

# CONTROL OF ECTOPARASITES IN DOGS AND CATS: THE ACTUAL SITUATION

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*Parasitic skin diseases in veterinary medicine include a wide range of organisms (arthropods, helminths and protozoa) whose many remain unrecognized or under-diagnosed. The relative importance of these parasites varies with countries. Arthropods are by far the most important in Veterinary Dermatology. The appropriate management of each case needs the good comprehension of the situation and appropriate steps for diagnosis and control.*

*The practitioner has to keep the best approach in the changing and challenging world of new ectoparasiticides.*

## I GENERAL INTRODUCTION

### **1 First of all « understand the parasite» (host parasite interaction)**

A variety of ectoparasites: insects, mites and ticks, helminths and even protozoa are adapted to live or to feed on the skin surface, often responsible for direct harmful effects and/or the transmission of an increasing number of pathogenic bacterias, viruses or parasites. The host defence mechanisms are both non-specific and specific and parasites have developed « strategies » to evade the response of their host. A parasitic “Skin disease” is the result of a complex host-ectoparasite interaction that changes with time.

**a - A parasite** (here arthropods) is basically:

Adapted to its host(s) – no profit for host but potential deleterious effects (Avoid the common confusion between a parasite and a **commensal...**) - The « most achieved » parasite is so adapted that practical no detectable effect in hosts (i.e. *Demodex* in the general situation in virtually all dogs).

#### Consequences:

The regular, “normal”, situation is « **asymptomatic carriage** » > « something wrong » if « parasitic disease ». This is important in terms of control, as sick animals have been in general infested from apparently healthy animals that are sources.

Invasion of a parasite results in initiation of this Host parasite relation-ship.

Young animals are logically exposed to new parasites and will be consequently the most affected group. Parasitic skin diseases are typically seen in young animals.

## **2 Ectoparasites have basically 3 strategies**

Understanding strategies are of huge important for the concept of treatment/control. The best product will do nothing if it doesn't interfere with the strategy of the parasite.

**a- Permanent parasites** complete their entire life cycle on the same host.

- They are most often really adapted and highly specific.
- Their development (successive cycles) induces a true infection.
- The resistance in environment is short (hours to days) and transmission mainly the consequence of direct contact between animals (= directly contagious).
- Transmission doesn't means disease.

**b- Temporary parasites** (=Stationary, Sessile)

Have one or several long parasitic phases (days to 2-weeks) with a part of development off the host:

- The life-cycle may involve several successive animal/hosts
- Reproduction an/or development of eggs occurs in the environment.
- The effect of parasitism is directly linked to the abundance of infesting stages from surrounding environment
- They generally resist a long time (weeks to years).
- The specificity of these parasites is variable

**c- intermittent ectoparasites** have multiple but very brief parasitic phases limited in time for necessary feeding (minutes).

- The role of environment is predominant.
- Many of them are adapted to haematophagy (rapid and nutritionally efficient meal, often necessary for moulting or egg laying).
- They spend most of the time off the host; their resistance in environment is long and specificity relatively low.

### Consequences:

These 3 strategies correspond to the 3 different approaches for control in terms of: animals to treat, importance of action in environment, importance of repellent products.

## **3 - The feeding process of ectoparasites and skin changes**

Understanding the feeding process is of help to understand how to reach the parasites (topical, systemic treatment)

### **1- Chewing:**

Many parasites bite or chew on the surface or within the skin, particularly “permanent “ones.

The direct effects are relatively mild if the parasites are in low number and/or not directly on the skin (hairshaft) but become very severe when they actively proliferate.

The alteration of *Stratum corneum* allows the passage of bioactive substances produced by the parasites or the damaged keratinocytes and immunogenic substances easily transferred to skin immune system.

### **2- Biting:**

Some superficial mites may bite epidermis although the chelicerae are not long enough to pierce the entire thickness. This process allows the ingestion of fluids and sometimes some blood cells resulting in both epidermal and dermal primary skin reaction.

### **3- Piercing the skin:**

Arthropods may feed by piercing the epidermis and dermis to ingest large amounts of fluids (often blood). In such cases the dermis is the principal skin compartment challenged.

### **4- Solenophagy (capillary feeder):**

These arthropods have relatively short feeding phases. Their mouthparts are thin and adapted to probe in the superficial dermis for blood vessels. The bite itself is almost painless (limited tissue damage, scarcity of nerve endings in the dermis). The probing process and feeding is accompanied (or preceded) by secretion of bioactive saliva. Direct lesional effect is minimal.

### **5- Telmatophagy (pool feeder):**

The epidermis and the dermis are actively attacked by mouthparts with saw and/or scissors movements until the broken vessels produce a haemorrhage (pool) that allows to feed. In some arthropods the pool is mainly formed by the action of saliva rather really the mouthparts (trombiculids) and not really haemorrhagic. The direct skin lesion (size of focus of lysis) is more or less linked to the size of the mouthparts.

### Consequences:

The feeding process will qualify the type of dermatitis (immunologically, histopathologically).

The insecticidal-acaricidal have no direct but an indirect effect on the regression of lesions and clinical cure.

## **4 Concepts for treatment/Control**

In many situations the choice of the most appropriate insecticide/acaricide treatment is difficult.

In other situation the owner and the practitioner perceive a feeling of “failure” of treatment.

Companies have developed a very active marketing approach to promote the qualities of their own product. However the best product will always fail if a series of steps have not is completed.

- 1 - an appropriate diagnosis: evidence vs. strong suspicion
- 2 - an appropriate evaluation of the situation (environment, number of animals.)
- 3 - an appropriate choice of the product(s) to use (spectrum, formulation adapted to the owner choice;)
- 4 - an appropriate “training” of the person that will treat the animals)
- 5 - a control of the compliance
- 6 - the follow-up of the case.

## II FLEAS AND FLEA CONTROL: WHAT IS IMPORTANT TO KNOW?

Fleas are the most common insect ectoparasites in dog and cats.

### 1 - Key facts on flea biology with applications for control

#### a – Life cycle

To remember the characteristics of the flea life cycle is one of the most important things for conceiving the flea control. Information given here are limited to the most useful ones.

- *Ctenocephalides felis* is by far the most common and the target. It feeds on many hosts. *C.canis* is more specific on dogs and not really adapted to cats. It will be useful in some situation to verify that the fleas present are really *C. felis*, not another anecdotic species.
- Adults of live permanently on the host and do not easily leave it. There is virtually no direct transmission between animals. The fleas reproduce very quickly onto the host and first eggs are obtained within the first day. The number of eggs produced will be maximum during the 3 first weeks. It is classically considered that a female produce 25-30 (*C. felis*) 8-15 (*C. canis*) eggs per day as an average. The average longevity on host is 3 weeks (although a flea may survive up to 3 months).
- Development of immature stages occurs in the environment of animals (i.e. all year round in household, spring to autumn outside). L1 (days 2 to 15 from eggs maturation) feed on organic debris (including adult flea dirt). Larvae express negative phototropism, positive geotropism and hygrotropism. L3 stage is obtained rapidly (0-20 days) then produce a cocoon in which metamorphosis occurs to produce pre-emerged adult (after 10 to 20 days).
- The global duration of life cycle is modulated by temperature, in 4 weeks as an average. The pre-emerged adults will survive 5 to 7 months (up to one year) in cocoons = resistant stage of the cycle.
- Adult fleas emerged from the cocoon survive 8 to 18 days.

#### Consequences:

- At one time it is considered that the flea population: only 1-5% adults on animals - The rest in the environment ( $\pm$  30% eggs,  $\pm$  50% larvae,  $\pm$  10% cocoons). When the parasitic phase is stopped the entire population in the environment will rapidly turn to 100% of pre-emerged adults in cocoons.

- Fleas are prolific insects: a light population ( ie. 15 fleas: 10 females, 5 males) on one dog or cat will produce easily 700 cocoons.

#### **b - Characteristics of the parasitic phase.**

- Emerged fleas will jump onto hosts. They immediately start to bite (18-20% after 5 minutes, virtually 100% at 40 min.). The duration of the blood meal is 5 to 20 minutes. A flea bites several times a day. A blood meal is followed by the production of one serie of eggs ( $\pm$  5-9).

- The bite itself produces minimal tissue lesion. Saliva is injected before (and during) the ingestion of blood. It contains bioactive substances some of them with immunogenic properties (antigens or haptens). The classical immune response to arthropod bite is observed composed mainly by HIS, HSIV, late phase reaction and basophils hypersensitivity. The sequence is variable amongst animals and clinical effects as well.

Consequence: A positive intradermal skin test to flea extracts should be considered first just as a marker of “presence of fleas”. Positive IDST are more frequent in dogs with flea bite Hypersensitivity (FBH).

#### **c- What about A few “myths”**

- Vets have often said “just one flea bite is enough to trigger and maintain clinical signs of “Flea Allergy Dermatitis FAD”. Our understanding of the role of fleas in what used to be called ‘summer eczema’ dates back to studies by Kissilef (1938), and subsequently the involvement of hypersensitivity mechanisms by Benjamini.

- FAD or FBH? The concept of allergy, often perceived as “non-dose dependent”, has become bound to this dogma. In fact, the hypersensitivity mechanisms involved are common to many ectoparasites and may develop in any dog or cat. “It takes just one bite”, can be used to motivate clients to treat their animals. In reality, there is not the slightest piece of evidence to back this up. On the contrary, most of information suggest that multiple, repeated bites are needed. Furthermore, all modern insecticides are effective (in carefully monitored studies) in controlling FAD, regardless of their speed of action or whether they act systemically. Most topical insecticides fall far short of preventing all (most) of flea-bites. These argument are in favour of FBH rather FAD.

The role of insecticides is to “reduce” the number of fleas then number of blood meals rather than prevent flea bites under the one necessary to overcome the pruritus threshold for each individual animal. Logically the most the product is rapid the best it is. However there is a limit of “speed of cure” that allows to relatively slow acting products (if perfectly used) to have (in monitored studies only?) the same efficacy as the faster ones.

#### - Consequences

Insecticidal treatment on animal is only one (little) part for the control

Cocoons are protected from any direct action of insecticides.

A short-term therapy has no chance to be effective.

Severity of skin effects and pruritus is a combination of number of bites and intensity of immunological reaction.

### III AVAILABLE PRODUCTS AGAINST FLEAS/ RULES FOR CONTROL

#### 1 General characteristics

All modern insecticides fulfil the “same” criteria to obtain the claim given by EMEA. Once the label is obtained all products may say “can participate to the control of flea allergy dermatitis”. The duration of efficacy is given by an insecticidal effect of “at least 95% at 24hours of time”.

#### 2 Flea – products: Topicals

Most of the commercial products are conceived (registered) for a monthly application

##### **a - Organophosphates and carbamates** (acaricidals and insecticidals)

(Propoxur Carbaryl) have disappeared from the market in most European countries.

##### **b- Phenylpyrazoles** (acaricidals and insecticidals)

Fipronil: in sprays and spot-on

in Frontline then Frontline combo (+ S methoprene), then Certifect (+ amitraze), then Broadline for cats (+ S methopren + eprinomectin + praziquantel). This last product includes a wide range of internal parasites (nematodes and cestodes)

a multitude of “generics” and combination ( not detailed here)

a recent combination with permethrin was proposed: Frontline TriAct/Frontect and Effitix

Pyriprole : in spot-on : Practic

##### **c- Neonicotinoids**: (insecticidals)

Imidaclopride: spot –on in Advantage

then extension to ixodicidal effect with Advantix (+ permethrin), then a new collar Seresto (+ flumethrin). This collar claims an activity up to 8 months in dogs and cats. The mots original point: this is the unique pyrethroid containing formulation that can be used in cats.

Nitenpyram : oral route in Capstar. A very effective, very rapid systemic action but no residual effect.

In the field, apart the curative effect, repeated weekly treatments can be used for flea control.

Dinetofuran : spot on (+ permethrin and Pyriproyfen) for dogs in : Vectra 3D.

(+ pyriproxyfen) for cat in Vectra felis

#### **d - Pyrethroids:** (insecticidal and acaricidal)

Permethrin: sprays, spot on

in Pulvex, Defendog, Duowin (combined to pyriproxyfen).....

This first molecule was used intensively until the 1990's. Then the development of new groups was accompanied by an argumentation and the message to consider it as an "old" drug. Interestingly the recent years have conducted to the reintroduction of permethrin to most of these new groups. Although known as one of the best "insecticidal" in many domains the reintroduction is associated to "strange" argumentations... focusing only on its ixodicidal properties or even just as a repellent!

Deltamethrin: collar Scalibor. A 6 months acting "flea and tick" collar in US. In Europe the marketing message focuses on ticks and sandflies.

Flumethrin: ( cf imidaclopride)

#### **e -Semicarbazone :** (insecticidal)

Metaflumizone: spot on in Promeris (cats) and Promeris Duo (+ amitraze) for dogs. These products launched in 2006 were stopped to be produced in 2011 after a publication of cases of drug induced pemphigus foliaceus in dogs.

#### **f - Oxadiazines:** (mainly insecticidal)

Indoxacarb: spot on in Activyl (cats) and Activyl plus (+ permethrin) for dogs. The original concept of this "green insecticide" is that activity is obtained after bioactivation by enzymatic metabolism in a decarboxymethylated insecticidal molecule. The combination with permethrin extends activity to ticks in dogs.

#### Consequences:

The common point of topically applied drugs is their variable resistance to shampoos, baths or interference with topical therapies. Very few papers are available on the real resistance of these molecules to bathing or shampooing. The data given from technical leaflet correspond usually to a very low challenge. Thus in case of frequent shampooing or baths it is recommended to reduce the interval of application.

### **3 Flea – products: Systemics**

#### **a -Macrocyclic lactones:** (insecticidal and acaricidal, nematocidal).

Most of the molecules of the group have no or very slight activity on fleas at usual dosage in veterinary medicine, with exception of

Selamectin: systemic spot-on in stronghold for dogs and cats.

**b - Spinosyns:** (insecticidal, acaricidal)

This family was quite recently discovered and used first in agriculture

The chemical compounds are produced by a bacteria actinomycete *Saccharopolyspora spinosa*. They exhibit a very favourable environmental and toxicological profile, and possess a mode of action on both nicotinic and gamma-aminobutyric acid receptor functions. They are active, by both contact and ingestion and can be used systemically. Insecticidal activity is higher than acaricidal spectrum at usual dose. The Spinosyns are the first group of systemic insecticidal demonstrating a very high speed of activity.

Spinosad: is available in tablets in Comfortis and Trifexis (+ milbemycin oxime for heartworm prevention).

Spinetoram: this molecule is not (yet?) available in Europe but already launched in US (Cheristin) for the treatment of fleas in cats as a spot on. It provides a control of fleas still 96% at day 37.

**c - Isoxazolines:** (insecticidal acaricidal)

This is the newest group of ectoparasiticides launched for dogs. Due to the very recent discovery and the direct use in veterinary medicine there are still few information on these molecules as compared to most of others groups with previous use in agriculture (insects, acari). Today the registration is done for dog only (likely for cats in the future depending on the molecules). They have a good tolerance profile that allows high dosages responsible for potentially long residual effect (3 months for Fluralaner). They are launched as oral palatable tablets. They received a considerable success both in US and Europe. They are launched for fleas and ticks but have their spectrum is obviously wider thanks to the huge concentration obtained at the beginning of the treatment. Also the concentration produces a rapid killing effect. Today 3 molecules are available:

Monthly treatment with Afoxolaner in Nexgard and Sarolaner in Semparica

Every 3 months treatment with Fluralaner in Bravecto.

Systemics are clearly recommended as a good option in the case of animals submitted to repeated topical treatments (rinses , shampoos).

The other advantage of systemics is the treatment for every part of the body surface as the blood concentration is the same everywhere on the body surface.

**4 Insect growth regulators**

Insect growth regulators and insect development inhibitors are widely used flea control products.). They do so by either interfering with the development of chitin (lufenuron) or by disrupting the hormonal signals necessary for successful development and/or molting (methoprene, pyriproxyfen). neither pets or



humans possess receptors for these molecules. The combination of adulticide and IGRs or IDIs is likely to decrease the time necessary to control flea infestations ( particularly important in the case of heavy flea infestations or when pet owners are experiencing flea bites). Moreover the likelihood of development of resistance is diminished considerably .

**a- Methoprene** : sprays, spot-on, and collar formulations for dogs and cats

A juvenile hormone mimic highly active at extremely low concentrations against eggs of a number insects including flea species. it can be used for topical administration to pets (and application to the environment) its sensitivity to oxidative and ultraviolet degradation render it less useful for environmental use. It is often combined with adulticidal compounds ( on-animal and premise flea control).

**b- Pyriproxyfen** in sprays, spot on, for dogs and cats. A pyridine-based juvenile hormone mimic ( structurally different) from juvenile hormone. It is a very safe active for application to pets (oral LD 50 is > 5g/kg. It has a very high stability ( UV light) making it a more reasonable choice for environmental flea control formulations.

**c - Lufenuron** oral and injectable formulations for dogs and cats

A benzoylphenyl urea class of insecticides. It is a strongly lipophilic compound, that accumulates in the adipose tissue (including intra-cellular fat) of treated animals. It is a very safe compound ( oral LD50 > 2g/kg). Its combination with milbemycin oxime and praziquantel make it an appealing choice for control of fleas, heartworms, intestinal parasites and tapeworms,

## 5 “Qualities” of molecules

### a - Mode of action (MoA)

- All the insecticides used today are “neurotoxic” to insects. They act mainly on 3 main targets but by different ways. Which, at least theoretically, reduce the risk of development of cross-resistances.

i) Sodium channel: Pyrethroids, Indoxacarb, Metaflumizone; ii) Gamma Amino Butyric Acid receptors/channels : Macrocyclic lactones, Isoxazolins, Fipronil; iii) nicotinic acid receptors: Neonicotinoids, Spinosyns. Most of insecticides have several MoA not necessarily known at the time of launching.

- Pyrethroids is the only group showing clear behavioural effects, mainly observed at sub-lethal concentration.

- It is difficult to rely the MoA to the visible effects (excitation vs. paralysis). These effects are likely to depend on the concentration, combination of MoAs and vary with the molecule.

- The combination of two molecules with different MoAs logically induces a kind of “synergy” and increases the efficacy of the product. i.e: combination of pyrethroids to imidaclopride (in Advantix) or to fipronil in Effitix / Frontect. This combination also reduces the risk to obtain tolerant strains of fleas.

### **b - Effects on insects**

-The effect cannot be anticipated from the MoA. In practice it is more important to evaluate the effects on insects. These effects are largely dose dependant thus time dependant.

**Repellency** : true repellency (= at distance), contact repellency (in practice the only observed. Also called “hot –foot effect or “flushing effect”).

**Expellency** : arthropods present onto the host when treatment I applied try to escape.

**Knock down effect (KD)**: Very rapid paralytic effect (loss of motricity). Mainly developed for flying insects (within minutes). Must be very rapid (less than one hour for fleas?). Followed or not by death (possible reactivation).

**Anti feeding effect**: Frequently confused with “prevention of bite” which is an indirect non specific “consequence” resulting from the combination of different actions (i.e: KD or repellency).

**Killing effect = *insecti*”cidal” sensu stricto.**

The efficacy (regulatory) is based on this effect ( $\geq 95\%$  in EU) obtained before a certain time (24h00 for fleas). The length of action is considered as long as this minimal 95% efficacy 24h00 is maintained. (US regulation can be different which explains sometimes different dosages for the same product. Thus information from publication can be different from the ones obtained in studies performed in Europe)

**“speed of kill** as been proposed = evaluation of percentage of dead fleas after contact/ingestion with the drug. It is still confusing to make the difference between a) the delay of killing effect for the first fleas or b) the minimal time to reach the efficacy ( $> 95\%$  of fleas killed). Speed of kill is maximal initially but decrease with time.

This recent terminology is now widely used in marketing arguments and mainly used in comparative studies by average % of efficacy at different times post infestation in experimental condition.

### Consequences :

The presence of fleas during “up to the 24<sup>th</sup>” hour doesn't mean lack of efficacy. This is easily seen in animals with a permanent flea challenge. Presence flea doesn't mean lack of efficacy.

Up to 5% of flea “may be present for more” than 24h00 without any significance of lack of efficacy.

This means also the possibility of multiple bites and that fleas may start to reproduce and lay eggs (= infestation of environment) within the first day (and slightly after) even with an active product.

Even in the best condition a “window” exist for fleas with many products.

### **Action on immature stages** : Ovicidal and Larvicidal

It is important to make the difference between i) an effect on eggs which is “just” the same “insecticidal effect”(not stage dependant) and ii) specific “ovicidal” or larvicidal effects by original mechanisms non active on adult fleas. Every insecticidal with the opportunity to be in contact of larvae will be non specifically larvicidal. However, efficacy can decrease as residual activity of the adulticide decreases. More importantly, efficacy results from exposure of multiple flea life cycle stages to the same active ingredient. Ovicidal efficacy is best achieved by IGR or IDI compounds

### **6 Integrated flea control**

Control of flea can be obtained with the use of one single molecule only in experimental or monitored studies. Thus it is important to combine” several approaches = integrated flea control.

- Combination of several methods (including mechanical destruction of stages in the environment i.e. by vacuuming)
- Combination of several MoA (this includes frequently the use of IGRs)
- Consider every stage
- Consider every potentially infested host
- Act during a long period

**Failure of treatment** is frequently perceived.

The causes are typically: Lack of integrated control, occasional or short treatment periods (reinfestation from the environment); poor treatment (choice of drug, tablet not properly ingested, spot on not properly applied)... There is a natural variation of sensitivity of flea strains (1 to 10?) that cannot be detected during the limited studies made for the development of the product. Topical spot-ons have revolutionised flea control in terms of apparent ease of administration. However, like other formulations, they have their limitations, in particular in relation to distribution. There has been virtually nothing published on the subject. It is important not to confuse overall efficacy on the whole animal with equal efficacy in each part of the body. On big dogs, when the same dose is split over several places on the body, a better performance is achieved in terms of residual effect. The persistence of insecticidal activity on the coat is excellent at the point of application and maintained for a very long time whereas only 20-25 cm away efficacy is very much lower, often inadequate. Consequently, it is more advisable to apply spot-ons at several sites. Sprays, in theory, offer many advantages because they provide, if well applied, much better insecticidal penetration. However, with sprays too, there is a big difference in efficacy when applied by owners to when applied under experimental conditions.

This is observed experimentally but also mainly when products are applied by owners. This may result in a long survival of fleas able to reproduce.

- In many cases fleas have not been detected previously by the owners or seen “occasionally” and treated sporadically. When they are a visible problem this means already a huge contamination in environment. In this case insecticides may appear non-active because slowly interfere with reinfesting fleas from the environment.

- **Variability** : Individual factors may influence variation in pharmacokinetics of drugs for systemic products. This variability is initially measured on a very limited number of experimental dogs and would be likely more important if a higher number of dogs was used. There is no doubt that in natural conditions this variability is much higher (huge number of treated dogs, interferences?, adipose tissues, sex ...). There is little consequences at the beginning of treatment but at the 3<sup>rd</sup> week (or later for longer claimed actions) and the result can be a decreased activity

There is virtually no evidence on real “resistance “ of fleas (*C. felis*) to veterinary insecticides in Europe.

**Tail effect** : The treatment with modern insecticides ( 1 month activity) induces “always” after the period of efficacy another period of decreasing efficacy until 0%. During this period fleas are not killed and individuals less sensitive may reproduce. This may lead to non-resistant but tolerant strains that progressively shorten the “length of efficacy” of the drug. To avoid this tail effect, animals have to be treated regularly every 4 weeks to limit the number of tail effects/year.

#### IV CHOOSING THE RIGHT PRODUCT FOR ECTOPARASITE CONTROL : I SARCOPTES AND OTHER CLASSICAL MITES: THE ICEBERG!

##### 1 Sarcoptes

A considered well-known ectoparasitosis, at least through its classical presentation. It does not decrease in many countries or even may increase (linked to fox sarcoptic mange?)

- Contagious. One species with host specific varieties: *Sarcoptes scabiei canis* in dogs (and *vulpes* variety), also common in companion rabbit, rare in ferret and rodents. (No variety adapted to cats). Host specificity is variable with strains (crossed contamination transient or not).

- Prevalence underestimated, under-diagnosed, more or less masked by the use of some anti-flea products also acaricidal.

- Most common in young animals, No breed predisposition; Pet stores, shelters, numerous animals in contact,

-Transmitted by direct contact (source : sick animals or asymptomatic carriers); low resistance in environment from hours to 1 week but infectivity is rapidly lost.

- A permanent parasite : Cycle is a succession of phases onto the surface or within thickened stratum corneum (protection). completed in 10-14 days. Feed on fluids and cell debris.

### Clinical signs ?

“Classical” aspect: Highly pruritic, chronic and extensive, papular (non-follicular) dermatitis with erythema secondary alopecia, crusts and self traumas. The lesions develop from head or lower parts of the body. chronicity is associated with lichenification, secondary pyoderma, renal complication, cachexia and death. The margin of ear pinnae and elbows are typically covered by yellowish, sand like, crusts.

*Juvenile form*: Less severe (mild to variable pruritus and moderate scaling) mainly in young dogs

*Florid form* : sometimes called “Norwegian scabies” : hyperkeratosis, variable pruritus and the presence of a huge number of mites.

*Carriage* (QUESTION: the more frequent situation !?)

- Recent articles have highlighted the role of asymptomatic carriers (more important than previously thought). Dogs could remain carrier after a “clinical cure” and a “good treatment”.

Regarding the immunology, a humoral is described response against at least 9 antigenic fractions taking maintained at least 4 months after clearance.

### Diagnosis

- The diagnosis from deep skin scrapings has a low sensitivity ( $\pm 20\%$  only).

- ELISA test, has been developed. Although the species share common antigens, with the house dust mites the sensitivity is 83- 94 % and specificity of 85. - 96 %. Seroconversion occurs rapidly after infection  $\pm 3-4$  wks and 1-3 weeks after the onset of clinical signs. False positive reaction can be measurable 1- 4.5 months post successful treatment

In dogs 68 – 100% of sarcoptic cases have a positive IDST (immediate) to Der.f

### Treatment

*Topical*: Many miticidal drugs are active. Applied twice a week for 3-4 weeks: amitraze 0,025% – 0,5%, (organophosphates). In case of abundant crusts and skin debris perform a shampoo before.

Fipronil spray applied with sponge is a possibility in very young puppies.

*Systemics*:

Sarcoptes are easily reachable by systemics

- Macrocyclic lactones were until now the most common therapy (sometimes off label ):

Milbemycin oxime (Interceptor). Orally 0,5 mg/kg every other day 2 weeks.

Selamectin (Stronghold) systemic spot on (6 mg/kg) or Moxidectin (Advocate) systemic spot on (2-3 times at 3 weeks interval)

Ivermectin (Off label) is active (200 à 400 µg/kg inj. or orally twice a week), but not recommended by the author (benefit/risk other molecules less toxic available)

Moxidectin (Cydectin for sheep) orally (same dose as Ivermectin) ( off labl) . Caution with moxidectin: “NEVER” use by injection in (potentially) sarcoptic dogs (anaphylactic reactions).

- There is little information on activities of Spinosyns.

- Isoxazolines will be likely new actives used for the treatment of Sarcoptic mange. Simparica (Sarolaner) is already registered for this indication.

Cure or not?

Most of labelled products have been demonstrated optimistically active through the absence of sarcoptes post treatment and apparent clinical cure after (short term follow up). These criterias are not really discriminant with a possible carriage with reappearance of milder but persistent pruritus and skin disease. This explains why these treatments fail in practical condition and protocols have been modified. A negative ELISA (4 months after treatment) could be proposed for control.

All in contact dogs have should be treated.

## **2 -Otodectes**

A primary otitis externa, frequently complicated by yeast and bacteria when the condition becomes chronic. It remains a frequent infection in dogs (1/3 of otitis externa?). Even more common on cats (75% of otitis) and ferrets.

The entire life cycle occurs in the ear canal but the parasite can be found occasionally in haircoat (need to leave the ear canal to infest by contact another animal).

### Clinical presentation:

Classically a bilateral, highly pruritic erythematous and ceruminous otitis. Audio-pedal reflex (not specific test but sensibility 50 -80%). The cerumen, when typical, is dark brown, dry and friable.

Other signs can be observed ( neurologic, cutaneous, othematoma).

A complete development occurs onto the skin = otodectic mange (mainly in cats)

Asymptomatic carriage is probably very frequent (adults that transmit to puppies or kittens the parasite)

### Diagnosis

Otodectes can be seen with an otoscope as whitish, mobile, points at the surface of the cerumen. Microscopic observation of cerumen reveals mites or eggs (variable abundance). Malassezia otitis can be associated. Possible confusion with house dust or storage mites when found on kin amples (similar size and

### Control

#### *Topical*

*Otodectes* is very sensitive to most products even to some non-acaricidal molecules (i.e. oily products)

Many molecules have been used with success containing: Lindane, benzyl benzoate, organophosphates, piperonyl butoxyde or topical ivermectin. Drops bilaterally twice a week at least 4 weeks

Off label uses include: amitraze, ivermectin, fipronil or pyriproxyfen (in Vectra felis), pyrethroids (dogs).

#### *Systemics*

The same treatments used as systemic therapy for Sarcoptes (macrocyclic lactone) are generally active also on *Otodectes*. Isoxazolines (afoxolaner, fluralaner, sarolaner)

The control of *Otodectes* can be very difficult in kennels or catteries. All animals have to be treated and an active disinfection in environment is performed.

### **3 Notoedres**

Feline notoedric mange is now uncommon to rare.

#### Clinical signs.

- Pruritus (intense at the beginning); Hyperkeratotic skin and lesions, on the face and the ears extending to the neck, limbs and rarely generalized. Secondary bacterial infections from self-trauma can even be lethal.
- In rats: variable pruritus. Lesions frequently localized (margin of ear pinnae: erythema. crust hyperkeratosis, necrosis), Tail ( $\pm$  genital) papules and crusts). A classical “nasal horn”.
- Occasionally generalized.

#### Diagnosis:

- Microscopic identification of the mite, from superficial skin scrapings is in general easy.

#### Treatment:

No treatment still licensed to treat notoedric mange in cats in Europe?

*Topical:* Not easy in cats. (Weekly total body lime sulphur dips in cats (“Elizabethan collar” until dry).

Amitraze active (Use with caution in cats),

*Systemic:*

Oral or subcutaneous application doramectin (long half life) or ivermectin

Spot on: selamectin (cf sarcoptes in dogs); combination imidacloprid/moxidectin 1 mg/kg body weight.

#### **4 Cheyletiella**

- A contagious infestation of cats, dogs, rabbits, (guinea pigs), wildlife (foxes, squirrels) and human.
- Prevalence underestimated because it is often misdiagnosed and responsive to treatment with many flea products.
- Disease most common in young animals in poor physical condition
- Longhaired cats?. Small breeds: Bichon, cavalier king Charles, Yorkshire T.... (Small breeds). Very frequent in rabbits.
- Origin: Pet stores, shelters, imported animals...
- 3 *Cheyletiella* species transmitted usually by direct contact (maternal transfer while nursing). Permanent parasites but could resist off the host for up to 10 days (even more?) Role of . Blankets, carpets, animal bedding
- *Cheyletiella* can be phoretic on fleas and transmitted.

Life cycle completed in 3 (5) weeks (Scott, 1980). Eggs on hairs 2-3 mm above the skin or free.

#### Clinical signs

- Asymptomatic in many animals (cats, adults)
- Pruritus often moderate (occasional pinnal-pedal reflex, frequent “truncal” pedal reflex positive).
- Scales, crusts, papular (military) dermatitis, erythema, diffuse or patchy. rarely otoacariosis,

#### Diagnosis

- observation of parasites or eggs quite easy (naked eye, combing, brushing, acetate tape test along the backline of the animal, Scraping).

#### Treatment

Topical

Every product except neonicotinoids and semicarbazone, oxadiazine(?) or “insecticides” used to treat for flea infestation is effective . Activity maintained 6 to 8 weeks?.

Systemics:

Ivermectin and other macrocyclic lactones: selamectin, moxidectin.

Still no indication on Isoxazolines ( but likely)

- Treat also all in-contact animals (dogs cats and rabbits) + environment.



## 5 Trombicula

- A non-infectious, non-contagious (pseudocontagious) ectoparasitosis.
- Seasonal dermatitis of sudden onset (essentially mid-summer to end of autumn; possibly any time except cold periods) .
- Only the larval stage is parasitic (nymphs and adults free living). Mainly *Trombicula Neotrombicula* (syn. *autumnalis* (Europe),
- Animals outdoors are exposed (meadows, lawns, corn field, wooded and marshy areas...) in patchy infested areas.
- The larvae feed (1-3 up to 10 days) on lymph through a canal (stylostome or histosiphon) that will stay after their departure.

Larvae are often in clusters on predilection sites (thin skin or in contact with the vegetation): eyelid, ear pinnae, chin, ventral thorax and abdomen, interdigital folds, legs, nares (horses) or perianal perigenital.

### Diagnosis

- quite easy if larvae are still present, but clinical signs persist after their departure.

### Treatment

- The curative treatment of trombiculosis is very easy ; prevention is very difficult and frustrating.
- Many topical acaricidal can be used i.e off label-use of 0.25% fipronil pump spray (Frontline™) in dogs and cats,
- In a limited study (8 infested cats) control was observed with selamectin spot-on at 6 mg/kg.

V CHOOSING THE RIGHT PRODUCT FOR ECTOPARASITE CONTROL :

DEMODEX: STILL SO MYSTERIOUS (AND MISUNDERSTOOD).

## 1 - Canine Demodicosis:

### a – Epidemiology parasite(s) and life cycle

- An infectious, non-contagious ectoparasitosis due to the proliferation of *Demodex* mites in predisposed animals. Transmission from the bitch to puppies (first hours to days of life). Possible at any time/age. The parasite doesn't significantly survive in the environment.
- Typically young dogs (1) 3months-1 year old; several cases in the same litter of puppies not rare = juvenile demodicosis. Second peak in older dogs (8-12 years) frequently associated to underlying disease (detectable or not).
- Mainly pure breeds (familial/lineage predisposed)(underexposed? Poodle, German Shepherd).

- Demodex present in (virtually) all dogs. Clinical classical demodicosis is associated to a defect in T lymphocyte mediated immune response genetically transmitted (demodicosis in young) or acquired (demodicosis in adult). - - Dogs that cure from a juvenile demodicosis may relapse when they get old.
- Role of corticosteroids frequently mentioned. Corticosteroids do not “induce” clinical demodicosis (even if they are able to stimulate the population of parasites) but worsen it (more frequent bacterial complications).

### Parasite(s)

- *Demodex canis* inhabits hair follicles and can be found on the surface of the skin. Life cycle egg, larva, 2 nymphal stages (controversial) and adults, completed in about 12 days.
- Morphology of *Demodex* is unique elongated body (total length 150 to 400 µm.) very short legs and an elongated opisthosoma (2/3 of the total length). In recent years other names proposed: *Demodex injai* if longer (also isolated from ear canals), *Demodex cornei* if shorter. Variants of *D. canis* or true species?. Molecular biology confirm the evidence that *D. cornei* is just identical to regular *D. canis* but suggest that *D. injai* is different (variant or subspecies or species, significance of the number of samples tested?).

In practice the deeper are the samples from the skin the longer are the Demodex. All sizes can be found from the shortest (*D. cornei* form) to the longest ( even longer than the *D. Injai* criteria). Long Demodex can be also isolated from ear canals.

### **b -Clinical presentation**

- A variety of clinical presentation of demodicosis. Very severe (late diagnosis) cases seen 30 years ago are now very rare; in return very subtle forms of the disease are better detected.
- *Localized demodicosis*: one little surface of the skin, non pruritic, generally only diffuse alopecia with minor skin changes (erythema, scaling). Most of these cases could spontaneously cure (?).
- *Demodectic otoacariosis*: combined to body involvement (60% in our data) or isolated. Generally a non-to moderate, ceruminous, erythematous, non-pruritic external otitis. *Malassezia* and bacterial complications may occur
- *Generalized demodicosis*: ( several definitions) Lesions and mite observed in several ( $\geq 5$ ), or large areas of skin, or at least two extremities.

\*Uninfected: alopecia (diffuse to annular), scaling, erythema (sometimes intense = « red mange ») and/or hyperpigmentation (= “black mange”), greasy and thickened skin. This is generally non-pruritic. seborrhoeic demodicosis : mildly alopecic and erythematous , mostly in Terriers breeds (?). Typically the expression due to longer and deeper ( low number in scrapings or histopathological findings) (*D. injai*).

\* Bacterial infection: (“ Pyodermatitis”): Proliferation of bacteria (Staph intermedius...), superficial (folliculitis), then deep pyoderma (furunculosis and cellulitis). Bacterial infection facilitates the proliferation of the parasites. Pruritic and accompanied by adenomegaly. Evolution is fatal.

\* Demodectic pododermatitis:

In general just an intense involvement of extremities combined to body involvement.

In some dogs demodicosis is only localized to extremities (most often quadrupedal).

Very painful. lymph nodes highly reactive. Digits are enlarged, oedematous, ulcers. Treatment difficult

### **c- diagnosis**

- Laboratory procedures:

\* Skin scrapings: The best. Deep skin scrapings and squeezing are necessary. Use a clearing agent (i.e. chloral lactophenol). In most cases parasites are abundant except when only long Demodex are detected.

\* Hair plucking: less sensitive but very useful in areas difficult to scrape (periocular, interdigital)

\* Histopathology: Occasionally skin scrapings are negative (i.e.: Shar-pei, seborrhoeic disorders associated to long Demodex...). In some cases the histopathological pattern only suggest Demodex (no visible mite).

- In adult dogs look for endocrinopathies, neoplasia, metabolic disorders or other immunosuppressive causes

### **d- Specific treatment:**

#### Topical

Amitraze rinses (Ectodex, Mitaban, Taktic), weekly/(every other week), 0.025 % to 0.6/00 (emulsion in water). Dip the entire body surface. Caution (or contraindicated) in diabetic dogs (or owners) (induced hyperglycaemia).

Amitraz spot on: (limited activity on demodectic pododermatitis)

Promeris Duo (amitraz + metaflumizone: surface spot-on) shown to be active (lunching stopped)

Certifect: (some observations suggest a good activity activity).

Systemic: Today the preferred treatment

Macrocyclic lactones are effective (mainly orally).

Milbemycin oxime: labelled for canine demodicosis (Interceptor). Initial dosage 0.5–1 mg/kg daily. A double dosage (2mg/kg) is necessary if the number of mites do not decrease during follow-up.

An expensive but safe and well-tolerated molecule (including in dogs sensitive to ivermectin).

Moxidectin (a milbemycin)

Advocate spot on (Bayer Lab) (combination with imidacloprid a pure insecticidal). Imidacloprid diffuse horizontally on the skin surface, whereas moxidectin is absorbed trans-dermally and acts systemically. It is proposed a monthly use (Claim) (2,5-6,25 mg/kg of moxidectin). Many cases do not respond even at biweekly treatments. It is now proposed as a “weekly spot-on” (milder forms of the disease) (Label in some countries).

Moxidectin (Cydectin off label) used by the author at daily oral dosages of 0.4–0.8 mg/kg (other authors propose 1 to 2 mg/kg) in Cydectin 0.1% for sheep.

Ivermectin (Ivomec Lab Merial...). Many protocols have been proposed i.e. daily 0.3 (0.6) mg/kg orally (many other protocols). May cause adverse neurologic effects in sensitive dogs.

Ivermectin and moxidectin should be initiated at lower doses and patients monitored for possible adverse effects during therapy. In case of use of Ivermectin (not proposed by the author) a test for MDR1 mutation (abnormal Pgp) is generally recommended.

The necessary test for MDR1 mutation in every dog from susceptible breed before using a macrocyclic lactone can be discussed (heartworm preventatives do not induce any risk due to their very low dosage) ( see chapter VII)

#### How to avoid the MDR1 test?

Avoid any use of Ivermectin (in practice the only molecule really at risk in accidents).

Start the treatment at a vary low dosage = 50 microg/kg and increase it progressively

Avoid or limit the use of potentially other Pgp inhibitors.

..... select DOGS without this mutation for reproduction!

Isoxazolines: There are still few studies on the efficacy and detailed spectrum of this group of molecules. The very high concentration (and dosage) makes just likely (evident) the activity on Demodex mites.

Fluralaner: This molecule is widely used in the treatment of canine demodicosis empirically at the label dosage. Results appear very interesting with most of case with enthusiastic comments but also some unsatisfied. The very long action and high dosage of the molecule makes the follow up scheme difficult to perform (evaluation?).

Afoxolaner : First observations are encouraging.....

Sarolaner : no information still available .....

No doubt that results of new studies will be soon produced.

#### **- Procedure for treatment and Follow-up:**

\* On day 0:

Perform 5 skin scrapings on 5 different lesional sites precisely identified. The mites are counted (separately for eggs). (Add one scraping in a clipped area non lesional). Treatment is prescribed for a one-month duration

\*Monthly follow-up:

- Skin scrapings performed in mineral oil on the same 5 (+1) areas (clip if coat regrows). Percentage of mites dead or alive is assessed as the presence of eggs. The dosage is maintained if the parasitic charge decrease and increased in other cases.
- The treatment is maintained at least one month after the last visit with apparent complete absence of mites.
- The clinical cure precedes always the parasitological cure.
- Average duration of treatment is 4 to 5 months although some dogs need a very long therapy.

\*Very few prognosis factors available:

- Pododermatitis is longer to control and extremities the last part of the body to cure;
- Better prognosis factors for a shorter treatment on Day 30 are:  $\geq 75\%$  of dead mites; absence of eggs and a complete control of pyoderma.

## **2 Feline Demodicosis**

- A very rare skin condition in the cat.
- Until recently one species, *Demodex cati* (Hirst, 1919) was described. It resembles *Demodex canis*. *D. cati* mites live within the hair follicles (especially eyelids, face, chin and neck).
- During the last two decades another species named *Demodex gatoi* was proposed. (Morphological, and molecular differences). (First observed in a cat in Louisiana, USA. Since it has been reported from other regions: USA, Austria, Finland, UK (France personal observations) *Much* smaller than *D. cati*. Inhabits the superficial skin layer (stratum corneum)? Life cycle is not described.
- A putative third Demodex species (*D. felis?*) suggested by some observations? Shorter than *D. cati* but longer than *D. gatoi* ? Additional studies are clearly needed.

### Diagnosis

Skin scrapings. Trichoscopy in areas difficult to scrape.

Sample cats in contact

Faecal flotation may reveal the presence of ingested parasites and could be even more sensitive than skin scrapings.

Recently a molecular technique on feline Demodex mites has been developed

## Treatment

Little information is available (no clear studies with comparative protocols):

- 2% lime sulphur dips at weekly intervals for 6 months
- Amitraz rinses at 0.0125-0.025% at weekly intervals for 2-3 months
- Oral ivermectin (0.2-0.3 mg/kg each day or every other day) effective in some *D. gatoi* cases (but failures also)
- Imidacloprid-moxidectin, selamectin or injected ivermectin once or twice a month = disappointing or contradictory results.
- Isoxazoline group of molecule likely to be used soon in cat (label or off label).

## VI CHOOSING THE RIGHT PRODUCT FOR ECTOPARASITE CONTROL : ADULT DIPTERA

- They are mainly “intermittent ectoparasites”. The classical hypersensitivity sequence they induce has been defined in laboratory animals (sensitization, HS: IV, IV+I, I, desensitization) but is not necessarily found in field conditions.
- In the dog and cat they will produce variable pruritus, papules, acute to ulcerative dermatitis, eosinophilic furunculosis and feline eosinophilic granuloma complex. Classically Mosquitoes, Sandflies, Stomoxes or even Tabanids are considered (Hippoboscidae, Ceratopogonidae also bite dogs and induce skin lesions) .

The discussion around flying insect target their vectorial role: Sandflies and *Leishmania*, Mosquitoes and *Dirofilaria*. These formulations should have the dual effect of both warding off and killing insects when they come into contact with a treated dog

Preparations contain different synthetic pyrethroids the only effective group of insecticides..

We will focus on Sandflies and *Leishmania*.

### *Collars*

Two collars are proven effective to prevent sandfly bites:

- Deltamethrin (Scalibor) which penetrates into the subcutaneous fatty tissue of the dog, reaching its maximum efficiency after 2 weeks and repellent effect that can last 6 months (has also been shown to significantly reduce canine and human seroprevalence of leishmaniosis).
- Flumethrin (+ imidacloprid-containing collar) Seresto. This collar was tested in a leishmaniosis hyperendemic area. After the one-year study period, 0% of treated shelter animals were seropositive compared to 35% in dogs without collars.

### *Spot-ons*

Topical preparations applied as a spot-on can provide adequate relatively rapid (24-48 h) spread of insecticide through the skin of the dog from which time they are considered effective. They all contain Permethrin

- Permethrin + imidacloprid 10% (Advantix): repellent effect against sandflies over 3 (4) weeks  
population-based application of these spot-ons to dogs was able to reduce *Leishmania* infection incidence over a 2-year period.

Permethrin (+dinotefuran, + pyriproxyfen) has repellency and insecticidal efficiencies of 96% and 88% at 2<sup>nd</sup> and 3<sup>rd</sup> week.

- Permethrin + indoxacarb (Activyl plus) has a repellent effect lasting 2 weeks against *Phlebotomus perniciosus*

- Permethrin + fipronil (phenylpyrazole) and permethrin against *Phlebotomus perniciosus* shown an effect of 96.3, 90.8 and 87% on Days 14, 21 and 28 respectively (Effitix). Another formulation shown a similar repellency 99.2, 90.9 and 90.3%, for Days 14, 21 and 29 respectively (Frontect).

Comments: It is important to mention that the effect is highly variable with the active dose of pyrethroid applied on the dog and not only the concentration in the formulation. i.e : efficacy maintained above 90% for 7 days 30mg/kg but, 29 days at 120mg/kg.

### *Sprays*

Insecticide lotions marketed as sprays based on permethrin 65% or combinations with pyriproxyfen offer good repellent and insecticidal properties. Their efficacy is immediate. Correct manual administration is necessary to avoid to leave unprotected zones on the animal. The residual effect is less than that of other products (one week).

## VII TOXIC AND ADVERSE CUTANEOUS DRUG REACTIONS TO PARASITICIDES

There is little information about effects on skin induced by ectoparasiticides in companion animals.

### **1 Classical observation of local intolerance**

-The most commonly related by owners is pruritus.

- Classical ones were related to a simple contact irritant dermatitis. The first described were those induced by the application of insecticide containing collars ( localized alopecia and erythema ).

Irritation due to spot on is also classical although the real incidence remains unknown. Finally a local alopecia is another secondary effect of spot ons.

In one recent case the condition was defined as a morphea-like lesion in a cat after topical application of a 'spot-on' solution containing praziquantel and emodepside.

It was considered s a possible idiosyncratic reaction to one of the applied substances

Scleroderma is a group of rare chronic disease of connective tissues that may affect the skin in humans. Although still unclear, its aetiology may be related to drug reactions This condition is very rarely described in veterinary literature

## **2 Pemphigus foliaceus (like?) localized or generalized**

Two publications mention the development of pustular lesions in dogs after the application of amitraz containing spot on.

- The first one described 22 cases of pemphigus foliaceus (like?) condition after application of novel topical flea and tick preventative for dogs containing amitraz combined to metaflumizone (Promeris Duo). The lesions appeared first on the site of application then possibly extended. Distant lesion was also present in 14 dogs. The lesions appeared after 1 to 8 applications.

The nature of lesions was histopathologically compatible with pemphigus foliaceus. Direct and indirect tests demonstrated anti-keratinocytes antibodies and desmosomal changes (desmoglein 1 markers).

- A second series of observations was made after launching of another spot on containing amitraz, fipronil, and S-methoprene (Certifect). It was associated with the development of an acantholytic pustular dermatitis similar to that of Promeris-triggered pemphigus foliaceus. Six dogs had local lesions and 15 others had also lesions at distant sites. One or two applications were sufficient to trigger PF-like lesions. Antikeratinocyte IgG was detected in most and serum antikeratinocyte IgG in 10 of 14 (. Autoantibodies targeted canine desmocollin-1 desmoglein-1.

- A third group of cases (3) was associated to another recently launched spot on (dinotefuran, pyriproxyfen permethrin)(Vectra 3D). The dogs exhibited rapid onset of papules, pustules and crusts at the site of application of the spot and expanded in 2 of them. Histology revealed subcorneal pustular dermatitis, with acantholysis of keratinocytes and focal to multifocal full-thickness epidermal necrosis. Tissue-bound IgG was detected and autodesmocollin-1 antibodies in one dog.



Pemphigus foliaceus (PF) can occur as a reaction pattern associated with cutaneous adverse drug reactions. Such pemphigus (mainly vulgaris type) adverse drug reaction have been described in humans. Contact with pesticides is suggested one of the risk factors for pemphigus in humans.

### 3 Genetically based Toxicity

- The MDR1 sensitivity is a genetic abnormality associated to the Multi-Drug Resistance gene, initially discovered in Collies (ivermectin neurotoxicity), then 10 other breeds.

-Transmission autosomal recessive (deletion of 4bp on MDR1): Heterozygotes are less sensitive (less severe clinical signs, higher dosages)

Studies in North America, Germany: (Gramer i et al., Vet J, 2011)

Collies (30-50% muted; 30-50% heterozygote;  $\pm$ 20% negative.), long haired Whippet (45%), Shetland (30%), Australian shepherds (22-24%), white Swiss shepherd (14%)... results on prevalence are highly influenced by the initial recruitment of animal tested.

- Mechanism: The gene modification induces the production of an abnormal transport protein (P-gp). P-gp is present in endothelial capillaries cells of haemato-meningeal barrier and plays a role of efflux pump for substances like Ivermectin. When the protein is abnormal the pump is modified and ivermectin (or other molecules transported by Pgp) accumulates and act on the nervous system.

Ivermectin stimulates GABA release from presynaptic neurons and blocks the nervous impulse.

Usual dosage in dermatology is 0,4-0,6 mg/kg/j. Dosages as little as 0.1mg/kg in susceptible (homozygous) collies can induce very severe signs (0.3mg/kg in heterozygous).

However not all the neurologic signs associated to the use of macrocyclic lactones are du to MDR1 mutation.

- Apart its roles of efflux pump (CNS and intestine) Pgp increases the renal (then biliary and intestinal) excretion

of drugs. In aged animals the expression of Pgp decreases and thus the risks increase.

- Other dugs are concerned by the efflux pump of Pgp = substrates. They may also induce neurologic signs. The list of Pgp substrates is mainly made of relatively Small molecules, lipophilic. This list is longer with time.

Apart Ivermectin the other macrocyclic lactones are also substrates but interestingly, molecules like selametin or milbemycins are much less concerned (label for susceptible breeds).

Spinosyns are also a substrate for Pgp

At intestinal level intestinal absorption is also modified for some molecules like Ciclosporin A (increase)

A list of molecules that could be substrates involved in dermatology:

Acepromazine, Amoxicillin, Cetirizin, Ciclosporin, Cimetidin, Dexamethasone, Doxycyclin, Itraconazole Ketoconazole, Spiramycin, Tetracyclins

- Blockers: These molecules make the Pgp less effective : (Ciclosporin, Hydroxyzin, Megestrol acetate, tamoxifene, verapamil). (risk of intoxication if used simultaneously to Ivermectin.

Inductors: these molecules reinforce the Pgp thus may reduce the effects of substrates (Dexamethasone, rifampicin ).

Some molecules are both substrates and inhibitors : thus there are even dangerous for use on heterozygous dogs. (Ivermectin, Ciclosporin, Itraconazole, Ketoconazole).