

Gastro-Intestinal Nematodes

General Information

The nematodes are a class in the animal kingdom with more than 20,000 species described. They have managed to live in a large variety of habitats. Most of these are parasites of plants, animal or humans. In veterinary medicine, parasitic nematodes comprise an important group of endoparasites. Their clinical importance relates to the diseases they may cause in the animal host, as well as the zoonotic potential for pet owners and others.



The Parasite

The term “roundworm” correctly refers to all the nematode parasites of dogs and cats. However, it is commonly used to refer to a family of the nematodes, the ascarids. Ascarids are well known nematodes infecting domestic animals and man. The genera of interest in cats and dogs are *Toxocara* and *Toxascaris* (Figure 1). Roundworms have adapted well to their particular host, which is reflected by their development pattern within the host and the routes of infection.





Figure 1: Mouth of *Toxascaris*

Life Cycle

The adult worms live in the small intestine of dogs and cats, feeding on the intestinal contents and desquamated epithelial cells. Female roundworms produce eggs that pass out in the faeces. The ascarid eggshell is capable of withstanding extreme environmental conditions and remains infective in soil for many years. The infective L3 larval stage develops within the eggshell and hosts can become infected by ingesting the egg with the infective larvae.

Toxascaris leonina:

Development to the infective larval stage occurs rapidly, in about one week. If ingested by the suitable host, the larvae is released in the stomach and enters the mucosa of the small intestine, where further development occurs. The larvae will leave the mucosa and return to the intestinal lumen to mature. In cases where the egg is ingested by animals such as rodents, the larvae will also migrate to the mucosa, but then go on to invade body tissues. Therein the larvae under

goes a encystation and remains as arrested infective stage. Rodents and other such unsuitable hosts thus function as intermediate or paratenic hosts. Infection with *T. leonina* in cats or dogs occurs by oral ingestion of the egg with the infective larvae (Figure 2), or by predation of small mammals such as rodents, with the encysted larvae.

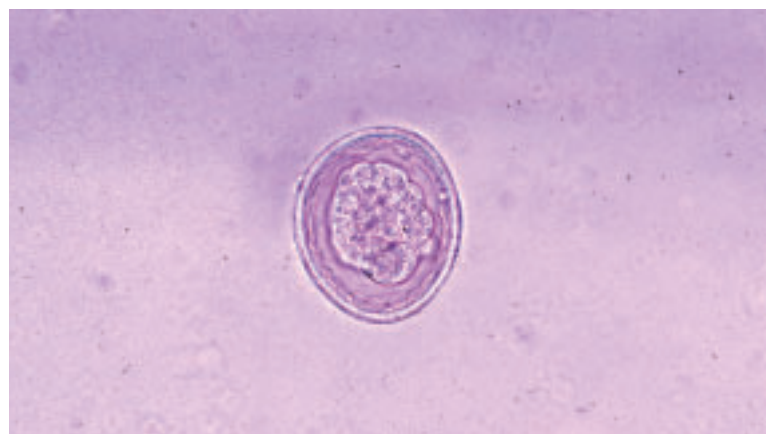


Figure 2: *Toxascaris leonina* egg

***Toxocara canis*:**

Larvae develop within the eggshell to the infective L3 stage within about 2 weeks time, however this is temperature dependent. The development of *T. canis* larvae within the dog is rather complex. Larvae undergo intensive migration within their host, while the route of migration differs depending on the dogs age as well as other factors. The larva hatches in the stomach or small intestine and enters the mucosa. From there the larva starts a migration through various body tissues, such as the liver or lungs. Within the lungs, the larvae may stay within the blood vessels and are then carried to other body tissues where they

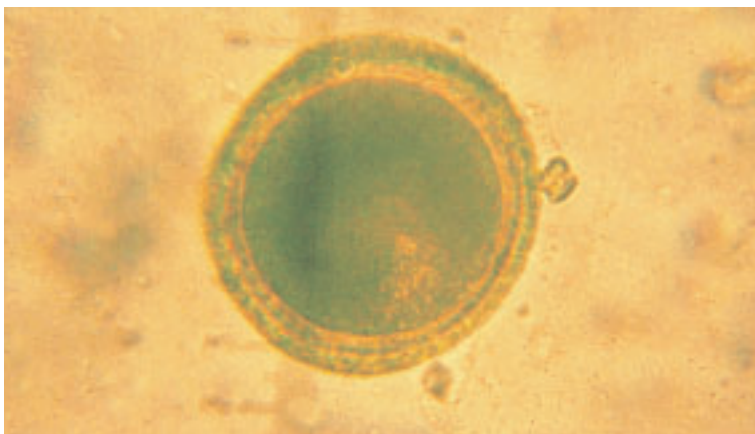


Figure 3: *Toxocara canis* egg

encyst. This developmental route is referred to as somatic migration and is the most common occurrence in adult dogs. Another pathway for the larvae is to break through the alveolar wall and enter the airway of the lungs, where they are coughed up and swallowed. This tracheal migration leads to sexual maturity within the gastrointestinal tract. The somatic migration is an important pathway for infection of paratenic or intermediate hosts. Thus, the prey-predator relationship used by *Toxocara* is a very important factor in epidemiology, in addition to the

resistance of the egg in the environment (Figure 3). This is even more so as the larvae undergoes changes within the paratenic host. When taken up by the definitive host, the dog, the larvae has shortened development and may go on to develop within the intestinal tract to maturity.

In addition to the various routes of migration, the infection of the female mature dog with arrested larvae is important as a route for passing the infection to the pups. In the last trimester of pregnancy, arrested larvae are reactivated by hormonal changes in the bitch. When the encysted larvae become reactivated, they begin migration with a tissue preference for the uterus as well as the mammary gland. In this way, they may enter the placenta and infect the puppies prior to parturition, or right after while the puppies are suckling milk. However, for *Toxocara*, the uterine route of infection is of primary importance. This is in contrast to the hookworm *A. caninum*, for which the galactogenic route is important for infection of puppies.

***Toxocara mystax (syn. T. cati)*:**

The migration pathway of *T. cati* in cats is very similar to the one of *T. canis* in dogs. However, some differences are seen. The most notable difference is that prenatal infection of the kitten via the placenta does not occur. Larvae entering cats via ingested eggs with infective larvae demonstrate the previously-described tracheal migration in both young as well as adult cats. Because the prey-predator relationship is even more prominent in cats than in dogs, the hunting of rodents is probably the most important way of cats acquiring roundworm infection. Although the probability of cats ingesting eggs via faeces or soil is limited, oral infection related to the intensive grooming activities of cats should not be ignored.

Pathogenesis and Clinical Appearance

Dogs, as well as cats, heavily infected with adult *Toxocara* (Figure 4) suffer from enteritis that can interfere with digestion and result in mal-absorption of food. Infection, especially in puppies and kittens, may be responsible for impaired growth and development, as well as clinical signs such as coughing, runny nose, vomiting after feeding, abdominal sensitivity to pressure, slimy unformed feces and even intestinal obstruction by entangled worms. Such heavily-infected animals commonly become jaundiced and emaciated and have a ruffled, unkempt coat. Young or adult dogs with mild infections are frequently asymptomatic or simply fail to gain weight. However, these animals remain important as a reservoir of infection, contaminating the environment and capable of passing the infection to other susceptible hosts, including man.

Prenatal infection with *T. canis* results in abdominal pain in newborn puppies. Often the whole litter is affected and puppies remain agitated, making shrieking noises even after feeding. Immature as well as adult worms are passed with the faeces or vomitus. However, this often goes unnoticed by the owner due to the bitches intensive cleaning habits. Death may occur in heavy infections due to rupture or obstruction of the intestine.

Infection and somatic migration of larvae may cause hypersensitivity and allergic reactions. On haematological examination, eosinophilia would be the characteristic sign of infection.

Zoonotic Significance

If a person accidentally swallows infective *T. canis* eggs from the environment, the parasite migrates through the

body without undergoing development into an adult worm in the gut. This migration, known as “*visceral larva migrans*”, can cause serious disease if the larvae reach body tissues such as the brain or the eye. The dog or cat is not a direct source of infection to people, rather it is the egg deposition in the environment that causes a potential source of infection. Because eggs of *T. canis* remain infective in the soil for years, contaminated areas may become a hazardous source of *visceral larva migrans* infection, especially for children. Cases of *visceral larva migrans* from *T. leonina* have been reported, however, it seems to be of less importance than the risk from *T. canis*.



Figure 4: *Toxocara canis*

Diagnosis

The eggs of *T. canis* are round in shape with a tick shell. The outer surface of this shell shows a characteristically rough surface (Figure 3). In contrast, the egg surface of *T. leonina* is smooth (Figure 2). These characteristics are used to differentiate between species. The eggs of both species measure 70 - 80 μm in diameter. Flotation methods are used to enrich eggs passed with the faeces. For larval infection with *Toxocara*, serologi-

cal enzyme-linked immunosorbent assay (ELISA) and indirect fluorescent antibody test (IFAT) methods have been described.

Clinical Efficacy of Advocate Against Adults

Dose-confirmation studies in dogs and cats

A large series of dose determination and dose confirmation studies have been conducted with Advocate in a range of endoparasites in dogs and cats¹. The dose rate and concentration of imidacloprid was fixed by the adoption of the Advantage formulation. This also had the effect of fixing the dose volume. Therefore, it was necessary to adjust the dose of moxidectin by adding different concentrations of moxidectin to this formulation. Initial

dose determination studies in dogs were conducted using *T. canis* and *A. caninum*, as it was recognised that larval *D. immitis* was not going to be a dose limiting species. The studies demonstrated, in fact, that the ascarid *T. canis* was the least sensitive species; thus, for dose finding/dose confirmation studies, *T. canis* was the roundworm species chosen. The initial dose determination studies in dogs were performed with moxidectin concentrations between 1.0 - 7.5%, corresponding to a dosage between 1.0 and 7.5 mg/kg b.w.. All studies were critical studies and efficacy was based on the number of worms remaining at final examination (Table 1).

Initial dose finding studies were also carried out in cats adding different moxidectin concentrations to the standard 10% imidacloprid formulation. Concen-

Table 1: Dose finding studies with 10% imidacloprid and different concentrations of moxidectin for treatment of *T. canis* in dogs

Concentrations 10% Imidacloprid +	Dosage (mg/ kg)	Efficacy % (arithmetic mean)
1.0 % Moxidectin	10/1.0	83.3
1.75 % Moxidectin	10/1.75	71.4
1.75 % Moxidectin	10/1.75	96.5
2.5 % Moxidectin	10/2.5	98.2

Table 2: Dose finding studies with 10% imidacloprid and different concentrations of moxidectin for treatment of *T. cati* in cats

Concentrations 10% Imidacloprid +	Dosage (mg/ kg)	Efficacy % (arithmetic mean)	
		<i>A. tubaeforme</i>	<i>T. cati</i>
0.25 % Moxidectin	10/0.25	-	72.6
1.0 % Moxidectin	10/1.0	100	98.4
1.75 % Moxidectin	10/1.75	-	99.5
2.5 % Moxidectin	10/2.5	100	100

trations of moxidectin tested were between 0.25 and 2.5%. All studies were critical studies conducted in accordance with international guidelines. As was determined to be the case for dogs, an ascarid, *T. cati*, was the dose-limiting nematode species for moxidectin in cats (Table 2).

Dose confirmation studies were carried out in Europe and the USA to confirm the efficacy of the 10% imidacloprid + 2.5% moxidectin in dogs and the 10% imidacloprid + 1.0 moxidectin in cats². The respective efficacies, which were calculated by comparing geometric mean worm counts from treated animals with those of untreated controls, confirmed a 100% efficacy against *T. canis* in dogs and *T. cati* in cats.

Dogs

In clinical as well as multi-centered field studies, the efficacy of Advocate was evaluated for treatment of natural patent *T. canis* and *T. leonina* infections in dogs³. Two studies for treatment of *T. canis* and two for *T. leonina* were performed. In the *T. canis* studies, the mean worm counts in the placebo treated groups were 6.3 and 18.1 respectively, in *T. leonina* studies a mean of 19.1 and 20.4 worms. The efficacies of Advocate was calculated as shown in Table 3.

One can conclude from the multi-centered field studies that Advocate is highly efficacious in dogs against natural infections with *T. canis* (98.8%), as well as hookworms (99.9%). A similar study was conducted to determine the Advocate efficacy under field conditions in cats.

Table 3: Efficacy of Advocate for treatment of patent infections of *T. canis* and *T. leonina* in dogs

Parasite	No. worms placebo/ Advocate groups	Geo. Mean no. worms		Efficacy (%)
		Placebo	Advocate	
<i>T. leonina</i>	70/ 0	20.4	0	100
<i>T. canis</i>	149/ 1	18.1	0.1	99.5
<i>T. leonina</i>	168/ 8	19.1	0.6	97.0
<i>T. canis</i>	91/ 0	6.3	0	100

Table 4: Efficacy of Advocate against L4 and immature adults of *T. canis* in dogs

<i>T. canis</i> Developmental stage		Efficacy (%)		Geo. mean worm counts at day 19 p.i.*		Geo. mean worm counts at day 29 p.i.	
Study		Day 20*	Day 29	Advocate	Control	Advocate	Control
1	L4	91.6	98.6	0.07	0.83	0.2	13.8
1	Immature adults	-	100	-	-	0.0	0.93
2	L4	97.6	99.0	0.15	3.51	0.0	3.27
2	Immature adults	-	99.0	-	-	0.15	12.6

* Study 1: counts performed on day 19; Study 2: counts performed on day 20.

Table 5: Efficacy of Advocate against L4 and immature adults of *T. cati*

<i>T. cati</i> Developmental stage	Efficacy (%)		Geo. mean worm counts at day 19 p.i. (SD ±)		Geo. mean worm counts at day 29 p.i. (SD ±)	
	Day 19	Day 29	Advocate	Control	Advocate	Control
L4	100	97	0	5.1 (3.7)	0.2 (0.01)	5.8 (7.3)
Immature adults	-	91	-	-	0.3 (0.02)	3.5 (5.3)

Advocate at the dosage of 1.0 mg/kg b.w. moxidectin was 99.9 % effective against *T. cati* and 99.6% against hookworms.

Cats

Clinical as well as multi-centered field studies have been conducted to evaluate the efficacy of Advocate for the treatment natural patent *T. cati* infections in cats³. The geometric mean numbers of *T. cati* from cats in the placebo treated control group and the imidacloprid group were 7.3 and 7.5 worms, respectively. The Advocate treated group and the moxidectin treated group had geometric mean counts of 0.0 worms. Therefore, Advocate demonstrated an efficacy of 100% for the treatment of *T. cati*.

Clinical Efficacy of Advocate Against Immature Worms

Dogs

The efficacy of Advocate in dogs against immature (L4 larval stage) and pre-adult stages of *T. canis* was evaluated in experimental infections³. Dogs were infected orally at study day 0 with 300 infective stages of *T. canis*. Advocate was then applied at either day 14 or 24 post infection. A placebo treated group served as a control. The worm burdens were determined in animals of both groups 5 or 6 days after treatment – i.e. on day 20 p.i. for efficacy against L4, and on day 29 p.i. for efficacy against immature adults. The two similar studies were conducted

in Europe and in North America. The efficacy of Advocate was calculated in comparison to the control group (Table 4).

Cats

To evaluate the efficacy of Advocate against immature and pre-adult stages of *T. cati*, cats were experimentally infected on study day 0⁴. Treatment was carried out at the time of expected maximum L4 population, on day 14 p.i., and for immature adults, which are in the small intestine on day 24 p.i. In general, days 14 and 24 p.i. represent times before patency is achieved for *T. cati*, which occurs from day 42 p.i. onwards. A placebo treated group served as a control. The worm burdens were determined for animals in both groups 5 days after treatment - on day 19 p.i. to determine efficacy against L4, and on day 29 p.i. for efficacy against immature adults. The efficacy of Advocate was calculated in comparison to the control group (Table 5).

References

1. Bayer internal research studies, data on file.
2. Hellmann K, Knoppe T, Radeloff I, Heine J. The anthelmintic efficacy and the safety of a combination of imidacloprid and moxidectin spot-on in cats and dogs under field conditions in Europe. *Parasitol Res* (2003) 90:S142-S143.
3. Bayer internal research studies, data on file.
4. Samson-Himmestjerna GV, Epe C, Schimmel A, Heine J. Larvicidal and persistent efficacy of an imidacloprid and moxidectin topical formulation against endoparasites in cats and dogs. *Parasitol Res* (2003) 90:S114-S115.

Further Reading

- Reinemeyer CR, Charles S. Evaluation of the efficacy of a combination of imidacloprid and moxidectin against immature *Toxocara cati* in cats. *Parasitol Res* (2003) 90:S140-S141.



Hookworm

The Parasite

Hookworms are blood sucking nematode parasites of many mammalian species, including man. Hookworms are distributed world-wide and a major nem-



Figure 5: *Ancylostoma caninum*

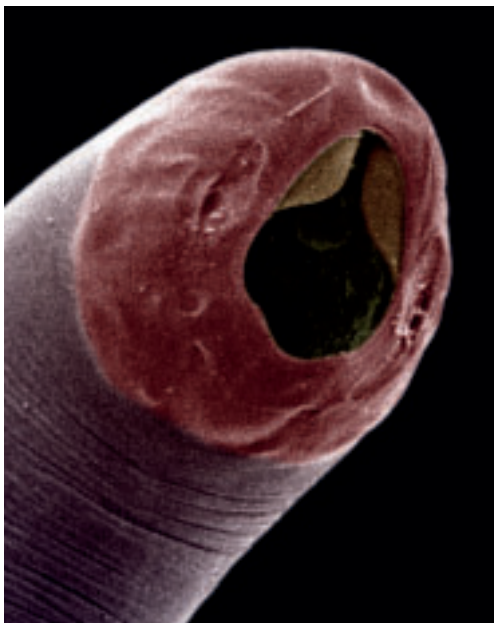


Figure 6: *Uncinaria stenocephala*

atode infection causing clinical signs in dogs of all ages. The name is derived from the distinctive “dentition” of the parasite. The mouth cavity of *A. caninum* (Figure 5) and *A. tubaeforme* has three pairs of sharp teeth at the ventral rim, while *U. stenocephala* lacks these teeth and the stoma is instead armed with rounded plates (Figure 6). *A. caninum* are the larger hookworms, with females measuring 15 - 18 mm (males 9 - 12 mm, Figure 7). In comparison, *U. stenocephala* females normally measure of 7 - 12 mm and males 4 - 5 mm in length.

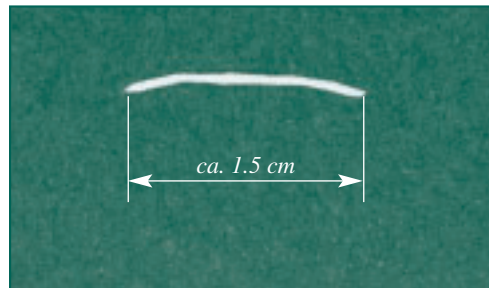


Figure 7: *Ancylostoma caninum*

Life Cycle

The development of all hookworm species in the environment is rather similar. Hookworm eggs passed in dog or cats faeces contain a 6 - 8 cell morula. The larva hatches from the egg and reaches the infectious stages after two moults. The development in the environment is highly temperature and humidity dependent and has been reported to be as short as 6 - 10 days. *Ancylostoma* is more prevalent in warmer climates, while *Uncinaria* is adapted well to the temperate climates and larvae are even able to survive over winter. It is these larvae in the environment that are the principle source of infection.

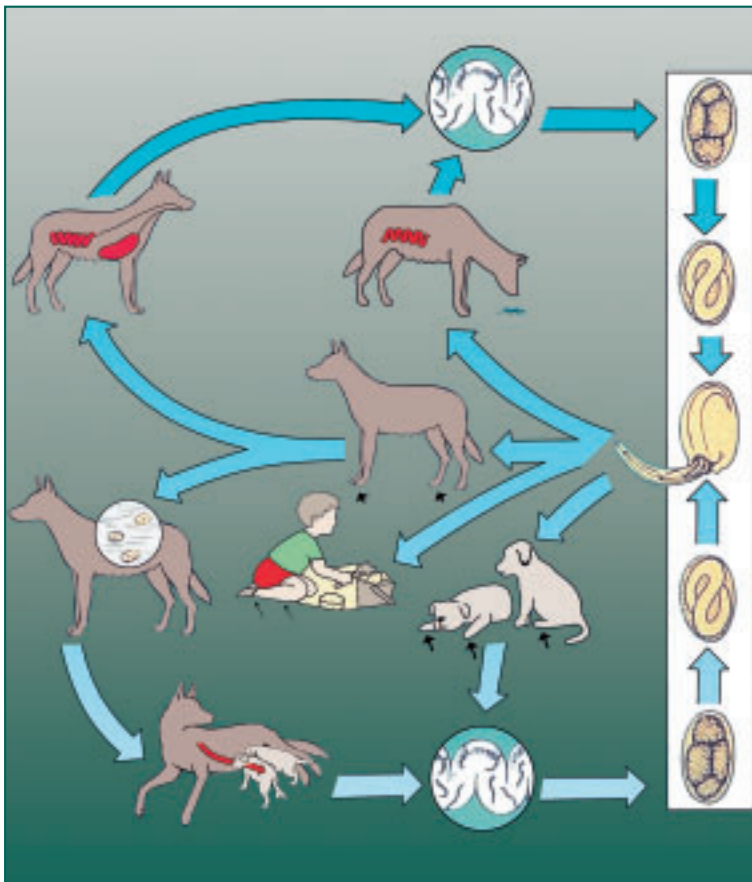


Figure 8: Routes of infection for hookworms

Infection of the definitive host, the dog or cat, occurs in different ways depending on the hookworm species and the age of the host animal (Figure 8). The most important way of hookworm larvae entering their host is by active penetration of the skin. This penetration occurs via the hair follicles and thus the larvae do not use any enzymes to break the skin barrier. Their migration is directed by positive chemotaxis towards blood or lymph fluids. Larvae are carried with the blood flow toward the gastrointestinal-tract or even migrate into the body tissues, primarily musculature. In pregnant and lactating bitches, larvae migrate toward the mammary glands and release with the milk to infect puppies via oral ingestion. Larvae are found in the milk for up to four weeks post partum, however, the majority are secreted within the first week after birth. In experimentally infected female dogs, it could be demonstrated that larvae were secreted in the milk for at least 3 consecutive lactations.



Figure 9: *Ancylostoma caninum*

Pathogenesis and Clinical Appearance

Hookworms are regarded as nematodes that feed on both blood and intestinal mucosa (Figure 9). Using the sharp teeth of the mouth cavity, they suck mucosal tissue and then digestion of the mucosa due to enzyme exposure occurs. While the mucosa is digested, underlying exposed small blood vessels burst and blood is released from the lesions. In a short time interval, the feeding nematode is attached to a new site, thus, after a brief period of time, mucosal lesions with petechial bleeding are visible. Experimental studies have shown daily blood intake from adult worms to be about 0.12 ml. The blood loss can lead to erythropenia, reduction of blood haemoglobin or decreased packed cell volumes. This

microcytic hypochrome anemia is due to the loss of iron. In addition, the loss of proteins adds to the severity of clinical signs.

Clinical signs are highly dependent on the severity of worm burden, as well as age and nutritional status of the animal. Low to medium worm burdens may lead to wasting and reduced growth in puppies. Heavy worm burdens result in diarrhoea containing fresh blood from mucosal lesions, and are a cause of death in highly infected litters.

Cutaneous infection with larvae may cause erythema at the penetration sites. The clinical signs that follow are dependent on the migration of the larvae within the body tissue. For example, when larvae reach the brain, ataxia may be seen. Some authors classify the clinical signs of hookworm infections into three categories. A peracute infection occurs as a result of infection in nursing puppies via the milk of their mothers. An acute form with sudden exposure of high numbers of larvae can be found in older puppies and up to adulthood. The chronic stage is characterised by dogs infected with low numbers and shedding eggs, while clinical signs may be absent.

It is commonly found with hookworms that their development in the host may be slowed by a variety of factors such as a sudden drop in temperature, hormonal imbalance of the host or intrinsic factors of the larvae itself. This is referred to as hypobiosis.



Figure 10: Creeping eruption caused by hookworm infection

Zoonotic Significance

Cutaneous larva migrans in man, also known as “creeping eruption”, is a dermatitis caused by migrating hookworm larvae (Figure 10). Infection occurs through skin contact with infective larvae and the most common sources of infection are shaded moist sandy areas or soil that has become contaminated via the faeces of infected dogs or cats. The clinical symptoms in humans are erythema at the sites of infection and intensive pruritus. The severity, and also persistence, of the skin lesions are related to the immune status of the individual person. Hypersensitivity related to previous infection has been reported. Although a few cases of adult dog hookworms in the intestines of

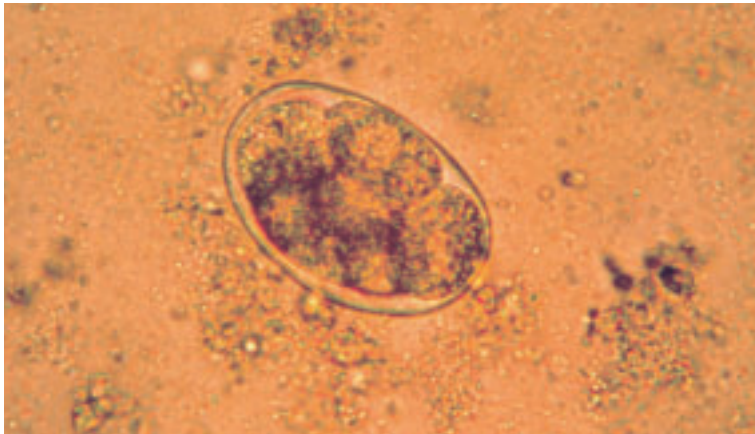


Figure 11: *Ancylostoma caninum* egg

man have been reported, the risk of such infections does not appear widespread.

Diagnosis

Diagnosis of hookworm infection in very young puppies by faecal egg count (FEC) may be hard to detect because the mothers clean up the puppies’ faeces right after defecation. Eggs of *A. caninum* (Figure 11) and *U. stenocephala* are soft-shelled nematode eggs, countaining 4 - 8 cell morulae in fresh faeces. In general, *A. caninum* eggs are shorter and larger in width than *U. stenocephala*.

The size is recorded at about 53 - 69 x 36 - 53 µm for *A. caninum* and 75 - 85 x 40 - 45 µm for *U. stenocephala*. However, although the diagnosis of a hookworm egg is easily done, species determination requires some experience. Today, polymerase chain reaction (PCR) techniques are in place to determine the presence of even low worm burdens and allow accurate species identification, although this is available in research or epidemiological studies, while and performed less in general diagnostics.

Clinical Efficacy of Advocate Against Adults

Dose-confirmation studies in dogs and cats

The dose confirmation studies confirmed the results from the dose titration studies, indicating that moxidectin is very effective against hookworms and that neither *A. caninum* and *U. stenocephala* in dogs, nor *A. tubaeforme* in cats, are dose-limiting nematode species. In dose titration studies using dosages of moxidectin between 1.0 and 7.5 % in the standard 10% imidacloprid formulation, the efficacy for treatment of hookworms in

Table 6: Efficacy of Advocate against *A. caninum* and *U. stenocephala* in dogs

Study No.	Treatment group	Hookworm	Infection	No. dogs	Geo. mean worm counts	Efficacy (%)
1	Advocate	<i>U. stenocephala</i>	experimentally	8	0.0	100
1	Placebo	<i>U. stenocephala</i>	experimentally	8	28.6	-
2	Advocate	<i>U. stenocephala</i>	natural	8	0.0	100
2	Placebo	<i>U. stenocephala</i>	natural	8	221.3	-
3	Advocate	<i>A. caninum</i>	natural	8	0.0	100
3	Advocate	<i>U. stenocephala</i>	natural		0.0	100
3	Placebo	<i>A. caninum</i>	natural	8	31.1	-
3	Placebo	<i>U. stenocephala</i>	natural		26.4	-

dogs was 100%¹. Several of these studies were conducted very early in the product development phase using experimental, as well as natural patent, hookworm infections in dogs. As was demonstrated with the studies in dogs, the efficacy against patent adult stages of *A. tubaeforme* hookworm species in cats was 100%.

Dogs

Studies were conducted evaluating both hookworm species, *A. caninum* and *U. stenocephala*, in dogs. While efficacy against *Ancylostoma* hookworms has been documented in many dose finding, dose confirmation, as well as multi-centered field studies², the efficacy of Advocate for treatment of *U. stenocephala* was evaluated in studies with natural and experimental infections. In the experimental study, dogs were infected orally with 300 infective larvae and treated with a dosage of 2.5 mg/kg b.w. 18 days post-infection to evaluate the persistent efficacy of the product. Final examination was performed at the end of the pre-

patent period, at 21 days p.i. Advocate demonstrated 100% efficacy against a patent hookworm infection, as well as 100% persistent efficacy³(Table 6).

Cats

Several efficacy studies have been conducted as critical tests to evaluate the efficacy of Advocate for treatment of *A. tubaeforme* in cats⁴. In one study, 20 cats were experimentally infected with hookworm larvae at day 0 of the study and randomised to either a placebo treated control or an Advocate treated group. Treatment was performed at day 21 post-infection at a dosage of 1.0 mg/ kg b.w. (moxidectin). Upon final examination in this critical test, a geometric mean of 16.9 worms were recovered from the placebo treated cats, while the ten cats treated with Advocate were free of worms. The efficacy was calculated as 100%. The efficacy of Advocate was evaluated in another study conducted in the South Africa, in 24 cats harbouring natural hookworm infections. Cats were randomised to placebo control or Advo-

Table 7: Efficacy of Advocate against natural hookworm infections in cats

Study Group	No. cats	Geo. mean worm counts		Efficacy (%)
		<i>A. tubaeforme</i>	<i>A. braziliense</i>	
Advocate	12	0.0	0.0	100
Placebo control	12	2.32	19.9	-

Table 8: Efficacy of Advocate against L4 and immature adult stages of *A. caninum* and *U. stenocephala* in dogs

Hookworm	Efficacy (%)		Geo. mean worm counts at day 12 p.i.		Geo. mean worm counts at day 17 p.i.	
	Day 12	Day 17	Advocate	Placebo	Advocate	Placebo
<i>A. caninum</i>	100	100	0.0	9.3	0.0	9.4
<i>U. stenocephala</i>	100	100	0.0	36.7	0.0	44.4

cate treatment groups and treated at day 0 according to label instructions. The results upon final examination 10 days post-treatment are shown in table 7.

Among the species diagnosed naturally infecting these cats was *Ancylostoma braziliense*. Even though evaluating *A. braziliense* was not the main propose of this study, the results showed a 100% efficacy against both hookworm species present in these cats (Figure 7).

Clinical Efficacy of Advocate Against Immature Worms

Dogs

The efficacy against immature stages of *A. caninum* and *U. stenocephala* was tested in experimentally infected dogs⁵. Dogs were infected with infective larvae of both hookworm species on study day 0. Treatment was performed using the recommended label dosage at day 7 post-infection to determine the efficacy against the L4 stage, and on day 11 p.i. for the immature and adult stages. On final examination 5 days p.t., the efficacy of treatment on both hookworm species was determined. Advocate proved to be

100% effective against larval and immature stages (Table 8).

Cats

To evaluate the efficacy of Advocate against immature stages of hookworms in cats, several studies have been conducted^{3, 4}. Cats were experimentally infected with 300 infective larvae of *A. tubaeforme* at study Day 0. Advocate was applied at a dosage of 1.0 mg/kg b.w. (moxidectin) at the time of maximum L3/L4 population, on day 7 p.i.. A second group in this study was treated at day 11 p.i. – a time when immature adults are present in the small intestine. Therefore, the Advocate treatment was well before patency is expected, from day 21 p.i. onwards. A control group was treated with a placebo only. The worm burdens were determined and the efficacy in Advocate treated cats compared to the control group was calculated in accordance with international guidelines. Thus, final examination was conducted 5 days p.t. – i.e. on day 12 p.i. for efficacy against L4 and on day 16 p.i. for efficacy against immature adults. Advocate was 100% effective against larval and immature stages of the cat hookworm (Table 9).

Table 9: Efficacy of Advocate against larval and immature adult stages of *A. tubaeforme* in experimentally infected cats

Developmental stage	Efficacy (%)		Geo. mean worm counts at day 12 p.i. (SD ±)		Geo. mean worm counts at day 16 p.i. (SD ±)	
	Day 12	Day 16	Advocate	Control	Advocate	Control
L3	100	100	0	9.1 (15.1)	0	5.0 (4.2)
L4	100	100	0	36.2 (23.3)	0	45.9 (26.4)
Immature adults	100	100	0	2.8 (3.8)	0	4.6 (7.0)

References

1. Bayer internal research studies, data on file.
2. Hellmann K, Knoppe T, Radloff I, Heine J. The anthelmintic efficacy and the safety of a combination of imidacloprid and moxidectin spot-on in cats and dogs under field conditions in Europe. *Parasitol Res* (2003) 90:S142-S143.
3. Samson-Himmestjerna GV, Epe C, Schimmel A, Heine J. Larvicidal and persistent efficacy of an imidacloprid and moxidectin topical formulation against endoparasites in cats and dogs. *Parasitol Res* (2003) 90:S114-S115.
4. Bayer internal research studies, data on file.
5. Bayer internal research study, data on file.



Whipworm

The Parasite

Whipworms are parasites of the caecum and, in heavy infections, the colon of many mammalian species. The canine whipworm, *Trichuris vulpis*, is found world-wide and is occasionally of considerable clinical significance. There is no evidence that *T. vulpis* is capable of infecting cats. *T. vulpis* measures 45 - 75 mm in length and the male worms possess a very long spiculum at the rear end. As for all whipworms, the *T. vulpis* body has the typical name-giving feature of a long and thin, hair-like anterior part and a short and thick posterior body part (Figure 12).

Life Cycle

The whipworm has a direct life cycle. Inside the excreted egg, the infective larval stage (L2) develops within 3 to 4 weeks. Under optimal conditions, this may occur in even less than 2 weeks. However this development can also be prolonged for as long as several months. Infective eggs may survive in soil for several years and be a source of re-infection for dogs exposed to a contaminated environment. After ingestion, the larvae hatch and penetrate the mucosa of the gastrointestinal tract. Here, development occurs and migration to the mucous glands of the caecum, where the adult stages can be found. The pre-patent period of *T. vulpis* is reported to be 70 - 100 days, and adults live for up to 16 months. There is no age restriction for whipworm infections.

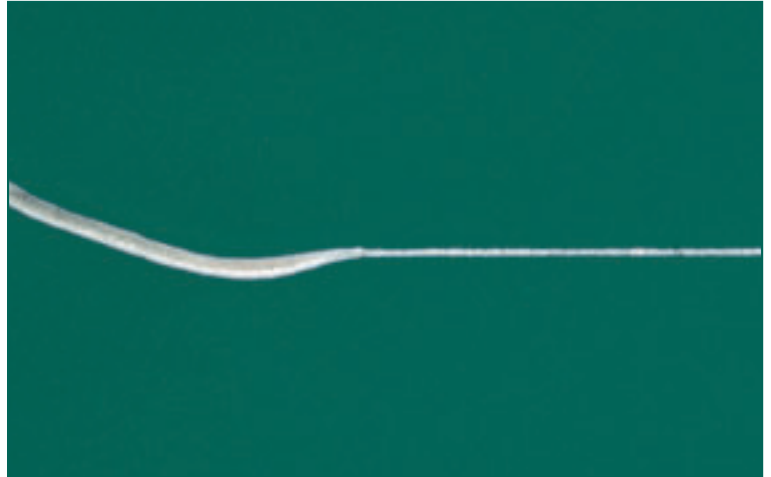


Figure 12: *Trichuris vulpis*

The eggs are in lemon-shaped with distinct plugs on both pole sides. As mentioned previously, the eggs can survive for long periods in the soil, however they are affected by desiccation.

Pathogenesis and Clinical Appearance

T. vulpis is a blood feeding nematode, with the anterior end of the body embedded in the mucosa of the caecum. In heavy infections, the mucosa may show thickening, oedema, and petechial bleeding. Clinical signs of massive infec-

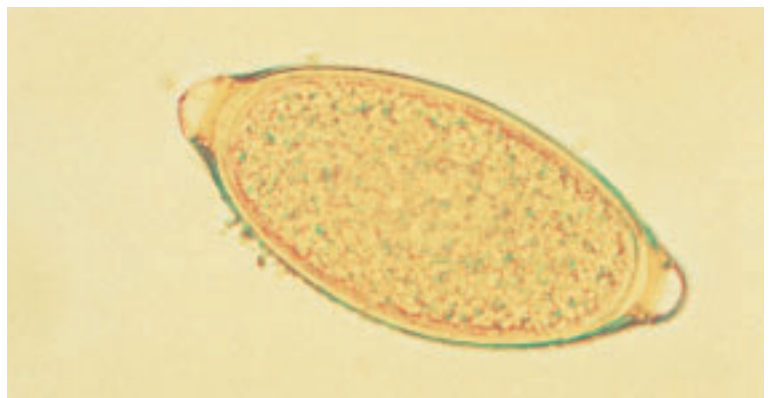


Figure 13: *Trichuris vulpis* egg

tions are hemorrhagic enteritis, with mucus and blood in the faeces and often foul smelling. Concurrent anaemia may also be present. The slow development time of *T. vulpis*, together with mainly sub-clinical signs, may be the reason for the general belief that whipworm infections in dogs may be less pathogenic. However, infections may cause reduced growth in young dogs and wasting.

Zoonotic Significance

On rare occasions, the common whipworm of dogs has been reported in man. However, in comparison to hook- and roundworms, *T. vulpis* does not play a zoonotic role of importance in transmission to humans.

Diagnosis

The lemon-shaped eggs with plugs on both ends are clearly distinguishable (Figure 13). The egg size is 70 - 85 µm in length and 35-40 µm in width.

Clinical Efficacy of Advocate

In a number of the pivotal dose-confirmation studies in dogs evaluating natural infections with other gastrointestinal nematodes, the whipworm *T. vulpis* was identified¹. In many of these studies, the faecal-egg counts on day 0 prior to treatment were of similar levels in the treatment and control groups. Out of 5 studies, a total of 830 worms were recovered from 20 control dogs, while only 2 worms were identified in one Advocate treated dog. All other Advocate-treated dogs were whipworm free. The efficacy against *T. vulpis* was 96 - 100% in all of these five studies.

This corresponded well with a specific study conducted in dogs naturally infected with whipworm². Twenty-two whipworm-positive dogs were randomly allocated to either a placebo treated control group or a Advocate treated group. On day 0 of the study, Advocate was applied using one of the four pipette sizes according to the respective body weight range of each of the dogs. All dogs were examined 10 days post-treatment. The efficacy of Advocate against patent whipworm infections was 97% (Table 10).

Table 10: Efficacy of Advocate against natural whipworm (*T. vulpis*) infection in dog

Study group	Dogs/group	Geo. mean worm counts	Efficacy (%)
Advocate	11	0.4	97
Control	11	15.5	-

References

1. Bayer internal research studies, data on file.
2. Bayer internal research study, data on file.