

Overview of Flea Allergy Dermatitis*

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Flea allergy dermatitis, or flea-bite hypersensitivity, is the most common small animal dermatologic condition.¹⁻³ In some regions of the world, it is the most commonly seen canine disease. This disease does not exist in locations that are inhospitable to fleas, such as those at elevations above 1500 ft or with low humidity (e.g., the desert).

Although there are more than 2000 documented species and subspecies of fleas, the cat flea (*Ctenocephalides felis felis*) is the species most frequently found infesting dogs, cats, and all caged pets in North America.

Flea Facts

The life cycle of the flea ranges from as few as 12 to as many as 190 days, with an average of 21 days. The time needed for development depends heavily on environmental conditions, particularly temperature and humidity. The optimal environment is a low-altitude geographic location, a temperature of 75°F (23.8°C), and a relative humidity of 78%.

An adult flea takes its first blood meal from a host within minutes of contact. Female fleas lay their first egg 24 to 36 hours after this blood meal. Flea eggs are smooth and slick. Only 30% of eggs remain on the haircoat; the remainder fall off the host into the environment. Hatching takes place within 1 to 10 days, again depending on humidity and temperature. A single female flea can lay 1000 eggs within 30 days, and most average 2000 eggs during their life.

Although eggs can hatch anywhere in the environment, development of the larvae that emerge from the eggs must take place off the host because mammalian body temperatures are too high for survival. Larvae are highly sensitive to heat and desiccation and therefore tend to move downward and away from direct light

sources. The larvae feed on adult flea feces (partially digested blood) in the environment. Within 5 to 11 days, a larva undergoes two separate molting stages before forming a pupa.

The pupal stage is the most resilient of all stages because the cocoon is highly resistant to desiccation. It also has a sticky surface that helps to prevent premature removal from the environment and accumulates dust and other household particulates to provide protection. On average, the pupal stage lasts 8 to 9 days; however, fleas can pupate for up to 6 months if the environmental conditions are not ideal for emergence. Only with proper environmental stimuli, such as an increase in carbon dioxide, warmth, physical pressure, and vibration, will an adult flea emerge from its cocoon.

After emerging from the cocoon, adult fleas search for an appropriate host. Adult fleas are attracted to light and tend to migrate upward toward surfaces where contact with an appropriate host is more likely. Once a host is found, feeding and mating take place within 8 to 24 hours. Female fleas can consume 15 times their body weight in blood per day. Adult fleas act as obligate, permanent ectoparasites, preferring to remain on a host rather than in the environment.

Pathogenesis

Flea saliva contains histamine-like compounds, proteolytic enzymes, and anticoagulants. These proteins are released into the host during feeding and can act as inflammatory or antigenic stimuli in sensitive animals. Various immunologic responses are provoked, including immediate and delayed hypersensitivity reactions,⁴ late-phase IgE-mediated responses, and cutaneous basophil hypersensitivity reactions.⁵ Dogs with atopic dermatitis appear to be predisposed to the development of flea allergy dermatitis.^{6,7}

At a Glance

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Dr. Yu (shown here with his dogs [left to right] Timmy, Joey, and Bitsy) is associate professor of dermatology at The University of Guelph Ontario Veterinary College in Canada.



FIGURE 1
Typical distribution pattern of flea allergy dermatitis affecting the caudodorsolumbar region and caudal thighs (caudal to the "waistline").



FIGURE 2
A fibropruritic nodule, a benign hyperplastic reaction to severe flea allergy dermatitis, on a dog.

QuickNotes

History and physical examination findings are the keys to making an appropriate diagnosis of flea allergy dermatitis.

Diagnosis

History and physical examination findings are the keys to making an appropriate diagnosis of flea allergy dermatitis. There is no breed or sex predilection, and flea allergy dermatitis can develop in animals of any age. Patients may exhibit seasonal or year-round pruritus, depending on their geographic location. The owner may report an increase in pruritus following the introduction of a new pet or a visit to a boarding or grooming facility.

Often, clinical signs manifest on the caudal aspect of the animal, especially in dogs (FIGURE 1). Evidence of self-induced alopecia; erythema; pyotraumatic dermatitis; dull, coarse

haircoat; hyperpigmentation; and/or lichenification may be observed affecting the dorsal lumbosacral region, tail base, caudomedial thighs, inguinal region, and umbilical fold.¹ Other physical examination findings include papules or encrusted papules, crusting, scaling, and, occasionally, fibropruritic nodules (FIGURE 2) in association with affected areas. Secondary superficial to deep pyodermas are common (FIGURE 3). Close examination of the skin and haircoat using a flea comb may reveal flea dirt or adult fleas (FIGURE 4). Some pets may even exhibit clinical anemia as a result of severe flea infestation (FIGURE 5). Pets that are fastidious groomers can ingest adult fleas



FIGURE 3
"Hot spot" or acute moist traumatic dermatitis. One of the common underlying etiologies of this condition is flea allergy or flea-bite hypersensitivity.



FIGURE 4
Flea comb. This is a useful tool to demonstrate fleas and flea dirt to clients who are in denial about the presence of fleas on their pet.

carrying the tapeworm *Dipylidium caninum* and may have segments of *D. caninum* in their feces.

Clinical manifestations of flea allergy dermatitis in cats can include miliary dermatitis, eosinophilic granulomas or plaques, or self-induced alopecia without active lesions (FIGURE 6). Affected areas may include the dorsum, inguinal region, caudomedial thighs, head, and neck.

A lack of fleas or flea dirt is commonly reported by owners and should not override a diagnosis of flea allergy dermatitis if clinical suspicion is high. Intradermal skin testing with flea allergen may reveal wheal formation with immediate and delayed hypersensitivity. Serum in vitro testing for flea-specific IgE has variable accuracy and does not identify animals with delayed hypersensitivity reactions. Histopathology is nonspecific and reveals a superficial perivascular inflammation, often containing eosinophils—a pattern that can be seen in other hypersensitivity reactions.

Treatment

Based on current knowledge of flea biology, topical or systemic flea adulticide therapy may be the only management required to establish adequate control over flea infestations. Many prescription flea control products are currently available (TABLE 1). Ideally, integrated pest management, including the use of flea adulticides along with insect growth regulators

(IGRs) or insect development inhibitors (IDIs), should be used as a long-term management program to effectively eradicate infestation while minimizing potential drug resistance. If the environment is heavily burdened with various stages of fleas, environmental control is also warranted. Vibrations from a vacuum cleaner help stimulate emergence of the adult flea from the impervious pupa and, hence, increase the likelihood of effective environmental ectoparasiticide control. One to two applications of a synthetic pyrethroid or fipronil as an environmental spray every 7 days should be sufficient, although the addition of a household IGR such as methoprene or pyriproxyfen and/or sodium polyborate in carpeted areas would produce the best results in the house. To avoid any potential adverse reactions, it is best to remove pets from the treated environment until the products have dried; therefore environmental treatment is often done in stages. Professionally licensed exterminators should be considered for yards and households that are heavily infested.

All blankets, bedding, and rugs that are favored by the affected pet should be laundered. All carpeted areas and furniture that can house preadult fleas should be vacuumed, and the vacuum bag should be disposed of immediately. All household pets should be prevented access to flea-dense areas, such as porches, garages, and crawl spaces. Contact

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FIGURE 5

Severe flea infestation.



Fleas on a dog before treatment.



When the dog was bathed, the water turned red from the extreme amount of flea dirt in the haircoat.

TABLE 1**Flea Control Products Approved by the US Environmental Protection Agency and/or the US Food and Drug Administration^a**

Product (Manufacturer)	Active Flea Control Ingredients ^b	Species and Minimum Age	Dosage/Administration	Mode of Action
Program/Sentinel (Novartis Animal Health)	▶ Lufenuron	▶ Dogs: 4 weeks ▶ Cats: 6 weeks	Monthly oral; also injectable q6mo feline product	▶ Inhibitor of chitin biosynthesis
Frontline Plus (Merial)	▶ Fipronil ▶ S-Methoprene	▶ Dogs: 8 weeks ▶ Cats: 8 weeks	Monthly spot-on	▶ Fipronil: GABA-gated chloride channel antagonist ▶ S-methoprene: Juvenile hormone analogue (IGR)
Advantage (Bayer Animal Health)	▶ Imidacloprid	▶ Dogs: 7 weeks ▶ Cats: 8 weeks	Monthly spot-on; can be used weekly	▶ Nicotinic acetylcholine-receptor antagonist
Advantage Multi (Bayer Animal Health)	▶ Imidacloprid	▶ Dogs: 7 weeks ▶ Cats: 9 weeks (do not use canine product on cats)	Monthly spot-on	▶ Nicotinic acetylcholine-receptor antagonist
K9 Advantix (Bayer Animal Health)	▶ Imidacloprid ▶ Permethrin	▶ Dogs: 7 weeks	Monthly spot-on	▶ Nicotinic acetylcholine-receptor antagonist ▶ Permethrin: Sodium channel modulator
Revolution (Pfizer Animal Health)	▶ Selamectin	▶ Dogs: 8 weeks ▶ Cats: 8 weeks	Monthly spot-on	▶ Chloride channel activator
ProMeris for dogs (Fort Dodge Animal Health)	▶ Metaflumizone	▶ Dogs: 8 weeks	Monthly spot-on	▶ Voltage-dependent sodium channel blocker
ProMeris for cats (Fort Dodge Animal Health)	▶ Metaflumizone	▶ Cats: 8 weeks	Monthly spot-on	▶ Voltage-dependent sodium channel blocker
Comfortis (Eli Lilly)	▶ Spinosad	▶ Dogs: 14 weeks	Monthly chewable tablet	▶ Nicotinic acetylcholine-receptor agonist (spinosyn)
Capstar (Novartis Animal Health)	▶ Nitenpyram	▶ Dogs: 4 weeks and 2+ lb ▶ Cats: 4 weeks and 2+ lb	One tablet prn or daily/EOD	▶ Nicotinic acetylcholine-receptor antagonist
Vectra 3D for Dogs^c (Summit VetPharm)	▶ Dinotefuran ▶ Permethrin ▶ Pyriproxyfen	▶ Dogs: 7 weeks	Monthly spot-on	▶ Dinotefuran: Nicotinic acetylcholine-receptor antagonist ▶ Permethrin: Sodium channel modulator ▶ Pyriproxyfen: Juvenile hormone analogue (IGR)
Vectra for Cats & Kittens (Summit VetPharm)	▶ Dinotefuran ▶ Pyriproxyfen	▶ Cats: 8 weeks	Monthly spot-on	▶ Dinotefuran: Nicotinic acetylcholine-receptor antagonist ▶ Pyriproxyfen: Juvenile hormone analogue (IGR)

^aAdapted with permission from Mark Grossman and Carol Foil, Veterinary Information Network 2008. For the complete chart, visit www.vin.com/Link.plx?ID=37277. (EOD = every other day; prn = as needed)

^bIngredients active against other parasites not listed.

^cThis chart reflects the latest revision by VIN in September 2008. Please note that the following product has since become available: Vectra for Dogs and Puppies.

FIGURE 6

Common reaction patterns associated with underlying flea allergy dermatitis in cats.



Miliary dermatitis of the dorsum.



Self-induced alopecia of the ventral abdomen.

QuickNotes

Topical or systemic flea adulticide therapy may be the only management required to establish adequate control over flea infestations.

with feral cats, wildlife, and other unknown neighborhood animals should be prevented.

Eliminating all secondary bacterial and *Malassezia* infections provides short-term relief of pruritus. Shampoo therapy and short courses of oral corticosteroids are good adjunctive therapies. Antihistamines and essential fatty acids are not effective in flea-allergic patients.

Finally, all animals in the household must be treated with ectoparasiticide therapy to prevent reestablishment of flea populations and perpetuation of disease.

Product Overview

Insect Growth Regulators and Insect Development Inhibitors

Juvenoid hormones are chemicals that control various aspects of insect metabolism, reproduction, and organ development and maturation. However, the final maturation process and pupation of the larva depends on the absence of the hormones that were required for earlier development. The presence of synthetic insect hormones or IGRs therefore prevents pupation of flea larvae.

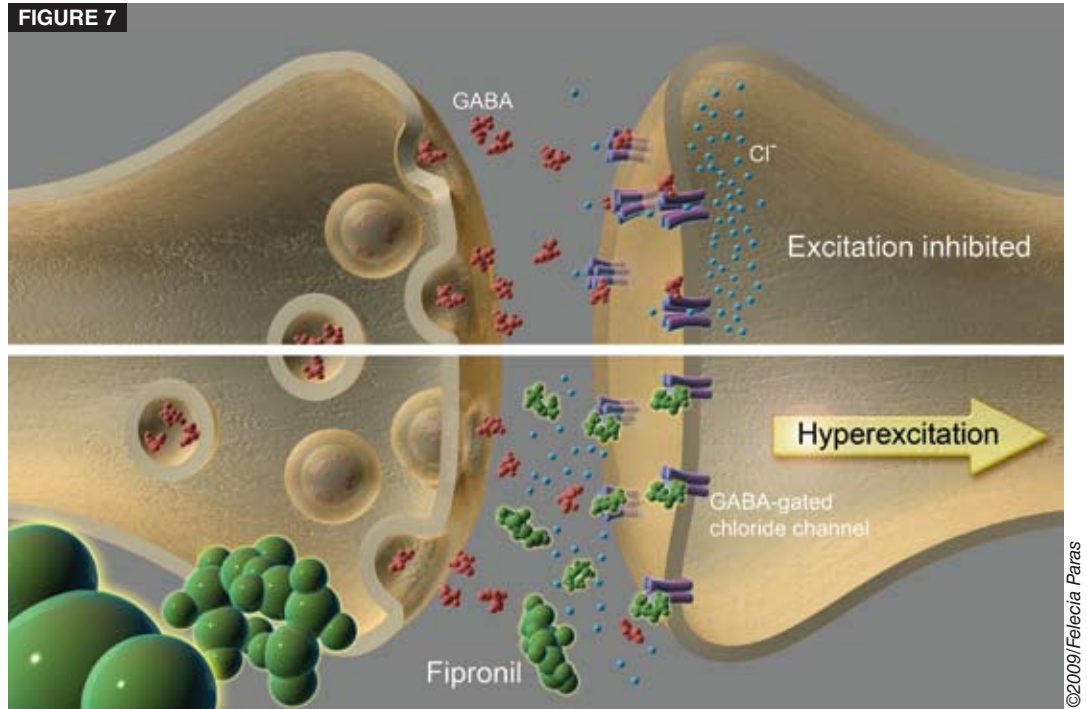
IDIs inhibit the development of adult fleas by disrupting the synthesis or development of chitin. Normal chitin development is essential for the survival and maturation of insect ova and larvae. Mammals do not produce chitin; therefore, IDIs are not toxic to mammals.

Lufenuron

Lufenuron is a benzoylphenyl urea compound providing IDI activity that should ideally be used in combination with adulticides when treating flea-allergic animals.⁸ Virtually no acute or chronic mammalian toxicity has been recorded. Lufenuron is poorly absorbed in tablet or liquid form unless it is administered with a fat-containing meal.

S-methoprene

S-methoprene is an IGR that may be combined with topical insecticides. It acts as a larvicide in the environment and an ovicide when female fleas on the pet are exposed. Its use in outdoor animals should be limited because it is inactivated by sunlight.



Fipronil disrupts the flea central nervous system by blocking the passage of chloride ions (Cl^-) through γ -aminobutyric acid (GABA) receptors, leading to hyperexcitation and death.

Pyriproxyfen

Pyriproxyfen is a traditional juvenoid IGR that is highly stable and efficacious. As an ovistilant, it remains 100% effective for 150 days after a single spray application. A residual effect was noted 3 to 4 months after pyriproxyfen-containing collars were removed from test animals.⁹ Although it is not toxic to adult fleas, eggs are not viable when laid.⁹

Adulticides

Flea adulticides interfere with flea nerve activity, specifically axonal and synaptic functions. Axonal adulticides impair the voltage-gated sodium channels or the γ -aminobutyric acid (GABA) or glutamate-gated chloride channels. Synaptic parasiticides include acetylcholinesterase inhibitors (organophosphates and carbamates) and products that target acetylcholine receptor-gated calcium channels and acetylcholine receptor-gated sodium channels.

Dinotefuran

Dinotefuran is a novel third-generation neonicotinoid adulticide that mimics the action of acetylcholine and binds permanently to acetylcholine receptors, resulting in tremors, uncoordinated movement, and death in fleas. For

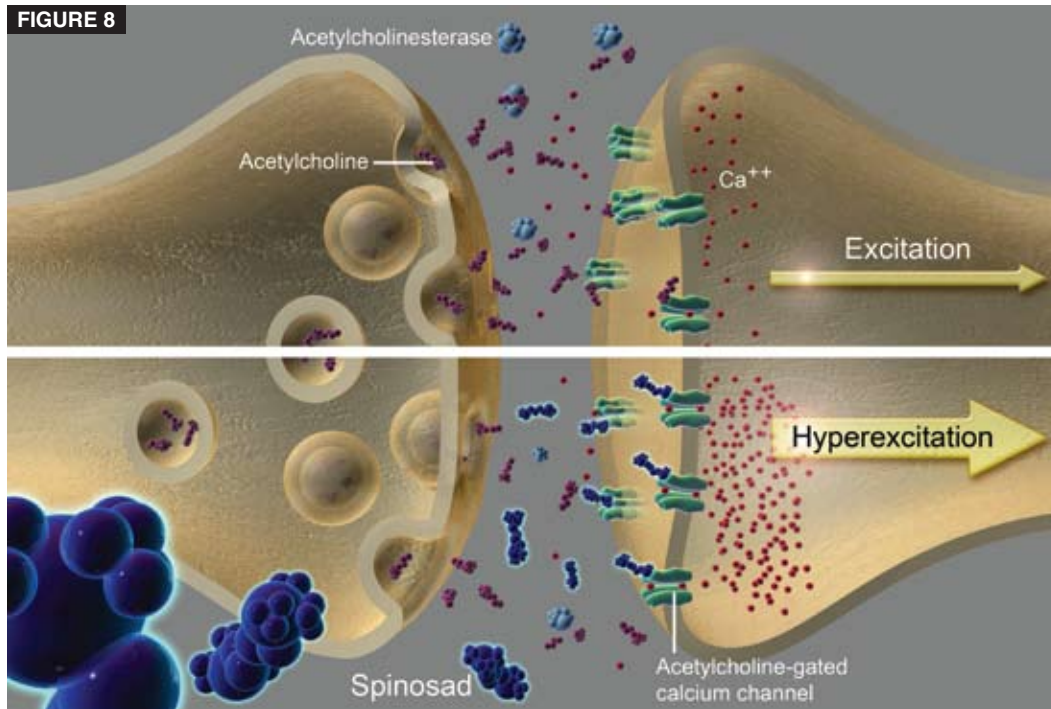
dogs, the product is combined with pyriproxyfen and permethrin to provide an integrated approach to pest management. Adult fleas, larvae, and ova, as well as four species of ticks and three species of mosquitoes, are targeted by this product. Because of concerns about potential toxicity, the feline product does not contain permethrin; hence, it primarily targets fleas. The manufacturer reports that 96% of fleas are killed within 6 hours and up to 100% are killed in 12 hours. Monthly application can begin in puppies as young as 7 weeks¹⁰ and in kittens as young as 8 weeks.

Fipronil

Fipronil is a GABA-receptor antagonist that works via chloride channel blockade in the central nervous system, causing hyperexcitation and death in adult fleas (**FIGURE 7**). It is a broad-spectrum phenylpyrazole insecticide with minimal systemic absorption. Fipronil translocates across the body, binds chemically to the hair and stratum corneum, and is absorbed into the sebaceous glands before being redistributed onto the skin surface. In one study,¹¹ topical sprays provided 100% kill in dogs for 16 days and 90% kill for the remainder of the month. In another study,¹² spot-on

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FIGURE 8



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Spinosad activates nicotinic acetylcholine receptors, causing rapid excitation of the flea central nervous system, paralysis, and death. Ca⁺⁺ = calcium ion

formulations provided >97% adult flea reduction on dogs and cats in a household environment within 24 hours, and this effect lasted for 1 month. Some products are combined with IGRs, such as *S*-methoprene.

Imidacloprid

Imidacloprid is a flea adulticidal and larvicidal neonicotinoid. Chloronicotinyl nitroguanidine compounds bind to acetylcholine receptor sites on postsynaptic nicotinic receptors, locking them open and resulting in stimulatory paralysis and death. The product kills rapidly (within 12 to 24 hours) due to rapid surface distribution. Topical application produces >95% protection against adult fleas for 28 to 37 days in dogs and cats.¹² Following application, contact transfer to bedding and other areas in the environment also prevents larvae development.¹³ Imidacloprid has been combined with other ingredients to enhance its spectrum of activity: 44% permethrin (for use on dogs only), for enhanced tick control, and moxidectin, a semisynthetic macrocyclic lactone, for an increased spectrum of activity against ecto- and endoparasites.

Metaflumizone

Metaflumizone is a semicarbazone insecticide

that blocks the influx of sodium through voltage-dependent sodium channels along the presynaptic and postsynaptic nerves, resulting in paralysis and death of adult fleas. The canine product contains amitraz for the control of ticks. A feline product without amitraz is also available. After translocation on the pet's skin, the product achieves full efficacy against fleas and ticks in 24 hours. It is lipophilic and water resistant. It has been reported that >95% control of fleas and >90% control of ticks remains 35 days after treatment.¹⁴ Monthly application is recommended; however, residual action has been seen against fleas for up to 6 weeks.¹⁴ Metaflumizone maintains >95% efficacy at 4 weeks against fipronil-resistant flea strains.¹⁴ The canine product has rarely been reported to cause a localized pemphigus foliaceus-like reaction that is under investigation.

The product has a "eucalyptus-like" scent that some people find undesirable; however, it can be used as a gauge for product distribution. Once the product has fully dried, the scent is no longer detectable. Clients should be made aware of the product's scent before purchase to decide whether it is acceptable to them. The manufacturer can supply test samples for this purpose.

Nitenpyram

Nitenpyram acts as an agonist to insect-specific nicotinic acetylcholine receptors in the post-synaptic membranes, causing paralysis and death of adult fleas. It is completely absorbed into the host's bloodstream in 90 minutes and requires a bite and blood ingestion by the adult flea to be effective. Nitenpyram begins to work within 15 minutes and kills >95% of fleas in 6 hours. The active product lasts up to 48 hours as a systemic insecticide.¹⁵ However, daily administration is recommended when treating highly sensitive flea-allergic patients, as it has low mammalian toxicity and rapid flea kill. It is also useful in treating pets with heavy and acute flea infestations within kennel, grooming, and veterinary facilities and provides a systemically distributed alternative for animals that are bathed frequently.

Pyrethrins and Pyrethroids

Pyrethrins and their synthetic counterparts (pyrethroids) are found in a variety of over-the-counter topical products. They cause hyperexcitation and death in fleas by increasing sodium channel permeability along axons. Some products are combined with IGRs (e.g., pyriproxyfen). While pyrethrins are safe in dogs and cats at the prescribed dose, higher-concentration pyrethroids should be used only in dogs because of high toxic potential in cats.

Selamectin

Selamectin is a broad-spectrum semisynthetic macrocyclic lactone with transdermal absorption and systemic delivery of a monthly topical application. It increases chloride permeability in glutamate-gated neuronal chloride chan-

nels to induce neuromuscular flaccid paralysis in fleas. Mammalian toxicity levels are very low because vertebrate cells do not have glutamate-gated chloride channels.

After selamectin is absorbed systemically, it is redistributed by the sebaceous glands to establish effective concentrations on the skin. Activity is not reported to be affected by bathing.¹⁶ As well as being an adulticide and larvicide, selamectin acts as an ovicide for fleas by preventing egg hatching. Selamectin applied topically reaches peak levels in the skin within 72 hours, and with each subsequent monthly application, it maintains steady-state concentrations for flea control. Contact transfer to bedding and other areas in the environment may also kill eggs and larvae.¹⁶ Selamectin is safe for ivermectin-sensitive dogs at the prescribed doses.

Spinosad

Spinosad is a neonicotinoid that acts as an agonist to insect-specific nicotinic acetylcholine receptors in the postsynaptic membranes, resulting in excitatory paralysis and death in fleas (**FIGURE 8**). Spinosad is the first US Food and Drug Administration–approved, oral, monthly systemic flea adulticide for dogs available in the United States. It must be given with food in order to achieve maximum systemic levels. Fleas start to die within 30 minutes, and close to 100% efficacy is achieved within 4 hours.¹⁷ Spinosad is not currently licensed for cats. Like nitenpyram, it is an alternative product for use in dogs that are bathed frequently to avoid the potential need to reapply a topical product. Spinosad is contraindicated in dogs receiving off-label high doses of systemic ivermectin used to treat unresponsive demodicosis. **C**

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