FELINE FLEA AND TICK CONTROL

A REFERENCE GUIDE TO EPA-APPROVED SPOT-ON PRODUCTS

TECHNICAL MONOGRAPH

by Michael K. Rust, PhD

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Email questions or comments to vetconnection@Hartz.com

DEAR DOCTOR:

When I first began studying fleas associated with cats some 30 years ago, the conventional wisdom suggested that cat fleas were simply a nuisance, vectors of the dog tapeworm, and causal agents of flea allergy dermatitis. However, with the aid of new molecular tools, cat fleas have been shown to be vectors of several human diseases, including cat-scratch disease and flea-borne typhus. In certain circumstances, they may also vector plague. With these emerging human health concerns, control of fleas and ticks to provide a pest-free environment takes on a new importance for pet owners.

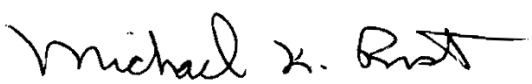
Most pet owners are aware of the important threat that fleas and ticks pose to their animals. However, the misconception that cats (particularly indoor cats) are not at risk for infestations by fleas and other parasites seems to be alive and well. As a result, many cats don't receive effective protection against parasites. This is a situation that veterinarians can help change.

A surprisingly large number of cat owners choose not to use parasite control products at all. Other owners may approach the problem in a reactionary manner—waiting until they see fleas or ticks before starting to address the problem. Still other cat owners use parasite control products seasonally or only treat some of their pets. Our current understanding of flea life cycles tells us that each of these parasite control strategies is likely to end in failure, even when attempted by the most diligent pet owner. Further, I am confronted every year by homeowners who don't have any pets, yet have cat fleas in their house. Feral animals that live near human dwellings are an important reservoir of fleas that humans and pets can bring indoors. Pet groomers, boarding kennels, and even veterinary clinics are also potential sources of cat fleas for indoor-only pets.

Although cat owners may know about fleas and ticks, they need your advice to protect their pets safely and effectively. This becomes even more important when we consider the pesticide-related safety issues that pertain specifically to cats. Most veterinarians have flea and tick control products that they are very comfortable with and likely to recommend to cat owners, but what about clients who choose to purchase parasite control products from other sources? Whether the reason is cost, convenience, or perception, retail outlets continue to be a popular option for purchasing flea and tick products. Unfortunately, the likelihood of purchasing an inappropriate product or using a product incorrectly increases when veterinarians are not part of the equation. To advise clients conscientiously, veterinarians need to become familiar with the products that cat owners may ask about—if for no other reason than to provide better counsel.

This monograph is intended to serve as an objective, quick-reference guide describing the active ingredients in currently available EPA-approved spot-on flea and tick control products for cats. It describes the major chemical classes, modes of action, absorption and distribution properties, and EPA safety designations for the individual active ingredients. It also provides an overview of, and references regarding, flea and tick biology and control strategies. The universe of feline parasite control products is constantly expanding with the introduction of new active ingredients, so veterinary professionals need to understand the different chemical agents on the market today. Becoming familiar with these ingredients is the first step toward helping cat owners understand how to use them to safely and effectively protect their pets.

Sincerely,



Michael K. Rust, PhD
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ABOUT THE AUTHOR

Michael K. Rust, PhD, was born in 1948 in Akron, Ohio. He spent his formative years in Parma, Ohio, a suburb of Cleveland. He has two children, Amy and Rachel, from his marriage to his first wife, Gayle, who passed away from cancer in 1998. He married his second wife, Mary, in 2002, and the family increased with the addition of her older children, Shannon, Shelly, and Shawn. Dr. Rust received his bachelor's degree in zoology from Hiram College in northeastern Ohio in 1970. His interest in entomology was sealed after spending a summer collecting insects at the University of Michigan's field station at Douglas Lake. He earned an MA and a PhD in entomology from the University of Kansas in 1973 and 1975, respectively.

Dr. Rust is an internationally recognized urban entomologist dealing with arthropods and insects of importance in and around urban structures. His research focuses on the integrated pest management (IPM) of important urban pest insects. He joined the faculty of the department of entomology at the University of California, Riverside, in 1975 and has been there ever since. His teaching assignments include courses on the natural history of insects for non-science majors, general entomology for science majors, and urban entomology. In his career, he has trained 14 PhD and 13 master's students specializing in urban entomology. He currently has three PhD candidates.

Dr. Rust's laboratory began conducting research on cat fleas in 1978. Since then, three students have completed dissertations on research dealing with fleas of importance in urban environments. Dr. Rust and his students have published some 17 scientific, technical, reviewed papers dealing with fleas. Their research has focused on flea biology and behavior, environmental control strategies, and insecticide resistance. Currently, the laboratory is part of a larger consortium of industry and veterinary professionals monitoring insecticide resistance to some commonly used adulticides and the susceptibility of field-collected cat flea isolates to imidacloprid. To date, more than 1,000 isolates have been screened in this worldwide monitoring program, funded in part by Bayer Animal HealthCare.

Dr. Rust was a University of California Presidential Scholar in Entomology in 1999 and 2000. He was elected a Fellow of the Entomological Society of America in 2001 and a Fellow of the American Association for the Advancement of Science in 2002. For his research on urban IPM, he has received numerous awards, including the Distinguished Achievement Award in Urban Entomology, Entomology Society of America, 1993; C. W. Woodworth Award, Pacific Branch Entomological Society of America, 1994; 1994 Excellence in Entomology Award—California Association, American Registry of Professional Entomologists; Entomological Society of America Recognition Award in Entomology, Pacific Branch, 2008; Lifetime Achievement Award—Association of Applied IPM Ecologists, 2009; and the IPM Team Award 2010 from the Entomological Society of America. Significant industry awards include the Orkin Research Award in 1990, 1995, and 1997; Book of Professional Services Award, Pi Chi Omega, 1995; Mallis Recognition Award, National Conference on Urban Entomology, 2000; *Pest Control Technology*'s 25 Most Influential People in the Industry, 2000; *Pest Control Technology*/Zeneca Leadership Award, 2002; and induction into the Pest Control Hall of Fame in 2007.

Dr. Rust has authored or coauthored 166 refereed research articles, book chapters, and reviews. He has also coauthored two books dealing with urban pest ants and their control. Current projects include a paper dealing with an extensive study of insecticide resistance profiles of field-collected isolates of cat fleas.

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FLEA BIOLOGY AND LIFE CYCLE

Fleas are successful ectoparasites of mammals and birds. Members of the order Siphonaptera (*Siphon* = tube and *aptera* = wingless), they evolved from snow flea (Boreidae) ancestors more than 35 million years ago, and many species have become highly adapted to single hosts. Of the 2525 identified flea species, approximately 96% infest mammals (74% on rodents); only 4% infest birds.[1]

Unlike most insects, adult fleas are laterally compressed. Both sexes have piercing–sucking mouthparts that enable them to feed on blood. A relatively small number of species have evolved or adapted to feed on domesticated pets and livestock. Only four species are regularly collected from domesticated felines: *Ctenocephalides felis felis* (Bouché), *Echidnophaga gallinacea* (Westwood), *Pulex irritans* L., and *Pulex simulans* Baker. The dog flea, *Ctenocephalides canis* (Curtis), is occasionally reported on cats, but cats are clearly not a significant host for this species.

The cat flea, *C. felis felis*, is the most important and prevalent ectoparasite of cats and dogs worldwide. Another *C. felis* subspecies, *Ctenocephalides felis strongylus* (Jordan), is restricted to sub-Saharan Africa and adjacent islands. *C. felis strongylus* infests dogs in rural areas; livestock such as sheep, goats, and cattle; and (probably accidentally) wild animals in South Africa, such as the caracal, *Caracal caracal*.[2,3] In Libya, *C. felis felis* is found on cats and dogs and *C. felis strongylus* is found on large farm animals.[4] Two former subspecies of cat flea—*C. orientis* (Jordan) and *C. damarensis* Jordan—have been given species status.[5] Considerably less is known about these two species. In this monograph, *C. felis felis* will be referred to as *C. felis* for brevity.

FLEA SPECIES OF IMPORTANCE IN DOMESTIC CATS

Cat Flea *(Ctenocephalides felis felis)*

Unlike most other flea species, the adult cat flea spends its entire life on the host—feeding, mating and laying eggs (Figure 1A). *C. felis* has been recovered from a broad range of domesticated and feral hosts.

A. Cat flea, *Ctenocephalides felis felis* (Bouché)
Distribution: Cosmopolitan
Hosts: Cats, dogs, opossums, raccoons, gray foxes, red foxes, coyotes, mongooses, hedgehogs
Vector of: *Rickettsia* spp, *Bartonella henselae, Yersinia pestis;* also causes feline allergy dermatitis
Intermediate host of: *Dipylidium caninum*

B. Dog flea, *Ctenocephalides canis* (Curtis)
Distribution: Northeastern United States, Europe
Hosts: Dogs, red foxes, coyotes; rarely cats
Vector of: *B. henselae;* also causes feline allergy dermatitis
Intermediate host of: *D. caninum*

C. Sticktight flea, *Echidnophaga gallinacea* (Westwood)
Distribution: Cosmopolitan
Hosts: Cats, dogs, rodents, foxes, coyotes, birds, more than 70 species of mammals and birds
Vector of: *Rickettsia felis, Rickettsia typhi*

D. Human flea, *Pulex irritans* L.[a]
Distribution: Cosmopolitan
Hosts: Cats, dogs, opossums, raccoons, pigs, rats, mule deer
Vector of: *R. typhi, D. caninum*

E. Oriental rat flea, *Xenopsylla cheopis* (Rothschild)
Distribution: Cosmopolitan
Hosts: Norway rats, roof rats, African grass rats, other rodents
Vector of: *Y. pestis, R. typhi*

Figure 1. *Adult flea species of importance in urban environments.*
[a]Often confused with *Pulex simulans*, a vector of *Y. pestis*.

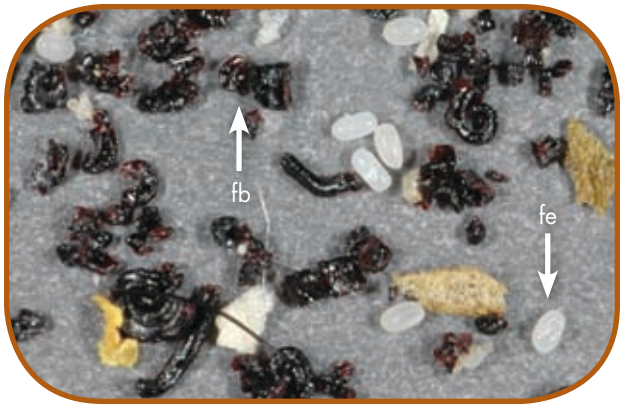


Figure 2. *The combination of cat dandruff, dried fecal blood droplets (fb), and flea eggs (fe) is sometimes referred to as "salt and pepper" and is a sure sign of flea infestation.*

In urban environments, opossums, raccoons, coyotes, foxes, mongooses, and skunks serve as suitable hosts and are natural reservoirs of fleas.[6–8] Typically, >90% of the fleas collected from cats are *C. felis*; an occasional sticktight or *Pulex* flea is collected from cats that roam and have access to more rural surroundings.[9] Heavy infestations of adult fleas on pets typically occur in the summer months, but adult *C. felis* has been collected from pets year-round. Consequently, inspection and treatment of cats are advised even in winter months.

Cat fleas are voracious blood feeders. In one study, 24.9% of fleas were engorged with blood within 5 minutes of being placed on a host.[10] By 1 hour, 97.2% had fed. Adult females fed for about 25 minutes, about 2.5 times longer than males. Female fleas consume copious amounts of blood, averaging about 13.6 µL—about 15 times their body weight—per day.[11] It is therefore not surprising that a heavy infestation of fleas on a small kitten can easily produce anemia. Adult fleas can excrete large amounts of nearly unaltered blood.[12] Dried, excreted blood accumulates in the environment and serves as the primary nutrient for flea larvae (Figure 2).

When cats are prevented from grooming, about 80% to 90% of female and 50% to 60% of male cat fleas live for at least 50 days.[13] Grooming can reduce the number of fleas on a cat by up to 50%.[13,14] Adult female fleas can lay about 27 eggs/day for 50 days, after which egg production declines; at day 113, they lay about 4 eggs/day.[13] Under favorable environmental conditions, cat flea populations can quickly overwhelm the host.

Environmental temperatures are probably the primary factor regulating population increases in cat fleas.[15] Flea eggs hatch in about 1 to 3 days at 80°F to 90°F, but hatching may be delayed for up to 6 days at 55°F. Flea eggs and, particularly, larvae are adversely

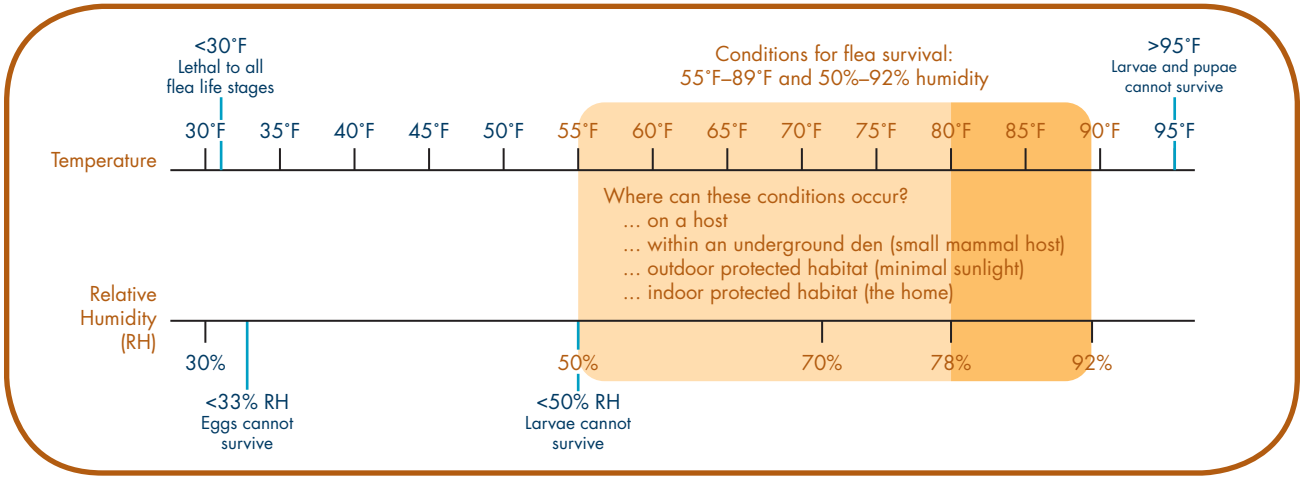


Figure 3. *Conditions for flea development and survival. This figure provides an overview of temperature (°F) and relative humidity (RH) conditions (orange shading) that support the stages of flea development and survival. Temperatures between 80°F and 89°F and RH between 78% and 92% (dark orange shading) are optimal for flea development. As shown, very high temperatures (>95°F) do not support the survival of larvae or pupae, and subfreezing temperatures (<30°F) for 5 days or longer are lethal to all stages of the parasite. Within that range, however, fleas can survive and adapt to modifications along the temperature–humidity continuum. For example, fleas can survive surprisingly low temperatures if there is adequate humidity. Even during times of suboptimal temperature and humidity, fleas can survive on a host, in under- or above-ground dens (with or without being on a host), and in outdoor habitats that are protected from direct sunlight and desiccation. An indoor environment can also provide microhabitats in which fleas can thrive and continue to reproduce.*[17,a–c]

[a]Wall R, Shearer D. Fleas (Siphonaptera). In: *Veterinary Ectoparasites: Biology, Pathology and Control.* 2nd ed. Osney Mead, Oxford: Blackwell Science Ltd; 2001:143-161.

[b]Dryden MW. Biology of fleas of dogs and cats. *Compend Contin Educ Pract Vet* 1993;15(4):569-578.

[c]Bowman DD, Lynn RC, Eberhard ML, Alcaraz A. Arthropods. In: Bowman DD, Lynn RC, Eberhard ML, Alcaraz A, eds. *Georgi's Parasitology for Veterinarians.* 8th ed. St. Louis: Saunders; 2003:1-81.

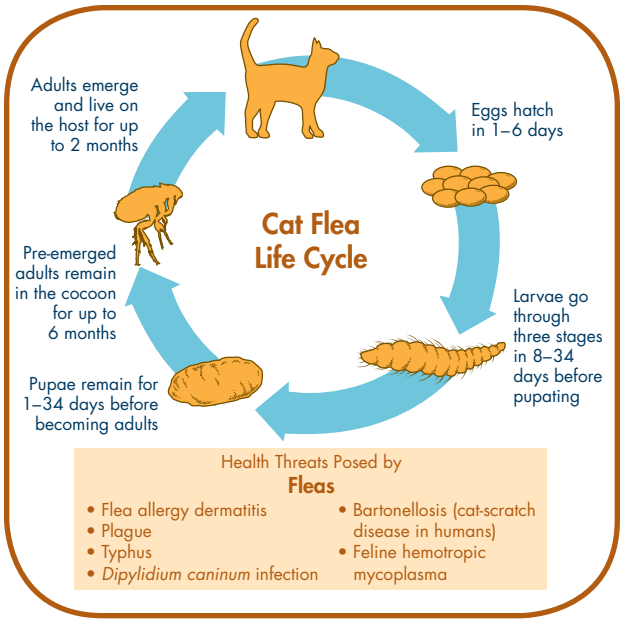


Figure 4. *Fleas are a one-host parasite, meaning that adult fleas can live and feed on a single host.*

affected by low relative humidity (RH): an RH <33% kills all eggs, and an RH <50% kills all larvae at any temperature[16] (Figure 3). However, overall RH and rainfall are not associated with increased numbers of *C. felis*, probably because the RH in the protected microhabitat, not the outdoor environment, dictates larval development. Protected microhabitats are habitats sheltered from environmental conditions in which the RH is higher than ambient conditions and temperatures are moderated. Outdoors, these habitats might exist in crawl spaces, dog houses or pet shelters, under bushes and vegetation surrounding a structure, and feral animal nests. Indoors, protected microhabitats might exist under beds, furniture, or cushions and in an animal's bedding. The pupal stage is resistant to

Figure 5. *Flea larvae are legless, and their mobility is greatly limited. This larva has ingested some dried fecal blood.*

desiccation, and pre-emerged adult fleas can remain quiescent in the cocoon for months. Under favorable conditions, the entire flea life cycle is completed in as quickly as 16 to 18 days. At cooler temperatures, adult emergence begins at 60 days and may take up to 140 days[16] (Figure 4).

Flea eggs are about 0.5 mm long, whitish, and ovoid (Figure 2). They are smooth and readily fall from the pelage of the host into the environment, where they hatch. The larvae are not very mobile and only move up to 46 cm in carpet from where they are deposited.[17] However, they are very sensitive to environmental conditions, RH <50% being lethal. Flea larvae feed on grains of dried blood excreted by adult fleas feeding on the host (Figure 5). Yeast has also been shown to be beneficial for larval development.[12] When confined together, larvae are cannibalistic, consuming other flea larvae and eggshells.[17] Larval development takes an average of 8 to 34 days depending on the temperature and RH[16] (Figure 4). The third instar voids the gut contents, forming a U-shaped larva that spins a pupal

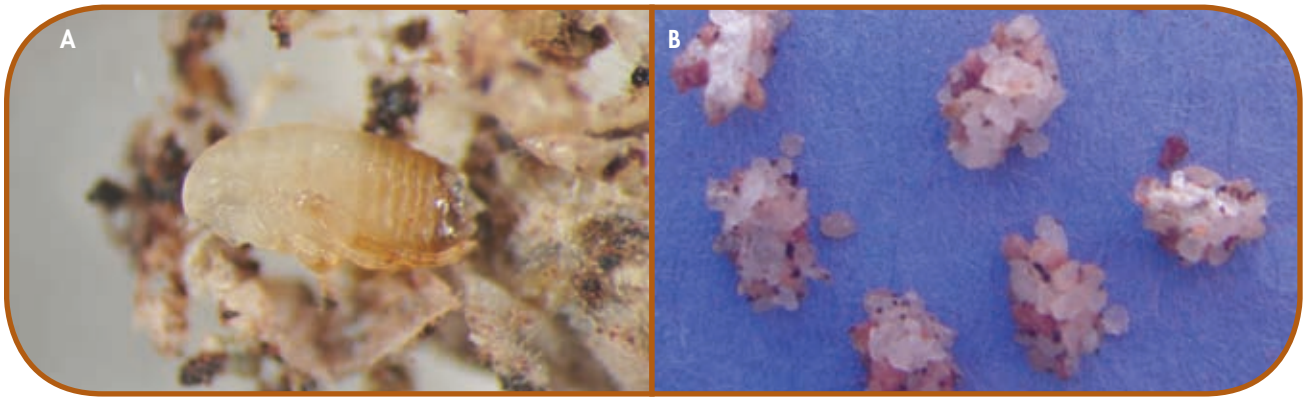


Figure 6. *The pupal stage of the cat flea life cycle can take 1 to 34 days.* ***(A)*** *The flea pupa may develop inside or outside of a silken cocoon.* ***(B)*** *Flea cocoons are constructed with silk and small grains of sand, fibers, and debris.*

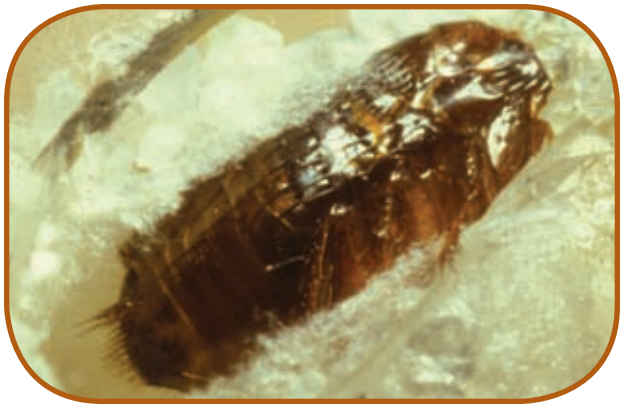


Figure 7. *Pre-emerged adult cat fleas can remain quiescent in the pupal cocoon for up to 6 months waiting for a host.*

cocoon (Figure 6). The average pupal stage lasts from about 1.2 to 23.5 days, depending on the temperature and RH. Places frequented by cats (i.e., resting and sleeping areas) where fecal blood droplets accumulate and the RH is >75% become flea developmental hot spots. It is important to treat these hot spots in the environment.

Once the adult flea develops in the cocoon (Figure 7), it is more protected against environmental conditions than the immature stages and may remain quiescent for up to 6 months waiting for a host.[16] Mechanical vibrations created by the host, increases in temperature, and increases in carbon dioxide stimulate fleas to emerge from cocoons.[18] Once emerged, adult fleas are attracted to movement and heat. They are most visually sensitive to green light (510 to 550 nm).[19] Fleas jump when their light source is suddenly interrupted (e.g., by a moving host).

Female adult fleas emerge several days before male fleas and are not ready to mate for several days. It is generally believed that the different emergence times help ensure that females mate with males from other flea populations, thereby reducing the likelihood of inbreeding.

Sticktight Flea (*Echidnophaga gallinacea*)

The sticktight flea is primarily a pest of gallinaceous and passerine birds but also infests various rodents worldwide[20] (Figure 1C). It has been found on peridomestic animals such as rats, opossums, skunks, raccoons, foxes, and coyotes, as well as cats and dogs.[21] In fact, it may hold the record for the most hosts in the Siphonaptera. In a study in southern California, most *E. gallinacea* were collected from feral cats in the spring.[21] Because of the adult's unique feeding habit of attaching and imbedding into the host's skin, cats most likely encounter these fleas when exploring animal burrows, nests, and dens of infested animals.

E. gallinacea can be a serious pest of domesticated chickens and has been reported to infest Florida scrub-jays,[22] reducing hematocrit levels to the point of anemia in severely infested birds. Infested birds were more likely to die than noninfested birds. In the western United States, *E. gallinacea* is commonly found on the California ground squirrel, *Spermophilus beecheyi*. This host is an important plague reservoir, but *E. gallinacea* has not been shown to be a vector for sylvatic plague.[21]

E. gallinacea is better adapted to xeric conditions than two other flea species that infest California ground squirrels and is similar to *C. felis*, with 30% to 50% of eggs hatching in conditions with RH as low as 31%.[21] In studies, larvae did not develop when the RH was <55%. Adults typically emerged from cocoons within 32 days at 70°F and 64 days at 60°F, and there appeared to be no quiescence in this stage like that in *C. felis*.[21] Like *C. felis*, female fleas develop faster and emerge from cocoons before males.

Adult female fleas attach themselves to the host and remain affixed where mating and oviposition occur. It is generally believed that the enlarged blades of their mandibles allow their attachment. They attach to lightly feathered or bare areas of skin (e.g., wattles) on birds or lightly haired areas such as the ventrum, eyelids, ears, and muzzle of mammals. Attachment around the eyes can lead to hyperkeratinization and perivascular mononuclear cell infiltration of the dermis.[23]

Pulex simulans and *Pulex irritans*

Considerable confusion in the literature exists regarding *P. simulans* and *P. irritans* because of the difficulty in identifying them. Many of the older literature citations with host records of the human flea, *P. irritans* (Figure 1D), probably refer to *P. simulans*. *P. irritans* infests hedgehogs and pigs and, consequently, humans who tend pigs. This may explain the misleading common name given to this species, since humans are not known hosts of any species of flea. Both *P. simulans* and *P. irritans* have been collected from swift, red, gray, and kit foxes.[24] They have also been collected from cats and dogs, especially animals permitted to roam in rural habitats. Cats probably obtain these fleas when visiting host nesting sites containing emerged adults.

P. simulans is an aggressive biter, and the bite is readily felt by humans. *P. simulans* is commonly found

on black-tailed prairie dogs (*Cynomys ludovicianus*) and is recovered from their burrows with greatest abundance in the fall.[25] Black-tailed prairie dogs are particularly susceptible to sylvatic plague, making *P. simulans* a potential vector to feral cats.

IMMUNOLOGIC REACTIONS TO FLEA BITES

Flea bite hypersensitivity (FBH) and flea allergy dermatitis (FAD) are two common feline responses to flea bites.[26] Cats with FBH typically have immediate reactions, whereas those with FAD have delayed hypersensitivity reactions. In cats with FBH or FAD, flea bites result in intercellular edema of the epidermis with an underlying infiltrate containing lymphocytes and white blood cells.[27] The immune response is highly variable from one animal to another and can intensify into a severe allergic reaction in affected cats and dogs. The clinical signs of FBH and FAD include miliary dermatitis (crusted papules), symmetrical alopecia, pruritus of the head and neck, and eosinophilic granuloma complex.[26]

TICK BIOLOGY AND LIFE CYCLE

Ticks belong to the class Arachnida and are separated into the families Ixodidae (hard ticks) and Argasidae (soft ticks). There are about 700 species of hard tick and 190 species of soft tick. Unlike fleas, the immature stages (larva and nymph) of ticks require blood meals. Except for *Amblyomma americanum,* nymphs and larvae fall off the host after feeding to molt.[28] The ticks then climb grasses, weeds, brush, and vegetation to wait for passing hosts. Most hard ticks have a three-host life cycle, each stage requiring a new host. Unlike fleas, ticks can survive for months or even years without feeding.[6,28]

The presence and incidence of ticks on cats are not well documented, but most reported species are hard ticks. *Rhipicephalus sanguineus*, *A. americanum*, *Dermacentor variabilis*, and *Ixodes scapularis* were documented on only 2.5% (5/200) of feral cats in Florida.[9] In an 8-year (2000 to 2007) survey in Kansas, *A. americanum*, *D. variabilis*, and *Otobius megnini* were the only ticks collected from cats.[a]

TICK SPECIES OF IMPORTANCE IN DOMESTIC CATS

Lone Star Tick (*Amblyomma americanum*)

Lone star ticks inhabit canopied or open-story woodlots of the southeastern and mid-central states. However, their range has been increasing, with reports in northern states such as Michigan, New York, and Maine.[6,28] This spread has been partly explained by the increase of white-tailed deer in urban and rural habitats. Nymphs and adult males are typically found in shaded areas, whereas adult females occupy adjacent sunlit areas.[29] These ticks feed on a wide variety of hosts, but the striped skunk, raccoon, and opossum are three species with large home ranges that might also be expected in urban settings.

American Dog Tick (*Dermacentor variabilis*)

The American dog tick inhabits grassy meadows, woodland areas, and spaces along roadways and trails.[6] Its range extends up the east coast of the United States, from Florida to southern New England, westward to the Plains states. Populations also extend along the Pacific Coast. Larval ticks feed on small rodents.[6] Nymphs feed on a variety of small mammals, including cats, dogs, opossums, and raccoons. Life cycles can vary from 3 months to 2 years depending on host availability and climate.

Ear tick (*Otobius megnini*)

The ear tick is typically found in the western and southwestern United States, in drier habitats than *Dermacentor* and *Amblyomma* spp. As its accepted common name suggests, the larvae and nymphs of this soft tick attach to the ears of their host for about 30 days. Engorged nymphs fall from the host and molt into adults. Adults do not feed, and mating and oviposition occur off the host. The entire life cycle is completed in 62 to 107 days.[29,30]

[a]Dryden MW. Personal communication. 2010.

DISEASES TRANSMITTED BY FLEAS AND TICKS

Adult male and female fleas require blood meals. In acquiring blood from their hosts, fleas are exposed to various animal and human pathogens. Fleas that spend much of their time in host burrows and nests, such as the oriental rat flea, *Xenopsylla cheopis* (Rothschild; Figure 1E), and the ground squirrel flea, *Oropyslla montana* (Baker), are likely to transfer pathogens to other hosts that visit these sites. Fleas such as the sticktight flea or chigoe flea, which remain affixed to their hosts, are less likely to horizontally transfer pathogens. However, fleas with numerous potential urban hosts, such as the cat flea or *Pulex* spp, may acquire pathogens and ultimately transfer them to cats. Ticks transmit a limited number of diseases to cats. *Cytauxzoon felis* is the primary tick-transmitted pathogen of concern in this species. Cat owners should be educated about the potential risk of exposure to vector-borne diseases, especially when their pets are allowed to roam outdoors in rural areas.

FELINE HEMOTROPIC MYCOPLASMA

Feline hemotropic mycoplasma can be caused by any of three bacteria: *Mycoplasma haemofelis*, "*Candidatus* Mycoplasma haemominutum," and "*Candidatus* Mycoplasma turicensis." These bacteria attach to red blood cells, ultimately causing their destruction by the host cat's immune system. This removal of red blood cells can lead to anemia. *M. haemofelis* is considered to be the most pathogenic species and most likely to cause clinical disease.[31]

Cat fleas have been reported as testing positive for "*Candidatus* M. haemominutum" and "*Candidatus* M. turicensis" with PCR analysis.[32,33] Fleas have been suggested as vectors of these bacteria, but transmission has occurred in areas where fleas or ticks are uncommon.[31,34] Cat-to-cat transmission through bite wounds and fighting injuries may also be an important avenue.[32]

CAT-SCRATCH DISEASE

Bartonella henselae is a gram-negative bacterium that is the causative agent of cat-scratch disease, also known as *cat-scratch fever* in humans. While cats are the primary reservoir and vector of this pathogen and infection is widespread in both pet and feral cat populations, cats show few clinical signs of disease.[35] It is unclear at this time whether *Bartonella* infection has any long-term consequences in cats.[36] The bacteria are shed in flea feces and are believed to enter humans through open wounds, scratches, or bites.[37] Clinical signs include reddening or a pustule at the scratch site within 7 to 12 days. Other signs include fever and mild headache. Swelling of the lymph nodes may last for several months and is common in children and young adults.

The number of human cases is probably underreported because cat-scratch disease is not a nationally reportable disease. However, veterinary professionals should avoid arthropod bites and feces, animal bites and scratches, and direct contact with body fluids of sick animals.[36] At least six species or subspecies of *Bartonella*, including *B. henselae*, are of concern. *Bartonella clarridgeiae* has also been detected in cats and humans. Cat blood samples (n = 92) revealed that about 12% were seropositive for *B. clarridgeiae*.[38] *C. felis* may serve as a vector of this bacterium.[35]

Cat owners should be educated about the risk of exposure to vector-borne diseases, especially when their pets are allowed to roam in rural areas.

FLEA-BORNE TYPHUS

With the advent of molecular tools such as polymerase chain reaction (PCR), the existence of flea-borne typhus caused by *Rickettsia felis* was discovered. Although *R. felis* was originally classified in the typhi group, there is evidence to suggest that it belongs in a transitional group. The prevalence of *R. felis* mirrors the distribution of *C. felis*.[39] Cats are probably not an effective reservoir, but *R. felis* can be maintained in cat fleas by vertical

transmission from one developmental stage to another or from adult fleas to eggs. *C. felis* is the primary vector.[38] *R. felis* DNA was recovered from 18% of opossums in a recent survey in California.[40] In one study, about 26% of adult *E. gallinacea* tested positive for *R. felis* and *Rickettsia typhi*. About 11% of pools of *P. irritans* have been reported to be positive for *R. felis* and *R. typhi*.[40] Transmission of rickettsiae in flea saliva during feeding is the most likely route. Larval fleas may also acquire *R. felis* when feeding on infected adult flea feces or cannibalizing infected eggs or immature larvae.[38]

Human plague cases have been associated with cats infected with Yersinia pestis.

Human cases of flea-borne typhus have been reported in a number of countries. The signs are typically milder than those of murine typhus, with fever, malaise, and myalgia being among the clinical signs.[27] Flea bites and close contact with infected animals are the primary means of transmission to humans.

MURINE TYPHUS

R. typhi is a gram-negative obligate intracellular bacterium that requires mammals and blood-feeding arthropods to complete its life cycle. It is the causative agent of murine typhus, which is characterized by high fever, headache, chills, and malaise beginning about 6 to 14 days after exposure.[37] Typically, it is spread from rats to other rats and to humans by the oriental rat flea, *X. cheopis*. However, *C. felis* has also been reported to be a vector. Roof and Norway rats are typically the primary reservoirs, but in urban areas, cats, dogs, and opossums may also play an important role.[41,42] Humans are infected when bacteria from fecal blood enter abraded skin or wounds from flea bites. The US incidence of human infection with *R. felis* or *R. typhi* is largely guesswork because these infections are not reported nationally. In Hawaii, only 1.9% of the oriental rat fleas collected from house mice, *Mus musculus*, were positive for *R. typhi*; 24.8% were positive for *R. felis*.[43] It is possible that *R. felis* was the causative agent in some previous reports of murine typhus.

Of 1200 pools of *C. felis* tested, about 21% were positive for *R. felis* or *R. typhi*.[40] However, cats do not appear to show any clinical signs of infection. Opossums in urban areas have been shown to be reservoirs of *R. felis* and *R. typhi* and may play a role in transmission to humans.[44] In Corpus Christi, Texas, 8% and 22% of tested opossums were seropositive for *R. typhi* and *R. felis*, respectively. More than 99% of the fleas collected from opossums in Texas were *C. felis*, of which 2.6% were positive for *R. typhi* and *R. felis* (3 and 11 fleas, respectively). Interactions between opossums, cats, and fleas may be important means of transferring rickettsial diseases in urban environments.

PLAGUE

Plague is a bacterial disease caused by *Yersinia pestis*, a gram-negative coccobacillus. In the United States, the disease is found in rodents such as ground squirrels, prairie dogs, chipmunks, and wood rats and in carnivores that prey on them. About 80% of human plague cases in the United States result from bites by infectious fleas.[45] *X. cheopis* and *O. montana* are considered to be primary vectors. Recent studies suggest that "early-phase" transmission may occur during the first few days after fleas acquire *Y. pestis* and before the flea gut is blocked. This greatly increases the number of potential flea vectors.[46]

In a 21-year period (1977 to 1998), 23 documented human plague cases were associated with cats infected with *Y. pestis*.[45] Plague epizootics were noted to have occurred in ground squirrels, prairie dogs, chipmunks, and wood rats in 47.8% of the sites where infected cats were found. However, transmission to humans was probably not via fleas. Additional vigilance in the future is warranted because of the increasing urbanization in the southwestern United States and the increased likelihood that free-roaming cats will encounter infected fleas or consume *Y. pestis*–infected animals.

While *C. felis* are capable of transmitting *Y. pestis*, the number required to maintain person-to-person transmission is very high (25 fleas per person) compared with *X. cheopis* (4.7 to 7.8 fleas per person). In Africa, the prevalence of *C. felis* indoors and occasionally infesting both roof rats and Nile rats increases the likelihood of transmission to humans.[47] *P. irritans* is also thought to be a potential vector, but standardized vector competency and efficiency studies have yet to be done.[46] *P. simulans* was collected from 95% of swift foxes (*Vulpes velox*) surveyed in a plague area.[48] Twenty-four percent of the foxes were seropositive for plague, but none of the fleas showed evidence of *Y. pestis*. However, in another

study, 8% of *P. simulans* tested positive for *Y. pestis;* therefore, this flea species may play a role in transmission to predators.[25]

TAPEWORM INFECTION

C. felis and *P. irritans* are intermediate hosts of the dog tapeworm, *Dipylidium caninum*.[49] Tapeworm eggs are voided in the feces of infected animals and consumed by flea larvae. The immature tapeworms develop in the body of the flea. Cats consume adult fleas during grooming, releasing the cysticercoids and thereby becoming infected. A survey of *C. felis* in Austria found that 2.3% were infected with *D. caninum.*[50] It has been my experience that the number of field-collected adult fleas infected with cysticercoids is less than 1%.

Humans, especially children, who swallow infected fleas or cysticercoids (e.g., if a pet with cysticercoids on its tongue licks a person's mouth) can be infected with tapeworms. More than 80% of human patients with tapeworms are <8 years of age.[49]

CYTAUXZOONOSIS

Cytauxzoon felis is a tick-transmitted protozoan parasite of cats in the southeastern and south-central US.[51] Cytauxzoonosis is characterized by fever, anorexia, listlessness, anemia, and jaundice and is particularly lethal to cats. The bobcat, *Lynx rufus*, is the natural reservoir for *Cytauxzoon felis*. Both the American dog tick and the lone star tick have been confirmed as vectors.[52] In wild-collected *A. americanum*, the minimum infection rate of *Cytauxzoon felis* was 0.5% to 1.5%, depending on the sex and stage of the tick.[52] Cats become infected when they interact with bobcats and tick vectors.[51] Urban edge habitats and areas close to natural or unmanaged spaces may be important locations where bobcats, free-roaming domestic cats, and tick vectors interact.[51,53] Chronically infected free-roaming cats could serve as a reservoir for *Cytauxzoon felis* in urban areas.[51] In endemic areas, minimizing cats' exposure to and regularly checking for ticks seems prudent.

ECTOPARASITE CONTROL

FLEA CONTROL STRATEGIES

Recent advances in detecting and understanding vector-transmitted pathogens have made the importance of minimizing exposure to fleas as a means to improve veterinary and public health greater today than it has ever been.[35,36] New products have revolutionized flea control and provided veterinarians and pet owners with a broad arsenal of weapons.

In all integrated control programs, the first step is to identify the pest and understand the biologic and environmental factors contributing to the problem. Adult cat fleas are typically confined to their host, and the immature stages develop in protected microhabitats in the environment. Thus, two distinctly different measures are taken to control fleas: on-animal flea treatments and environmental treatments. While a variety of insecticidal shampoos, dips, sprays, collars, and dusts are available, it is the advent of oral and topical spot-on products that has revolutionized flea control. These products are easy to use, generally fast acting, and provide residual activity for up to 30 days.

While a variety of other flea control products are available, oral and topical spot-on products have revolutionized flea control.

Vacuuming and Flea Traps

With the rise of on-animal treatments in the past 15 years, indoor and outdoor environmental treatments have been largely ignored. However, eliminating fleas in the environment helps to reduce the likelihood of reinfestation and to provide much quicker control. Methods that do not involve pesticides include vacuuming and using flea traps. Vacuuming kills eggs, larvae, and adult fleas and eliminates them from carpeting. Fleas do not survive in the vacuum bag, so additional steps to kill the fleas in the bag (e.g., freezing, discarding, adding insecticides to the bag) are not necessary.[54] Intensive vacuuming stimulates adults to emerge from cocoons and eliminates them from inside the home. Vacuuming does not affect the residual activity of sprays applied to potential flea breeding sites. In one study, traps using a green-yellow light on a cycle of 10 minutes on, 5 seconds off collected more than 86% of the fleas in a room over a 20-hour period.[19] However, not all flea traps are effective in trapping adult fleas.

Indoor Sprays and Aerosols

The effectiveness of most sprays and aerosols applied indoors to control adult fleas is limited. However, sprays containing the insect growth regulators (IGRs) methoprene and pyriproxyfen prevent eggs from hatching, disrupt larval development, and affect the survival of emerged adults. A study of the mortality of adult fleas emerging from pupae inside cocoons sprayed with methoprene and pyriproxyfen found that these IGRs killed 45.8% and 48.4% of emerging fleas, respectively.[55] Methoprene and pyriproxyfen are extremely active against immature stages and provide residual activity for months. A combination of vacuuming and an indoor application of an aerosol with an IGR provided control for at least 60 days in one study.[56]

Outdoor Treatments

In recent years, a need has developed for additional outdoor treatments. Areas frequented by feral hosts and cats, such as crawl spaces under mobile home trailers, houses, temporary structures, and modular buildings, have proven especially difficult to control with existing products. Many active ingredients in the on-animal products are not registered or effective for flea control outdoors. However, pyriproxyfen has been shown to have good residual activity when applied outdoors and is an effective way of treating larval breeding sites.

On-Animal Treatments

Oral and topical treatments have revolutionized cat flea control on cats and dogs. Some products provide contact kill of adult fleas, whereas others require fleas to ingest the active ingredient.[6,8,57] Some products have been combined with the IGRs methoprene or pyriproxyfen. Pyriproxyfen applied to cat hair is extremely active, with as little as 0.1 ppb inhibiting egg and larval development[58] and having a residual activity of at least 8 weeks.[59] Continuous exposure to pyriproxyfen is lethal to adult fleas, with 100% kill being achieved in about 7 days.[60] Methoprene provides similar residual activity when applied to cats.[61] The IGRs remain active long after the residual activity of the adulticide has dissipated.

Cats are particularly sensitive to some insecticides, such as permethrin and fenvalerate.[62] The feline liver cannot conjugate pyrethroid metabolites with glucuronide, and cats' small body mass, high hair density, and grooming habits probably contribute to the toxicity. There are reports of cats acquiring toxic doses from the hair of treated dogs. Newer active ingredients exploit physiologic differences between insects and mammals and provide a wider margin of safety.[63] Insecticides such as imidacloprid, nitenpyram, and dinotefuran target the insect nicotinic acetylcholine receptors (nAChRs) and have a low affinity for vertebrate nAChRs; thus, they provide a margin of safety when applied to cats.[64] Even so, pet owners should carefully read and comply with all label directions. Products labeled for use on dogs should never be used on cats.

Active ingredients that rapidly inhibit and prevent flea feeding or that repel fleas may be especially important for animals with FAD and in preventing disease transmission.[65] When fleas are confined to a cat, they can ingest a quantifiable amount of blood within 5 minutes. However, substantial blood consumption does not occur until about 2 to 4 hours after the cat is infested.[66] Imidacloprid and fipronil did not totally prevent fleas from feeding within 1 hour after being released on treated cats.[66] It remains to be seen how quickly flea feeding must be suspended in order to prevent disease transmission.

Rapid inhibition or prevention of flea feeding may be especially important for animals with FAD.

In addition to having direct effects against adult cat fleas and eggs on the host, many flea treatments indirectly control the flea population by contaminating the fleas' developmental microhabitats. Debris from dogs treated with imidacloprid reduced the numbers of pupae and adults in rooms by 98.6% for 4 weeks.[67] Spot-on treatments of pyriproxyfen on cats resulted in 88% of the cats being free of fleas at day 180.[68]

TICK CONTROL STRATEGIES

Control of ticks on cats is challenging because of the limited number of active ingredients that kill or repel ticks[69] and the limited number of pesticides that can be safely applied to cats. Fipronil and etofenprox are registered for tick control on cats. Fipronil applied to cats provided control for 30 days against *Ixodes ricinus*.[70]

Tick control in the environment is nearly impossible unless drastic alterations of vegetation and feral hosts can be achieved. In the case of cats, the most effective strategy might be to confine them indoors during tick season and prevent them from accessing woodlots, fields, and other areas likely to harbor ticks.

EPA SAFETY AND APPROVAL CRITERIA FOR SPOT-ON REGISTRATIONS

Ectoparasiticides used on cats are approved and regulated by the FDA or the EPA. Unlike FDA-regulated ectoparasiticides, which generally require a prescription, EPA-regulated ectoparasiticides can be available through veterinary channels or through retail outlets.[71] This has led some to assume that there is an inherent difference in safety between EPA-regulated ectoparasiticides that are sold through veterinarians and those that are not. To clarify the facts, the FDA and the EPA approval and regulation processes are detailed below.

The FDA regulates active ingredients that are systemically distributed as they exert their effects. These agents are classified as drugs and can be administered by various routes (e.g., spot-on, oral, injectable). Examples of FDA-regulated parasiticides include nitenpyram and selamectin. The FDA approval process involves submission of specific drug information to the FDA's Center for Veterinary Medicine (CVM). A new animal drug application (NADA) is complex, requiring submission of (1) important background information for the drug, including chemical composition, manufacturing processes, and labeling specifics and (2) a Freedom of Information (FOI) summary, which includes the efficacy and target animal safety data.

The EPA regulates (1) ectoparasiticides that remain within the layers of the skin and do not exert their effect through systemic absorption and (2) the effect of chemical agents on soil, air, and water quality.[71] All EPA-approved ectoparasiticides are subjected to rigorous safety testing before being registered (see chart below[71,72]). They must demonstrate on-animal efficacy and safety, which are evaluated through several exposure routes, including required companion animal safety studies.[72] Acute oral, acute dermal, and acute inhalation studies evaluate active ingredients for systemic toxicity. Primary eye and primary skin irritation studies evaluate irritation or corrosion associated with exposure, and a dermal sensitization study evaluates the potential for allergic contact dermatitis associated with exposure to the parasiticide.[73] Each chemical tested receives a score for each safety evaluation.

The EPA then uses results from five evaluations—acute oral, acute dermal, acute inhalation, primary eye irritation, and primary skin irritation—to assign an overall safety profile designation for regulated agents. The overall safety profile designation is contingent on the worst category score across all five safety tests and is indicated by a Roman numeral. This categorization then determines what level of precautionary language (called *signal words*) is required to appear on the product label[73]:

I = Danger
II = Warning
III = Caution
IV = No signal word required; "Caution" is acceptable

A signal word is required on all EPA-registered pesticides, except for Category IV, and must be displayed on the front label, in other precise locations on the product's label, and on other informational documents pertaining to the product. Category IV is considered the least severe toxicity category, whereas Category I is considered the most severe category

Summary of EPA Registration Considerations[71,72]	
Approval process	APR (Application for Pesticide Registration) submitted to the EPA
Active ingredient distribution (mode of action)	Concerned with chemicals that are applied topically and that are not systemically absorbed
Active ingredient safety	Safety of active ingredients is tested on target animals and in laboratory animals
Active ingredient efficacy	Practical efficacy on target animals is required
Product availability	No prescription required; products may be available over the counter through veterinary channels or through retail outlets at the discretion of the manufacturer

assignment. Table 1 (page 18) lists the EPA's overall toxicity classification categories for several active ingredients of feline flea and tick products. Appendix I (page 28) provides a summary of commonly used EPA-registered feline spot-on flea and tick control products, and Appendix II (page 32) provides an overview of potential toxic effects and treatment guidelines for some of the major active ingredients.

The EPA also has a reregistration process for chemical agents that were licensed for use before 1984.[74] The reregistration eligibility decision (RED) is a comprehensive review of older pesticides and is conducted to help ensure that these chemicals continue to meet current industry health, environmental, and safety standards. The current EPA safety standards for pesticides also incorporate standards outlined in the Food Quality Protection Act of 1996. The RED process includes a thorough review of the entire scientific database underlying an agent's registration to determine whether that agent is eligible for reregistration and continued use.[75] Some newer products that were approved since 1996 are not subject to the current RED process and instead will be reviewed in the future under a new registration review program. The EPA reviews pesticides every 15 years using updated testing, scientific, and regulatory standards in an effort to protect the general public and the environment.

EPA-registered flea and tick products are tested and monitored rigorously, since all of them can be sold over the counter directly to the final consumer. As with any drug or product, the user has the responsibility of reading the product information and using the product appropriately to minimize the risk for treatment failure and other adverse events. Even if clients choose to purchase flea and tick control products outside of veterinary channels, veterinary professionals can still help educate clients about selecting products and using them appropriately. The best sources for information about EPA-regulated parasiticides, including safety warnings and toxicity information, are the veterinarian and the package or product information sheet for that specific product.

TABLE 1.
Summary of Active Ingredients in Feline EPA-Registered Spot-On Flea and Tick Products

Class/ Chemical/ Mode of Action	Acute Oral LD_{50} (Rat) (mg/kg)*	EPA Acute Oral Toxicity Class	Acute Dermal LD_{50} (Rat) (mg/kg)*	EPA Acute Dermal Toxicity Class	Overall Active Ingredient Safety Profile Designation†	EPA Registration No.	EPA Registration Date‡
Ether Pyrethroid: Sodium channel modulator							
Etofenprox	>5000[a]	IV	>2100[a]	IV	III[b]	33657-6[a]	September 2001[a]
Neonicotinoid: Nicotinic acetylcholine receptor agonists							
Dinotefuran	>5000[c]	III	>2000[c]	III	II	33657-10[d]	December 2006[d]
Imidacloprid	450[e]	II	>5000[e]	IV	II	264-755[d]	March 1996[d]
Phenylpyrazole: GABA-gated chloride channel antagonist							
Fipronil	97[f]	II	>2000[f]	III	II	7969-243[d]	June 1996[d]
Semicarbazone: Voltage-dependent sodium channel blocker							
Metaflumizone	>5000[g]	IV	>5000[g]	IV	III	7969-226[d]	August 2007[d]
Insect Growth Regulator: Juvenile hormone mimics							
Pyriproxyfen	>5000[c]	IV	>2000[c]	III	III	1021-1864[d]	February 1996[d]
(*S*)-Methoprene	>5000[h]	IV	>3038[h] (rabbit)	III	III	2724-442[d]	June 1995[d]

*Toxicity information (oral LD_{50} and dermal LD_{50}) contained in this table may vary for a particular active ingredient depending on the concentration of that ingredient in the final commercial product and the combined effect of other active ingredients within the same formulation. Practitioners are advised to consult the package information, product manufacturer, or the ASPCA Poison Control Center (888-426-4435) for more specific toxicity data.

†Overall active safety designations include: Class I, Danger; Class II, Warning; Class III, Caution; Class IV, no signal word required. Designations are based on five tests: acute oral toxicity, acute dermal toxicity, acute inhalation, primary eye irritation, and primary skin irritation.

‡Date of first use in a companion animal flea and tick control product. Products that were approved since 1996 are not subject to the current RED process and will be reviewed in the future under a new registration review program.

a. Etofenprox technical formulation acute oral LD_{50} (rat) = 42,880 mg/kg. US Environmental Protection Agency. Report on acute toxicity study of MTI-500 (ethofenprox) in rats. Data Evaluation Report. November 10, 1987. Accessed 12/22/10 at http://www.epa.gov/pesticides/chemical/foia/cleared-reviews/reviews/128965/128965-001.pdf.

b. McAndrew E. United States Environmental Protection Agency Memorandum February 4, 2009; Pesticide Product RF2042[CDSO]. http://www.epa.gov/pesticides/chemical/foia/cleared-reviews/reviews/128965/128965-105402-067501-2009-02-04a.pdf. Accessed 10/19/10.

c. Vectra 3D Material Safety Data Sheet. Accessed 10/21/10 at www.summitvetpharm.com/File/MSDS%20Vectra%203D.pdf.

d. National Pesticide Information Retrieval System. West Lafayette, IN: Purdue University. Databases available by subscription at http://ppis.ceris.purdue.edu/htm/databases.htm.

e. Lynn RC. Antiparasitic drugs. In: Bowman DD, ed. *Georgi's Parasitology for Veterinarians*. 9th ed. St. Louis, MO: Saunders; 2009: 254-294.

f. Frontline Top Spot Material Safety Data Sheet. Accessed December 2010 at http://www.freshpets.com/v/vspfiles/assets/pdfs/ZX390.pdf.

g. Backus BT. United States Environmental Protection Agency Memorandum June 10, 2005; EPA File Symbol: 80490-G Promeris Spot-On for Cats. Accessed 12/22/10 at http://www.epa.gov/pesticides/chemical/foia/cleared-reviews/reviews/281250/281250-2005-06-10a.pdf.

h. (*S*)-Methoprene technical formulation acute oral LD_{50} (rat) = 34,600 mg/kg. Advisory Committee on Pesticides. *Evaluation on S-Methoprene*. 1993. Accessed 10/26/10 at www.pesticides.gov.uk/PSD_PDFs/Evaluations/085_s-methoprene_(1).pdf.

SPOT-ON PARASITICIDES: THE CHEMICAL CLASSES

In the past 15 years, the advent of new chemistries has led to a paradigm shift in the way flea control is practiced. Previously, a flea problem required a combination of on-animal and premise treatments, but now many practitioners primarily recommend on-animal products alone. However, in situations where feral animals are infested and serve as a potential source for reinfesting domestic pets, on-animal treatments may not be enough to provide complete control. Treatment strategies that incorporate compounds with different modes of action are often necessary to eradicate flea infestations, especially outdoor infestations. Given the variety of available products, veterinarians need to understand the various chemical classes of parasiticides and how their mechanisms of action differ.

Before the current spot-on treatments were introduced, IGRs were used to kill the immature stages of fleas on animals and in the environment.

An integrated approach to flea control, which uses two compounds with different mechanisms of action, may include an adulticide, which kills newly acquired fleas, combined with an IGR having ovicidal and/or larvicidal activity. This approach breaks the flea life cycle at multiple stages for enhanced flea control. Advances in tick control products for cats have led to the development of several spot-on formulations with combined efficacy, so that a single active ingredient (e.g., etofenprox) targets fleas as well as ticks.

Multiple flea products may be recommended for heavy infestations or to control severe environmental infestations. Cats are particularly sensitive to many organophosphate, carbamate, and pyrethroid insecticides, and care should be taken when suggesting environmental treatments. Pet owners need to read labels of insecticides to be used in and around the perimeter of their home to be sure that they are safe for cats.

Although the issue of whether insecticidal resistance affects current on-animal therapies is controversial, it is important to use flea control products judiciously to help minimize and delay the development of resistance to our current arsenal of products. To help delay resistance, veterinarians could periodically alternate or rotate flea products with different mechanisms of action. The mode of action of the active ingredient, not the product's commercial name, is the key to selecting an alternative product. Pet owners should be advised to use all ectoparasiticide products in a responsible manner that is consistent with label recommendations. Veterinary professionals have an important role in educating pet owners on the safe and effective use of insecticides to control fleas.

The following is an overview (not an all-inclusive listing) of the major parasiticide chemical classes and their mechanisms of action. This monograph focuses solely on EPA-approved active ingredients used in feline spot-on products.

Currently, all the spot-on adulticides target the parasite's nervous system. These active ingredients can be divided into two broad categories based on the site where nerve function is affected:

- **Synaptic insecticides** moderate or block neurotransmitters, affecting the nerve impulse conduction between neurons
- **Axonal insecticides** affect ion influx along the nerve axons, which in turn influences the nerve impulse

Rather than affecting nerves, the topical IGRs, which target developing flea stages, raise hormone levels in the insects.

PYRETHRINS AND PYRETHROIDS

Pyrethrins are natural adulticides derived from the pyrethrum plant (*Chrysanthemum cinerariaefolium*) or related species. Pyrethrins are typically combined with synergists such as piperonyl butoxide (PBO) or N-octyl bicycloheptene dicarboximide (MGK 264) to enhance their activity. These botanicals provide fast insect

knockdown with low mammalian toxicity, but they tend to break down when exposed to air, moisture, and sunlight.[62,69,71,76] In recent years, pyrethrins have largely been replaced by synthetic pyrethroids, which retain the knockdown activity of pyrethrins but have been modified to provide greater potency and longer residual activity.[69,77] Although pyrethroids have many proposed mechanisms of action, all these agents primarily work by disrupting the voltage-sensitive sodium channel function in the nerve axons of the peripheral and central nervous system of the arthropod.[62,78] During normal arthropod nerve function, the voltage-gated sodium channels open and allow an influx of sodium ions, which produces a nerve impulse. The sodium channels then close to terminate the nerve signal. Pyrethroids exert their influence by preventing the sodium channel from closing.[71] The effectiveness of natural pyrethrins and pyrethroids has been adversely affected by the widespread development of insecticide resistance in cat fleas.

Compared with dogs, cats are more sensitive to pyrethroids because cats cannot effectively clear chemicals by hepatic glucuronidation.[77] Consequently, some pyrethroids, such as permethrin and phenothrin, are labeled for use in dogs only. If a cat grooms a recently treated dog, or an owner inadvertently applies a canine product to a cat, pyrethroid toxicosis can occur.

Etofenprox has been shown to be safe for application on cats.[79] Etofenprox differs from most pyrethroids because it contains an ether and not an ester bond, lacks a cyclopropane moiety and an alpha-cyano moiety, and is not halogenated. These molecular differences enhance the mammalian safety profile for ether pyrethroids.

NEONICOTINOIDS

Nicotine has been used as a natural insecticide since the 1700s. Just as synthetic pyrethroids are modeled after botanical pyrethrins, neonicotinoids are synthetic compounds based on the activity of natural nicotine. The neonicotinoids developed in the early 1990s are the only new major class of insecticides in the past 3 decades. They offer greater insecticidal activity and lower mammalian toxicity than natural nicotinoids.[71,78]

Neonicotinoids are synaptic insecticides that mimic the actions of the excitatory neurotransmitter, acetylcholine, at nAChRs in the insect central nervous system. Normally, acetylcholine is released from the presynaptic membrane and binds to the postsynaptic membrane, resulting in the depolarization of the neuron and propagation of a nerve impulse. Following the nerve impulse, acetylcholine is degraded by acetylcholinesterase and is removed from the receptor.

Like acetylcholine, neonicotinoids bind to postsynaptic nAChRs, but neonicotinoids lock the receptors in the open position. The resultant increase in the frequency of spontaneous discharge is followed by a block in the nerve impulse. This overstimulation of the cholinergic synapses leads to hyperexcitation and eventual paralysis and death of the parasite.[71,78] Some neonicotinoids, such as imidacloprid, are 500 times more active against nAChRs in insects than mammals, which minimizes potential animal toxicities and increases their safety factor.[71,80]

PHENYLPYRAZOLES

Phenylpyrazoles are synaptic adulticides with activity against fleas and ticks. Fipronil, the first chemical agent in this category, was introduced in the United States in 1996.[71]

Normally, GABA functions as an inhibitory neurotransmitter in the arthropod central nervous system. When released from a presynaptic nerve terminal, GABA binds to a postsynaptic receptor, causing the chloride ion channel to open. Chloride ions flow into the postsynaptic neuron, thereby diminishing nerve impulse firing.

Fipronil antagonizes the damping effects of GABA by binding to the GABA receptors in neurons and blocking the flow of chloride.[71,78] This results in nerve hyperexcitation and death of the arthropod.

SEMICARBAZONES

Metaflumizone works as a novel sodium channel blocker and is the first chemical agent in this class of axonal adulticides.

In normal insect nerve function, the influx of sodium ions in the nerve axon leads to the propagation of a nerve impulse. Metaflumizone binds to the voltage-dependent sodium channels in the axon and blocks the flow of sodium ions across the nerve cell membrane. As a result, nerve impulses fail to propagate, resulting in paralysis and death of the parasite.[81]

INSECT GROWTH REGULATORS

Because adult fleas account for only a small percentage of the parasite population and the flea life cycle, IGRs were introduced in the 1980s and 1990s to address the developmental flea stages found in the environment.[71]

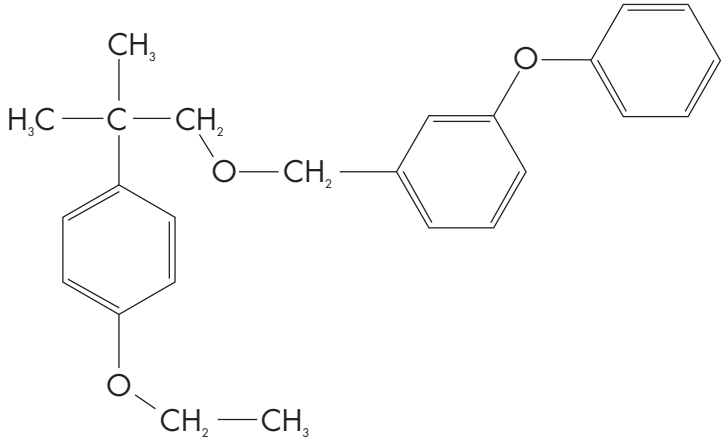
IGRs interfere with the growth and development of the immature flea stages—the eggs, larvae, and pupae.[71] Because these agents do not kill the adult flea directly, they are often combined with an adulticide for more rapid control of established flea infestations.

The IGRs currently used in topical flea products, such as (*S*)-methoprene and pyriproxyfen, are categorized as juvenile hormone analogues because they mimic the activity of naturally occurring hormones in the flea. During normal flea development, enzymes in the flea's circulatory system destroy endogenous juvenile hormones, allowing the larva to molt to a pupa and then to an adult. Juvenile hormone analogues bind to the juvenile hormone receptor sites, but structural differences protect them from enzyme degradation. As a result, these chemicals arrest flea development by preventing insects from molting to the next stage.[69] When applied to indoor carpets, methoprene and pyriproxyfen provided control of cat flea larvae for >12 months.[82] Pyriproxyfen is stable enough to provide control of cat flea larvae outdoors for 3 weeks.[83]

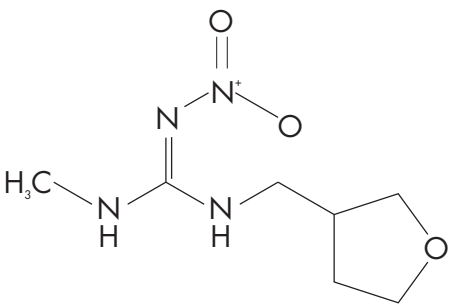
ACTIVE INGREDIENTS OF COMMON ECTOPARASITICIDES

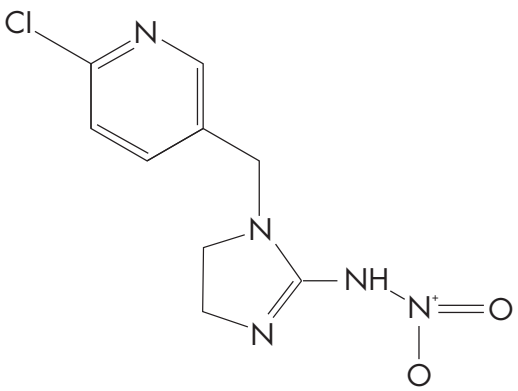
Within each chemical class described in the previous section, there are active ingredients represented in the current EPA-registered spot-on feline ectoparasiticides. Some products contain only one active ingredient, whereas others combine an adulticide with an IGR to expand the spectrum of activity for the product. Interactions (e.g., synergy) between active ingredients can vary, but such a discussion is beyond the scope of this monograph. The following tables summarize the most common active ingredients used in EPA-registered feline spot-on products, describe their modes of action, and indicate absorption and distribution properties. Additional tables listing products that contain these active ingredients and toxicity and/or antidotal information can be found in Appendix I (page 28) and Appendix II (page 32).

ETHER PYRETHROID

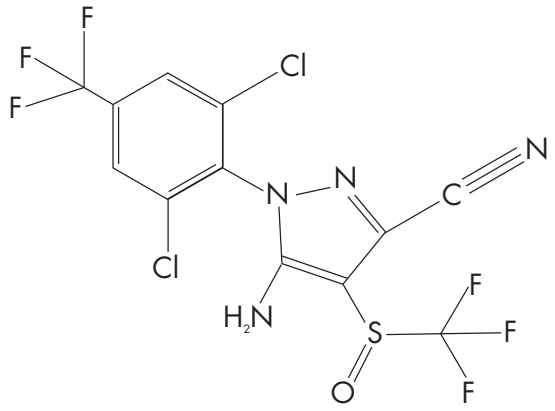
Etofenprox[84–86]	
Molecule	
Molecular Formula	$C_{25}H_{28}O_3$
Classification	Ether pyrethroid (contains an ether moiety, instead of an ester moiety like other pyrethroids; lacks the cyclopropane, alpha-cyano, and halogen moities); sodium channel modulator
Mode of Action	This axonal adulticide affects the parasite's nervous system at the nerve cell sodium channels. While these channels normally close after transmission of a nerve impulse, this chemical keeps the channels open longer. As a result, the nerves keep discharging, leading to death of the parasite.
Absorption and Distribution	After topical application, the agent is dispersed over the entire body surface by translocation. The arthropod is killed by contact, without the need to ingest the active ingredient.

NEONICOTINOID

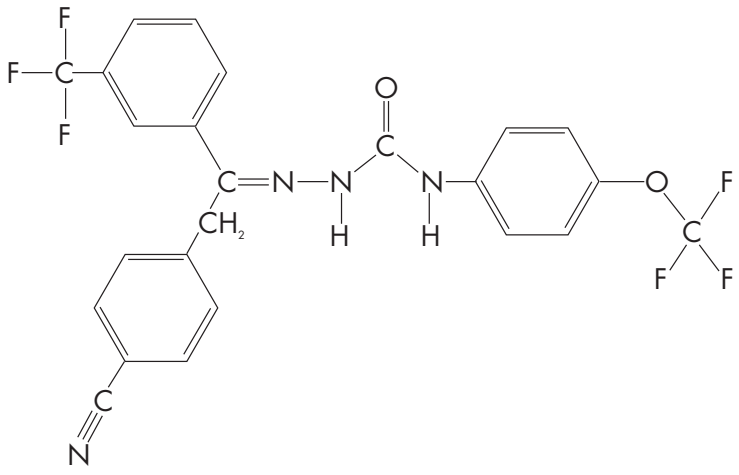
Dinotefuran[71,78,80,87]	
Molecule	
Molecular Formula	$C_7H_{14}N_4O_3$
Classification	Nicotinic acetylcholine receptor agonist/antagonist; third-generation neonicotinoid
Mode of Action	This chemical works as a competitive inhibitor at the nicotinic acetylcholine receptors in the nervous system. Dinotefuran binds to the postsynaptic nicotinic receptor sites, locking the receptor into the open position. The result is hyperstimulation of the nerve cell and ultimately the death of the insect. Unlike other chemicals in this class, which are based on the nicotine molecule, this chemical is derived from the acetylcholine molecule. It binds to unique sites as compared with other neonicotinoids.
Absorption and Distribution	After topical application, the agent is dispersed over the entire body surface by translocation. The insect is killed by contact, without the need to ingest the active ingredient.

Imidacloprid[71,78,80,86–88]	
Molecule	
Molecular Formula	$C_9H_{10}ClN_5O_2$
Classification	Nicotinic acetylcholine receptor agonist/antagonist; neonicotinoid
Mode of Action	This chemical works as a competitive inhibitor at the nicotinic acetylcholine receptors in the nervous system. Imidacloprid binds to the postsynaptic nicotinic receptor sites, locking the receptor into the open position. This results in hyperstimulation of the nerve cell and ultimately the death of the insect.
Absorption and Distribution	After topical application, the agent is dispersed over the entire body surface by translocation. The compound is absorbed through the insect's intersegmental membrane, where it then comes into contact with the insect's nervous system. Imidacloprid is effective against fleas by either contact or ingestion.

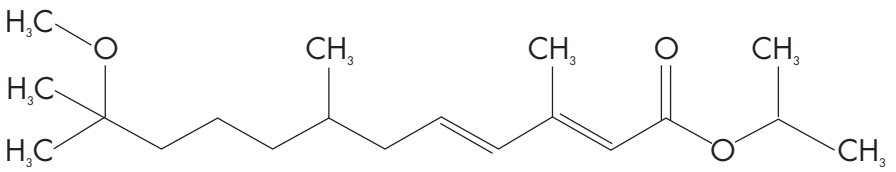
PHENYLPYRAZOLE

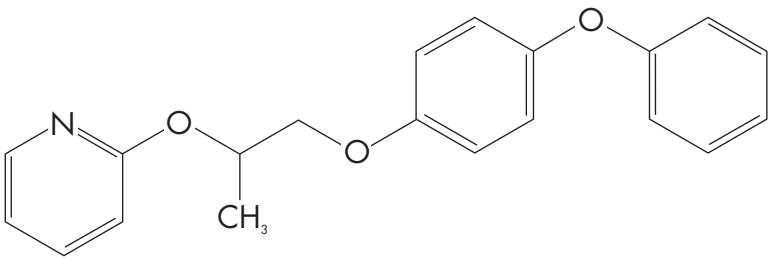
Fipronil[71,78,89–91]	
Molecule	
Molecular Formula	$C_{12}H_4Cl_2F_6N_4OS$
Classification	GABA-gated chloride channel antagonist; phenylpyrazole
Mode of Action	This synaptic adulticide blocks GABA-regulated chloride channels in the postsynaptic neuron, antagonizing the calming effects of GABA. As a result, the arthropod neuron is hyperstimulated, resulting in death.
Absorption and Distribution	After topical application, the agent is dispersed over the entire body surface by translocation. Fipronil collects in the sebaceous glands, hair follicles, and sebum and is continuously secreted from the hair follicles onto the stratum corneum and hair. The chemical is toxic to the arthropods by contact or ingestion.

SEMICARBAZONE

Metaflumizone[81,92]	
Molecule	
Molecular Formula	$C_{24}H_{16}F_6N_4O_2$
Classification	Voltage-dependent sodium channel blocker
Mode of Action	This axonal insecticide blocks the influx of sodium ions, which prevents the propagation of nerve impulses. The result is paralysis and death of the parasite.
Absorption and Distribution	After topical application, the agent is dispersed over the entire body surface by translocation. The insect is killed by contact, without the need to ingest the active ingredient.

INSECT GROWTH REGULATOR

(S)-Methoprene[69,71,93]	
Molecule	
Molecular Formula	$C_{19}H_{34}O_3$
Classification	Juvenile hormone mimic; juvenile hormone analogue
Mode of Action	This chemical mimics the action of juvenile hormone, arresting flea development before the adult stage. (*S*)-Methoprene is directly and indirectly ovicidal, embryocidal, and larvicidal.
Absorption and Distribution	After topical application, the agent is dispersed over the entire body surface by translocation. The insect is affected by contact, without the need to ingest the active ingredient.

Pyriproxyfen[69,71,94]	
Molecule	
Molecular Formula	$C_{20}H_{19}NO_3$
Classification	Juvenile hormone mimic
Mode of Action	This chemical mimics the action of juvenile hormone, arresting flea development before the adult stage. Pyriproxyfen is both ovicidal and larvicidal.
Absorption and Distribution	After topical application, the agent is dispersed over the entire body surface by translocation. The insect is affected by contact, without the need to ingest the active ingredient.

CONCLUSION

Pet owners today have more choices for ectoparasite control than ever before, and the US market for flea and tick control products has risen to the $1 billion mark.[95] The growth of this industry testifies to veterinarians' ongoing efforts to educate their clients about the medical issues surrounding ectoparasite infestation and to diagnose and control parasitic infestations in their patients. However, some owners may feel that products to control fleas and ticks constitute an unnecessary expense, especially in a difficult economy. Increasing client awareness about the health benefits of ectoparasite control for all their family members—animal and human—therefore continues to be important.

From a financial perspective, the cost of preventing flea and tick infestations can be compared with the cost of treating vector-borne disease or dermatologic conditions, such as FAD. However, the greater impact of parasite infestation may be felt in the effect on the human–animal bond. Infestation of the home may lead owners to perceive their pets as inconvenient or to attempt to distance themselves and their family from the pet.[95–98] Added to this is the potential for zoonotic disease that can particularly affect children (tapeworms) or owners who are immunocompromised (e.g., bartonellosis). Measures to prevent transmission of these diseases to humans that involve reducing contact with the pet can decrease the emotional attachment of the owner to the pet, thereby decreasing the benefits of animal companionship.[99] Preventing and controlling ectoparasite infestations may, therefore, have a positive effect not only on animal health but also on owners' commitment to their pets as members of their family.

Because many cats are kept indoors, cat owners may need more education on the potential for parasite infestation than dog owners. They may not take into account factors such as parasites entering the home on their own clothing or on other animals that live in or visit the household and may consider regular parasite control unnecessary for their pets.

Another aspect of client education involves improving compliance, even among owners who have purchased flea and tick control products. Establishing a routine for administering parasiticides may be useful. Fortunately, there are now many products on the market that are safe, effective, and formulated to make administration quick and simple. Spot-on flea and tick control products are preferred by many clients for these reasons.[100] Choosing one from all the available options, however, may be overwhelming or confusing for some owners. Veterinarians can be invaluable in assisting cat owners with choosing a product that is appropriate to their pet's exposure risk, increases the likelihood of compliance, and, most importantly, is formulated for use on cats.

Great strides have been made in increasing pet owner awareness of the health benefits of ectoparasite control,

Because many cats are kept indoors, cat owners may need more education on the potential for parasite infestation than dog owners.

but educational efforts need to continue. Owners of indoor cats, in particular, may not consider their pets to be at risk for medical conditions or diseases associated with fleas and ticks. Use of educational materials, such as Companion Animal Parasite Council recommendations, may help veterinary professionals in their ongoing communication with these clients. As with any other area of medicine, professional advice about flea and tick control should be based on current scientific information (such as the evidence reported in this monograph) and sound medical judgment. Only when armed with accurate information can cat owners successfully understand and institute an effective parasite control program for their pets.

APPENDIX I

SUMMARY OF COMMONLY USED EPA-REGISTERED FELINE SPOT-ON FLEA AND TICK CONTROL PRODUCTS*

Brand Name (Manufacturer)	Active Ingredients (%)	Chemical Classes	EPA Registration No.
Adams™ Spot On® Flea & Tick Control For Cats and Kittens (Farnam Companies, Inc.)	Etofenprox (40%) (*S*)-Methoprene (3.6%)	Ether pyrethroid (Etofenprox)‡ IGR [(*S*)-Methoprene]	2724-504-270
Advantage® Topical Solution (Bayer HealthCare LLC)	Imidacloprid (9.1%)	Neonicotinoid	11556-116 11556-118
Bio Spot® for Cats One-Step (Farnam Companies, Inc.)	Etofenprox (55%), Pyriproxyfen (2.2%)	Ether pyrethroid (Etofenprox)‡ IGR (Pyriproxyfen)	69332-3-270
Bio Spot® Spot On® Flea & Tick Control For Cats and Kittens (Farnam Companies, Inc.)	Etofenprox (40%) (*S*)-Methoprene (3.6%)	Ether pyrethroid (Etofenprox)‡ IGR [(*S*)-Methoprene]	2724-504-270
Bio Spot® Stripe-On® Flea Control for Cats & Ferrets (Farnam Companies, Inc.)	Pyriproxyfen (5.3%)	IGR	270-308
First Shield™ (Schuyler, LLC)	Dinotefuran (22%), Pyriproxyfen (3.0%)	Neonicotinoid (Dinotefuran) IGR (Pyriproxyfen)	83399-9-85581
Frontline® Plus For Cats & Kittens (Merial Ltd.)	Fipronil (9.8%) (*S*)-Methoprene (11.8%)	Phenylpyrazole (Fipronil) IGR [(*S*)-Methoprene]	65331-4
Frontline® Top Spot® For Cats & Kittens (Merial Ltd.)	Fipronil (9.7%)	Phenylpyrazole (Fipronil)	65331-2
Hartz® InControl Advanced™ Flea & Tick Drops for Cats (The Hartz Mountain Corporation)	Etofenprox (40%) (*S*)-Methoprene (3.6%)	Ether pyrethroid (Etofenprox)‡ IGR [(*S*)-Methoprene]	2724-504-2596
Hartz® InControl™ Flea & Tick Drops for Cats (The Hartz Mountain Corporation)	Etofenprox (40%) (*S*)-Methoprene (3.6%)	Ether pyrethroid (Etofenprox)‡ IGR [(*S*)-Methoprene]	2724-504-2596
Hartz® UltraGuard® OneSpot® Treatment for Cats & Kittens (The Hartz Mountain Corporation)	(S)-Methoprene (2.9%)	IGR	2596-147
Hartz® UltraGuard Plus® Drops for Cats (The Hartz Mountain Corporation)	Etofenprox (40%) (*S*)-Methoprene (3.6%)	Ether pyrethroid (Etofenprox)‡ IGR [(*S*)-Methoprene]	2724-504-2596
Hartz® UltraGuard Pro™ Flea & Tick Drops for Cats (The Hartz Mountain Corporation)	Etofenprox (40%) (*S*)-Methoprene (3.6%)	Ether pyrethroid (Etofenprox)‡ IGR [(*S*)-Methoprene]	2724-504-2596
ProMeris® For Cats (Fort Dodge Animal Health)	Metaflumizone (18.53%)	Semicarbazone	80490-3

	Minimum Age (Weight)	Target Parasites						
		Flea Adults	Flea Eggs	Flea Larvae	Flea Pupae	Mosquitoes† (*K* = Kills; *R* = Repels)	Ticks†	Chewing Lice
	12 weeks	X	X			X K&R	X	
	8 weeks	X		X				
	12 weeks (5 lb)	X	X	X		X R	X	
	12 weeks	X	X			X K&R	X	
	12 weeks		X					
	8 weeks	X	X	X	X			
	8 weeks	X	X	X	X		X	X
	8 weeks	X					X	X
	12 weeks (5 lb)	X	X	X		X K&R	X	
	12 weeks	X	X			X K&R	X	
	12 weeks		X	X				
	12 weeks	X	X			X K&R	X	
	12 weeks (5 lb)	X	X	X		X K&R	X	
	8 weeks	X						

SUMMARY OF COMMONLY USED EPA-REGISTERED FELINE SPOT-ON FLEA AND TICK CONTROL PRODUCTS* *(cont.)*

Brand Name (Manufacturer)	Active Ingredients (%)	Chemical Classes	EPA Registration No.
Sentry® PurrScriptions® Squeeze-On for Cats and Kittens (Sergeant's Pet Care Products, Inc.)	Etofenprox (55%)	Ether pyrethroid‡	69332-4-2517
Sentry® PurrScriptions™ Plus Squeeze-On for Cats and Kittens (Sergeant's Pet Care Products, Inc.)	Etofenprox (55%) Pyriproxyfen (2.2%)	Ether pyrethroid (Etofenprox)‡ IGR (Pyriproxyfen)	69332-3-2517
Sergeant's® Gold® Squeeze-On for Cats and Kittens (Sergeant's Pet Care Products, Inc.)	Etofenprox (55%) Pyriproxyfen (2.2%)	Ether pyrethroid (Etofenprox)‡ IGR (Pyriproxyfen)	69332-3-2517
Sergeant's® Silver® Squeeze-On for Cats and Kittens (Sergeant's Pet Care Products, Inc.)	Etofenprox (55%)	Ether pyrethroid‡	69332-4-2517
TriForce™ Feline Squeeze-On (Tradewinds, Inc.)	Etofenprox (55%) Pyriproxyfen (2.2%)	Ether pyrethroid (Etofenprox)‡ IGR (Pyriproxyfen)	69332-3-83333
Vectra For Cats® (Summit VetPharm LLC)	Dinotefuran (22%) Pyriproxyfen (3.0%)	Neonicotinoid (Dinotefuran) IGR (Pyriproxyfen)	83399-9
Vectra For Cats & Kittens™ (Summit VetPharm LLC)	Dinotefuran (22%) Pyriproxyfen (3.0%)	Neonicotinoid (Dinotefuran) IGR (Pyriproxyfen)	83399-9
Zodiac® Spot On® Flea Control For Cats and Kittens (Wellmark International)	(*S*)-Methoprene (3.6%)	IGR	2724-488
Zodiac® Spot On® Plus Flea & Tick Control (Wellmark International)	Etofenprox (40%) (*S*)-Methoprene (3.6%)	Ether pyrethroid (Etofenprox)‡ IGR [(*S*)-Methoprene]	2724-504

*This chart represents the most commonly used EPA-regulated topical spot-on parasiticides for use in cats as of August 31, 2010. All products are applied monthly unless otherwise indicated. Please refer to individual product labels and package information for details on target parasites, contraindications, and safety information. Products listed here are for use only on cats.

Inclusion of parasites in this table indicates that the product "controls," "kills," "prevents," or "repels" the parasite listed.

†Refer to product labels for specific tick and mosquito species affected.

‡Ether pyrethroid is a sodium channel modulator that contains an ether moiety instead of an ester moiety (like other pyrethroids), lacks a cyclopropane moiety and an alpha-cyano moiety, and is not halogenated. These attributes decrease mammalian toxicity.

IGR = insect growth regulator.

Sources: Package labels of individual products and *Compendium of Veterinary Products*. 11th ed. Port Huron, MI: North American Compendiums Inc. Accessed August 2010 at https://www.bayerdvm.com/Resources/cvp_main.cfm.

	Minimum Age (Weight)	Target Parasites						
		Flea Adults	Flea Eggs	Flea Larvae	Flea Pupae	Mosquitoes† (*K* = Kills; *R* = Repels)	Ticks†	Chewing Lice
	12 weeks	X				X R	X	
	12 weeks (2.2 lb)	X	X	X		X R	X	
	12 weeks	X	X	X		X R	X	
	12 weeks	X				X R	X	
	12 weeks (2.2 lb)	X	X	X		X R	X	
	9 lb	X	X	X	X			
	8 weeks	X	X	X	X			
	12 weeks		X					
	12 weeks	X	X			X K	X	

APPENDIX II

POTENTIAL TOXIC EFFECTS OF ACTIVE INGREDIENTS AND TREATMENT GUIDELINES[a]

Active Ingredient	Systems Involved	Treatment
Dinotefuran	Central nervous (low toxicity potential)	**Specific treatment:** None **Decontamination:** • Dermal: Bathe with a liquid dishwashing detergent • Oral ingestion: Emesis and activated charcoal usually not needed **Supportive:** • IV fluids if needed • Monitor for central nervous system signs • Treat symptomatically • Antihistamines or steroids for dermal reaction
Etofenprox	Central nervous (low toxicity potential) Gastrointestinal Integumentary	**Specific treatment:** None **Decontamination:** • Dermal: Bathe with a liquid dishwashing detergent • Oral ingestion: Dilution with milk or water; emesis and activated charcoal are not needed **Supportive:** • IV fluids if needed • Treat symptomatically • Antihistamines or steroids for dermal reaction
Fipronil	Central nervous Gastrointestinal Integumentary	**Specific treatment:** None **Decontamination:** • Dermal: Bathe with a liquid dishwashing detergent • Oral ingestion: Dilution with milk or water; emesis or activated charcoal not needed **Supportive:** • IV fluids if needed • Treat symptomatically • Antihistamines or steroids for dermal reaction
Imidacloprid	Gastrointestinal Integumentary	**Specific treatment:** None **Decontamination:** • Dermal: Bathe with a liquid dishwashing detergent • Oral ingestion: Dilution with milk or water **Supportive:** • IV fluids if needed • Treat symptomatically • Antihistamines or steroids for dermal reaction

[a]If a feline patient displays sensitivity to a spot-on chemical, or if accidental ingestion occurs, please contact the ASPCA Animal Poison Control Center immediately at 888-426-4435. It is available 24 hours a day, 365 days a year. For additional information, visit the ASPCA Animal Poison Control Center's web site at: http://www.aspca.org/pet-care/poison-control/.

Active Ingredient	Systems Involved	Treatment
Metaflumizone	Cardiovascular Central nervous Gastrointestinal	**Specific treatment:** None **Decontamination:** • Dermal: Bathe with a liquid dishwashing detergent • Oral ingestion: Dilution with milk or water; emesis or activated charcoal usually not needed **Supportive:** • IV fluids if needed • Treat symptomatically • Antihistamines or steroids for dermal reaction
(*S*)-Methoprene	Central nervous Gastrointestinal Integumentary (low toxicity potential)	**Specific treatment:** None **Decontamination:** • Dermal: Bathe with a liquid dishwashing detergent • Oral ingestion: Dilution with milk or water **Supportive:** • Antihistamines or steroids for dermal reaction
Pyriproxyfen	When used alone: Integumentary (low toxicity potential)	**Specific treatment:** None **Decontamination:** • Dermal: Bathe with a liquid dishwashing detergent • Oral exposure: Dilution with milk or water **Supportive:** • Antihistamines or steroids for dermal reaction

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