

Parasite Prevention

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1. Introduction

Parasiticides include *ectoparasiticides*, *endoparasiticides*, and *endectocides*.

Ectoparasiticides are used to kill parasites on the skin, and include amitraz, pyrethroids, phenylpyrazoles (such as fipronil), neonicotinoids (such as imidacloprid), macrocyclic lactones (such as ivermectin), isoxazolines, and insect growth regulators (such as S-methoprene and lufenuron). Endoparasiticides, also known as internal parasiticides, are used to kill internal parasites. Commonly used endoparasiticides in companion animals are the benzimidazoles (such as fenbendazole), tetrahydropyrimidines (such as pyrantel), and macrocyclic lactones (avermectins and milbemycins). Macrocyclic lactones have activity against both nematodes and arthropods, and so are referred to as *endectoparasiticides*; *endectocides* is another term used to refer to products with activity against both internal and external parasites. Products that target fleas are *insecticides*, whereas products that target ticks are *acaracides*, because ticks are not insects. Combination products that target both internal and external parasites are also examples of endectocides.

In the US, the global market for veterinary parasiticides is projected to grow from USD \$10.6B in 2022 to \$14.1B in 2027. In 2019, it was estimated that parasiticides accounted for 23% of the global animal health market; in 2021, ectoparasiticides accounted for the highest share of the market. In the UK, animal parasiticides accounted for 39% of the market, or £725 million. Pet ownership continues to rise; around two-thirds of households in the US currently own a dog or a cat, and there is widespread use of parasite preventatives among these animals. Parasiticides are widely available from veterinary clinics, online, and over-the-counter. They also come in a variety of formulations, with recent availability of ultra-long-acting products that offer the convenience of heartworm prevention for up to one year. In the United States, there has also been strong guidance based on input from both academia and industry to “administer year-round broad-spectrum parasite control with efficacy against heartworm, intestinal parasites, fleas, and ticks (Companion Animal Parasite Council).” In Europe, the European Scientific Counsel Companion Animal Parasites (ESCCAP) has

lifestyle-based recommendations for flea and tick prevention

(https://www.esccap.org/uploads/docs/cgqtqpf1_0720_ESCCAP_GL3_English_v19_1p.pdf), with regular prevention recommended for all animals with outdoor access. Unfortunately, evidence of resistance has emerged in the literature for both endoparasites and ectoparasites. This has primarily been an issue in livestock but is increasingly of concern for companion animal parasites. Just as there is for antimicrobials, there is a need for antiparasitics with novel mechanisms of action, but there is a lack of new drugs in the pipeline. Other suggested routes have been the development of other approaches, such as parasite vaccines, for prevention. Such approaches may take many years to reach the consumer. In the meantime, given the growth of resistance, concerns regarding environmental contamination, and recommendations for blanket prevention protocols (even in regions where some parasitic diseases are extremely rare), it may be time to re-evaluate recommendations. While use of preventatives in companion animals is critical for human and animal health, indiscriminate use may ultimately lead to such widespread resistance that products are rendered useless. Note that the terms *resistance* and *tolerance* are often used interchangeably, but in contrast to resistance, true tolerance is an intrinsic tendency to be less susceptible to a drug's activity (e.g., ticks are more tolerant of imidacloprid than fleas), whereas true resistance is a heritable trait (Coles and Dryden, 2014).

2. Resistance to Ectoparasiticides in Companion Animals

2.1 Imidacloprid and Pyrethroids

One of the most significant studies of ectoparasiticide resistance took place over 17 years and involved testing of a quarter of a million eggs from over 3000 populations of *Ctenocephalides felis felis* across 10 countries. The drug tested was imidacloprid, which is a nicotine-like compound that blocks nicotinic cholinergic receptors, resulting in insect paralysis and death. Imidacloprid binds insect receptors more strongly than mammalian receptors, accounting for its reduced toxicity in animals. Despite the fact that imidacloprid was the most widely used insecticide in the world between 1999 and 2018, no evidence of resistance to imidacloprid was found in cat fleas. However, imidacloprid is a component of topical products that also contain either pyrethroids (for tick prevention) or moxidectin (for endoparasite prevention). There is widespread evidence of pyrethroid resistance in *C. felis felis* (Rust et al, 2015) and *Rhipicephalus sanguineus* sensu lato (Eidan et al, 2015; Tian et al, 2023). Ongoing drug exposure has the potential to select for pyrethroid-resistant *Ixodes scapularis* (Burtis et al, 2021) and *Amblyomma* spp. ticks (Cardoso et al, 2023). There is also evidence of macrocyclic lactone resistance among *Dirofilaria immitis* and *Ancylostoma caninum*.

Thus, indiscriminate use of imidacloprid in combination products has the potential to select for pyrethroid- or macrocyclic lactone-resistant parasites.

Pyrethroids act by preventing voltage-gated sodium channel closure in axonal membranes. This prevents repolarization, with resultant insect paralysis. They may also have effects on other voltage-gated channels. Examples of pyrethroids used in parasiticides for dogs and cats include permethrin, cyphenothrin, deltamethrin, flumethrin, and etofenprox. Flumethrin and etofenprox have lower toxicity for cats than other pyrethroids.

2.2 Fipronil

Fipronil is a phenylpyrazole. It acts by blocking the ligand-gated ion channel of the GABA_A receptor and glutamate-gated chloride (GluCl) channels, with resultant nerve and muscle hyperexcitation. The lower toxicity for mammals is thought to result from decreased affinity for mammalian GABA_A receptors and the absence of GluCl channels. Although veterinarians have reported apparent lack of efficacy of fipronil against fleas over the last decade, resistance studies showed no evidence of resistance, so reasons other than resistance were thought to explain this (Rust 2020). However, recently phenotypic resistance was identified in the laboratory as a result of increased detoxification by resistant fleas (Ramon-Portugal et al, 2023). The possible existence of fipronil tolerance in *Rh. sanguineus* s.l. has been identified, but fipronil resistance has not been detected in *A. americanum* (Kaplan et al, 2020). Fipronil is often used in combination products with S-methoprene or pyrethroids.

2.3 Macrocyclic Lactones

Macrocyclic lactones consist of the avermectins (such as selamectin, ivermectin, eprinomectin, doramectin) and milbemycins (such as moxidectin and milbemycin oxime). The macrocyclic lactones work by binding glutamate-gated chloride channels in nerve and muscle cells of invertebrates, increasing permeability to chloride ions and causing hyperpolarization, parasite paralysis, and death. Selamectin is used for prevention of a variety of external and internal parasites (Revolution[®], Zoetis). As noted above, moxidectin is included in topical products that contain imidacloprid. Lack of efficacy of macrocyclic lactones against *Dirofilaria immitis* was first suspected around 2005 based on FDA reporting, with definitive evidence of resistance being documented in studies published between 2011 and 2017 (Prichard 2021). Recent research has focused on development of genetic tests to detect and monitor resistance (Kumar et al, 2023), so that the epidemiology of macrocyclic lactone resistance in *Dirofilaria immitis* can be better understood. Evidence of macrocyclic lactone resistance in *Ancylostoma caninum* has grown in the last 5 years, with evidence of spread from greyhound dogs

to the general dog population; such isolates are typically also resistant to benzimidazoles (such as fenbendazole) and imidazothiazoles/tetrahydropyrimidines (pyrantel) (multi-anthelmintic drug resistance [MADR]) (McKean et al, 2024). Resistance to benzimidazoles has been associated with a single nucleotide polymorphism (SNP) F167Y; a recent study showed a polymorphism prevalence ranging from 4% in Canada to 13.4% in the western US.

2.4 Isoxazolines

Examples of isoxazolines are afoxaloner, fluralaner, lotilaner, and sarolaner. Isoxazolines are the newest class of parasiticides and have potent inhibitory effects on glutamate- and GABA-gated chloride channels in invertebrates. Both oral and topical (fluralaner) products are available for prevention of flea and tick infestations in dogs and cats. When used off-label, these products also have efficacy for treatment of mite infestations (Zhu et al, 2021). At the time of writing, no evidence of resistance to isoxazolines exist in parasites from dogs and cats. However, a genetic pathway to resistance in arthropods has been demonstrated *in vitro* (Zhang et al, 2023). Several combination products with isoxazolines exist; these include either moxidectin alone or moxidectin and pyrantel.

3. Pathways to Improved Stewardship

In conclusion, veterinarians now have more highly active parasiticides for dogs and cats than ever before. For optimal effects, these should be used in conjunction with other efforts to control parasites (such as general hygiene, reducing exposure, controlling population density, promoting immunity through good nutrition). For some parasite-parasiticide combinations, the literature provides evidence of a growing resistance problem, but for others, resistance has not yet been reported. Resistance among parasites from companion animals and concerns about environmental impacts of parasiticides suggest that more discussion is needed by veterinary organizations regarding the future of recommendations for parasite prevention in dogs and cats.

References

Available upon request