CANINE FLEA AND TICK CONTROL

A REFERENCE GUIDE TO EPA-APPROVED SPOT-ON PRODUCTS

TECHNICAL MONOGRAPH

by Jorge Guerrero, DVM, MSc, PhD

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Email questions or comments to SpotOnMonograph@vetdata.com

DEAR DOCTOR:

The results are in. A recent survey[1] indicated that pet owners are more concerned about fleas and ticks than any other parasites. Unfortunately, this concern does not always translate to judicious use of effective parasite control methods. In May 2009, the EPA issued an advisory reinforcing the importance of using spot-on flea and tick control products correctly and following the label instructions carefully. This increased scrutiny from the EPA on all spot-on products will require increased education for your clients.

A surprisingly large percentage of pet owners choose not to use parasite control products at all. Others may approach parasite control in a reactionary manner—waiting until they see fleas or ticks on their pet before taking action. Similarly, some pet owners may use flea and tick control products only seasonally. Our current understanding of flea and tick life cycles and these pests' ability to survive seasonal temperature changes tell us that each of these strategies is likely to be unsuccessful, even for the most diligent pet owner.

In short, pet owners may know about fleas and ticks, but they need your advice to protect their pets safely and effectively. As veterinarians, we all have flea and tick control products that we are very comfortable with and like to recommend. However, we should acknowledge that some of our clients will choose not to purchase flea and tick control products from us. Whether the reason is cost, convenience, or perception, some of our clients will elect to purchase over-the-counter parasite control products through retail outlets. To advise clients conscientiously, we should become familiar with all the products our clients may be using or asking about—if for no other reason than to be able to provide sound counsel. Veterinary professionals can also benefit from having a better understanding of the broad range of available parasite control products. Our duty to protect our patients must remain a primary goal of clinical practice. This remains as true in the area of parasite control as in any other area of practice.

This monograph is intended to serve as an objective, quick reference guide describing the active ingredients in the currently available EPA-approved spot-on flea and tick control products for dogs. Although the diversity of available products includes several active ingredients for cats, data presented in this monograph are limited to agents registered for use on dogs. The major chemical classes are described, as are the mode of action and absorption and distribution properties for the individual active ingredients; EPA safety designations are also covered.

The universe of canine parasite control products seems to be expanding on a regular basis with the frequent introduction of new active ingredients. It is important for veterinarians to understand the different chemical agents on the market today, including how they work and their similarities and differences. Becoming familiar with these products is the first step toward helping clients understand how to use them safely and effectively to protect their dogs from fleas and ticks.

Sincerely,

Jorge Guerrero, DVM, MSc, PhD
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ABOUT THE AUTHOR

Jorge Guerrero, DVM, MSc, PhD, was born in 1942 in Andahuaylas, a small town in the middle of the Peruvian Andes. His family later moved to Lima, the capital of Peru, where Dr. Guerrero earned his early education and spent his formative years. He is also a US citizen and has resided in Pennington, New Jersey, since 1976. He and his wife, Mary Anne, have two children, Regina and Sebastian, both born in São Paulo, Brazil. Dr. Guerrero received his bachelor and DVM degrees from San Marcos University, Lima, Peru, in 1965 and his MS and PhD from the University of Illinois, Urbana, in 1968 and 1971, respectively.

Dr. Guerrero is an internationally recognized veterinary parasitologist, with a unique blend of experience in the animal health industry and academia. He has been Adjunct Professor of Parasitology at the University of Pennsylvania since 1983, with teaching duties in the professional veterinary program as well as in the graduate program in parasitology. His early teaching duties were at San Marcos University in Lima, Peru, and the Escola Paulista de Medicina and the Universidade de São Paulo in Brazil. In 2004, he was honored with the title of Honorary (Emeritus) Professor at San Marcos University. He has served as Visiting Professor of Veterinary Parasitology and Parasitic Diseases for the Facolta de Medicina Veterinaria, Universita degli Studi di Milano, Milan, Italy (1991); Facultad de Medicina Veterinaria, Universidad Nacional Mayor de San Marcos, Lima, Peru (2001 to 2004); Faculdade de Medicina Veterinaria, Universidade Federal Fluminense, Niteroi, Rio de Janeiro, Brazil (2002); Facultad de Medicina Veterinaria, Universidad Peruana Cayetano Heredia, Lima, Peru (2003 to present); and Facultad de Veterinaria, Universidad de Santiago de Compostela, Lugo, Spain (2004).

Upon leaving Pitman Moore, Inc. (a Johnson & Johnson Company) as Director of their Pre-Clinical Research Department in 1984, he joined Merck and Co., Inc. as Associate Director of Technical Services and remained with Merck (later, Merial) until his retirement as an Executive Director in 2001. In 1993 and 1994, he was Director of Operations for MSD AGVET Spain, and the following year he was made Regional Managing Director of MSD AGVET Spain and Portugal (Iberian Region). In 1996, he returned to the United States and was later promoted to Executive Director of Veterinary Professional Services (VPS) at Merial. While at Merck, he was recipient of the Award for Creativity from the *Art Direction Magazine* for creation of *Momentum*, an MSD AGVET magazine (1992), and the Chairman's Award for his participation in the development of PARABAN, a computer program for design of strategic anthelmintic treatments of cattle (1993).

Among other academic accomplishments, he received a Fulbright Scholarship to study in the United States from 1967 to1972 and was appointed to membership on the Board of Directors of the Latin American Professorship Program of the American Society for Microbiology from 1985 to 1994. More recently, he has served the veterinary community in a wide variety of roles: He served on the Board of Directors of the Eastern States Veterinary Association and The North American Veterinary Conference (2002); was Director on the Executive Board of the American Heartworm Society; was in charge of continuing education and organization of the triennial Heartworm Symposium from 2004 to 2007; was elected to a second term as President of the New Jersey Society for Parasitology (2001); was appointed Editor-in-Chief of the *International Journal of Applied Research in Veterinary Medicine* (2004); has been a member of the Editorial Review Board of the journal *Veterinary Therapeutics: Research in Applied Veterinary Medicine* (since 2003); was appointed to the National External Advisory Committee of the College of Veterinary Medicine of the University of Illinois (2003); was appointed to the Board of Directors of the Southern European Veterinary Conference; and was elected to the Nominating Committee of the American Association of Veterinary Parasitologists (2004).

Dr. Guerrero has authored or co-authored more than 170 refereed original research articles and book chapters, and he is currently co-authoring a book on helminth parasite infections of dogs and cats. He is the recipient of the Distinguished Veterinary Parasitologists Award for 2005 given by the American Association of Veterinary Parasitologists.

Dr. Guerrero was the North American Veterinary Conference President from 2007 to 2008 and is currently the President of the Latin American Veterinary Conference.

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OVERVIEW: FLEA AND TICK BIOLOGY AND LIFE CYCLES

FLEAS—STILL THE WORLD'S MOST IMPORTANT ECTOPARASITE

Fleas are extremely successful parasites that have been among us for millions of years.[2] Despite decades of research yielding a variety of insecticidal options, fleas continue to pose a problem for dogs, their owners, and their veterinarians. The cat flea, *Ctenocephalides felis,* is the most important ectoparasite of pet dogs and cats[2–4] and is the primary flea species infesting dogs. *Ctenocephalides canis* (the dog flea) also infests dogs but is much less common. *Ctenocephalides* fleas are voraciously hematophagous. Females can consume approximately 15 times their body weight—about 13.6 µl of blood—in a day.[2,5] An infestation by as few as 72 female fleas can result in a loss of 1 ml of blood from a host in a single day.[2,6] Needless to say, a heavily infested animal can become dangerously anemic if left untreated. Fleas also cause flea allergy dermatitis (FAD) and transmit a variety of diseases to dogs, humans, and other species. These factors contribute to the importance of fleas as parasites that threaten companion animals and create concern among pet owners and veterinary professionals.

C. felis LIFE CYCLE

C. felis fleas begin feeding on blood and subsequently producing feces within minutes of finding a host. Mating occurs within 8 to 24 hours after feeding, and both male and female fleas take blood meals before mating.[7] Egg production begins 24 to 48 hours after feeding and can continue for up to 90 days.[2,3,8] Flea eggs can hatch within a few days under a surprisingly wide range of acceptable temperature and relative humidity conditions (Figure 1).[2,4,6,8] Further development and environmental infestation can be well under way before a pet owner even notices fleas on his or her dog.

Flea eggs are small (0.5 mm) and easily fall off the host within a few hours of being laid.[4] They tend to remain in the environment, and the first of three larval stages emerges after 2 to 3 days. *C. felis* larvae are mobile and negatively phototactic. Because they are vulnerable to heat and desiccation, the larvae prefer darker, protected areas such as carpeting, bedding, furniture, leaves and grass, or soil.[4,6] They feed on adult flea feces and other organic debris in the environment and have also been shown to be cannibalistic.[4] The third stage of flea development is the pupa. Flea pupae

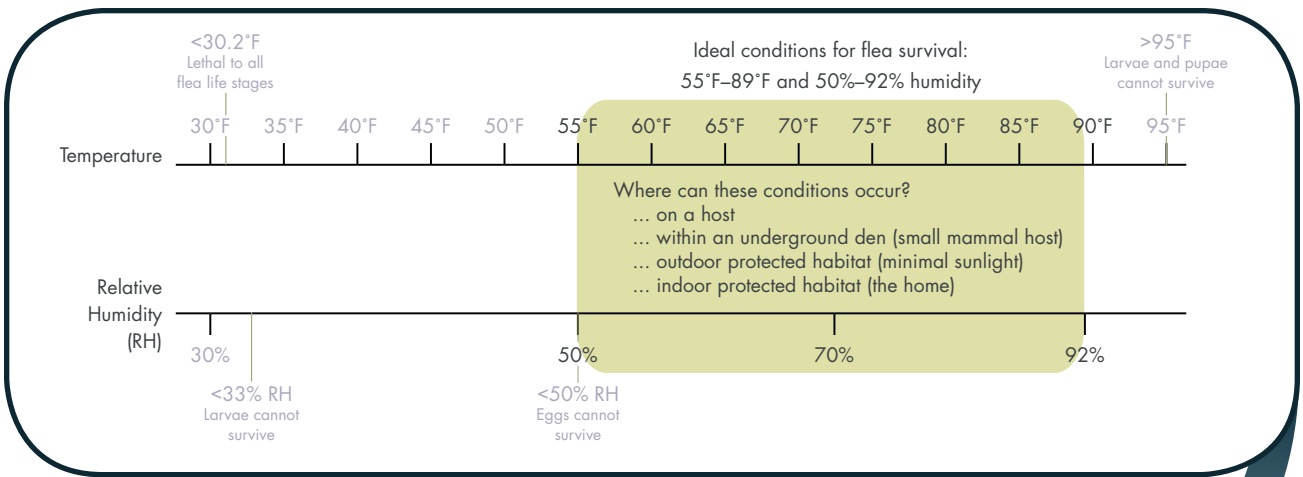


Figure 1. *Optimal conditions for flea development and survival. This figure provides an overview of ideal temperature (°F) and relative humidity (RH) conditions that support the stages of flea development and survival. As shown, very high temperatures (>95°F) do not support the survival of larvae or pupae, and subfreezing temperatures (<30.2°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.*[2,4,6,8]

can be found in many of the same areas where larvae reside (e.g., carpeting, soil, bedding); however, pupae are much less susceptible to desiccation and can survive in environments with humidity as low as 2%.[4] Pupae can remain in the environment for several months, until the proximity of a new host triggers emergence of new adult fleas that begin feeding immediately and continue the parasite's life cycle.

Once adult fleas find a host, they tend to remain on that host. Fleas *can* move from one host to another nearby host, thereby exposing humans and other pets; however, most fleas that infest a new host come from the environment, not from another host.[4,8]

C. felis feed on a variety of hosts, including dogs, cats, and humans. Under ideal conditions, *C. felis* can survive for months, feeding and producing eggs by the thousands at a rate of up to 50 per day.[3,9] Environmental infestation is an important component of the flea's survival strategy: For every visible adult flea, many more eggs, larvae, and pupae are in the environment (Figure 2). The complex biology of *C. felis* and its ability to infest indoor habitats makes the parasite well adapted to environments where humans and companion animals share living space (Figure 3, page 8).

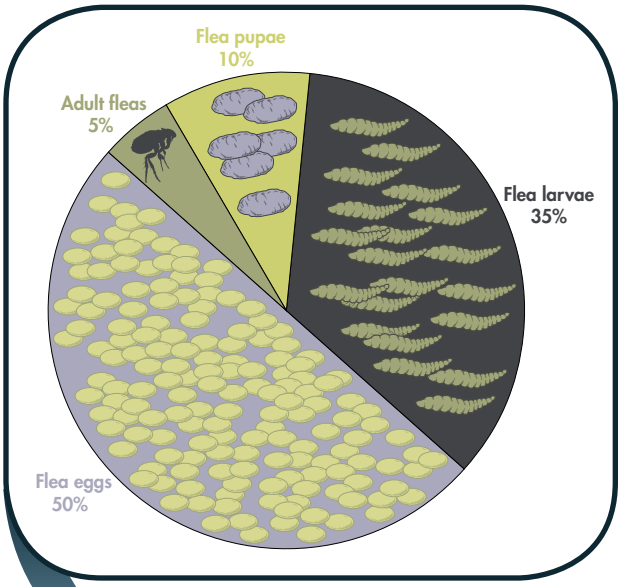


Figure 2. *Flea life stages. For every visible adult flea, many more eggs, larvae, and pupae are in the environment. As shown here, adult fleas account for only about 5% of the total flea infestation. This means that eggs, larvae, and pupae comprise the other 95% of a flea infestation.*

FLEAS AS CAUSES OF DISEASE

Fleas are much more than a nuisance parasite. Heavy infestations can cause anemia, and flea bites are a source of tremendous distress for affected dogs. "Hot spots" and pyoderma lesions can result from increased scratching and grooming. FAD is also caused by flea infestation. FAD creates a serious problem for dogs that have developed an allergy to flea saliva injected during feeding. Fortunately, the use of some topical flea control products has been associated with reductions in severity and incidence of this condition.[7,10]

FLEAS AS VECTORS OF DISEASE

The hematophagous behavior of fleas and their willingness to feed on multiple hosts makes them well-adapted to being efficient vectors of disease. *C. felis* is a vector for the transmission of the filarial parasite *Acanthocheilonema reconditum* (formerly *Dipetalonema reconditum*) to dogs and the tapeworm *Dipylidium caninum* to dogs and humans.[8,11]

Bartonelloses are receiving interest as emerging zoonotic diseases.[12,13] This group of infectious diseases includes cat scratch disease (caused by *Bartonella henselae*), which is thought to be the most common bacterial zoonotic infection acquired from companion animals. Because bartonelloses and several other vector-borne diseases are transmissible by both fleas and ticks, control measures directed at both parasites are recommended to protect dogs from these infections.[12] Dogs can become infected with *B. henselae* when exposed to *C. felis*, and insect vectors can also transmit disease directly to humans.[3] *Bartonella vinsonii* in dogs is most likely transmitted by ticks, with *Amblyomma* and *Dermacentor* spp having been implicated.[12]

Human cases of murine typhus, caused by the organism *Rickettsia typhi*, are traditionally transmitted by the rat flea (*Xenopsylla cheopis*), but investigators in the United States have linked outbreaks of the disease in Texas and California during the past decade to transmission by *C. felis*, even though *C. felis* is considered to be a poor vector of this disease.[14,15] Additionally, investigators researching human cases of plague (*Yersinia pestis*) in the United States have identified intimate contact with household pet dogs (such as sleeping in the same bed) as an independent risk factor for contracting the disease. These investigators suggested that dogs can facilitate the transport of rat fleas (the common vector for *Y. pestis*) into the home. Other research of plague cases in Africa has also implicated *C. felis* as being a capable vector

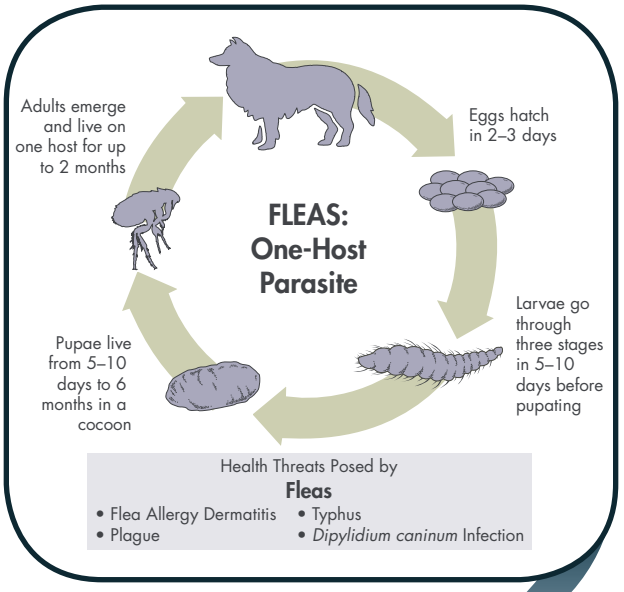


Figure 3. *Fleas are a one-host parasite, meaning that adult fleas can live and feed on a single host.*

for this disease in humans.[16,17] The message is clear—protecting veterinary patients from fleas and ticks also protects humans from dangerous diseases. Pet owners also need to be educated about the risk of exposure to vector-borne diseases and the best ways to minimize disease transmission.

CHALLENGES OF FLEA CONTROL

Scientific advances have provided numerous methods for controlling flea infestations on pets and in domiciles, but fleas continue to be a primary focus of parasite management efforts for pet owners and companion animal veterinarians.

The first challenge of flea control is recognizing and diagnosing the problem. This may not be as straightforward as it seems. Even pet owners who know about fleas may not believe that their dog could be infested, and fleas continue to be a frequently diagnosed medical concern. In a 1999 study involving more than 31,000 dogs at 52 private veterinary hospitals in the United States, the prevalence of confirmed flea infestation was approximately 4.4%.[18] This may not seem like a large percentage, but flea infestation was diagnosed nearly twice as often as such other common conditions as vomiting (2.1%), diarrhea (2.2%), and arthritis (2.4%). Additionally, this number may be on the low side because some dogs with dermatitis or other skin conditions may have had a flea infestation that was undetected at the time of physical examination. Client communication can be a delicate matter when discussing fleas and other parasites, but the conversation is worth having. A thorough physical examination should include checking the dog for fleas. If evidence of infestation is detected, clients need help addressing the issue and they also need sound recommendations about which products to select and how to best manage the problem for their particular situation.

Another challenge in the fight against fleas is recognizing the importance of treating all life stages of the parasite. Not long ago, pet-focused flea control efforts were limited to killing adult fleas on pets. Our current understanding of the flea life cycle makes it clear that the other stages of infestation must not be ignored if flea control is to be successful. The persistence of flea infestation among pet dogs may be related in part to failure to address all stages of the flea life cycle (Figure 2). The development of insect growth regulators (IGRs) has addressed this need, but communication is still important, as clients should understand that IGRs do not kill adult fleas but rather act by preventing the development of flea eggs and larvae. Many flea control products combine an IGR with an adulticide to eliminate the adults while reducing the likelihood of further reproduction and infestation.

Since most of the flea life stages live in the environment, controlling the entire infestation involves reducing flea populations in the environment. This includes treating all the pets in the home, even if no fleas are seen on the other animals. Historically, "treating the environment" meant using a premise spray or fogger to control fleas that were not on the pet, but a new treatment paradigm has emerged with the increased use of spot-on flea products. Several of the spot-on products currently available control the off-host stages of the fleas in addition to reducing flea populations on the pet.[19,20] In one study, monthly application of a spot-on flea product reduced flea populations both on the pet and in the home by more than 95%.[19]

Owner compliance is yet another challenge in controlling fleas. Traditional methods to control fleas on pets were limited to insecticidal shampoos, dips, sprays, powders, and collars, many of which were messy and time-consuming to use. Although traditional flea control products are still available, pet owners now have a much larger variety of products and delivery routes, including oral and topical spot-on products. Since spot-on products became available in the

mid-1990s, they have become the preferred flea control method for pet owners. Research has also shown that the availability of easily applied spot-on products can increase owner compliance.[20–22] Despite these options, the prevalence of flea infestations among dogs remains much higher than it should be.[11] In a 2006 survey, pet owners indicated that they were more concerned about fleas and ticks than other parasites, but only 32% of respondents indicated that they regularly used flea and tick preventive products on their dogs.[23] The reasons for poor owner compliance may involve misperceptions about product safety or effectiveness, or an assumption that well-cared-for household dogs do not get fleas. Whatever the reason, veterinarians need to continue focusing on client education and stressing the importance of using safe and effective flea control products.

TICKS AS PARASITES AND VECTORS OF DISEASE

There are more than 800 species of ticks worldwide and approximately 80 species found in the United States.[24] Of these, only a handful of species routinely infest dogs in the United States. Yet ticks share the stage with fleas as being the parasites that cause the most concern among pet owners.[23]

The consequences of ticks on canine hosts can be divided into cutaneous effects (e.g., infection and inflammation associated with tick bites) and systemic effects (e.g., tick paralysis, anemia, disease transmission),[25] but the primary concern about ticks is their ability to serve as vectors of disease. Like fleas, ticks are hematophagous parasites; however, three stages of tick development (larvae, nymphs, and adults) need to feed on the blood of hosts, whereas only adult fleas feed on blood. During feeding and engorgement, a female *Amblyomma* tick can increase in size from 10 mm to more than 25 mm and increase in weight by nearly 100%.[25] As our understanding of ticks as disease vectors grows and new tick-borne diseases emerge, the importance of ticks as parasites is likely to increase in the future.

The two major families of ticks are the soft ticks (family Argasidae), which are primarily parasites of birds, and the hard ticks (family Ixodidae), which can infest a variety of mammalian hosts.[8] The tick species that most frequently affect dogs in North America include *Rhipicephalus sanguineus* (brown dog tick), *Dermacentor variabilis* (American dog tick), *Dermacentor andersoni* (Rocky Mountain wood tick), *Ixodes scapularis* (black-legged tick or deer tick; northeastern species were previously known as *Ixodes dammini*), *Ixodes pacificus* (western black-legged tick), *Amblyomma maculatum* (Gulf Coast tick), and *Amblyomma americanum* (lone star tick).[26,27] Of these, *R. sanguineus* is the most ubiquitous, having the largest global distribution of any tick species[28,29] (Figure 4, page 10).

TICK LIFE CYCLE

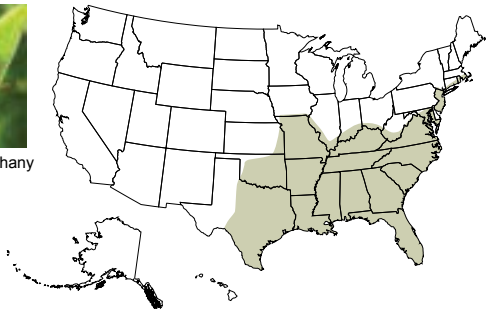
Ticks have four life stages: eggs, larvae, nymphs, and adults. Except for the eggs, all life stages feed on the blood of hosts. After the eggs hatch, the larvae need to feed on blood and then molt to nymphs; after a blood meal, the nymphs then molt again to adults. In addition to being identified by genus and species, ticks can be further categorized based on how many hosts are involved in their development. One-host ticks complete both molts without leaving the original host. For two-host ticks, engorged nymphs drop off the host to molt to adults; for three-host ticks, both larvae and nymphs drop off the host to molt to the next stage of development.[8] Most of the Ixodid ticks affecting companion animals are three-host ticks[25] and as such are the main concern for veterinarians.

The primary concern about ticks is their ability to serve as vectors of disease.

Even within these designations, there can be tremendous variety in terms of host adaptability. For example, *D. variabilis* is a three-host tick whose larvae and nymphs feed on small mammals, but the adults feed on dogs. In contrast, *R. sanguineus* is also a three-host tick, but all three stages feed primarily on dogs.[8] These distinctions become important in terms of parasite control and disease transmission. If all the tick life stages develop on a single host, parasite control is potentially less complicated because only one animal (dogs, for example) needs to be the focus of treatment. Conversely, controlling ticks becomes more of a challenge when multiple hosts (particularly wild animals) are involved in the developmental stages because treating all the host species involved and/or reducing the patient's exposure to several other species of potential hosts can be difficult. The number of potential hosts for a tick species also influences disease transmission. In interstadial transmission, a tick can

Amblyomma americanum

CDC/James Gathany



Amblyomma maculatum

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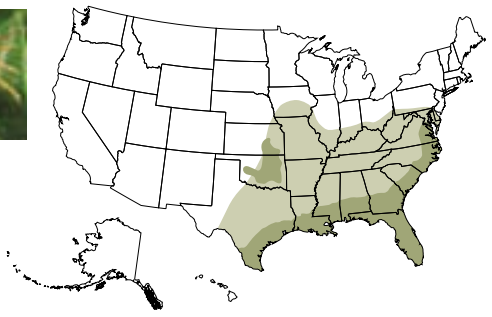
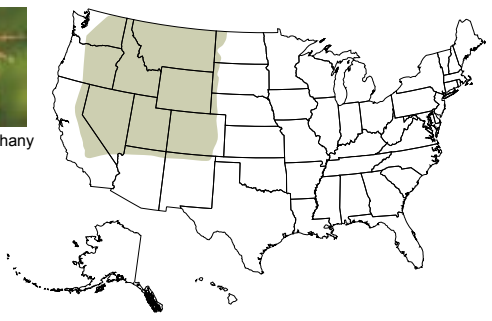


Dermacentor andersoni

CDC/James Gathany



Dermacentor variabilis

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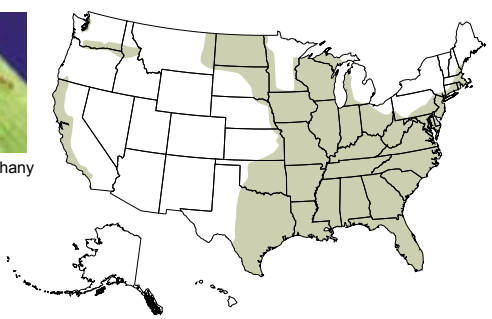

Ixodes pacificus

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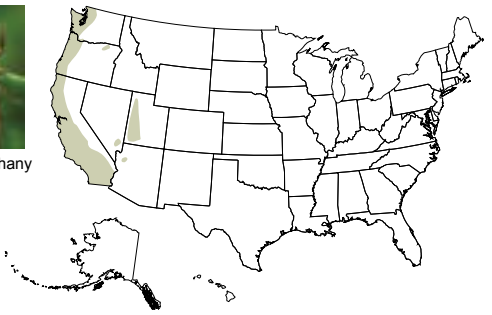
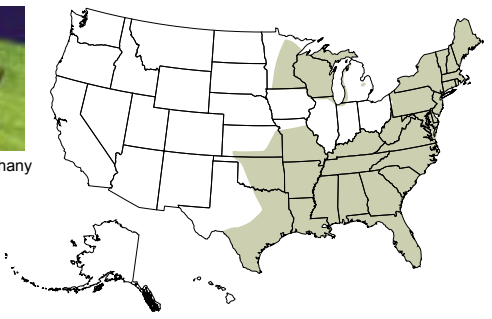


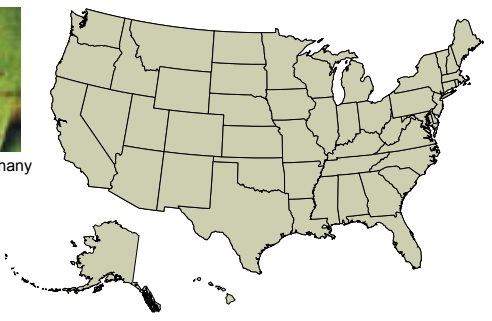
Ixodes scapularis

CDC/James Gathany



Rhipicephalus sanguineus

CDC/James Gathany



Sources for maps: *A. americanum*, *I. scapularis*, and *I. pacificus*, www.cdc.gov/ncidod/dvrd/ehrlichia/natural_Hx/Natural_Hx.htm; *A. maculatum* (darker shading indicates historic distribution; lighter areas indicate current proposed distribution), Paddock CD, Finley RW, Wright CS, et al: *Rickettsia parkeri rickettsiosis* and its clinical distinction from Rocky Mountain spotted fever. *Clin Infect Dis* 2008;47(9):1188-1196 and Dr. Pete Teel; used with permission of the author; *D. andersoni*, *D. variabilis*, and *R. sanguineus*, Stafford KC: *Tick Management Handbook*. New Haven, CT: The Connecticut Agricultural Experiment Station, 2004, and Drummond R: *Ticks and What You Can Do About Them*. Berkeley, CA: Wilderness Press, 2004.

Figure 4. *Identifying tick species can be difficult for pet owners and even for experienced clinicians. The variation in size among species is tremendous. A female* Amblyomma *tick can be as long as 10 mm, whereas a female* I. scapularis *tick may be only 2.5 mm. Also, nymphs, larvae, and adults all feed on hosts and can look different. Larvae have six legs and are sometimes called* seed ticks*; nymphs and adults have eight legs. Some very small ticks can easily be mistaken for mites. The above images illustrate the general appearance of several tick species, and the adjacent maps show their current areas of distribution.*

become infected with a disease as a larva or nymph and carry the infection through the molt to the next life stage (nymph or adult, respectively).

Unlike fleas, which spend large amounts of time on the host, ticks may spend as little as 10% of their lifetime on a host.[25] Several tick species drop off the host to molt and lay eggs and must then await the arrival of another host before blood feeding and further development can continue. Ixodid ticks can be found in fields, weeds or tall grass, or shrub areas. When a host brushes against an occupied piece of vegetation, the tick climbs on and eventually attaches to the host. Attachment and feeding may be delayed for as long as a few days while the tick locates an acceptable site for attachment. Once attachment has occurred, feeding may be further delayed for a day or more.[27,29] After feeding and mating, ticks drop off the host and the females lay eggs in the environment. A single female can produce up to 18,000 eggs.[24] Within a few weeks, the eggs hatch to larvae and the cycle continues. Depending on the tick species, the life cycle can take 1 to 3 years to complete[24] (Figure 5).

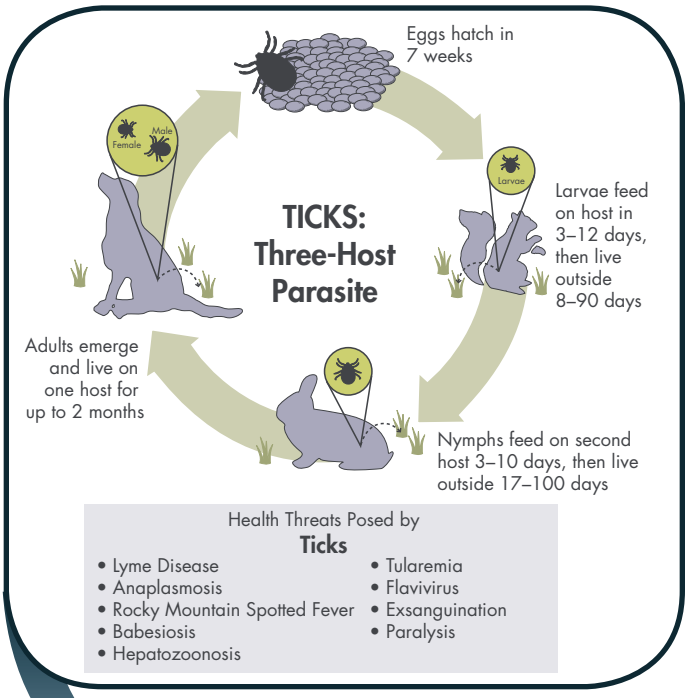


Figure 5. *Three-host tick life cycle. Both larvae and engorged nymphs drop off the host to molt to the next stage of development. Although* R. sanguineus *is a three-host tick, all three stages feed primarily on dogs. In contrast, the larvae and nymphs of* D. variabilis *feed on small mammals and the adults feed on dogs.*

TICKS AS VECTORS OF DISEASE

Tick bites can be painful and can become infected and irritated; a heavy infestation can also cause anemia. However, the primary importance of ticks as parasites stems from their ability to serve as vectors for transmission of bacterial, viral, rickettsial, and protozoal pathogens.[8,25,27,28] Ticks have several characteristics that improve their capacity to serve as vectors, including being persistent blood suckers, being slow feeders, requiring blood at most stages of their developmental cycle, feeding on different hosts, producing large numbers of eggs, and remaining viable in the environment for long periods between blood meals. Most of the important vector tick species are three-host ticks. With the exception of *R. sanguineus*, they tend to feed on multiple hosts at different stages of development, increasing their efficiency as vectors of disease.[28]

Table 1 (page 12) summarizes some of the common tick-borne diseases and the tick species associated with their transmission.[8,25,27,29,30] Rocky Mountain spotted fever and tick paralysis can be transmitted or caused by a variety of tick species. However, Lyme disease (transmitted primarily by *I. scapularis* and *I. pacificus*) remains the most common vector-borne disease in the United States despite increased awareness of the disease and the availability of effective control measures. Practitioners also have to keep in mind that the pathologic relevance of tick-transmitted infections increases when pathogens are transmitted by the same vector. For example, *Borrelia burgdorferi* and *Anaplasma phagocytophilium* are both transmitted by *I. scapularis* and *I. pacificus*.[31] This theoretically allows a single tick to transmit more than one disease to a host. Dogs concurrently infected with both organisms may exhibit more severe clinical signs and have more pathologic changes than dogs infected with either organism alone. Understanding the vector potential for ticks is challenging because both the vectors and the diseases are changing. Climate change, altered host migratory patterns, and other factors have modified the geographic range for ticks and some other arthropod vectors.[32] In some cases, as vectors migrate to a new geographic area, they bring new diseases with them. Tracking the prevalence of flea- and tick-borne diseases is difficult because some of these diseases (e.g., bartonellosis) are not reportable and multiple factors, such as suburban development and altered vector

TABLE 1.

SUMMARY OF NORTH AMERICAN TICKS AS VECTORS FOR CANINE DISEASE[8,25,27,29,30]

Species	Rocky Mountain Spotted Fever	Borreliosis	Ehrlichiosis	Anaplasmosis	Tick Paralysis	Babesiosis	Hepatozoonosis	Tularemia
Rhipicephalus sanguineus	X		X	X (*Anaplasma platys*)		X	X	
Dermacentor variabilis	X				X			X
Dermacentor andersoni	X				X			X
Ixodes scapularis		X		X (*A. phagocytophilum*)	X	X		
Ixodes pacificus		X		X (*A. phagocytophilum*)	X			X
Amblyomma maculatum	X		X		X		X	
Amblyomma americanum	X	X[a]	X		X			X

[a]*A. americanum* has been found to transmit *Borrelia burgdorferi* in parts of the eastern United States (New Jersey).[25]

migration, influence whether incidence increases, decreases, or remains static. The emergence of new diseases further complicates this picture.

CHALLENGES OF TICK CONTROL

Controlling ticks is a complex exercise because of the frequent involvement of multiple host species, the high reproductive capability of ticks, and variations in tick habitat. Longevity of ticks in the environment can also be a factor.[27] Some species of Ixodid adult ticks can survive unfed for more than a year; thus, a prolonged control strategy is required.[8,27]

Logically, it would seem that success in controlling ticks could be linked to success in controlling the diseases they transmit; however, evidence shows that improved tick control does not seem to have the expected influence on the incidence of tick-borne diseases. For example, the incidence of Lyme disease has increased relatively steadily since the 1980s, and the incidence of ehrlichiosis increased during the 1990s[33]; during that same era, use of spot-on tick control products increased. Experimental data have shown that use of flea and tick control products can reduce the incidence of certain vector-associated illnesses,[7,34] but, unfortunately, current data do not seem to indicate conclusively that tick-borne diseases are decreasing in pet dogs. Owner compliance may be an issue, as only 32% of pet owners regularly use products to prevent their dogs from getting ticks.[23] Another factor may be the increased diagnostics available to veterinarians. Routine rapid screening tests for such diseases as Lyme disease, anaplasmosis, and ehrlichiosis have been developed, meaning veterinarians are now able to detect diseases among populations of dogs that would have remained undiagnosed 20 years ago. It is therefore difficult to tell whether an increase in the diagnosis of tick-borne diseases is a result of an actual increase in disease prevalence or a perceptual increase resulting from an improved ability to diagnose these diseases. Other variables may include the emergence of new diseases and expanding tick vector habitats.

A positive outcome from the past 20 years of diagnostic achievements and parasiticide development has been the increased owner awareness of ticks and the dangers they pose to pets and humans. Regardless of whether tick-borne diseases are increasing or decreasing, the duty of veterinarians to educate pet owners about parasite control remains a critically important component of public health and veterinary clinical practice.

THE EFFECTS OF FLEA AND TICK INFESTATIONS

The medical and financial effects of flea and tick infestations can be significant for pet owners. Treating medical conditions such as FAD and Lyme borreliosis generally requires medications and follow-up visits with the veterinarian. Even if a pet does not develop a serious

medical problem, the costs associated with controlling fleas and ticks can add up over time; current data indicate that Americans spend more than $1 billion annually on products targeted at controlling fleas and ticks on their pets.[35] However, the influence of parasite infestation on the lives of pets and their owners is not entirely measurable in dollars. The presence of fleas and ticks on pets and subsequent infestation of the home (and perhaps the surrounding environment) negatively affects the human–animal bond. Pet owners themselves may sustain flea or tick bites and, in a society where more than 40% of dogs share a bed with their owners, the presence of parasites can strain the critically important relationship between pets and their families.[16,21,36] Pet owners who are elderly, ill, or immunocompromised can have an increased risk of contracting potentially zoonotic diseases as a result of their altered immunocompetency. The natural inclination is to limit the exposure of such pet owners to dogs that may be infested with fleas or ticks (or other parasites). This is particularly concerning because interacting with a pet provides much-needed mental and emotional benefits for people who are ill or elderly; thus, limiting contact with pets can have unintended consequences for this population of pet owners.[37]

Veterinarians have made tremendous strides in client education over the past two decades. Ectoparasite infestation, once largely considered a nuisance, is increasingly being treated as a medical issue, and a significant amount of the average veterinary office appointment is dedicated to educating clients about parasites and performing physical and diagnostic examinations to detect them. Manufacturers of parasiticides have also risen to the challenge of improving ectoparasite control methods by developing safe and effective products for controlling fleas and ticks and formulating them to be easier to use than products of the past. Today, clients prefer spot-on flea and tick control products over other delivery methods and, even within this category of agents, pet owners have many brands and products from which to choose.[22]

Thanks to the educational efforts of veterinary professionals, product manufacturers, and organizations such as the Companion Animal Parasite Council, pet owner awareness of fleas and ticks as vectors of disease and a potential cause of serious illness has increased. Consequently, pet owners today are less likely to consider fleas and ticks merely nuisance parasites. However, the educational process needs to continue, as increased awareness has not consistently resulted in effective use of parasite control methods. Clients who think that their pet is not at risk for exposure to parasites should be further educated about exposure risk. Pet owners who are confused or overwhelmed by the variety of treatment options can benefit from continued support and education about the best products for their pet. Pet owners who are frustrated by failed parasite control efforts can also benefit from learning how to properly target fleas and ticks to achieve better therapeutic results. For veterinary professionals in all areas of clinical practice, providing accurate and effective client education will remain a cornerstone of parasite control strategy—an aspect of medical care that continues to be important for our patients' overall health and well-being.

Controlling ticks is a complex exercise because of the frequent involvement of multiple host species, the high reproductive capability of ticks, and variations in tick habitat.

SUMMARY OF EPA SAFETY AND APPROVAL CRITERIA (SPOT-ON REGISTRATIONS)

Ectoparasiticides used on dogs are approved and regulated by either the FDA or the EPA. 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, orally, by injection). The FDA approval process involves submission of specific drug information to the FDA's Center for Veterinary Medicine (CVM). The complex application procedure is called the new animal drug application (NADA) and requires submission of important background information for the drug including chemical composition, manufacturing processes, and labeling specifics. Additionally, a summary of efficacy and target animal safety data known as a Freedom of Information (FOI) summary is also required as part of the NADA process. Examples of FDA-regulated parasiticides include nitenpyram and selamectin.

The EPA regulates ectoparasiticides that do not exert their effect by systemic absorption but that remain within the layers of the skin. The EPA also concerns itself with the effect of chemical agents on soil, air, and water quality.[38]

Unlike FDA-regulated ectoparasiticides, which generally require a prescription, EPA-regulated ectoparasiticides can be available through veterinary channels or through retail outlets.[38] 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. A closer look at the EPA approval and regulation processes shows us the facts.

All EPA-approved ectoparasiticides are subjected to rigorous safety testing before being registered (see chart below[38,39]). They must demonstrate on-animal efficacy and safety, which are evaluated through several exposure routes, including required companion animal safety studies.[39] 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.[40] 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 is required to appear on the product label:

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

The EPA has designated the above words as "signal words."[40] 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

SUMMARY OF EPA REGISTRATION CONSIDERATIONS[38,39]	
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

informational documents pertaining to the product. Category IV is considered the least severe toxicity category, whereas Category I is considered the most severe category assignment. Table 2 (page 16) lists the EPA's overall toxicity classification categories for several canine flea and tick ectoparasiticides. Appendix I (page 28) provides a summary of commonly used EPA-registered canine 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 re-registration process for chemical agents that were licensed for use before 1984.[41] The re-registration 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 re-registration and continued use.[42] 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. Table 2 (page 16) indicates which spot-on ectoparasiticide active ingredients currently in use have been re-registered under the RED process and which are not subject to the process at this time.

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 2.

SUMMARY OF ACTIVE INGREDIENTS IN CANINE EPA-LICENSED 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‡	Last RED Process Approval§
Pyrethroid: Sodium channel modulators								
Cyphenothrin	318[a]	II	>5,000[b]	IV	II	2517-80[c]	November 2006[c]	N/A
Permethrin	1,660 (female rats); 2,614 (male rats)[d]	II	>4,000[e]	III	II	59-198[c]	December 1984[c]	2006
Phenothrin	>10,000[f,g]	IV	>10,000[f,g]	IV	III	2596-150[c]	January 2000[c]	2008
Neonicotinoid: Nicotinic acetylcholine receptor agonists								
Dinotefuran	>5,000[h]	III	>2,000[h]	III	II	83399-1[c]	December 2006[c]	N/A
Imidacloprid	450[g]	II	>5,000[i]	IV	II	11556-116[c]	March 1996[c]	N/A
Phenylpyrazole: GABA-gated chloride channel antagonist								
Fipronil	97[j]	II	>2,000[k]	III	II	65331-3[c]	June 1996[c]	N/A
Semicarbazone: Voltage-dependent sodium channel blocker								
Metaflumizone	>5,000[l]	IV	>5,000[l]	IV	III	80490-2[c]	August 2007[c]	N/A
Insect Growth Regulator: Juvenile hormone mimics								
Pyriproxyfen	>5,000[h]	IV	>2,000[h]	III	III	270-358[c]	February 1996[c]	N/A
(*S*)-Methoprene	>34,600[m]	IV	>3,038[m] (rabbit)	III	III	2596-139[c]	June 1995[c]	1991
Formamidine: Octopamine receptor agonist								
Amitraz	800[g]	III	>1,600[n] (mice)	II	II	54022-4[c]	February 1992[c]	1995

*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 or 800-548-2423) 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 canine 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.

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SPOT-ON PARASITICIDES: UNDERSTANDING THE CHEMICAL CLASSES

In the past decade, advances in flea control products have led to a paradigm shift in flea treatment. Whereas eradicating a flea problem used to require a combination of on-animal and premise treatments, current treatments primarily focus on host-targeted products alone.[5,19] With a more diverse arsenal of products from which to choose, it is important for veterinarians to understand the various chemical classes of parasiticides and how their mechanisms of action differ.

An integrated approach to flea control, which uses two compounds with different mechanisms of action, is often necessary to eradicate flea infestations. For instance, an adulticide, which kills newly acquired fleas, is often combined with an insect growth regulator (IGR) having ovicidal and/or larvacidal activity. This approach breaks the flea life cycle at two different stages for more effective flea control. Advances in tick control products have led to the development of several spot-on formulations with combined efficacy or that combine a flea adulticide with an active ingredient that targets ticks.

To minimize potential toxic effects when combining parasiticide products, care should be taken to avoid using multiple products with the same mechanism of action.

Some veterinarians may recommend multiple flea products for heavy infestations or to control severe environmental infestations. To minimize potential toxic effects when combining parasiticide products, care should be taken to avoid using multiple products with the same mechanism of action. For instance, the concurrent use of the neonicotinoids imidacloprid and dinotefuran should be avoided because they share similar mechanisms of action.

Finally, given the ubiquitous nature of *C. felis*, the judicious use of flea products is important to help prevent the development of resistance among fleas and to safeguard the efficacy and longevity of current flea products. Although at present time the issue of resistance is controversial, to help prevent or delay its development, veterinarians should select appropriate parasiticides with proven efficacy; if necessary, veterinarians can periodically alternate or rotate flea products by mechanism of action.[38] It is worth emphasizing that the mode of action of the active ingredient—not the product's commercial name—is the key issue in alternating among products. Pet owners should be advised to use all ectoparasiticide products in a responsible manner that is consistent with label recommendations. Veterinary professionals share the important obligation of educating pet owners on this point and promoting the safe use of parasite control products in our patients.

EACH CHEMICAL CLASS IS UNIQUE

The following discussion provides an overview of major chemical classes and their mechanisms of action, but it is not intended to be all-inclusive. This monograph focuses solely on EPA-approved active ingredients used in canine 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. These botanicals provide fast insect knockdown with low mammalian toxicity, but they tend to break down when exposed to air, moisture, and sunlight.[38,43–45]

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.[45,46]

Allethrin, a first-generation pyrethroid, was developed in 1949.[47] Despite undergoing 22 chemical reactions to reach the final product, it still lacked environmental stability.[43,47] In 1965, the second-generation pyrethroids tetramethrin, followed by resmethrin and phenothrin, were introduced to the market; these products offered greater killing capacity and stability.[38,47] Third-generation pyrethroids, such as fenvalerate and permethrin, were introduced between 1972 and 1973. These chemicals brought even greater killing power and photostability.[47,48] The addition of permethrin to some topical flea control products makes them active against ticks as well. The most potent and longest-lasting pyrethroids include cypermethrin and cyphenothrin and are considered fourth-generation pyrethroids.[38,43,47] While some pyrethroids, such as permethrin, are labeled for use only in dogs, owners may inadvertently apply a dog product on a cat, or the cat may groom a recently treated dog, potentially leading to pyrethroid toxicosis. Cats are more sensitive than dogs to pyrethroids because they cannot effectively clear chemicals by hepatic glucuronidation.[46]

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 insect.[44,47] During normal insect 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.[38]

The effect of pyrethroids on the sodium channel depends on the chemical structure. Type I pyrethroids, such as permethrin, lack the alpha-cyano moiety found in Type II pyrethroids (see chart below).[38] As a result, Type I pyrethroids delay the closing of the sodium channel to cause repetitive nerve discharges. Type II pyrethroids, on the other hand, hold the sodium channel open even longer, so that the nerve eventually becomes depolarized and no nerve impulses are sent.[44,49] Some pyrethroids, especially Type II pyrethroids, may also suppress γ-aminobutyric acid (GABA) and glutamate receptor-channel complexes.[38]

PYRETHROID CLASSIFICATION EXAMPLES

Type I	Type II
Allethrin	Cyfluthrin
Bioallethrin	Cyhalothrin
Bioresmethrin	Cypermethrin
Permethrin	Cyphenothrin
Phenothrin	Deltamethrin
Resmethrin	Fenvalerate
Tetramethrin	Fluvalinate

NEONICOTINOIDS

Nicotine has been used as a natural insecticide since the mid-1700s. Just as synthetic pyrethroids are modeled after botanical pyrethrins, neonicotinoids are synthetic agents based on the activity of natural nicotine. The neonicotinoids developed in the early 1990s offered greater insecticidal activity and less mammalian toxicity than natural nicotinoids.[38,47]

Neonicotinoids are synaptic insecticides that mimic the actions of acetylcholine, an excitatory neurotransmitter, at nicotinic acetylcholine receptors 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 nicotinic acetylcholine receptors, but neonicotinoids lock the receptors in the open position. This causes an increase in the frequency of spontaneous discharge, 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.[38,47] Some neonicotinoids, such as imidacloprid, are more selective to nicotinic receptors on insects than mammals, which minimizes potential animal toxicities and increases its safety factor.[38]

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.[38]

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.[38,47] This results in nerve hyperexcitation and death of the arthropod.

SEMICARBAZONES

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

Pet owners should be advised to use all ectoparasiticide products in a responsible manner that is consistent with label recommendations.

In normal insect nerve function, the influx of sodium ions in the nerve axon leads to the propagation of a nerve impulse. This agent 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.[50]

FORMAMIDINES

Formamidines are used in animals for the control of ticks, mites, and lice; they have no known activity against fleas. Amitraz is the only formamidine used on dogs.

Although the specific actions of this agent are not fully understood, it is believed that there are two mechanisms of action. First, it is thought that amitraz inhibits the enzyme monoamine oxidase[38]; this enzyme degrades the neurotransmitters norepinephrine and serotonin, resulting in an accumulation of these amines. Amitraz may also act as an octopamine agonist, which is a neurotransmitter found in ticks and mites[45]; by agonizing arthropod octopamine receptors, amitraz has the effect of increasing nervous activity while decreasing feeding and reproductive behavior, ultimately resulting in death.

INSECT GROWTH REGULATORS (IGRs)

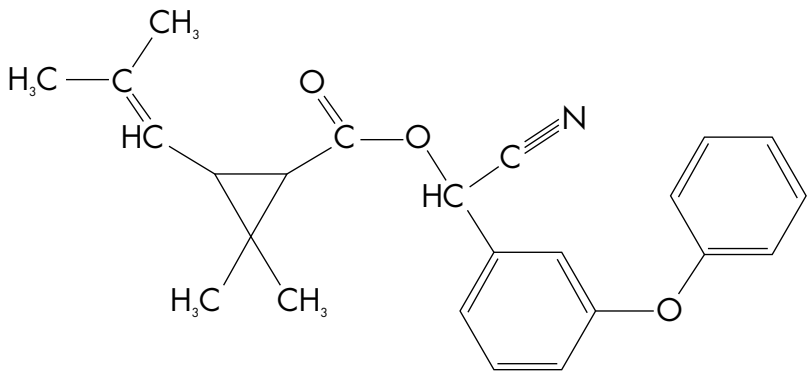
Because adult fleas account for only a small percentage of the parasite population and the flea life cycle, IGRs were introduced in the 1980s and 1990s to address the developmental flea stages found in the environment.[38] IGRs interfere with the growth and development of the immature flea stages—the eggs, larvae, and pupae.[38] Since these agents do not kill the adult flea directly, they are often combined with an adulticide for more rapid control of established flea infestations.

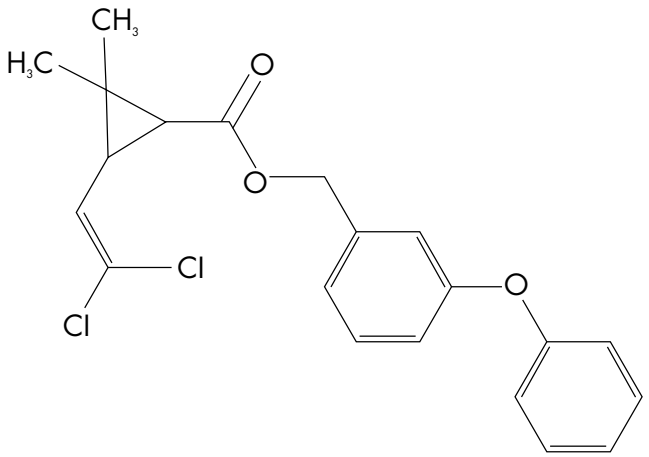
The IGRs currently used in topical flea products, such as (*S*)-methoprene and pyriproxyfen, are categorized as juvenile hormone analogs because they mimic the activity of naturally occurring hormones in the flea. During normal flea development, enzymes in the flea's circulatory system destroy endogenous juvenile hormones, allowing the larva to molt to a pupa and then to an adult. Juvenile hormone analogs 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.[45]

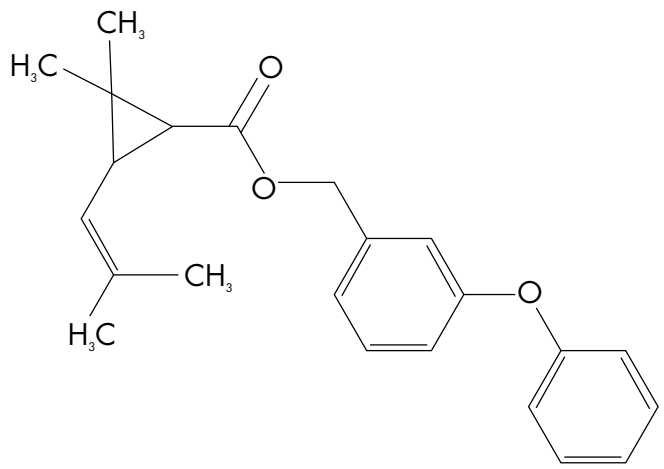
SUMMARY OF COMMON ECTOPARASITICIDE ACTIVE INGREDIENTS

Within each chemical class described in the previous section, there are active ingredients represented in the current EPA-registered spot-on canine ectoparasiticides. Some products contain only one active ingredient (usually an adulticide), whereas others combine an adulticide with an IGR or another active ingredient that expands the spectrum of activity for the product. Interactions (e.g., synergy) between active ingredients can vary, and such a discussion is beyond the scope of this monograph. The following tables summarize the most common active ingredients used today in EPA-registered canine 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).

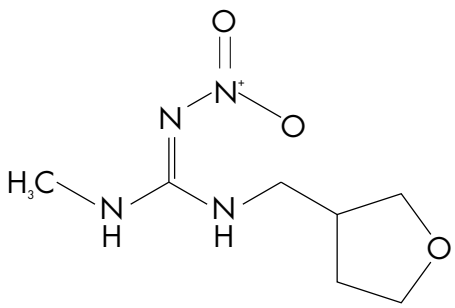
PYRETHROIDS

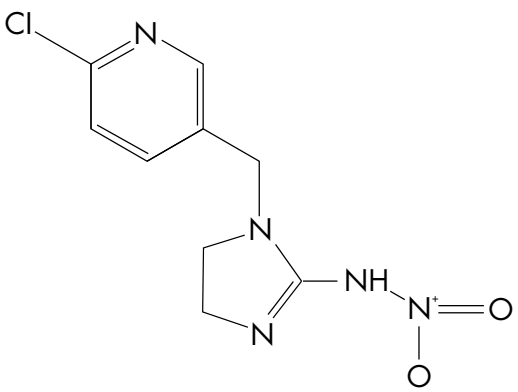
Cyphenothrin[38,44,49,51]	
Molecule	
Molecular Formula	$C_{24}H_{25}NO_3$ Unlike many other pyrethroids, this molecule has an added alpha-cyano moiety.
Classification	Sodium channel modulator; fourth-generation, Type II pyrethroid
Mode of Action	This axonal adulticide targets the sodium channels along the cell membrane. While these channels normally close after the transmission of a nerve impulse, this chemical keeps the channels open so long that the nerves do not fire impulses at all, which leads to 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.

Permethrin[38,44,47,49]	
Molecule	
Molecular Formula	$C_{21}H_{20}Cl_2O_3$
Classification	Sodium channel modulator; third-generation, Type I pyrethroid
Mode of Action	This axonal adulticide targets the sodium channels along the cell membrane. Whereas these channels normally close after the 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 by surface translocation. The insect is killed by contact, without the need to ingest the active ingredient.

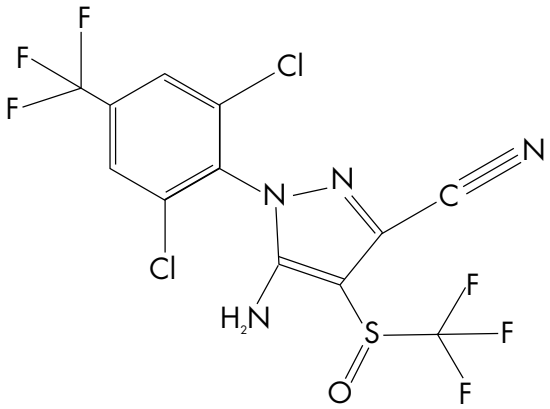
Phenothrin[38,44,47]	
Molecule	
Molecular Formula	$C_{23}H_{26}O_3$
Classification	Sodium channel modulator; second-generation, Type I pyrethroid
Mode of Action	This axonal adulticide targets the sodium channels along the cell membrane. While these channels normally close after the transmission of a 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 insect is killed by contact, without the need to ingest the active ingredient.

NEONICOTINOIDS

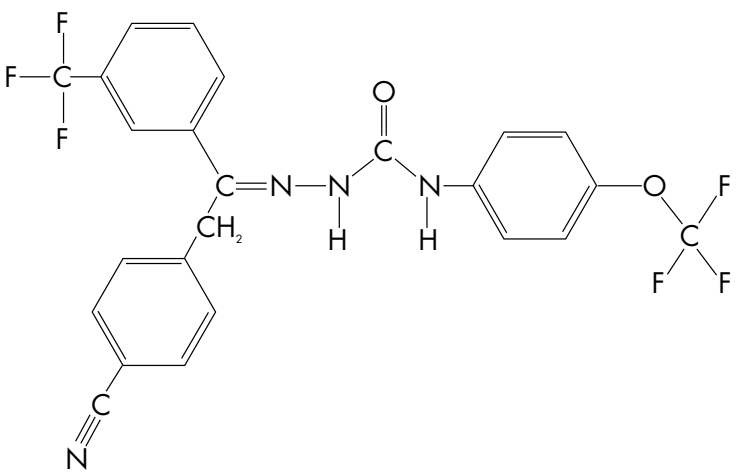
Dinotefuran[38,47,52,53]	
Molecule	
Molecular Formula	$C_7H_{14}N_4O_3$
Classification	Nicotinic acetylcholine receptor agonist/antagonist; third-generation neonicotinoid
Mode of Action	This chemical works as a competitive inhibitor at the nicotinic acetylcholine receptors in the nervous system. Dinotefuran 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[38,47,54]	
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.

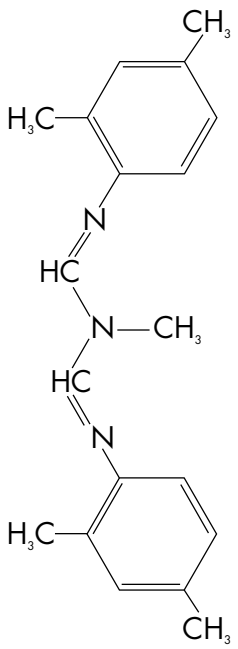
PHENYLPYRAZOLE

Fipronil[38,47,55,56]	
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 insect 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.

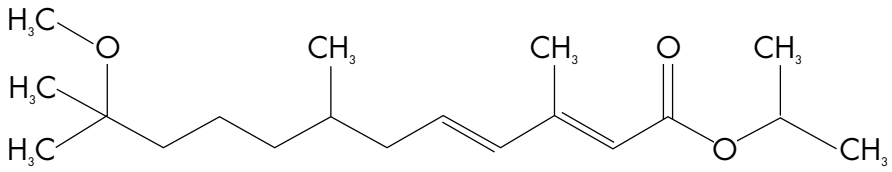
SEMICARBAZONE

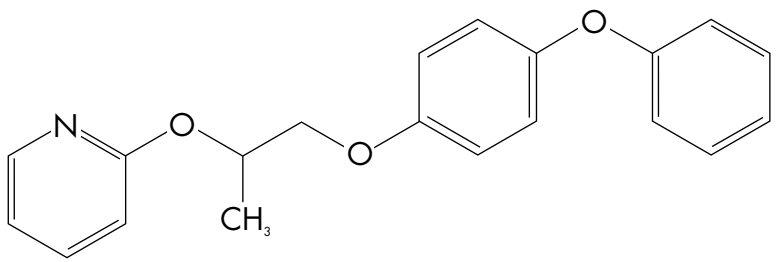
Metaflumizone[50,57]	
Molecule	
Molecular Formula	$C_{24}H_{16}F_6N_4O_2$
Classification	Voltage-dependent sodium channel blocker
Mode of Action	This axonal insecticide blocks the influx of sodium ions, which prevents the propagation of nerve impulses. The result is paralysis and death of the parasite.
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.

FORMAMIDINE

***Amitraz*[38,45]**	
Molecule	
Molecular Formula	$C_{19}H_{23}N_3$
Classification	Formamidine; octopamine receptor agonist
Mode of Action	Amitraz works by inhibiting the enzyme monoamine oxidase, preventing the degradation of neurotransmitters in the arthropod nervous system. It also agonizes octopamine receptors, leading to the death of exposed arthropods. Amitraz is also thought to act on the insect mouthparts, reducing feeding activity.
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 REGULATORS

***(S)-Methoprene*[38,45,58]**	
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*[38,45,59]**	
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

Over the past two decades, pet owners have gradually but consistently increased the amount of money they spend on their pets, including on flea and tick products.[60] Today, Americans spend in excess of $1 billion annually to control fleas and ticks on companion animals.[35] Controlling parasites is becoming a goal that pet owners understand and want to accomplish. They are also learning that protecting pets from certain parasites has the added advantage of reducing the risk for the spread of zoonotic diseases. Fortunately, parasite control has never been easier and pet owners have never had as many options as they currently have. But with so many choices, it is easy for pet owners to become confused about which products to use and for veterinarians to become complacent about which products to recommend. Pet owners must consider several factors when deciding which flea and tick control product is best for their pet. Route of delivery and ease of administration are important, as are product availability, cost, efficacy, and safety. Sales of parasiticides, whether distributed through veterinary practices or sold over the counter, continue to grow each year. This reinforces an important point—for whatever reason (cost, accessibility, or other), many pet owners continue to purchase flea and tick control products from sources other than their veterinarians. Consequently, this means that for veterinarians to continue providing accurate and up-to-date advice to pet owners, the veterinary community must be familiar with products that are sold outside the practice.

Before being approved and marketed, all EPA-regulated flea and tick products undergo the same rigorous testing and approval process. This means that pet owners can purchase effective parasite control products over the counter through veterinary channels or through retail outlets. Veterinarians and veterinary support staff continue to play a pivotal role in educating clients about how to select the most appropriate product for their pet. This does not need to diminish or stop if a client elects to purchase an over-the-counter product. Clients still need to be educated about how to read product labels carefully, choose the correct product for the level of parasite control they need, and apply products safely and correctly. The best way for veterinary professionals to continue to be an important part of this process is to become better educated about the various products available over the counter and decide how to best counsel pet owners who seek professional advice. This technical monograph is intended to provide an overall summary of the available active ingredients, but veterinary professionals are advised to consult the technical manuals for individual products to learn more about these chemicals. If pet owners or veterinarians witness an adverse event associated with the use of any EPA-approved flea or tick control product, it is highly recommended that the product manufacturer be notified. The product and active ingredient will need to be confirmed, along with how the product was administered. The manufacturer submits this information to the EPA, and adverse effect data are available from the EPA through a Freedom of Information Act request.

Clients still need to be educated about how to read product labels carefully, choose the correct product for the level of parasite control they need, and apply products safely and correctly.

In conclusion, pet owners deserve the best advice veterinary professionals can provide. As with any other issue, professional advice and recommendations about flea and tick control products should be based on accurate, current scientific information and sound medical judgment. Such conversations should incorporate a wider discussion of EPA-approved products available through all sources. EPA-regulated parasiticides have shown themselves to be effective against fleas, ticks, and other ectoparasites, but accurate veterinary information is the single most important weapon that can protect pets from parasites and the dangers they pose.

APPENDIX I

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

Brand Name (Manufacturer)	Active Ingredients (%)	Chemical Classes	EPA Registration No.
Adams™ Flea & Tick Control for Dogs (Farnam Companies, Inc.)	Permethrin (45%) Pyriproxyfen (5%)	Pyrethroid (Permethrin) IGR (Pyriproxyfen)	270-278
Adams™ Spot on® Flea & Tick Control for Dogs (Farnam Companies, Inc.)	Permethrin (45%) (*S*)-Methoprene (3%)	Pyrethroid (Permethrin) IGR [(*S*)-Methoprene]	2724-497-270
Advantage® Topical Solution for Dogs and Puppies (Bayer HealthCare LLC)	Imidacloprid (9.1%)	Neonicotinoid	11556-117, 11556-119, 11556-120, 11556-122
Bansect® Squeeze-On Flea & Tick Control for Dogs (Sergeant's Pet Care Products, Inc.)	Permethrin (45%)	Pyrethroid	69332-1-2517
Bio Spot® Spot On® Flea & Tick Control for Dogs (Farnam Companies, Inc.)	Permethrin (45%) (*S*)-Methoprene (3%)	Pyrethroid (Permethrin) IGR [(*S*)-Methoprene]	2724-497-270
Bio Spot® Spot On® Flea & Tick Control for Puppies (Farnam Companies, Inc.)	Permethrin (45%) (*S*)-Methoprene (3%)	Pyrethroid (Permethrin) IGR [(*S*)-Methoprene]	2724-497-270
First Shield™ Trio (Schuyler, LLC)	Dinotefuran (4.95%) Pyriproxyfen (0.44%) Permethrin (36.08%)	Neonicotinoid (Dinotefuran) IGR (Pyriproxyfen) Pyrethroid (Permethrin)	83399-6-85581
Frontline® Plus for Dogs & Puppies (Merial Ltd.)	Fipronil (9.8%) (*S*)-Methoprene (8.8%)	Phenylpyrazole (Fipronil) IGR [(*S*)-Methoprene]	65331-5
Frontline® Top Spot® for Dogs & Puppies (Merial Ltd.)	Fipronil (9.7%)	Phenylpyrazole	65331-3
Happy Jack® Kennelspot™ for Dogs (Happy Jack, Inc.)	Permethrin (45%)	Pyrethroid	69332-1-2781
Hartz® InControl advanced® Flea & Tick Drops for Dogs (The Hartz Mountain Corporation)	Phenothrin (85.7%) (*S*)-Methoprene (2.3%)	Pyrethroid (Phenothrin) IGR [(*S*)-Methoprene]	2596-150
Hartz® InControl® Flea & Tick Drops for Dogs (The Hartz Mountain Corporation)	Phenothrin (85.7%) (*S*)-Methoprene (2.3%)	Pyrethroid (Phenothrin) IGR [(*S*)-Methoprene]	2596-150
Hartz® UltraGuard® Flea & Tick Drops for Dogs and Puppies (The Hartz Mountain Corporation)	Phenothrin (85.7%)	Pyrethroid	2596-151
Hartz® UltraGuard Plus® Flea & Tick Drops for Dogs and Puppies (The Hartz Mountain Corporation)	Phenothrin (85.7%) (*S*)-Methoprene (2.3%)	Pyrethroid (Phenothrin) IGR [(*S*)-Methoprene]	2596-150
Hartz® UltraGuard Pro® Flea & Tick Drops for Dogs and Puppies (The Hartz Mountain Corporation)	Phenothrin (85.7%) (*S*)-Methoprene (2.3%)	Pyrethroid (Phenothrin) IGR [(*S*)-Methoprene]	2596-150

	Target Parasites							
	Flea Adults	**Flea Eggs**	**Flea Larvae**	**Ticks†**	**Mosquitoes†**	**Flies†**	**Mites†**	**Lice**
	X	X	X	X	X			
	X	X		X	X			
	X		X					X
	X			X				
	X	X		X	X			
	X	X		X	X			
	X	X	X	X	X			
	X	X	X	X			X	X
	X			X			X	X
	X			X				
	X	X	X	X	X			
	X	X		X	X			
	X			X	X			
	X	X		X	X			
	X	X	X	X	X			

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

Brand Name (Manufacturer)	Active Ingredients (%)	Chemical Classes	EPA Registration No.
K9 Advantix® (Bayer HealthCare LLC)	Imidacloprid (8.8%) Permethrin (44.0%)	Neonicotinoid (Imidacloprid) Pyrethroid (Permethrin)	11556-132, 11556-133, 11556-134, 11556-135
OmniTrol™ Spot-On for Dogs Plus IGR (Vedco, Inc.)	Permethrin (50%) Pyriproxyfen (1.20%)	Pyrethroid (Permethrin) IGR (Pyriproxyfen)	75844-8-44084
ProMeris® for dogs (Fort Dodge Animal Health)	Metaflumizone (14.34%) Amitraz (14.34%)	Semicarbazone (Metaflumizone) Formamidine (Amitraz)	80490-2
Proticall® Insecticide for Dogs (Schering-Plough Animal Health)	Permethrin (65%)	Pyrethroid	773-73
Sentry® Value Squeeze-On Flea & Tick Control for Dogs (Sergeant's Pet Care Products, Inc.)	Permethrin (45%)	Pyrethroid	69332-1-2517
SentryPro™ Squeeze-On Flea & Tick Control for Dogs (Sergeant's Pet Care Products, Inc.)	Permethrin (45%) Pyriproxyfen (1.9%)	Pyrethroid (Permethrin) IGR (Pyriproxyfen)	2517-87
SentryPro® XFC® Flea & Tick Squeeze-On for Dogs (Sergeant's Pet Care Products, Inc.)	Cyphenothrin (40%) Pyriproxyfen (2%)	Pyrethroid (Cyphenothrin) IGR (Pyriproxyfen)	2517-80
Sergeant's® Gold® Flea & Tick Squeeze-On for Dogs (Sergeant's Pet Care Products, Inc.)	Cyphenothrin (40%) Pyriproxyfen (2%)	Pyrethroid (Cyphenothrin) IGR (Pyriproxyfen)	2517-80
Sergeant's® Silver® Flea & Tick Squeeze-On for Dogs (Sergeant's Pet Care Products, Inc.)	Cyphenothrin (40%)	Pyrethroid	2517-85
Sergeant's® Squeeze-On for dogs and puppies (Sergeant's Pet Care Products, Inc.)	Permethrin (45%) Pyriproxyfen (1.9%)	Pyrethroid (Permethrin) IGR (Pyriproxyfen)	2517-94
TriForce™ Canine Squeeze-On (Tradewinds, Inc)	Cyphenothrin (40%) Pyriproxyfen (2%)	Pyrethroid (Cyphenothrin) IGR (Pyriproxyfen)	2517-80-83333
Vectra 3D™ (Summit VetPharm)	Dinotefuran (4.95%) Pyriproxyfen (0.44%) Permethrin (36.08%)	Neonicotinoid (Dinotefuran) IGR (Pyriproxyfen) Pyrethroid (Permethrin)	83399-6
Zodiac® Spot On Flea & Tick Control (Wellmark International)	Permethrin (45%) (*S*)-Methoprene (3%)	Pyrethroid (Permethrin) IGR [(*S*)-Methoprene]	2724-497

*Products listed here are not for use in cats. Target parasites are based on label indications. Inclusion of parasites in this list indicates that the product "controls," "kills," "prevents," or "repels" the parasite listed. Products listed represent the most commonly used EPA-regulated canine spot-on products as of June 30, 2009. All products are applied monthly unless otherwise indicated. Please refer to individual product labels and package information for contraindications and safety information.

†Refer to product label for specific tick, mosquito, fly, and mite species affected.

Sources: Package labels of individual products and *Compendium of Veterinary Products*. 11th ed. Port Huron, MI: North American Compendiums Inc. Accessed June 2009 at https://www.bayerdvm.com/Resources/cvp_main.cfm.

IGR = insect growth regulator.

	Target Parasites							
	Flea Adults	**Flea Eggs**	**Flea Larvae**	**Ticks†**	**Mosquitoes†**	**Flies†**	**Mites†**	**Lice**
	X		X	X	X	X		X
	X	X	X	X	X		X	X
	X			X			X	X
	X			X	X		X	X
	X			X				
	X	X	X	X	X			
	X	X	X	X	X			
	X	X	X	X	X			
	X			X	X			
	X	X	X	X	X			
	X	X	X	X	X			
	X	X	X	X	X	X	X	X
	X	X		X	X			

APPENDIX II

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

Active Ingredient	Systems Involved	Treatment
Amitraz	Cardiovascular Central nervous Gastrointestinal Integumentary Respiratory Thermoregulation	**Specific treatment:** • Yohimbine, 0.11 mg/kg slow IV, *or* • Atipamezole, 50 µg/kg IM, repeat q3–4h as needed **Decontamination:** • Dermal: Bathe with a liquid dish-washing detergent • Oral ingestion: Emesis and activated charcoal usually not needed **Supportive:** • IV fluids • Monitor temperature, cardiovascular system, respiration, and central nervous system
Cyphenothrin	Central nervous Gastrointestinal Integumentary Respiratory	**Specific treatment:** None **Decontamination:** • Dermal: Bathe with a liquid dish-washing detergent • Oral ingestion: Emesis and activated charcoal usually not needed **Supportive:** • IV fluids if needed • Monitor for central nervous system effects • Treat symptomatically (diazepam, methocarbamol if needed) • Antihistamines or steroids for dermal reaction
Dinotefuran	Central nervous (low toxicity potential)	**Specific treatment:** None **Decontamination:** • Dermal: Bathe with a liquid dish-washing 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
Fipronil	Central nervous Gastrointestinal Integumentary	**Specific treatment:** None **Decontamination:** • Dermal: Bathe with a liquid dish-washing 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 dish-washing detergent • Oral ingestion: Dilution with milk or water **Supportive:** • IV fluids if needed • Treat symptomatically • Antihistamines or steroids for dermal reaction

[a]Adapted from Côté E, ed. *Clinical Veterinary Advisor: Cats and Dogs*. St. Louis: Mosby; 2007.
[b]If a canine 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 or 800-548-2423. They are available 24 hours a day, 365 days a year.

Active Ingredient	Systems Involved	Treatment
Metaflumizone (may be used in combination with amitraz)	Cardiovascular Central nervous Gastrointestinal	**Specific treatment:** • Yohimbine or atipamezole for amitraz **Decontamination:** • Dermal: Bathe with a liquid dish-washing 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 (usually used in combination with permethrin or other pyrethrin/ pyrethroid)	Central nervous Gastrointestinal Integumentary (low toxicity potential)	**Specific treatment:** None **Decontamination:** • Dermal: Bathe with a liquid dish-washing detergent • Oral ingestion: Dilution with milk or water **Supportive:** • Antihistamines or steroids for dermal reaction
Permethrin	Central nervous Gastrointestinal Integumentary Respiratory	**Specific treatment:** None **Decontamination:** • Dermal: Bathe with a liquid dish-washing detergent • Oral ingestion: Emesis or activated charcoal usually not needed **Supportive:** • IV fluids • Monitor temperature, respiration, and central nervous system • Treat symptomatically (diazepam, methocarbamol if needed) • Antihistamines or steroids for dermal reaction
Phenothrin	Central nervous Gastrointestinal Integumentary Respiratory	**Specific treatment:** None **Decontamination:** • Dermal: Bathe with a liquid dish-washing detergent • Oral ingestion: Emesis or activated charcoal usually not needed **Supportive:** • IV fluids • Monitor temperature, respiration, and central nervous system • Treat symptomatically (diazepam, methocarbamol if needed) • Antihistamines or steroids for dermal reaction
Pyriproxyfen (often found in products containing permethrin)	When used alone: Integumentary (low toxicity potential)	**Specific treatment:** None **Decontamination:** • Dermal: Bathe with a liquid dish-washing detergent • Oral exposure: Dilution with milk or water **Supportive:** • Antihistamines or steroids for dermal reaction • Treat for permethrin toxicosis if present

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