Challenges and Solutions to Flea Control

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Fleas are a common and important external parasite of dogs and cats. The most common flea species infesting dogs and cats in North America and in many areas of the world is *Ctenocephalides felis felis*, the cat flea.[1,2] Cat fleas are voracious blood feeders consuming up to 15 times their body weight in blood daily and female fleas use that blood to produce up to twice their bodyweight in eggs daily.[1-3] So it does not take long before a flea infestation can get completely out of hand. These fleas can cause allergic skin disease (FAD), produce anemia through their blood feeding activities, and transmit tapeworms and bacterial pathogens.[1,2] It is therefore important for the health and well-being of our pets that we control these harmful parasites.

It must be understand that it often takes several weeks to eliminate a flea infestation. That is because all flea infestations of dogs and cats originated from a flea-infested environment and it takes time to eradicate the immature stages living in the carpet or outdoors. Once these fleas jump on a dog or cat they will feed, mate and female fleas will begin laying eggs within 24 hours.[1-3] Then within a few days each female flea will be producing 40 – 50 eggs per day, with hundreds and potentially thousands of eggs being deposited into the home or yard.[3] The in-home and potentially outdoor premises rapidly become infested with egg, larvae, pupae and emerging adult fleas, often referred to as the flea biomass.

Historically veterinarians and pet owner treated the premises directly through the application of insecticides and insect growth regulators into the carpet and yard.[4] This was done in an attempt to kill emerging fleas and prevent development of eggs & larvae. Premises treatments were considered necessary to break the flea lifecycle. The primary reason that premises treatments were necessary was that prior to the mid-1990s topical products (dips, sprays, collars, powders etc..) had no substantial duration of residual activity.[5] Premises treatments were difficult to conduct, time consuming, expensive, environmentally unfriendly and often ineffective.

However, with modern topical and systemic residual flea products, control of infestations in the premises is now achieved by preventing flea reproduction.[6,7] Reproduction is halted either through the use of highly effective residual adulticides that kill most newly acquired fleas before they begin reproduction (killing fleas within 24 hours after jumping on treated pet) or through the use of insect growth regulators (or insecticides) with ovicidal activity to kill any eggs that might be produced.[6,7] Simply stated, if you cannot reproduce as a species you go extinct in the local premises.

When focusing on residual adulticides it is the residual speed of kill of a product that is of utmost importance.[8] Residual speed of kill relates to how rapidly a product kills newly acquired fleas at some time point (days or weeks) after administration. If a product can kill newly acquired fleas fast enough it can prevent flea reproduction and markedly reduce the amount of salivary proteins injected by the fleas, thus minimizing or eliminate FAD symptoms.[5,8]

Although modern residual flea adulticides provide prolonged adulticidal activity, it has been determined that efficacy and speed of kill of most products will decrease over time following administration.[5,9-12] As the residual efficacy decreases and fleas are not killed within 24 hours, female fleas can live long enough to produce eggs.[5,9,10] Therefore, it is important to use a product that is effective enough to suppress reproduction between scheduled reapplications. Residual efficacy can also be affected by under-dosing by clients, bathing or swimming that can reduce insecticide levels of topical formulations, poor G.I. absorption with oral products and natural variability in susceptibility or outright resistance.[13]

Proper administration of effective residual flea products to all dogs and cats means no more fleas reproducing and no more eggs dropping into the environment. Therefore, within 2 to 7 days, eggs that were previously deposited have developed into larvae, within 1 to 2 weeks the larvae have now developed into pupae, and 1 to 4 weeks later those pupae are now adult fleas. As these fleas emerge and jump on treated pets they are hopefully being killed by the flea product. Therefore within 3 to 8 weeks or occasionally as long as 3 months, all the adult fleas and immature life stage biomass should be gone.[6,7]

How bad a flea infestation becomes and how rapidly a flea infestation is eliminated is not only affected by the product used, but also by environmental conditions. Relative humidity in the microenvironment is primary determining factor in flea populations. This is because flea larvae are weak link in the life-cycle chain and are very susceptible to heat and desiccation.[1,2] In addition, the rate of flea development and therefore how rapidly the biomass is exhausted can be very temperature dependent.[1,2]

If a flea infestation continues beyond the expected 3 to 8 weeks (or longer), commonly encountered problems can be an untreated flea host in the home or maybe that the product itself is not stopping reproduction. An interesting assessment of product performance entails the evaluation of gender structure of newly emerged fleas in these homes.[14] While most insect species exhibit protrandry (males tend to emerge before females), *C. felis* belong to a much smaller group that exhibits protogny (females tend to develop before males).[15] The first fleas to emerge from a cohort of eggs are females, followed by both males and females and then lastly almost exclusively males. It has been demonstrated that if flea reproduction is inhibited by insecticidal treatments administered to a pet, then a gender shift in premises flea population takes place overtime from a female dominated population towards a more male dominated

population.[14] In a recent field investigation, 60% of the unfed fleas collected in premises light traps on day 0 were female, whereas by 28-30 days following treatment with oral afoxolaner, 78% of the unfed fleas collected in the traps were male. This was a clear and rapid gender shift, indicative of cessation of flea reproduction.

Another issue that must be expected in a small number of homes is that the flea infestation may get worse before it gets better.[7] These cases are referred to as "Red-line homes". By definition a red-line home is a house were premises trap flea counts increase > 20% over day 0 trap counts within 1 to 4 weeks post-treatment.[14] These surges in emerging fleas occurs because of a large preexisting biomass in the indoor premises. Such surges in emerging fleas and resulting increase in flea numbers on household pets can give the perception of product failure. Often extensive and frequent mechanical intervention (vacuuming, washing pet bedding and area and throw rugs, etc.) and even application of insecticides into the premises may be necessary in these cases.

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Understanding speed of kill of flea adulticides

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Numerous manufacturers of flea products often tout the speed of flea kill of their formulations. So what does speed of kill actually mean and why is it important? Understanding differences in residual flea adulticide flea treatments requires understanding the methods used in flea product evaluations. The important speed of kill evaluations of flea adulticides are "initial speed of kill" and "residual speed of kill ".[1-5] These evaluations sound similar, but are actually quite different and the results of the different evaluations are extremely important. With "Initial speed of kill" evaluations the aim is to determine how quickly an adulticide kills fleas when it is first administered (topically or orally), and it may or may not be a predictor of the speed at other times during the post-treatment period. In contrast the goal of a "residual speed of kill" study is to determine the rate at which the product kills fleas that jump on the treated pet at some time

point after treatment, often days or weeks. Residual speed of kill is likely far more clinically relevant, as will be discussed later. In addition, a third type of study that may be combined with a residual speed of kill evaluation is called a "reproductive breakpoint" study.[6-9] This type of evaluation provides information on the impact of a residual flea control treatment to prevent a flea population from maintaining itself.

"Speed of kill" studies tend to follow the same basic pattern. Efficacy of the product against fleas is calculated by comparing the number of fleas remaining on animals in one or more treatment groups compared with the number of fleas remaining on animals in a negative control group at pre-selected time points. Often a different group of treated and control animals is used for each of the pre-selected time points, but less commonly repeated measurements are made on the same animals over time.

The typical "speed of kill" experimental protocol involves the following steps: Control group animals and treatment group(s) animals are initially infested with fleas 1 or 2 days prior to treatment application so that the infestation more closely mimics treatment of naturally infested animals having actively reproducing fleas. Animals (dogs or cats) are then treated on what is usually called "Day 0".

Fleas are carefully counted on animals from the treated and control groups at subsequent pre-selected time points (example 4, 8, 12, 24 & 48 hours; more or fewer time points may be chosen). Efficacy is calculated at each time point based on the number of fleas on control animals compared with treated animals. This is called an "Initial Speed of Kill" study and provides efficacy evaluations at specific time points post treatment.

This is contrasted with a "Residual Speed of Kill" study when at selected time-points after treatment the control and treatment group animals are re-infested with new fleas, and the process of counting fleas at each time point is repeated. These post-infestation time points are often 12 and 24 hours or 24 and 48 hours, however earlier time periods are occasionally used.

As an example the residual speed of kill of a monthly flea treatment for dogs could be measured by infesting dogs on days 0, 7, 14, 21 and 28 post-treatment and removing fleas on treated and control dogs at 12 and 24 hours after each infestation. Because speed of kill of residual adulticides slows with time[2-9], this portion of the study gives an indication of the time required to kill newly arriving fleas throughout the treatment period. For example, a flea treatment that kills 100% of fleas within 8 hours 7 days post-treatment, typically does not kill newly arriving fleas with the same speed 30 days later.

To get a clearer understanding of the importance of flea adulticide residual speed of kill it is necessary to understand a few facts concerning the

reproduction of the cat flea, *Ctenocephalides felis*. Cat fleas initiate feeding within seconds to minutes of acquiring a host, mate within the first 12 hours and females typically starting to produce eggs at 24 hours post-infestation.[10] These females will continue to produce eggs every day for several months, producing up to 40 eggs/day.[11] Therefore, a topical or systemic flea treatment that has a rapid residual speed of kill, killing or rendering moribund all fleas within 24 hours of them jumping on the dog or cat, can prevent egg production. Preventing flea reproduction then allows the environmental flea population load to steadily decrease.[11] However, this rapid 24 hour kill rate must be maintained at or close to 100% throughout the entire post-treatment period; otherwise fleas will survive and egg laying will start. Historically that was difficult to accomplish and insect growth regulators were often needed to kill the few eggs that were laid by female fleas living longer than 24 hours.[7,12] If the reproduction inhibition drops below 100% before the 24 hour mark on any day during the treatment interval, then fleas will reproduce and will re-seed the environment with eggs. A topical or systemic flea treatment succeeds or fails based on its ability to control or not control flea reproduction.[13] If fleas can reproduce in spite of the flea treatment, then no amount of treatment will eliminate fleas from the household.

So how do we evaluate a product's ability to prevent reproduction between treatment applications? That can be accomplished by conducting a "reproductive break point" study. The aim of this type of study is to determine the time point following product administration when the residual speed of kill of the formulation slows sufficiently or ovicidal activity drops below 100%, to allow for viable egg production.[7-9] In this study design treated and control animals are infested with fleas at specific intervals post-treatment, and then 48 to 72 hours after each re-infestation researchers carefully collect and count any flea eggs falling from the treated and control animals. The eggs are then incubated to determine viability, as indicated by the percent of eggs emerging to adult fleas. The study is designed to identify the approximately time post-treatment when viable flea eggs are first produced from fleas that re-infest treated animals, the "reproductive break point". When evaluating the residual performance of a flea product, an effective product will have its "reproductive break point" at some time point after the next labeled reapplication interval. If a product is labeled for administration once a month and the reproductive break occurs around day 21, then the product likely will not be effective in eliminating a flea infestation. Considering the results of "residual speed of kill" and "reproductive break point" study together gives the best indication of the real value of a flea treatment. A treatment that can control 100% or close to 100% of flea adults within 24 hours for the full duration of its treatment interval (as shown in a speed of kill study), and that also does not allow a production of viable flea eggs within its treatment interval, can be used to drive

fleas in a household into extinction. This is because the treatment will not allow adult fleas to survive long enough to reproduce; and there are no new viable flea eggs being added to the environment.

The use of a flea treatment that drives fleas into extinction within a household is still not quite the end of the story because there is a constant possibility of reintroducing fleas into the household from outdoor flea populations maintained on wildlife or in untreated households. Owners need to routinely reapply an effective treatment at the recommended retreatment interval, and in most places this needs to be continued year round. A treatment gap will allow fleas to re-seed the environment with viable eggs.

Another important aspect of residual speed of kill is the potential impact it has on managing flea allergy dermatitis (FAD). Historically, products containing fipronil, imidacloprid, metaflumizone, selamectin and spinosad have clearly demonstrated their ability had a major impact on reducing the occurrence of FAD.[14-17] However, the data from the several studies as reviewed by Dryden 2009 demonstrate that these compounds neither stop flea bites nor completely stop flea feeding.[18] These compounds are very likely managing FAD because they decrease prolonged flea feeding and reduce the amount of salivary protein delivered to the allergic pet and in the long-term reducing flea numbers. It is also worth noting that whether an insecticide works topically or systemically may be irrelevant in the management of fleas or FAD; what is most important is rapid *residual* speed of kill.

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