm and mitochondrial membrane).

Benzimidazoles bind to tubulin dimers and prevents them from polymerizing.

- **this action on microtubules is translated by:**
- **inhibition of glucose uptake by the parasite and**
- **reduction of reserve of glycogen,**
- ***reduced secretion of acetylcholinesterase by parasites.***

Depolymerization

- **takes place by binding to beta-tubulin.**
- **this explains the low toxicity for the vertebrate cell cytoskeleton.**

In the reactions of *phase I* the participating enzymes are:

- flavin monooxygenase (catalyses the oxidation of N or S);
- dehydrogenase;
- xanthine dehydrogenase;
- glutathione peroxidases from mitochondria;
- esterases = break the esteric and amidic intermolecular bonds, resulting in conjugation (phase II).

In phase II is not important only the drug, but also bilirubin, bile acids, steroid hormones occurring from the conjugation reaction in the endoplasmic reticulum in the presence of glucuronyl transferase, acetyl-transferase, sulfo and methyl transferase.

The metabolization occurs especially in the liver and is *biphasic.*

a. Initial biotransformation:

- oxidation,
- reductions and
- hydrolysis (catalyzed by microsomal enzymes).

Monooxygenase have mixed functions with catalytic role of oxidation of exogenous lipophilic substances.

Cytochrome P450 is (usually) in helminths the terminal catalytic element of the oxidant system.

The enzymatic induction of anthelmintics

Those containing imidazole nucleus are *inducers of biotransformation enzymes*: levamisole, benzimidazole, clotrimazole, miconazole.

Antiparasitics are subjected in particular to *hepatic oxidative* metabolization: - molecules or their metabolites become substrates for flavin monooxygenase and cytochrome P450.

The toxicity of antiparasitic products

New substances have a better electivity against parasites and are generally well tolerated in the body of the host animal.

- Tetramisole= toxicity especially in horses (cholinergic);
- Metyridine= local reactions when administered sc;
- The association: metyridine + trovamil = deadly effects.
- Rafoxanide = safety average margin, may produce amaurosis even at low or medium doses.
- Niclofolan, bromo-salycilinide, in to a lesser extent oxyclozanide, Nitroxinil should be administered with caution.
- New cestocidal substances generally have low toxicity.
- In all cases, you must pay a special attention to the animals that are tired, weakened, cachectic and debilitated, with chronic diseases, to pregnant females or young groups.

Classification of antiparasitic substances

Antiparasitics are: internal and external.

The internal ones have action on nemathelminthes and platyhelminthes.

A. Affect nematodes (old):

Santonin

Alkaloid from the plant *Artemisia cinae.*

Photosensitive turning from white to yellow.

Needs to be conserved into darkness: ***Separanda***.

Acts especially on those with well developed muscles, causing their paralysis.

Good results in: ascaridiosis, in swine and dogs.

Has no effect on immature or larval migrans forms.

Phenothiazines- synthetic substance.

Very sensitive to moisture and light, this is the reason why is kept in tightly closed vessels in the dark.

Has hemolytic action.

Phenobent

66% phenothiazine, 33% bentonite, 1% zinc stearate.

Excellent on hematophagous nematodes.

Does not act on cestodes and trematodes.

In ruminants 100% effect against adults of Haemonchus and Oesophagostomum and 75% against the adult form of Ostertagia and Trichostrongylus

In *birds,* very good activity in heterakidosis in turkey chickens and hens, 50% activity in ascaridiosis in hens.

Mechanism of action= blocking the enzymatic components of adult parasites = paralysis or death.

- Acts on the ovigerous function of nematodes, causing its enzymatic inhibition.
- In the body is absorbed and then metabolized in thionol causing redness of urine and milk.
- Phenothiazine is administered as Phenobent and Phenosar (lighters with one part phenothiazine and 9 parts salt).
- Phenothiazine and Phenobent are presented as: tablets, bowls, pills, suspensions.
- Horses are highly sensible.

Piperazine

In our country: piperazine *adipate* *(Ascatrix)* and piperazine sulphate *(Ascatrix S).*

Crystalline powder, very hygroscopic, white, salty-sour taste, characteristic odor.

Easily *absorbed* in the intestine.

Acts on neuromuscular junctions of worms, causing its blocking.

Low *toxicity*, DL_{50} is high -11,4/kg, indicates large limits of safe.

Spectrum: ascarids, pinworms, strongyles, esophagostomy.

- in: ascaridiosis in calves, swine, birds and carnivores.
- as well as in other helminthiasis.

Trovamil

- diethyl carbamyl derivative of piperazine citrate.
- as: injectable solution (44,5%) associated with xilin (0,43%).

Very active in dictyocaulosis in bovine and ovine.

Nematocton

- tablets containing piperazine adipate and
- syrup containing piperazine hidrate.

Sodium fluoride

- crystalline white powder, odorless, slightly salty taste,
- soluble in water in a ratio of 1:25,
- kept at *Separanda.*

- very good action in ascaridiosis in pigs.
- disadvantages: highly toxic when solubilised in water.
- after administration water *is not* given for 6-12 h.

Fluorosil

- preparation based on sodium fluorosilicate.
- white crystalline water soluble powder with high specific gravity,
- sour taste, slightly soluble in water, therefore less toxic.
- kept at Separanda.

Great efficacy in ascaridiosis in pigs!

■ Benzimidazoles

- Methyl- carbamate benzimidazoles

Thiabendazole (TBZ)

Benzimidazoles first appeared in the 70s.

- **white powder, odorless, insoluble in water;**
- **soluble: in D.M.S.O. and in diluted hydrochloric acid, at heat.**

Mechanism of action **: prevents incorporation of glucose and blocking the *enzymatic succinate* and *fumarate reductaze system* in the body of helminths.**

Elimination: **through faeces, urine and a small percentage in milk.**

Absorption: **rapidly in the digestive tract.**

Acts:

- **vermicidal,**
- **larvicidal and**
- **ovicidal.**

Action:

vermicide: adult death. *Ireversibile* lesions;

larvicide: death of the larvae, generally, in higher proportions;

ovocide: lethally on all evolutionary stages of the egg.

The action *in vitro* is much stronger than the one *in vivo*.

Spectrum: *Strongyloides, Bunostomum, Trichostrongylus, Ostertagia, Cooperia, Nematodirus, Chabertia.*

- in swine: efficacy on H. rubidus and S. ransomi;
- in horses: strongiloidiasis (AM), foals: oxyuriasis and ascariasis;
- in birds: syngamiasis in pheasants and in amidostomiasis in geese;
- commercials: Cevasol, Nemapal, Tibenzol, Vormguard

Tiprazol: thiabendazole (4%) + picadex (piperazine 8%).

- in: human, birds in syngamiasis, amidostomiasis and, nematodosis.

Cambendazole (CBZ)

- powder, odorless and tasteless, insoluble in water but soluble in alcohol;
- *absorption:* reduced in the digestive tract.

Action:

- prevents incorporation of glucose;
- does not interfere the glucose level from the host organism.
- on: nemathelminthes in bovine, great action on:
  Dictyocaulus (90% = adults and 50-85% = larvae).

Very active in gastrointestinal nematodosis.

In horses: active on Habronema muscae.

In birds: in respiratory parasites, ovicidal action.

Mebendazole (MBZ)

Metabolism: ***partial absorption*: it is absorb less than 10% in plasma, of which 95% is coupled to plasma proteins and is metabolized in the liver.**

Excretion: especially through feces, but also through: urine, bile.

Toxicity- is not embryotoxic.

Mechanism of action= ***inhibition of glucose uptake.***

- **Interferes with the passive diffusion.**

***Spectrum*: g.i. nematodes, especially in: horses and birds, but also in other species, on adults and larvae, activity knows as anti-filaria.**

- **in: parasitosis with strongyloides and oxyures;**
- **birds: syngamiasis, ascaridiasis, uncinariosis, capillariasis.**

Ciclobendazole (CyBZ)

- new product used against all nematodes.
- high toxicity, the product presenting teratogenicity;
- interdiction period: 20-30 days

Oxibendazole (OBZ)

- best anthelmintic in horses;
- good activity in gastric and pulmonary nematodes;
- *the excretion* is realized through urine;
- not recommended in stallions during mating.

Luxabendazole (LBZ)

- great product with good effectiveness;
- on all young and adults nematodes and trematodes .

Albendazole (ABZ)

- most used in combating nematodes,
- including hypobiotic forms;
- with good activity on cestodes and nematodes;
- very rapidly metabolized: in sulfone and then in sulfoxide.

Parbendazole(PBZ)

known teratogenicity, not in use.

Fenbendazole (FBZ)

- broad spectrum with good activity;
- against all important nematodes and hypobiotic larvae;
- the major metabolites are: sulfones and sulfoxides;
- over 35% of the dose is eliminated through urine, the remainders through feces.

Oxfendazole (OFZ)

- effective on nematodes and inhibited forms;
- and on adult cestodes;
- is present also in bowls.
- high doses: embryotoxic effects;
- in pregnant sheep: enteritis, hyperthermia, mortality = 20% of cases.

- **Halogenated thiabendazole**

Triclabendazole(TcBZ)

- one of the best products;
- excellent activity on trematodes;
- excreted 40-45% through bile and 46% through urine;
- interdiction period - 28 days.

Flubendazole (FlBZ)

- used more in human therapy and in swine.
- fluorinated analog of mebendazole
- from: reduction of the ketone and hydrolysis of the carbamate.

Metabolism - weakly absorbed.

Metabolites: in urine and feces.

Interdiction period = 14 days

Source: http://peticious.com/images/flubenvet_banner.jpg

- **Pro-benzimidazole**

The ability to cyclize *in vivo* and then converting itself in benzimidazoles.

Thiophanate (TPT)

- **it is rapidly transformed into its major metabolite *lobendazole*,**
- **good activity: most young and adult nematodes.**

Febantel (FBT)

- **precursor fenbendazole.**
- **very good activity on: gastrointestinal nematodes;**
- **commercials: *Ryntal, Ryntal plus*.**
- **rapidly absorbed and metabolized.**

Netobimin (NTB)

- by cyclization in the body will turn to albendazole.
- active against all gastrointestinal nematodes and on cestodes and trematodes, especially in adults.
- oral: netobimin is metabolized by intestinal flora in albendazole, then is converted to albendazole sulfoxide.
- will be metabolized in the liver, in a specific sulfone.

Other actions of benzimidazoles

Benzimidazoles

- high efficiency in the intestinal phase (at a week after exposure) or in the migration phase (2-3 weeks).
- the treatment is difficult when dealing with the encysted larvae stage, it can be realized with: thiabendazole, fenbendazole, albendazole, oxibendazole.

In human medicine, thiabendazole was used successfully against nematodes with percutaneous penetration, in which case, the topical application is more effective than the oral treatment (creams 10-15%).

■ New solutions in the use of benzimidazoles

Safe and effective drugs, but due to injudicious utilization, the resistance phenomenon appears.

Two alternatives: use combinations of anthelmintics and introduction of slow-release and sequential devices (intraluminal bolus treatment).

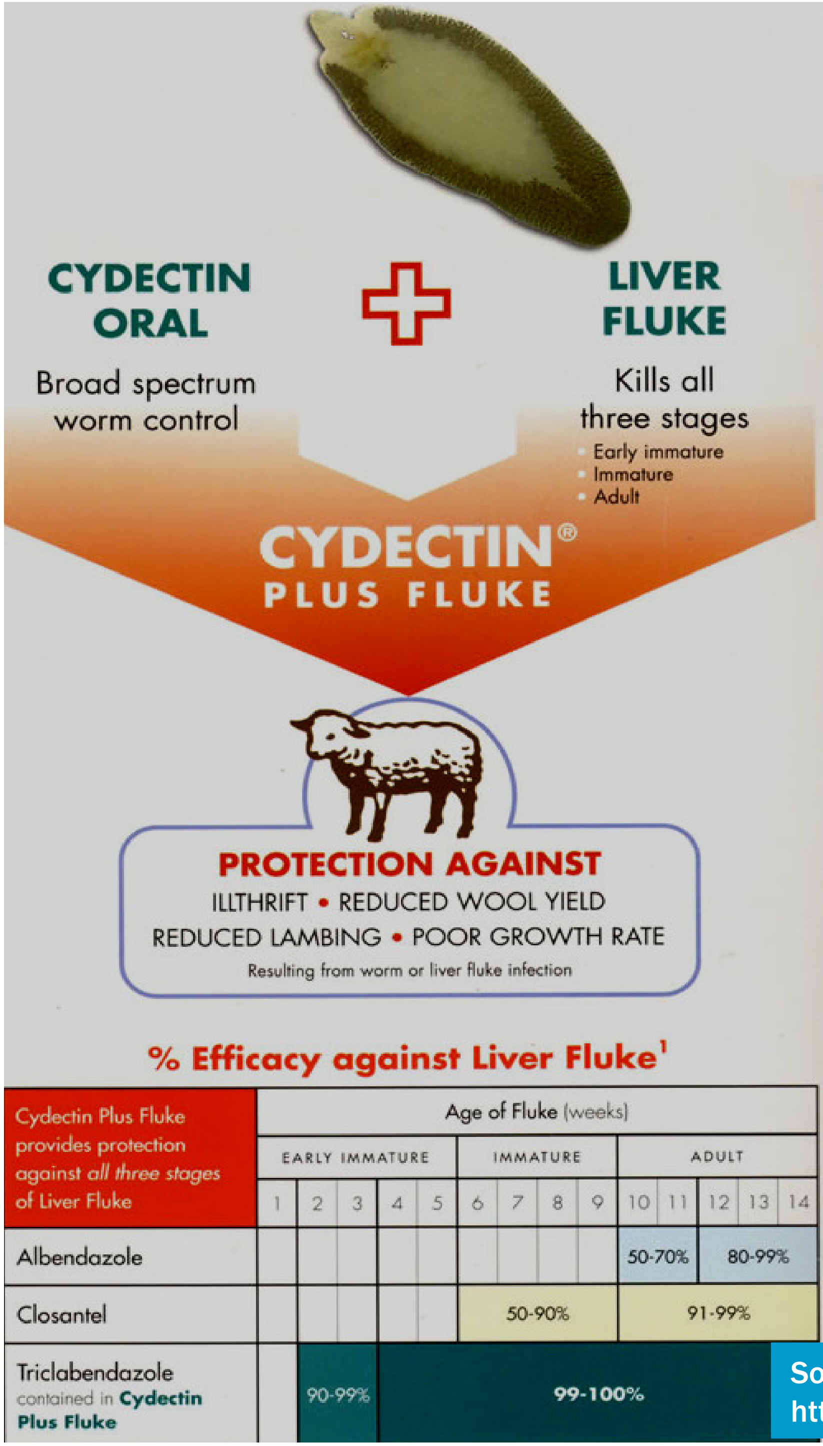
***Combinations of anthelmintics*:**

- **thiabendazole+ rafoxanid;**
- **thiophanate + brotianide;**
- **tetramisole + bithionol;**
- **levamisole+ rafoxanid + Co + Se;**
- **thiabendazole + febantel + Co + Se;**
- **morantel + diethylcarbamazine;**
- **mebendazole + triclorfon;**
- **pyrantel + oxantel;**
- **oxibendazole + niclosamide.**

Combinaţii uzuale de antihelmintice *(după Brander, 1991)*

Combination	Activity	Target species
Ivermectin+Clorsulon	Nematodes, adult trematodes	Ruminants
Thiabendazole+Rafoxanid	Nematodes, adult trematodes	Ruminants
Tetramisole+Bithionol	Nematodes, adult trematodes	Ruminants
Tiophanate+Brotianide	Nematodes, adult trematodes	Sheep
Levamisole+Oxiclozanid+Co+Se	Nematodes, trematodes adults, micronutrients deficiency	Ruminants
Oxibendazole+Rafoxanid+Co	Nematodes, trematodes adults, micronutrients deficiency	Ruminants
Albendazole+Co	Nematodes, trematodes adults, micronutrients deficiency	Ruminants
Fenbendazole+Co+Se	Nematodes, micronutrients deficiency	Ruminants
Febantel+Co+Se	Nematodes, micronutrients deficiency	Ruminants
Thiabendazole+Co	Nematodes, micronutrients deficiency	Ruminants
LEV + anti-clostridium vaccine	Nematodes, *Clostridia*	Sheep
Morantel+Diethylcarbamazine	Nematodes, including the pulmonary forms	Ruminants
Mebendazole+Triclorfon	Nematodes,	Horse
Febantel+Triclorfon	Nematodes,	Horse
Thiabendazole+Piperazine	Nematodes, iincluding *Ascaris*	Horse
Tiophanate+Piperazine	Nematodes,	Pig
Pyrantel+Oxantel	Nematodes, including *Ancylostoma*	Dog
Febantel+Praziquantel	Nematodes, Cestodes	Dog
Pyrantel+Epsiprantel	Nematodes, Cestodes	Dog
Toluen+Diclorofen	Nematodes, Cestodes	Dog
Thenium+Piperazine (synergism)	Nematodes	Dog

	Dedicated use	The active substance
	Adult hepatic trematodes (ruminants)	Bithionol Bromophenophos Bromoxanid Brotianid Carbon tetrachloride Clioxanid Dichlorophenol Hexachlorethane Menichlofolan Metryphonate Resorantel Tribrom Salicylanilide
	Nematodes (ruminants)	Bephenium Methitidine
	Nematodes (horses, pets)	Coumaphos Fenclorphos Fosfirat Naftalophos
	Nematodes (dogs and cats)	Amidatel Butamisol
	Nematodes (Trichuris)	Diphetarsone Dithiazanine Vincophos
Devoted activity of other anthelmintics (after Brander, 1991)	Nematodes and cestodes (dogs and cats)	Nidanthel Ticarbodin Uredophos
	Nematodes (Ancylostoma)	Thiacetarsamide
	Cestodes (dogs and cats)	Arecoline Paromomycin



Source:
http://www.crtkyneton.com.au/animalhealth/drench/cydectinfluke0002.jpg

1 . Systems with continuous release

Release systems for ABZ

Proftril bolus

- bowl, cylindrical
- corresponding to: 3,85g ABZ for ovine and 18,44g for bovine.
- in acid medium the operculum solubilizes = puts in contact the first tablet of albendazole.
- three months longevity

Sustained-release system for morantel tartrate

Paratect (Pfizer)

- first continuous release bolus containing morantel tartrate;
- gradually slow dissolution of the morantel;
- protects the animal between 60 and 80 days.

Sustained-release system of ivermectin

Enzec and Alzet- Osmotic-pump (MSD)

consisting of a container *containing micellar solution of ivomec and a water-permeable vesicle* which contains a concentrated solution (high osmolarity) under pressure (pump).

Entering of water into pump (blister) = will increase the volume = compression on the ivomec tank = release in the rumen (ROP) of the active substance.

Doses: determined by the concentration of the vesicle solution.

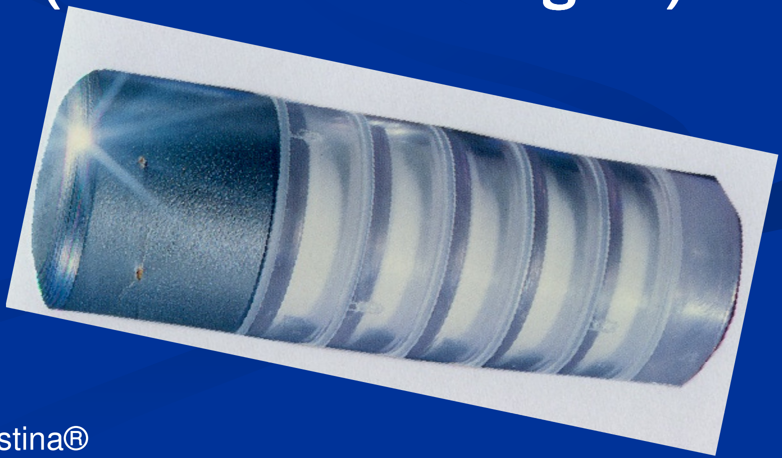
delivered doses during 40 days ranged between: 3,2 - 16, 6 - 24,4 şi 33,7 μg/kgb/day,

- corresponding to plasma concentrations: 5, 9, 12, 17 mg/ml

Sustained-release system of oxfendazole (OFZ)

Synanthic multidose bolus (Pitman Moore)

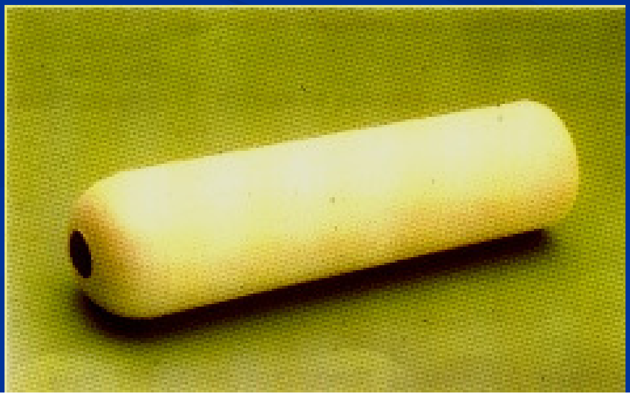
- similar to Proftril (ABZ),
- provides: OFZ 0,25-0,50 mg /bw. for 40 days;
- after administration of two bowls at an interval of 40 days, the effect lasted 114 days after administration.
- using bowls were net favorable for *oral administration* (drench type) with the same product (SMZ is 50-70% higher).



Sustained-release system for levamisole

Cronominthic bolus (Virbac)

- bowl, cylindrical (the wall consists of polymers);
- ensures continuous diffusion of incorporated levamisole;
- the concentration of anthelmintic = in relation to the amount of antiparasitic daily released and the duration of desired treatment.
- the system will be given five weeks before the onset of verminous bronchitis, animals carrying bowls does not require therapeutic intervention during the grazing season.



Sustained-release system for ivomec:

Ivomec SR Bolus (*Merial)*

- the newest sustained release systems;
- ensures: 12 mg ivermectin/day, for 135 days,
- preventive and curative: nematodosis, lice and ticks in cattle.

Sustained-release system for fenbendazole

Panacur Bolus (Hoechst Roussel)

- ensures 0,2-0,4mg/kgb/day;
- is active for 140 days after administration;
- prevention and therapy of nematode infestations in cattle

2. Periodic scheduled delivery systems

- the latest achievements in the field,
- represented by:
  - Electronic bowl and
  - Repidose system (Autoworm).

Electronic bowl

Intra Ruminal Pulse Release Electronic Device (IPRED)

- composed of a undegradable coated and two mini batteries.
- has three compartments, each one presenting a thermosensible operculum and a resistance with two electrodes.
- each compartment contains 2g albendazole.
- by heating the resistance is suddenly released CO_2 or NO_2 = explosion of the operculum.
- assures the albendazole release at: 21, 62 and 90 days.

Oxfendazole Pulsed Release Bolus

Autoworm (Pitman Moore)

- is based on the *progressive erosion* principle and
- cylinder 19/2,5 cm of 130g consisting of a Mg rod driven on its entire length by a steel ring.
- divided in five circular compartments of polyvinyl chloride = each compartment: 750mg OFZ.
- on the effect of the electro discharge pile between the ruminal juice and magnesium axis, after three weeks of contact will open the first of five opercula, allowing access to the active substance in the rumen.
- the erosion continues until day 124, the operculum opening at average intervals of 23,5 days.
- determines the decrease of the G.I. parasitism (95% towards *Ostertagia* and *Cooperia*),
- remarkable weight gain.

■ Imidazole derivatives (imidazoles)

Tetramisole

- on: gastrointestinal and pulmonary nematodes.
- white powder, a mixture of two optically active isomers.
- fast absorption.
- action: blocking the fumarate and succinate reductase enzymes.
- by irreversible paralysis of worms.
- constant effect *in vitro* on all types of helminths.

Spectrum:

In bovine - active on Ostertagia, Trichostrongylus, Cooperia, Bunostomum, Strongyloides, Oesophagostomum, Dictyocaulus

In ovine - Haemonchus, Cooperia, Nematodirus, Strongyloides, Chabertia, Trichocephalus.

In swine - ascaridiosis, hyostrongylosis, metastrongylidosis strongylosis, trichocefalosis, esophagostomosis.

In birds - capillariasis, ascaridiosis, heterakidiasis and in amidostomiasis in palmipeds.

In horses - Oxyuris, Para-scaris.

In dogs & cats - Toxascaris, Toxocara, Uncinaria, Ancylostoma, Trichocephalus.

In ruminants- 15mg/kgbw, active on dictyocaulosis.

Levamisole (LEV)

- levorotatory form of tetramisole.
- soluble, administered both orally and parenterally.
- very effective on nematodes, larval and adult forms.
- often used in the form of chlorhydrate salt.
- commercials: Decaris, Paglisol, Nemisol, Anthelson.

Tetrahydropyrimidine derivatives

Current treatments use:
- **morantel,**
- **pyrantel,**
- **oxantel.**

- **initially, pyrantel was produced under the form of:**
- **tartrate salt ('70) followed by**
- **pamoate salt in ruminants,**
- **Injectable form= inactive towards pulmonary nematodes.**

Mode of action:

linked to *affecting the neuromuscular system* of worms resulting in: paralysis, death and expulsion.

Pamoate= more active and used in current therapy.

Tartrate = used in nematodes, more effective in strongylosis and oxyuriasis in horses, ascaridiosis in swine.

good effects are obtained in trichinellosis!

In ovine and bovine, effect on all G.I. nematodes with lower efficacy on: Oesophagostomum and Chabertia.

Due to its cholinergic activity (nicotinic type), the treatment with pamoate is not associated with the organophosphate therapy!

It is delivered as liquid or powder of 5%.

Morantel

- methyl derivative of pyrantel, used in the form of salts (fumarate and tartrate),
- used as bowls (Paratect bolus and Paratect flex)
- providing antiparasitic protection for a period of 90 days,
- the product *does not* have toxicity (x 30 times the therapeutic dose),
- there were not found any teratogenic effects,
- commercials: *Ovihelm, Bovhelm, Glyox* (for swine)

Pyridine derivatives

Metyridine

- colorless liquid miscible in water,
- good organic solvent, not administered with rubber objects!
- sterile solutions 90% for s.c. and i.p. administrations.
- very active in: nematodes, efficacy on adults and larvae of the species: Trichostrongylus, Nematodirus, Ostertagia, Cooperia, Trichocephalus.
- very active in capillariasis in birds,
- preparations: *Methyridin, Prominthic*

■ Antiparasitic macrolides

Avermectins and milbemycins

antibiotics produced by actinomycetes, classified as macrocyclic lactones.

Avermectins exhibit highly efficient activity on the parasitic species from nematodes to arthropods.

Are known 8 major avermectins produced by Streptomyces avermitilis and over 30 de milbemycins produced by different species of Streptomyces.

Natural avermectins are known as abamectine.

Ivermectin is a semisynthetic product.

Milbemycin: Milbermicin D, Milbermicin-oxime in SUA and in Japan, Moxidectin.

Avermectins (ivomec, abamectin, doramectin)

- GABA-ergic activity,
- but will stimulate the production of GABA and
- will potentialise the acid fixation on the postsynaptic receptors.

Avermectins = paralysis affecting GABA mediator, cestodes and trematodes do not use this mediator as a neurotransmitter!

- in mammals, GABAergic neurons are located in the CNS.
- avermectins *does not cross the hematoencephalic barrier.*
- easy to explain the low toxicity for mammals.
- some dog breeds (Collie, Shepherd's) are sensible to injectable Ivomec.

Ivermectin (Ivomec)

- association of 22-23 dihydro-avermectin B1a and B1b.
- used: oral and parenteral.
- effective in all major nematodes.
- strong ectoparasiticide.

Excretion

- through: 98% feces and 2% urine .
- residues in: liver and fat tissue.
- Ivermectin *is not recommended* in dairy cows!
- Safety index is 30 times the dose.
- do not administer parenteral in: horses and some dog breeds!
- is not embryotoxic, but has teratogenic effects in rats.
- therapeutic dose= 0,2mg/kgbw.

Moxidectin

- synthetic milbemycin derived from the metabolite of:
- Streptomyces aurolacrimosus noncianogeus.
- similar activity to ivermectin and with the metabolites potentiating of the GABA inhibitory effect.

Milbemycin D

- natural product of *Streptomyces hygroscopicus*.

Milbemycin-oxime

- contains 80% milbemycin A4 and 20% milbemycin A3.
- used only in dog.

Doramectin (Dectomax)

- new product studied only in pigs.
- sustained activity on Ascaris and Metastrongylus.

Other antiparasitic substances (old)

Bephenium (Alcopar)

- quaternary ammonium derivative,
- in: gastrointestinal strongyloides.

Oxiuran

- human product use in human nematodes.
- pioctanin acts on the nematodes of the digestive tract in animals.

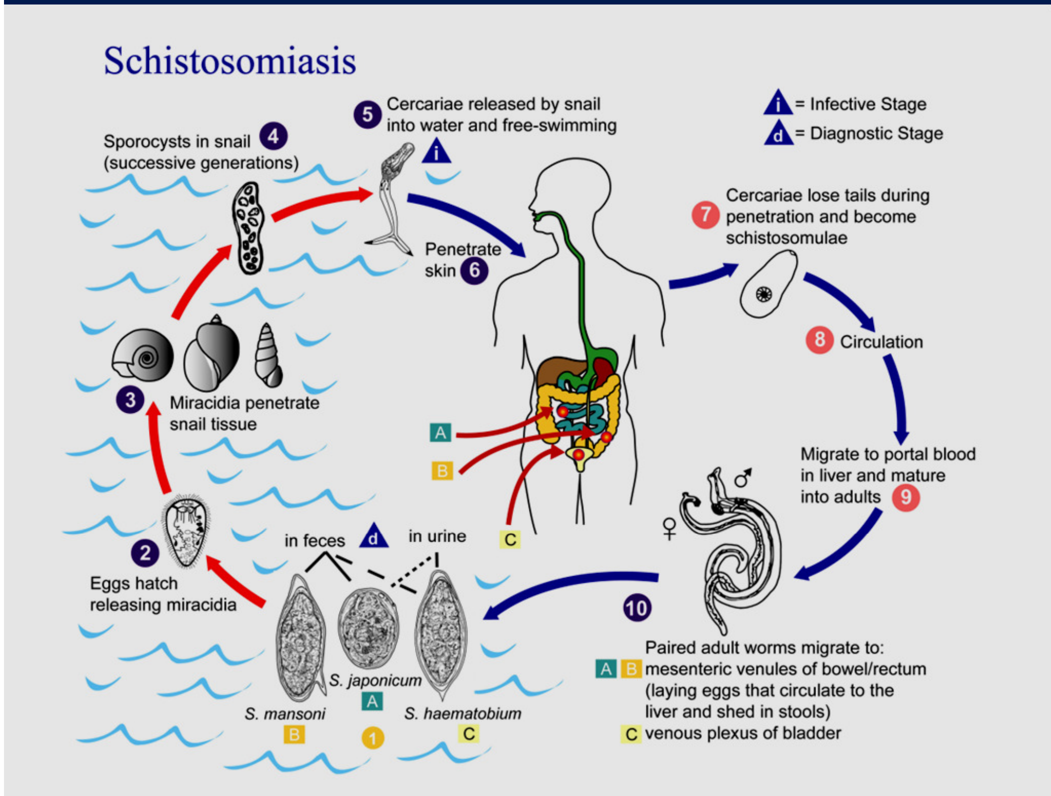
Turpentine oil

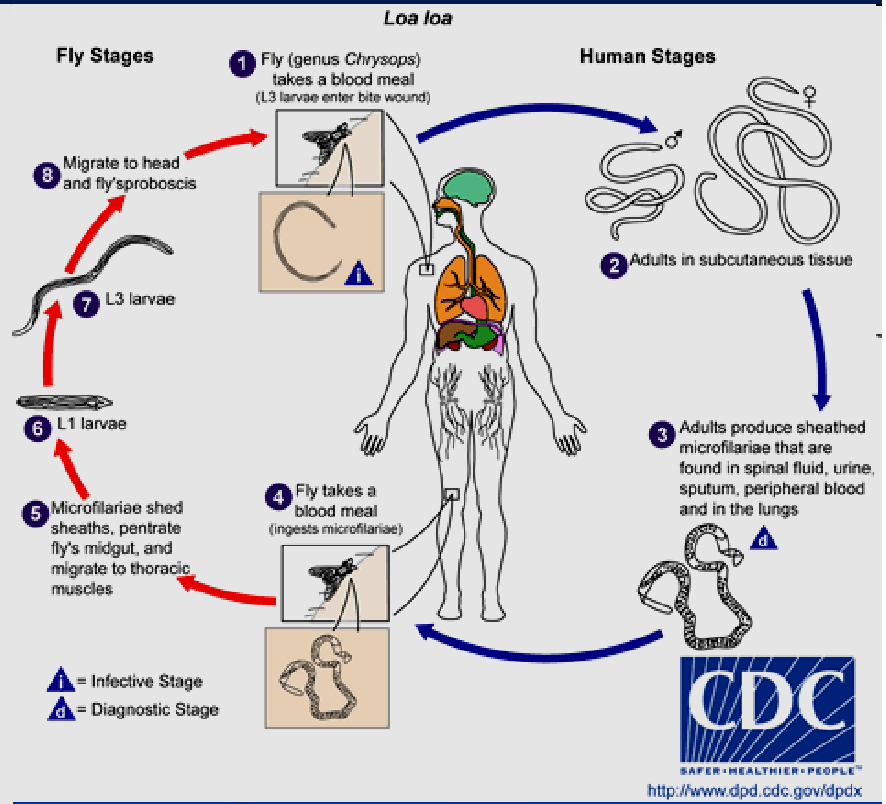
In horses, administered with the naso-oesophageal probe 30 ml associated with 20 ml CCl_4.

Lugol solution

- in dictyocaulosis is sheep, calves, using intratracheal injections.

http://upload.wikimedia.org/wikipedia/commons/8/80/Schistosomiasis_Life_Cycle.jpeg





http://lamarck.unl.edu/zoo/lifecycles/Loa.gif

Therapy

of trematodes and cestodes

Old products (chlorinated derivatives and hydrocarbons)

Carbon tetrachloride (CCl4)

colorless liquid, sweet, spent taste, volatile, chloroform-like appearance with which is structurally related.

- ***toxic*, especially on the central nervous system.**
- ***cumulates* in the liver leading to serious liver dystrophy.**
- **bovines are sensitive, therefore the p.o. *administration is Forbidden!***
- **are used: injectable formulations.**

Fasciozan ovin, gelatin capsules of 1,25 ml, respectively 2 g CCl_4 + paraffinic oil.

Vitolin

- injectable, photosensitive! 73% CCl_4, xilin 1%, 26% vaseline oil.

Avipar

- in birds, three dimensions (A, B, C), they contain: 0,5, 1 and 2ml CCl_4.

Hexachloroethane

- ethane derivative, white, unpleasant odor, insoluble in water, soluble in alcohol and oil.
- acts: on adult facioles.

Fasciozone (ovine or bovine)

- contains 60 parts Hexachloroethane and 40 parts bentonite.
- susceptible: pregnant cows and those with high milk production!

Hexachlorophene

- white powder, odorless, insoluble in water, soluble in alkali.
- in: nematodes, cestodes, fasciolosis in sheep and cattle.

Diclorphene

- product: antiparasitic, antiseptic, antifungic.
- on: flat worms, except fasciolosis.
- commercials: *Dicestal, Taeniaphene, Diphentan*.

Hethol

- white powder, insoluble in water.
- usage: ovine and bovine fasciolosis, more active and less toxic.

Hetholin

- very active on Dicrocoelium lanceolatum.
- along with *diamphenethyl* it is the drug of choice when dealing with dicroceliasis.

Salicylamide derivates

Effectiveness when dealing with trematodes known since '60s.

Has no activity on young forms of 6-8 weeks.

Activity on:

- **hematophagous nematodes (*Haemonchus spp* and *Ancylostoma*)**
- **larvae of the *Oestrus and Hypoderma genera.***
- **after absorption (except Niclosamide) are tightly coupled affecting phosphorylases participation within the energetic metabolism of parasites.**
- **this group of substances may inhibit *fumarate reductase.***

Good activity on *Haemonchus* allowed the use of salicylanilides, as an alternative medication, in cases of resistance to benzilidazole anthelmintics.

Salicylanilides are insoluble in water, but are also known injectable formulations (rafoxanide and closantel).

***Lower safety index*: about 4-7 time the dose.**

The latest analog = Closantel = low safety limits (only six times the therapeutic dose).

Rafoxanide (Rafoxanide, Flukanide, Ranide)

- yellowish-white powder with a characteristic odor, insoluble in water.
- but gives stable suspensions if the water has a slightly acidic pH.
- action: fasciolicide.
- destroys: adult forms and young forms of 6 weeks 99%!
- the younger the parasitic forms are, the proportion will decrease to 50%.
- commercials: *Rafoxanid, Flukanide, Ranide, Ranidzol*
- doses: 10-12,5mg/bw.
- are known: incorporable powder suspensions, tablets, bowls and injectable formulas, 2,5%, 10%,

associations:

Ranidzol: association of Rafoxanide + Thiabendazole in suspension.

Closantel

- formulated as: oral or injectable formulations;
- *activity:* young and adult forms (6-10 weeks), trematodes, hematophagous nematodes, insect larvae;
- some effects: on cestodes, scabies and even ticks;
- *metabolism:* well absorbed, p.o. doses: 10 mg/kgbw, reaching after 24h, plasma, value of: 55 mcg/kgbw;
- the half-life time: 15 days;
- after the injectable administration the plasma peak is achieved at: 24-48h.
- *toxicity:* is not carcinogenic, teratogenic or embryotoxic;
- the safety limit is just over 6 times the therapeutic dose;
- *dosage:* ovine and bovine: 10 mg/kgbw p.o. and 5 mg/kgbw s.c.

Clioxanide (Tremerad)

- very active in acute forms;
- on: adult forms of F. hepatica (15mg/bw) where these forms are 100% eliminated;
- in young forms, doses are increased to 130mg/kgbw;
- signs of intoxication may occur after 2-3 d. of treatment;
- because the usual doses have a good tolerance it can be used in lactating and pregnant sheep.
- much more active in the treatment of chronic fasciolosis, being able to ascertain health improvement;
- Clioxanide can be associated with thiabendazole.

Oxyclozanide (Zanil)

- absorption: high, high concentrations in: liver and kidneys.
- elimination: glucuronoconjugation through bile.
- action: interfering glucuronide-reductases.
- fasciolicide: towards adults, in young: 60-64% action.
- toxicity: relatively low, low therapeutic index.
- dose x 4 times higher = toxic effects.
- the restriction period of meat = 14 days.
- milk = doesn't have a restriction period.
- dose: 10-15mg/bw in ovine and bovine.
- bovine: do not exceed 100ml, regardless of weight.
- rare accidents in animals with massive acute fasciolosis.

Associations:

Nilzan = Nilverm (tetramisole) + Zanil 50%/50% (3,4%).

Loditac = Zanil + oxibendazole, 10-15mg/kgbw.

Niclosanide

(Cestocid, Fenasal, Mansonil, Yomesan, Dogoten, Lintex, Niclocide, Sulqui, Tenizan, Vermitid,)

- excellent against: Echinococcus spp. and Taenia spp.,
- weaker against: Dypilidium spp.,
- nematodes in dogs and cats in intestinal trematodes;
- ruminants: in Paramphistomum.
- metabolism: absorbed very little in the digestive tract;
- the absorbed amounts will be metabolized in aminoclosamide (amine without pharmacodynamic activity).

- action: inhibition of glucose uptake = blockage of the Krebs cycle= accumulation of lactic acid= death of trematodes.
- elimination: particular towards other representatives, niclosamide is rapidly eliminated.

Safety limit:

- High in: bovine and ovine, doses x 40 times, well tolerated;
- Small in: dogs and cats.

Usual doses:

- 150-200 mg/kgbw: dog, cat and horse.
- 80-100 mg/bw. in ruminants.
- most efficient: particle of 2-3μm.
- in treatment: diet for 12h., does not requires any purgative.
- toxicity: doses can be exceeded by 5-7 times.

- **Bromosalicylanilides**

Includes two substances:

Dibromsalan and Tribromsalan

- gray white powder, insoluble in water,
- used in the treatment of fasciolosis in sheep and cattle,
- alone, or often associated in commercial conditionings.

Hilomid

association between: dibromsalan + tribromsalan in 1:1 ratio.

Diafen

- association 3:1 tribromsalan + dibromsalan.
- advantages: effective on adult and young forms, of 6-12 weeks.
- IT = 3.
- dose= 30mg/bw, for the young forms the dosage is doubled.

Substituted phenol derivatives

Numerous group with importance for a.u.v.

compounds: of thiodiphenol, chlorophenoldiole, acetonitrile, benzonitrile, phenyl thiocyanate and niclopholan.

- good effects against: cestodes and trematodes.
- in general has a small safety index,
- due to this considerate, it is replaced with safer drugs.
- however, their effectiveness, considered good, has an important role in the current anthelmintic arsenal.
- as halogenated hydrocarbons, substituted phenols act as: inhibitors of phosphorylation phase in the mitochondrial cell of the helminths, blocking its energetic metabolism.

Hexachlorophene

(Dermadex, Distolin, Douveoside, Exofene, Hexosan Fasciophene, Surofene)

- with powder, odorless, insoluble in water, soluble in alkali.
- in: nematodes, cestodes, fasciolosis in ovine and bovine.
- dose in sheep and cattle: 10-15mg/kgbw.

Diclorophene

(Diclorophene, Dicestal, Taeniaphene, Diphentan)

- **safe cestodicide, used a.u.v.**
- **antiseptic or antifungal with narrow spectrum,**
- **moderat on *Taenia* and *Dipylidium* in carnivores,**
- **has no activity against *Echinococcus.***
- **slowly absorbed, activity in the intestine =**
- **worms are disintegrated before removing through feces.**
- ***toxicity:* very well tolerated by carnivores.**
- **in extremely rare cases: vomiting or diarrhea in dog.**
- **dog and cat: 200 mg/bw, with diet prior to 24 h.**
- **used also in horse with some efficiency in fasciolosis.**

Diamphenetide (Coriban)

- most effective on immature forms, from day 3!
- the activity decreases proportionally with the increasing in age of fasciolosis.
- the adult forms are less affected.
- principal effect: vacuolization of the helminth's skin and the production of its irreversible paralysis.
- spectrum: trematodes in sheep.
- has no activity on trematodes in cattle.
- p.o. is absorbed and distributed, by circulatory path.
- at 3 days after treatment = highest concentration: liver and gallbladder.
- activity: depends on the amidic metabolite (by the deacetylation of enzymes of the liver cells) that is responsible for the anthelmintic activity of the product.

- this metabolite = death of the immature forms of fasciolosis.
- in: acute fasciolosis, by the invasion of young forms.
- 100% effectiveness.
- interdiction period: 7 days for meat.
- not recommended in: lactating sheep when milk will be used for consumption.
- toxicity: the substance is safe up to x 4 dose
- visible toxic dose, from: 1 g/kg body weight.
- dose: 100 mg/kgbw in sheep, well tolerated by pregnant females, weak animals and with a compromised growth.
- repeat treatment: after 1 week., in the temperate zone after 4 weeks.
- diamphenetide is irritant for skin and mucosa.

Menichlopholane (Niclofolan, Bilevon-M)

- crystalline substance, yellowish, insoluble in water,
- great activity on : adult forms.
- weaker on: younger forms, the doses should be gradually increased.
- in: sheep, cattle, swine.
- action: blocking of glucose uptake + decoupling of oxidative phosphorylation, high absorption and maximum blood concentrations in 24-48 h.
- after 3mg/kgbw= 100% effectiveness in adults.
- interdiction period= 7-14 days.
- no residues in: milk, tissue, organs.
- delivered as: M: sheep and goats and R: cattle.
- Bilevon M = 4mg/bw.,
- Bilevon R = 3 mg/bw.,
- toxic and irritating for the one who handles the drug.

Cursuri Prof. Romeo T. Cristina®

Brotiamide (Dirian)

- **activity:** active on F. hepatica, adults and larvae and
- **in:** paramfistomosis with immature and adult forms.
- **dosage:** 10-15 mg/kgbw.
- **toxicity:** small safety index 1,7 (retired).
- **weighing** the animal is indicated in order to avoid overdosing.
- **precautions:** do not use in cattle!

Nitroscanate

- **activity:** on all cestodes and nematodes specific in dogs.
- **not recommended in cats!**
- in animals **with emptied digestive tract,** the medicine will pass **too fast** the intestinal segment = **acting only partially.**
- **the maximum effect, contrary to the rules:** the medicine will be administered **after feeding** the animals, when due to plenitude, **the intestinal drug absorption rate** will be slowed = amplified effect.
- **side effect: vomiting.**
- **dosage:** dog **50 mg/kgbw.**

Nitroxinil (Dovenil and Trodax)

- effective fasciolicide only by injection.
- yellow powder, soluble in water.
- administration: parenteral, s.c. or i.m. existing also p.o. forms.
- s.c. on the sides of the neck in cattle and in areas without wool in sheep.
- parenteral effectiveness is several times higher than the local administration, excellent results in fasciolosis, including young forms, comparable efficiency to that of Rafoxanide.
- dose: 10 mg/kgbw , s.c. in sheep and cattle.

- **Organophosphoric derivatives**

- act as parasiticide,
- action: blocking acetylcholine esterase,
- the organophosphorus binds stable to the enzyme,
- produces: its irreversible blocking,
- the chemical mediator, *acetylcholine,* remains unhydrolyzed.
- accumulates = paralysis of the neuromuscular system of the parasite.

action: toxic, of contact and digestion.

act: by combining and neutralizing the cholinesterase.

Elimination: by products of metabolism.

Toxicity: dadue to the cholinesterase activity, are more toxic.

The OP activity can be counteracted by use of atropine.

It is not recommended the administration, at the same time, of insecticides and anthelmintics with choline esterase inhibitory activity!

Spectrum

Nematodes in: horse, swine, carnivores, to some extent, in ruminants.

Triclorfon present in: *Dipterex, Neguvon, Metrifonate*.

White powder in crystal form, with particular odor, soluble in water, ether, chloroform, soluble in alcohol.

Official name: Metrifonate.

In horse – as boluses or granules in parasitism with: Gasterophylus, Paraascaris, Oxiuris.

Commercial product: Dyrex TF.

In carnivores, *good results in infection with* Toxocara canis, Ancylostoma, fleas, ticks and in demodicosis.(75%).

Dichlorvos (DDVP)

- volatile, easily decomposed by oxidation and hydrolysis.
- advantage: the only OP anthelmintic that can be incorporated into rezine (e.g. polyvinyl chloride).

In swine, the Atgard product with broad spectrum anthelmintic.

Active on: Ascaris, Oesophagostomum, Trichocephalus, on both adult and larvae form.

In horses is used the product: *Equigard.*

Contraindicated in animals with pulmonary emphysema (produces bronchospasm) or enteritis (increase peristalsis).

Broad spectrum: large and small strongyles, ascarids, pinworms, gasterophilus.

Haloxon

- white powder, odorless, insoluble in water,
- soluble in chloroform, acetone, oil.
- Formulations: wettable powders, suspensions or pasta.
- sheep – adult forms: *Haemonchus, Trichostrongylus, Cooperia, Strongyloides.* Relatively active on *Ostertagia and Bunostomum.* Less active on: *Trichocephalus and Chabertia.*

In cattle – same spectrum.

Commercials: *Cevoxon* and *Galloxon.*

In horse – good effects: large and small ascarids and strongyles.

In cattle – same spectrum.

Commercial: Cevoxon şi Galloxon.

Coumaphos

- yellow powder, insoluble in water, sparingly soluble: ether and methanol
- mainly used in ruminant because does not leave residues in milk.

Naftalophos

- organophosphoric product with average spectrum.
- used in: sheep and cattle.
- very active on: adult and larvae forms of Haemonchus, Trichostrongylus, Ostertagia, Neoascaris.
- white powder, aromatic odor, insoluble: water, soluble: chloroform.
- commercial: *Maretin* and *Rametin*.

- **Antiparasitic sulfonamides**

- with activity on *Fasciola spp.*
- mainly on adult form and on young forms up to six weeks parasitic in sheep, respectively, eight weeks (cow).
- usually a single injectable administration is sufficient.
- fast absorption, couples to erythrocytes.
- great effectiveness on haematophagous trematodes.
- action = impaired energy production of enzymes by interfering two important enzymes: *phosphoglycerol kinase* and *phosphoglycerol-mutase,* essential in the glycolytic phase of the carbohydrate metabolism of worms.

The most important representative of the group:

Clorsulon (presented in the sulfonamides chapter)

- Very good activity on young and adult trematodes (of 6-8 weeks).
- metabolism: well absorbed, 75% of the circulant drug can be found in plasma, which is 25% coupled to erythrocytes.
- forbidden period: 8 days for meat.
- the drug cannot be administered in dairy cows!
- toxicity: is not embryotoxic or mutagenic.
- high doses, even 25 times higher, do not induce any side effects in animals.
- dose: sheep and cow7 mg/bw., p.o. and 4 mg/bw., s.c.

- Pyrazine - isoquinolines and benzodiazepines

- the most efficient and reliable cestodicide group of all.
- effective against all cestodes in dog and cat.
- inclusively *Echinococcus*,
- and on cestodes of mammals,
- at increased dose destroys the larvae form of the intermediate host and is
- less effective against hydatid cyst of *Echinococcus.*

Praziquantel (Droncit, Drontal, Kuma, Cestal)

- oral or parenteral formulations.
- best activity in dogs and cats.
- activity on the helminths form: lung, intestine and blood.
- on: all species of cestodes, adults and larvae.
- not on: hydatid cyst!
- on trematodes (but not on Fasciola) = injectable.
- muscle contraction by altering the ionic balance of the cell = by vacuolization and then disruption of worm's cuticle.
- acts by: blocking the cuticular functions of the parasite = its permeability and high losses of glucose.
- the parasite will become susceptible to the attack of proteolytic enzymes.
- metabolization: quickly absorbed and is almost completely metabolized nearly as fast = first-pass effect.

http://www.vetdepot.com/store/i/is.aspx?path=/images/
Droncit-Praziquantel-Injectable-10-mL.jpg&lr=t&bw=340&bh=340

- in dog 60-80% of dose is excreted in the urine, the rest through bile and feces.
- a very small part of the drug (0,1-0,3%) will be excreted unchanged.
- praziquantel has a very good safety limit.
- the dose x 40 times higher= occasional vomiting.
- the substance can be administered safely in gestation.
- not recommended to puppies under a month, or kittens under 6 weeks.
- injectables can cause allergies and transient algia.
- dog and cat: 5 mg/kgbw. p.o. and 5,5 mg/kgbw. s.c. or i.m.

Epsiprantel

- among the latest cestodicide remedies appeared on the market.
- excellent activity against cestodes from dog, cat, sheep and horses.
- perhaps better than praziquantel,
- activity against schistosome is restricted.
- dog: 5,5 mg/kgbw, cat: 2,25 mg/kgbw.
- toxicity = very safe.
- no signs of toxicity were observed in dog or at 90 times increasing doses.

Bunamidine (Buban, Scolaban)

There are three salts of bunamidine:

- chloride,
- toluen-sulfonate and
- hydroxynaphthoate, a.u.v., first and last are commonly used.
- chloride is a valuable cestodicide in carnassiers.
- active only on cestodes, including E. granulosus,
- very good results: 25-50 mg/kgbw., in dog and cat.

Hydroxynaphthoate

- yellow powder, insoluble in water.
- remarkable cestodicide effects are quite common.
- used especially in sheep and goats.
- in monesiasis in dogs, birds and other species.
- 50 mg/kgbw in ruminants and birds.
- 25 mg/kgbw in equine.
- 50-100 mg/kgbw in dogs.
- oral administration without diet and purgative.

Ectoparasiticide

(insecticides, pesticides)

The **ectoparasitic** name = attributed to those substances active against the parasitic arthropods: **skin** and **appendages** or **adjacent areas** (larvae forms).

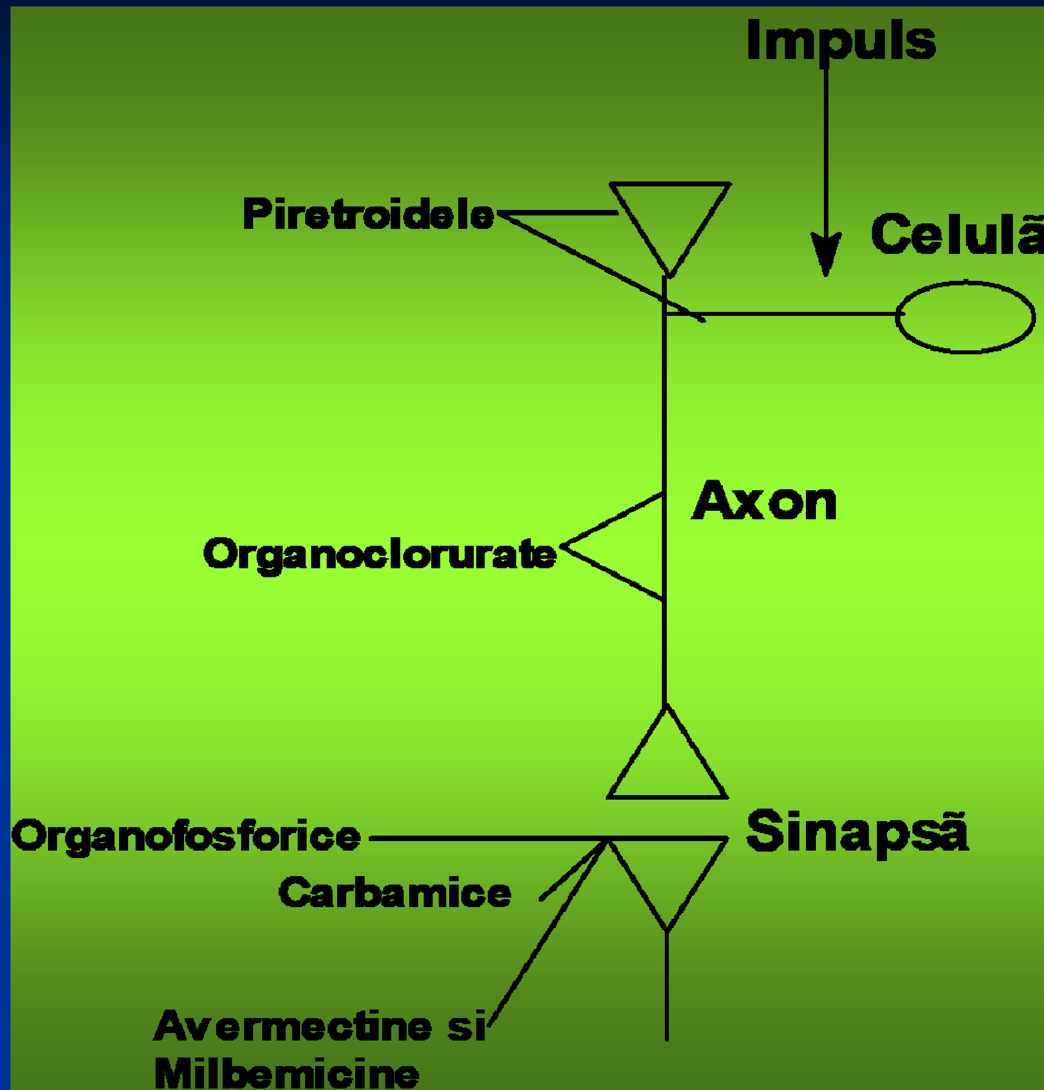
The ectoparasites of animals include **members of the groups:**

- ► Arachnida (ticks and scabies)
- ► Insecta (Diptera and hematophagous flies, gasterophilus lice).

- in this group: old minerals, OC, OP, carbamate, formamidines, piretrinoids fermentation products etc.
- the site of action of ectoparasiticides:
- *migrating during their larval stage through the host's body,*
- *that perforates the cutis and its layers,*
- *living in the skin and its depth.*

An ideal ectoparasiticide must:

- *destroy any parasites regardless of their stage of life,*
- *have a quick action,*
- *be non-toxic or with low toxicity,*
- *be compatible with various excipients,*
- *be economical and practical,*
- *not polluting the environment and*
- *not present residues in the host's tissues.*


Impuls
Piretroidele
Celulã
Axon
Organoclorurate
Sinapsã
Organofosforice
Carbamice
Avermectine si
Milbemicine

Therapeutic strategy against ectoparasitosis

The timing and pace of the treatment

It will be based on:

- acaricide in use,
- target species,
- season and
- the objective of the combat program

reduces infestation at bearable levels, the interval between the acaricides treatments is 2-4 weeks.

1. Seasonal treatments
2. Extempore treatment

Old inorganic products

Sulphur and derivatives

- Sodium sulfide
- Sulfur sublimatum
- Sulfur praecipitatum
- Sulfur pulveratum lotum
- Solutio calcii sulfurati
- Natrium thiosulfuricum,

Arsenic and derivatives

- Calcium arsenate
- Copper acetoarsenite
- Copper arsenate
- Lead arsenate
- Potassium arsenite
- Sodium arsenite

■ Organochlorine

DDT (Dicophane, Clorophenotane, Agritan, Neocid)

- Contact toxic and neurotoxic affecting motor and sensitive neurons, with the installation of paralysis and hyperexcitation.
- The knock-down effect: in minutes, a half an hour.
- due to the toxic effects, the host may be also affected.
- The toxicity is higher in pets due to their hygiene habits (licking) that in large animals is absent.
- possibility of residues in milk.
- the intoxication: hyperexcitability, convulsions, paralysis and death.
- To control the nervous simptomatology: sedation (e.g. phenobarbital) and detoxification: calcium borogluconate (antidot in dog) i.v. in high dose2-3g /animal.

HCH

(Lindan, γBHC, Gammexane, Lindavet, Quelada, Viton)

- paralysis and death of insects, rapid effect.
- pure gamma isomers, devoid of toxicity.
- compared to dicophane, x 4 times less toxic.
- danger of intoxication in young animals = increased.
- diverse antiparasitic spectrum: fleas, lice and sarcoptic mange.
- dosage: 0,2% bathing and 0.2-0.5% dusting, animals will be cleaned after a contact of 30 min.
- in some countries, for pets, insecticide associations with pyrethrins (0,4%) and conditioning for antiparasitic administrations, parasitic otitis (0,1%), antiparasitic ointment (0,2%).
- in birds, fumigations (7,7 mg izomer gamma/m^3).
- young cats are sensible to increasing concentrations (over 0,2%).
- residual effect of 3-6 weeks, but depending on the environmental conditions this period can increase.

Toxaphene

(Alltox, Geniphene, Phenatox, Motox, Toxakil)

- complex cyclodiene obtained by chlorination of *camphene*.
- viscous or waxy consistence, yellow, pine odor.
- insoluble in water, but soluble in organic solvents.
- the strong alkalies decompose easily toxaphene.
- toxic by ingestion and contact but
- requires association with agents having knock-down effect.
- consecrated use against ticks and lice.
- the acute toxicity is four times higher than dicophane.
- the chronic toxicity is much lesser.
- intoxication: dyspnea, cyanosis, muscle tremors and convulsions.

Organochlorine a.u.v.

Historical organochlorine	Bromo-DDT Camphechlor DDT - pp'-DDT - ethyl-DDD HCH - gamma-HCH - Lindan Methoxychlor Pentachlorophenol
Cyclodiene	Aldrin Bromocyclen Chlorbicyclen Chlordan Chlordecon Dieldrin Dilor Endosulfan Endrin Heptachlor Isobenzan Isodrin Kelevan Mirex

Inorganic insecticides

- Borax,
- Boric acid,
- Calcium polysulfide,
- Copper oleate,
- Diatoms,
- Mercury chloride,
- Potassium thiocyanate,
- Silica gel,
- Sodium thiocyanate.

- **Organophosphorus**

represented by:

- ***Azamethiphos (Alfacron; Snip)***
- ***Bromclophos (Bromex, Naled)***
- ***Cythioate (Proban)***
- ***Chlorfenvinphos (Supona)***
- ***Chlorpyrifos (Piridane, Pyrinex, Scout, Stipend)***
- ***Crotoxyphos (Ciodrin)***
- ***Coumaphos (Asuntol)***
- ***Diazinon (Dimpylate, Droplix Dimpygal)***
- ***Diclorvos (Atgard, Canogard, Equigard, Nogos)***
- ***Dioxathin (Delvan)***
- ***Dimethoate (Fostion, Rogor,Roxior)***
- ***Fenthion (Tiguvon, Pro Spot)***
- ***Quintiofos (Oxinothiophos, Bacdip)***
- ***Neguvon (Metriphonat)***
- ***Phoxim (Sebacil)***
- ***Malathion (Cythion, Malamar, Prioderm)***

Source:
http://bayeranimal.com.vn/tiny_mce/plugins/imagemanager/files/Sebacil_491x248.jpg

Phoxim (Sebacil)

- Very active in sarcoptic and psoroptic mange.

Warbex (Fanfur)

- thiophosphoric compound, well tolerated by organisms.
- with high activity in hypodermosis.

External applications

For these applications a.u.v. are utilized over 20 compounds with activity on: mange, lice and myiasis.

Organophosphorus used in bathing and spraying (after Brander, 1991)

Insecticide	Concentration (%)	Protection (weeks)
Bromophos	0,02	8
Diclorfenthion	0,025	8
Carbofenthion *bathing* *spraying*	0,045 0,002	8 12
Chlorfenvinphos	0,04	26
Diazinon (bathing)	0,025	6-8
Phosmet (both)	0,02	8

Organophosphorus used against ticks
(after Brander, 1991)

Insecticide	Concentration (%)
Coumaphos	0,05
Clorfenvinphos	0,05
Dioxathion	0,15
Ethion	0,075

Organophosphorus used against mange is sheep
(after Brander, 1991)

Insecticide	Concentration (ppm)
Diazinon	100-125
Flumethrin	55
Propetamphos	125

Organophosphorus and associations used pour-on
(after Brander, 1991)

Insecticide	Applied dose *(mg/kgcorp)*
Coumaphos	10
Deltamethrin*	1%
Fenclorphos	150
Fenthion	7,5
Ivermectin*	0,5%
Trichlorfon	50
Permethrin*	1%
Phosmet	20

Spot-on products applied on the dorsal line of the back

Administration in feed

- in combating systemic , low dose (75-125 ppm).
- used: Dichlorfenthion Dimethoate and Trichlorphon.
- effective in: gasterophilus in horses, administered with the naso-oesophageal probe, in single doses.

Organophosphates used in necklaces in carnivores
(after Brander, 1991)

Insecticide	Concentration (%)	Animal
Diclorvos	8,9 4,65	Dog Cat
Fospirate	15	Dog
Propoxur	9,4	Dog

Organophosphorus used in gasterophilus in horse
(after Brander, 1991)

Insecticide	Administered with the probe *(mg/bw)*
Diclorvos	50
Ruelen	100
Trichlorphon	75

■ Group of carbamates

The group contains about 25 basic compounds classified into several subgroups.

Action – similar to organophosphorus also based on cholinesterase blocking.

Carbaryl (Arylam, Dicarbam, Ravion, Seffein, Sevin)

- excellent external acaricide as suspension or
- emulsions 1-5% and powders 5%.
- carbaryl used massively in conditionings as powders, spray, collars for dogs and cats = good contact insecticide..
- the carbaryl's activity in collars for dogs and cats in long-term, even reaching over 4 months.
- against: fleas, ticks, mosquitoes, lice, mange.
- concentrations of 0,1-0,2%,
- inappropriate utilization may cause resistance.
- signs of intoxication: nosea, vomiting, diarrhea, bronchoconstriction, salivation, cyanosis, convulsions and coma.

Clorphenamide (Clordimephorm, Galeron)

- very active against resistant arthropods at 0,5-1‰ OP ;
- three days remanence,
- toxic and even has a carcinogenic potential.
- can be associated in low concentrations with OP and pyrethrins where inhibits its degradation by esterases and oxidases of arthropods.

Cymiazole (Tifatol)

- a *carbamyl-methyl naphthyl-carbamate.*
- used in: bathing or incorporated into medallions.
- *the action is based on* cholinesterase blocking.
- non-systemic ectoparasiticide : contact and respiratory
- good action on ticks and eggs of ticks.

Bendiocarb

(Ficam Dycarb, Garvox, Multamat, Multimet, Niomil, Rotate, Seedox, Tattoo, Turcam)

- contact insecticide with the same indications.
- spectrum and toxicity as carbaryl.
- against: mosquitoes, fleas, lice and ticks.

Methomyl

(Acinate, Agrinate, Flytek, Kipsin, Lannate, Lanox, Methavin, Methomex, Nudrin, NuBait, Pillarmate)

- introduced in 1966 as pesticide and as insecticide in 1998,
- does not determine risks to humans, animals and environment,
- until now are known 15 base products of methomyl,
- soluble powder, of pulverization, emulsifiable or baits,
- can be conditioned in: necklaces, with permethrin,
- activity: contact or systemic insecticide.
- great against ticks and fleas.
- toxicity: moderate to high for human and high for fish and bees.

Propoxur

(Aprocarb, Baygon, Bifex, Blattanex, Brifur, Bolfo, Pillargon, Prentox Carbamate, Propogon, Propyon, Rhoden, Suncide, Sendran, Tendex, Unden, Undene)

- introduced in the 60s as pesticide, and then as insecticide.
- broad spectrum especially against insects and its larvae.
- contact insecticide, as well as systemic.
- activity: a very fast knock-down effect and a broad residual spectrum = a means to control mites highly appreciated.
- wide variety of formulations for veterinary use: emulsifiable concentrates, soluble powder, for pulverizations, granules, aerosols, baits, and fumigation.
- moderate toxicity: inhaled or swallowed.
- but less toxic: topical applications.
- do not use in combination with carbamates: phenothiazines, morphine, neostigmine, pyridostigmine, succinylcholine!

- **Formamidine (Triazopentadienes)**

- halide salts of formamidine and fenamidone,
- activity in cases of resistance to OP and carbamate compounds.
- octopamine receptor agonists in the NS of arthropods.
- activity: increased nerve activity, feeding reduction of muscle cell and disruption of the contraction mechanism.
- may act: inhibiting the monoamine oxidase enzyme, responsible for the degradation of specific neurotransmitters (norepinephrine and serotonin) = accumulation (biogenic amines).
- the toxicity on insects, different compared to other ectoparasitic structures, the affected insects become quiescent, their death is fast installed.

Amitraz
(Taktic, Mitaban, Mitac, Ovasyn, Ridd, Triatox, Ectodex)

- action: contact and on respiratory path;
- in: 5% impregnated collars, retain their effectiveness 4 months.
- in: Sarcoptes, Chorioptes, Psoroptes, Demodex and ticks.
- metabolization: organism and on skin: 4-amino-methylbenzoic acid.

- toxicity: low, broad safety limits in mammals,,
- signs: sedation, associated with activity on α2-receptors.
- as: bathing solutions and sprinkling.
- sheep 0,05%, cattle 0,075%, swine 0,005%, bees (Varrescens)
- amitraz is contraindicated in horses!
- is not carcinogen and does not accumulate into the body.
- one of the metabolites (BTS-27271) = biological activity on amitraz.
- amitraz is considered a: pro-insecticide and pro-acaricide.
- interdiction period = 14days meat , 24 h. milk.

Chlorodimeform

(Acaron; Carzol Bellotion Especial; Bermat Fundal, Galecron Ovatoxion Spanon)

Synonyms:

Chlorophedine, Chlorophenamide, Chlorophenamidine

- **Interferes the amine regulatory mechanisms.**
- **Toxicity: moderate–high.**
- **Signs of intoxication: miosis, vomiting, bronchoconstriction, which limits the use of the product for dogs of less than 3 months.**
- **in intoxications: lavage with activated charcoal, atropine 0,2mg/kgbw diazepam, PAM.**

A dog with demodectic mange before and after treatment with ProMeris.

Source: http://www.vetlearn.com/Media/images/2009vf/05_09/VF_0509_22.png

Fenamidone isethionate

- is 4,4 '- oxydibenzamidine-isethionic,
- he product was initially used as anti-infective,
- then against Babesia spp.
- was enshrined in demodectic mange.

Antiparasitic macrolides

In this class, with ectocid activity:

- Doramectin,
- Eprinomectin,
- Ivermectin,
- Selamectin,
- Milbemycin oxime,
- Moxidectin.

The modality of action of the group = GABA agonistic activity modulation,

Major target:

- binding glutamate to the chlorine channels, and
- causing the paralysis of the insects.

- ivermectin and abamectin = avermectines,
- first endectocide structures.

Ivermectin (Ivomec)

- potent insecticide and acaricide with contact activity and orally
- introduced in 1981 as anthelmintics and then as insecticide.

Abamectin

- first introduced as an injectable formulation a.u.v.
- in: nematodes and lice in cattles.
- formulations: injectable pour-on, spot-on, even as bowls.
- the forbidden period for meat and milk, considered prolonged : 20-28 days.
- Excreted through feces= toxic to coprofagic insects!

Milbemycin-oxime (Interceptor)

- insecticide, acaricide and nematodicide with
- contact and digestive action,
- produced by Streptomyces hygroscopicus.

Moxidectin

- endectocide resulting from fermentation and synthesis,
- from Str. cyanogriseus nocynogenus.

Selamectin (Revolution, Stronghold)

- semisynthetic product analogues to doramectin.
- used in the newest conditionings as spot-on and pour-on
- in the prevention and treatment of ticks and fleas.

Doramectine

- **broad spectrum** insecticide and acaricide,
- action by ingestion and contact,
- produced by the fermentation of a mutant strain of *Str. avermitilis*,
- as systemic endectocide with ectoparasitic activity against many insects and ticks, including multi-resistant strains.

Eprinomectin (Eprinex)

- introduced in 1997, in parasites in the cattle including the lactating ones,
- the only representative of the group of avermectins-milbemycins which can be placed in the strategic programs against endo and ectoparasites!
- **low risk of residues,** without withdrawal condition.

- **Pyrethrins**

Are insecticides of contact, a little toxic for animals.

Divided in two groups:

- ➔ natural pyrethroids;
- ➔ derived synthetic pyrethroids.

Pyrethrins (natural pyrethroids;)

Pyrethrum powder

- from the dried calatides, pulverized by the Chrysantemum species.
- in the powder are found esters (0,5-3%):
- pyrethrin I and II;
- cinerin I and II
- colorless liquid, oily, immiscible in water, liposoluble.

Pyrethrins can be combined with organochlorine, organophosphorus, which have a slower action but are more toxic.

Pyrethrins (synthetic derivatives)

- with chemical compounds similar to pyrethrins,
- not photosensitive!
- *some have even a repellent action.*
- combating cockroaches, ants, lice,
- by prinkler and pulverization,
- against: Stomoxys calcitrans, Musca autumnalis,
- on scabies: Psoroptes bovis, Sarcoptes suis.

Pyrethroid esters

Fenvalerate (Acadex 60, Pydrin, Sumicidin, Belmark),
Permethrin (Ambush, Ectiban, Pounce, Exspot),
Flumethrin (Bayticol),
Acrinathrin,
Cyhalothrin (Grenade),
Cypermethrin (Barricade, Ripcord),
Flucythrinate (Pay-off),
Fluvalinate
Tau-fluvalinate

Products and associations a.u.v.:

- Stomosan EC (permethrin);
- Neo-Stomosan (tetramethrin + permethrin);
- Butox B 12,5 (deltamethrin).
- Chemotox (tetramethrin);

Rotenone

- from the plant *Lonchocarpus nicou* (fam. *Leguminosae*),
- known as *the Derris* powder (5% rotenone),
- insoluble in water, but soluble in organic solvents.
- under the influence of light and air oxidizes.
- from transparency, becomes yellow, orange, then red,
- can crystallize in: *dehydro rotenone and rotenone* toxic for insects, acting faster than *hexachlorocyclohexane* but slower than the Pyrethrum powder.

- act as toxic: of surface and ingestion.
- used as: powder (1%), or as oily solution (2%).
- inhibiting the transport activity of mitochondria of the arthropods.
- in: demodectic mange in dogs and good antiprotozoal.
- administrations will be made at intervals of 7-10 days.
- the massive ingestion or inhalation: nosea, vomiting, tachypnea, esthesia loss and muscle tremors.
- death: respiratory spasm, preceded by convulsions.
- fish are very sensitive to rotenone poisoning!
- chronic toxicity= modification of fat deposits in the liver and kidneys.
- the direct contact of the skin and mucosa = moderate irritations.
- inhalation = more harmful than ingestion.

Biopesticides

- these substances constitutes the therapy of future,
- these substances does not influence other organismsother than insects,

Advantages:

- are not toxic and
- does not seem plausible that insecticides can adapt and create forms of resistance in the coming years.

Juvenile hormones

- delay the onset of sexual maturity in arthropods.
- development: *egg –larvae –pupa –imago* of the insects = directed by hormones.
- a sustained treatment= death of the insects.
- hormones produced by the neurosecretory cells reach through circulation at the endocrine glands from prothorax activating the secretion of a hormone, *ecdysone which determines the rapid growth and development of insects.*

In *corpus allatum* is secreted *the juvenile hormone* which prevents precocious sexual maturation and impupation.

Methoprene (Altosid, Viodat)

- stimulates the juvenile hormone of larvae from animal feces.
- prevents the formation of chitin coating.
- in: combating the populations of flies from peacocks.
- slightly toxic,
- cattle: 0,02-0,03 mg/kgbw./day.
- in 10-14 days = 95-98% decrease of flies population.
- indirect: prevent the infectious keratoconjunctivitis produced by Moraxella bovis.

Substances that mimic juvenile hormones:

- Epofenonane
- Fenoxycarb
- Hydroprene
- Kinoprene
- Pyriproxyfen
- Triprene

Repellents

- external antiparasitic substances that repel insects.
- does not produce death of insects.
- sanitar: a good repellent worth as an insecticide.
- prevents: transmitting diseases by insects.
- ensures: the peacefulness of animals.

Representatives:

- diethyl toluamide,
- dimethyl-toluamide (Protect B, Moszkito, Szuku)
- dimethyl phthalate (Szura).
- dibutyl phthalate.
- 5-40%, as: ointments, solutions or aerosols.
- on skin: a few hours protection.
- impregnation of textiles = long-term action.

- Other modern means

Sterilization of insects

Apholate

Pheromones (attractors)

Dimethoxybenzamide (DEET)

Citrus extracts (Citronella)

Tricosene

Chitin-inhibitors

Flufenoxuron

Cyromazine (Neporex, Larvadex)

Fluazuron (Akatak)

Clofentezine

Diflovidazine (Pestanal)

Insecticidal bacteria

- Thuringiensin

- Alosamidin

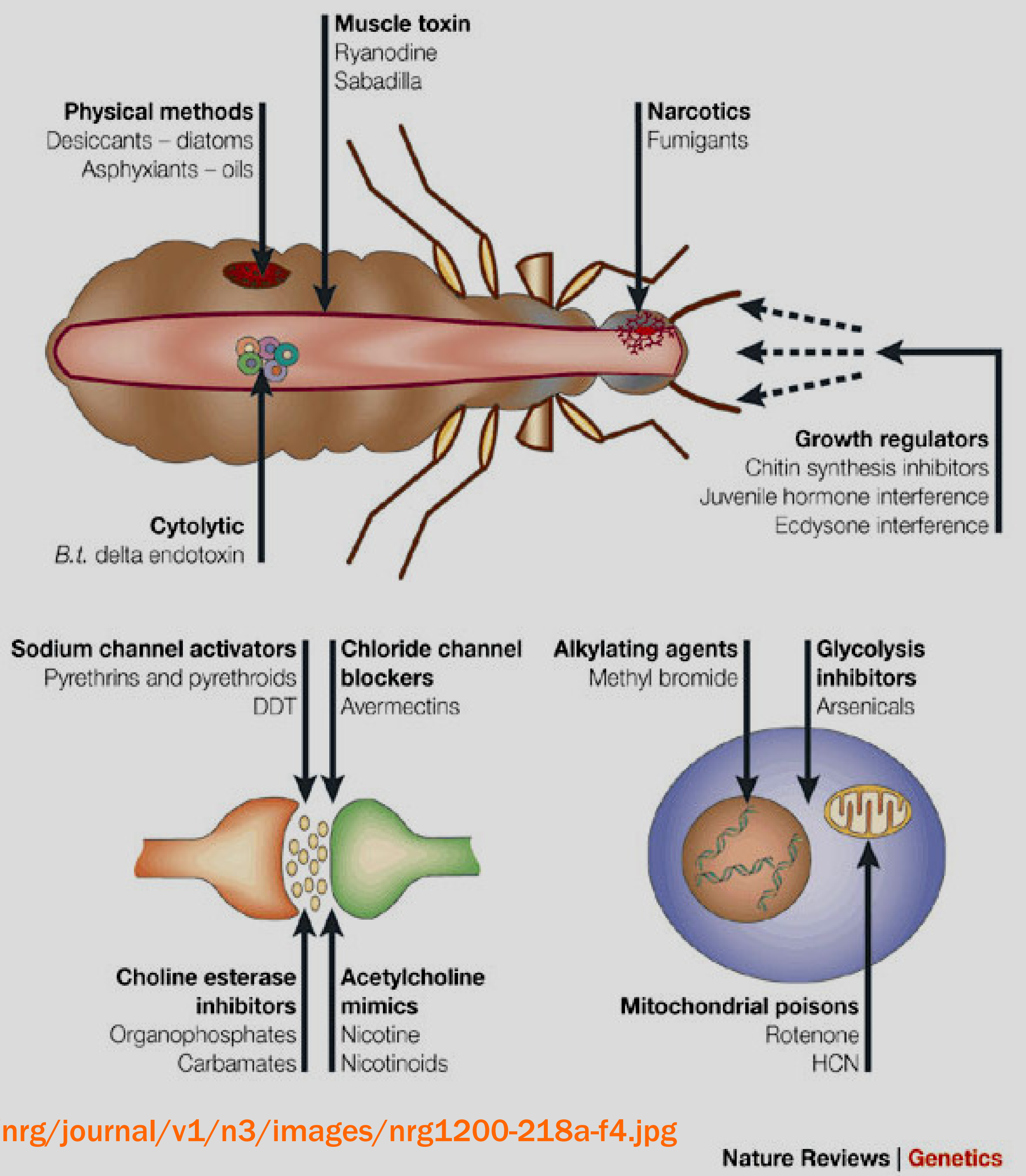
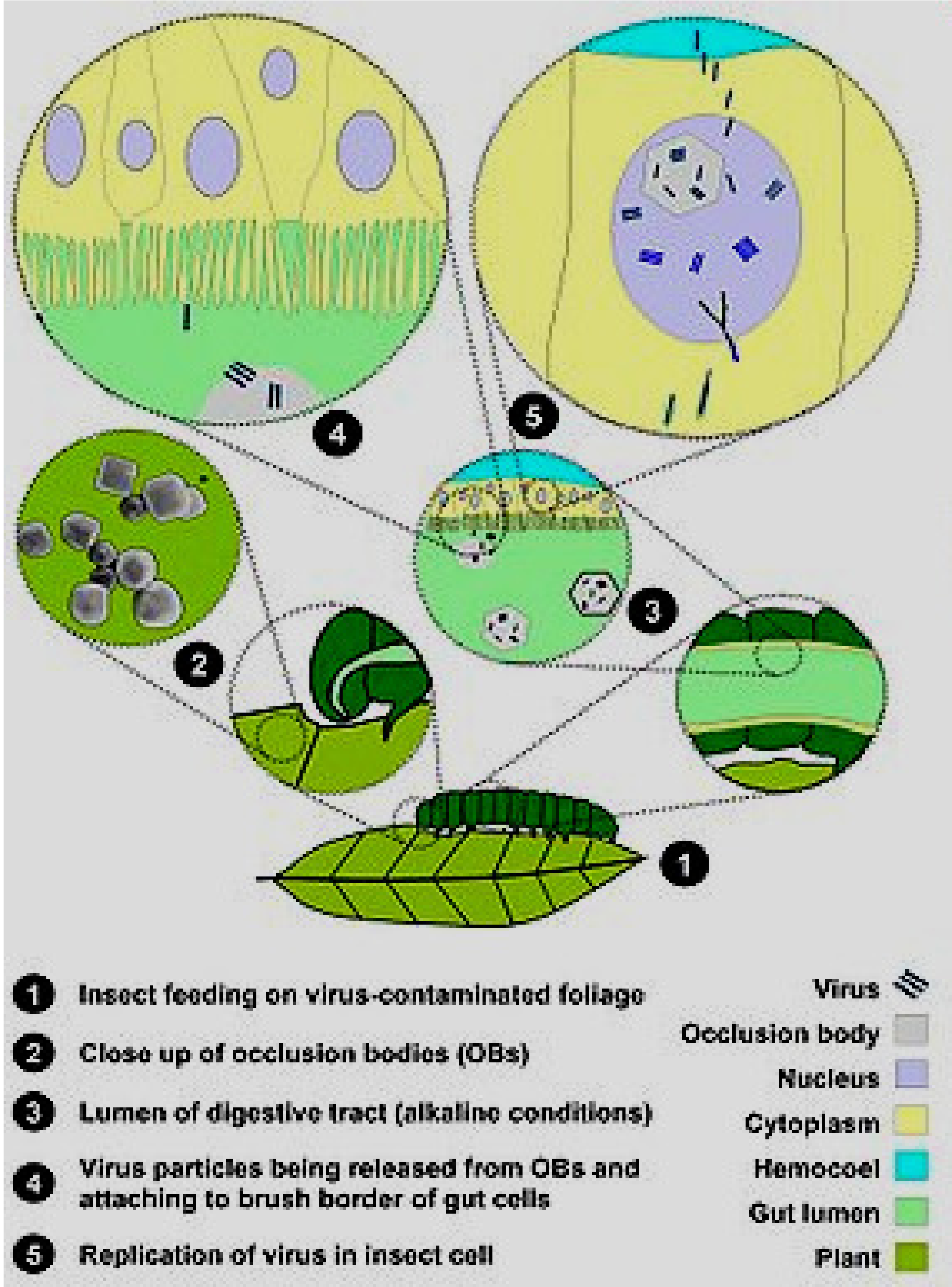


Image source: http://www.nature.com/nrg/journal/v1/n3/images/nrg1200-218a-f4.jpg



http://image.absoluteastronomy.com/images/encyclopediaimages/n/np/npv-life_cycle.jpg

Baculovirus

vibrions assembled in protein formations: super virion capsida (SPVC).

Action:

The baculovirus enters the insect by ingestion.

from here: reaches the medium intestine, under the action of enzymes, will proteinizes releasing virions which will develop in the epithelial cells of insects on which they will destroy .

Cristina®

Acaricidal fungus

- **produced by:** penetrating the host by the pathogen.
- **dual action:** mechanical and enzymatic.

Stages:

1. penetration of the cuticular tegument.
2. fungi will penetrate the insect hemocell.
3. Quick multiplication.
4. Insect colonization, by proliferation of blastopore.
5. continued growth the micelles of fungus,
6. thereby blocking the circulation of the haemolymph,
7. will totally disintegrate tissues.

Insecticide synergists

Piperonyl butoxide(Butancide, Launol)

- synergistically associated with : pyrethrins, OC, OP = increased efficiency.
- no side effects.
- low toxicity when administered on skin.
- toxic: by inhalation or swallowing large quantities.
- does not exercise pollutant effects on environment: desintegrates in the environment.
- the more the proportion of piperonyl butoxide is higher, the lower will be the concentration of the associated pyrethrins.
- the knock-down classic effect , will be significantly amplified.
- inhibits: the microsomal enzymatic system of arthropods and mange

Other representatives:

sesamex (Sesoxane), piprotal, propylisome, sesamolin.

Fermentation products

Spinosad

(Entrust, Spintor, Comfort)

mixture: spinosyn A + spinosyn D.

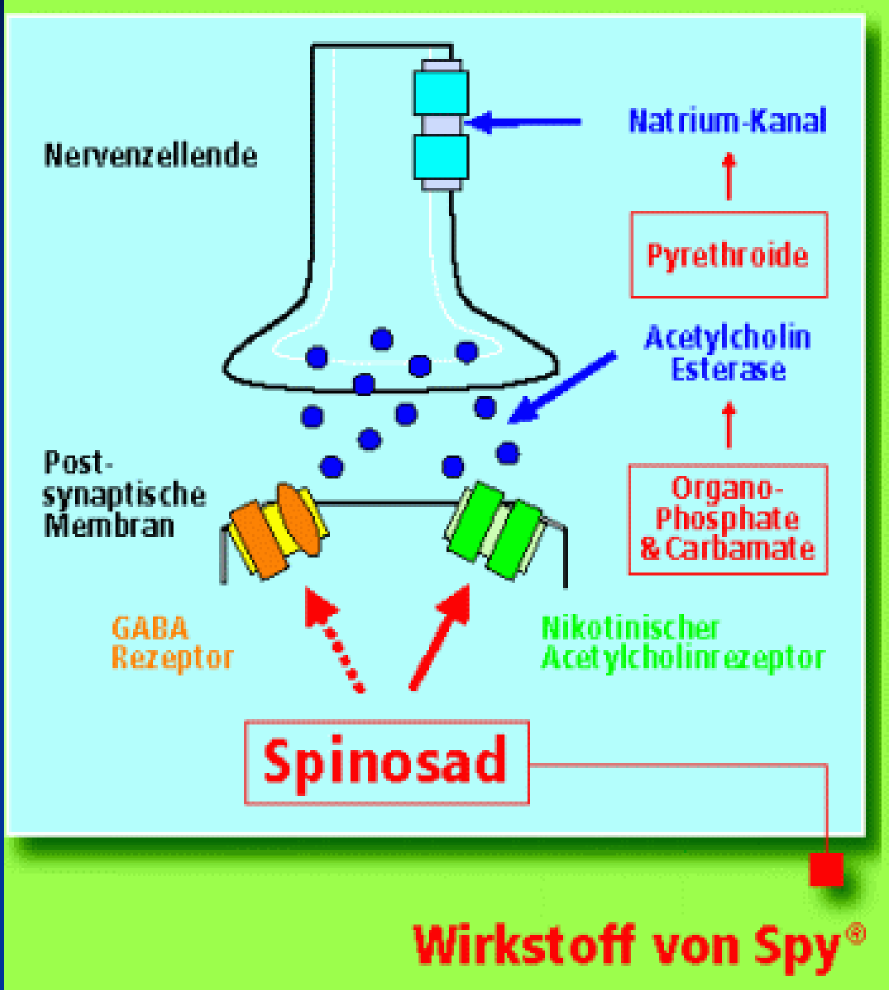
Metabolites:Sacharopolyspora spinosa

great contact activity,

most toxic when ingested.

Spectrum:

- diptera,
- thysanoptera,
- syphonaptera and
- best results: lepidoptera.
- seems more effective against immature stages (larvae, nymphs) than against adult forms present on the animal.



Source: http://www.animal-health-online.de/gross/wp-content/uploads/2008/07/spy_nerven.gif

Phenylpyrazoles

Fipronil (Frontline, Top spot)

- non-systemic insecticide and acaricide of next generation.
- broad spectrum: contact and digestive action.
- acts: on the GABA inhibitor receptors of insects.
- inhibit the flow of Cl-ions in the nervous cell.
- will result: neuromuscular hyperexcitability, paresis, paralysis and death of insects.
- broad spectrum: fleas, ticks and lice.
- are not yet known fipronil resistance phenomena.
- Fipronil is toxic for bees (direct contact and ingestion)!

Source: http://www.vetrxdirect.com/images/358-1.jpg

Currently are known three formulations of fipronil:

- aerosols 0.25%,
- solution 10%,
- spot-on, associated with (methoprene).

Rapidly and well absorbed, concentration dependent in all species of mammals and will accumulate in the sebaceous glands.

A single dose is efficient!

Excretion: feces, both biotransformed and conjugated.

Restricted urinary excretion: only conjugated metabolites.

Toxicity: considerated low.

Recent phenylpyrazoles:

- Acetoprole
- Ehtiprole
- Pyrafluprole

Other known structures:

- Pyrachlophos
- Pyriprole
- Tebufenpyrad
- Tolfenpyrad
- Vaniliprole

New acaricide structures
(synthesis Cristina)

Structural group	Substance
Pyrimidinamine	Pyrimidifen
Pyrrole	Chlorfenapyr
Quinoxaline	Chinomethionat; Thioquinox
Sulfate esters	Propargite
Tetrazine	Clofentezine; Diflovidazin
Tetronic acid compounds	Spirodiclofen
Thioureas	Chloromethiuron; Diafenthiuron
Orphan acaricides (unclassified)	Acequinocyl; Amidoflumet; Bifenazate; Crotamiton

Conclusions

Internal therapy

- diet,
- weighing the animal,
- weigh the heaviest animal in the flock.
- in large herds, performing a sample group .
- cheese is not fermented by benzimidazoles.
- when administering *Ivomec* be careful in dogs and horses!

External therapy

- volume of water for bathing should be know exactly
- is done a test on animals (the weakest).
- after bathing, animals are not kept in sunlight or stream of air.
- the completing water for bathing is more concentrated than the initial one.
- for dog and cat there are different anti-flea collars.

Thanks for your attention!

Image source: http://www.zooplus.es/bilder/1/109211_karlie_hundespielzeu_1.jpg