HealthforAnimals: “White Paper” of the Cross Functional Team on the Anthelmintic Resistance in Companion Animals

I. Executive Summary

The close contact between pet owners and their dogs or cats imposes a risk of transmission of zoonotic diseases and has to be taken into account for good animal hygiene and health management. Control of infection with gastrointestinal worms (helminths), either with roundworms (nematodes) or tapeworms (cestodes), is important not only to keep the animals healthy, but also to avoid any risk to pet owners. Most worm species in pets are host specific, but a few species have the potential to infect humans. Despite the frequent use of anthelmintics, there is so far no anthelmintic resistance known to occur in dogs or cats except for one historical report on pyrantel resistance of hookworms from Australia. The biology and epidemiology of worms in dogs and cats makes development of anthelmintic resistance in these species very unlikely, in contrast to livestock (cattle, sheep, and horses). Therefore, there is limited risk to select for anthelmintic resistance when using the currently available products. Moreover, there is no risk of the transfer of resistance from animal worms to human pathogenic worm species or other infectives. We strongly recommend following the guidelines of the representative organizations (CAPC, ESCCAP, and TroCCAP) for the prevention or control of worm infections in dogs and cats.

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II. Health for Animals White Paper on Anthelmintic Resistance in Companion Animals

1. *Scope of white paper*

This position paper aims to provide an overview of the current knowledge on anthelmintic resistance in gastrointestinal helminths (worms) in companion animals, with a focus on dogs and cats. This position paper does not focus on external parasites (ectoparasites - ticks, fleas) or heartworm of dogs and cats.

2. *Background*

Pet ownership, especially of dogs and cats, is increasing in all parts of the world year over year. Dogs and cats are often considered to be family members, thus they are true companion animals. The human-animal bond is very strong and these companion animals belong to households almost like if not equal to other family members and share close interactions with their owners. This close contact imposes a risk of transmission of zoonotic diseases and has to be taken into account for good animal hygiene and health management. The importance of adequate internal parasite (endoparasite) control, particularly worms (helminths), is outlined in this paper. The control of infection with worms (helminths), either with nematodes, also known as roundworms, or with cestodes, (known as tapeworms) is important for health management not only to keep the animals healthy, but also to avoid risks to their owners. Guidelines on deworming with regard to anthelmintic use have been established around the globe covering the different challenges associated with the species of parasites present in various regions. For Europe the ESCCAP* guidelines, North America those from CAPC* and just recently for the tropics and subtropics guidelines established by TroCCAP* clearly define helminth distribution and frequency of deworming. In this paper, we focus on the potential anthelmintic resistance in companion animals, which appears to be different from that in farm animals due to major differences in treatment protocols and parasite biology.

3. *What is anthelmintic resistance ?*

Anthelmintic resistance can be defined as the heritable ability of a parasite to withstand the usual effects of concentrations of an anthelmintic agent achieved after recommended therapeutic doses were administered. This is due either to the presence of specific alleles of genes in the original, susceptible population, which can confer at least partial resistance, or to the production of new alleles (via mutation or recombination) or new combination of alleles which are then selected preferentially. This selection process results from the imposition of selection pressure, i.e. the repeated administration of anthelmintics, whether highly or partially effective. Anthelmintic resistance is present when there is a greater frequency of individuals within a population with a heritable ability to tolerate therapeutic doses of an agent than in a normal population of the same species (Prichard et al., 1980).

4. *Biology of gastrointestinal (GI) helminths of dogs and cats*

Dogs and cats can become infected with a large spectrum of worms located in the gastro-intestinal tract. Of most relevance are roundworms (*Toxocara* spp. and *Toxascaris* spp.), hookworms (*Ancylostoma* spp. and *Uncinaria* spp.), whipworms (*Trichuris* spp.) and tapeworms (*Taenia* spp., *Echinococcus* spp., *Dipylidium caninum*, *Mesocestoides* spp., *Diphyllobothrium latum*). While these parasites are all located in the small or large intestine as adult stages and shed eggs with the feces, their morphology, biology and life cycles vary considerably.

a. Roundworms, hookworms and whipworms

Oral uptake of infectious *Toxocara* and *Toxascaris* eggs or of larvae in paratenic hosts (hosts that are not necessary for the development of a particular species of parasite, but can serve as an accidental host) may lead to infection in dogs and cats. Of much more relevance in *Toxocara* is the transplacental infection of fetuses with migrating 3rd-stage larvae (L3) (*T. canis*), as well as the oral uptake of L3 with the milk after birth. The *Toxocara* larvae migrate through different organs (liver, heart, lungs) during their development and reach the intestine as (pre-) adult stage. The prepatent period (the time between uptakes of infectious stages of parasites until shedding of

eggs) depends on the mode of infection and ranges from 21 to 39 days. *Toxascaris*, which remains in the intestinal walls during its larval development, has a prepatent period of 48 to 77 days.

Infective hookworm larvae can penetrate the skin (*Ancylostoma* spp.) of their host and migrate through tissue and bloodstream to the lungs and finally to the small intestine. Oral uptake of free living larvae or larvae in paratenic hosts also leads to infection of the small intestine. The former infection mode results in a high proportion of hypobiotic tissue larvae (in the developmentally arrested stages) that are re-activated during pregnancy and migrate to the milk-glands. Like *Toxocara*, they can be transmitted to puppies and kittens immediately after birth via suckling milk. The prepatent period depends on the mode of infection and the age of the host, but ranges between 14 to 26 days.

In order *Trichuris* infection to occur in dogs and cats, the eggs containing infective larvae must be taken up orally. The 3rd-stage larvae (L3) will be released in the gut lumen of the animal and migrate into the intestinal mucosa where they develop to the adult stage. The prepatent period lasts 74 to 87 days, after which the female worms, with their rear-end sticking out of the caecum-mucosa, release eggs that are shed with the feces.

b. Tapeworms (Cestodes)

All major tapeworms require at least one intermediate host. Such intermediate hosts can be mammals (*Taenia*, *Echinococcus*, *Mesocestoides*), fish (*Diphyllobothrium*, while crustaceans serve as intermediate hosts to infect the fish), and insects (*Dipylidium caninum*). Dogs and cats become infected when eating larvae-containing tissues of these intermediate hosts. The further development in the final host occurs in the small intestine. After a prepatent period of 16 days up to more than 4 months (depending on the species), the worms start shedding proglottids which are heavily loaded with infective eggs and have to be taken up by the intermediate host to complete the life cycle.

c. Host specificity

In general, the above listed parasites show a high specificity for their definitive hosts. Thus, they must infect a dog or a cat in order to reach the sexually mature stage and to produce offspring. In some cases, the same parasite species (e.g. *Dipylidium caninum*, *Toxascaris leonina*) may occur in cats and dogs and in closely related hosts such as wolves, foxes, and others. However, in most

cases such infections between different host-families do not occur. On the other hand, paratenic hosts may become infected by roundworms and hookworms. In such cases, the larvae do not develop to the adult stage, but remain in a "stand-by" position in the tissue until they get ingested by a definitive host. Tapeworms are generally very specific for their definitive host, while the spectrum of intermediate hosts is less restricted.

d. Zoonotic risk

Most of the nematodes and tapeworms in dogs and cats are host specific. Thus, it is very unlikely that humans could develop a patent infection. An exception is *Dipylidium caninum*, which can reach the adult stage in the intestine of humans after (accidental) ingestion of cysticercoid-containing fleas. In addition, humans can become paratenic hosts for roundworms and hookworms ("larva migrans") after oral uptake of infective eggs or exposure to 3rd-stage larvae, respectively. Of great concern is the development of metacestodes after infection with *Echinococcus* eggs. Humans may become incidental hosts for this tapeworm, i.e. the larvae do not reach an infective stage, but they can cause severe health problems due to the development of large cystic swellings.

5. *Anthelmintics used in dogs and cats*

a. Drug classes

Several classes of drugs are registered for anthelmintic use in dogs and cats in Europe: Benzimidazoles (fenbendazole, flubendazole, including the probenzimidazole febantel), pyrimidines (pyrantel, oxantel), cyclooctadepsipeptides (emodepside), and macrocyclic lactones (ivermectin, selamectin, milbemycin oxime, moxidectin). All have broad-spectrum activity against gastrointestinal (GI) nematodes and others, and depending on their mode of action and formulation, complete or partial efficacy against migrating larval stages. Macrocyclic lactones as endectocides do also show efficacy against a spectrum of ectoparasites. Additionally, cestode (tapeworm) infections are specifically treated with pyrazinoisoquinolines (praziquantel, epsiprantel).

b. Shared anthelmintic drug classes between human and animals

In contrast to several anthelmintic molecules that are registered for veterinary use, only a limited number of compounds are available for human use. Albendazole or mebendazole as molecules of the benzimidazole class, as well as pyrantel and the macrocylic lactone ivermectin are registered for use in humans against various nematode infections. Cestode infections in humans and some trematode infections are treated with praziquantel.

c. Required and proven efficacy

For the registration of pharmaceutical products, the efficacy of the respective product has to be demonstrated. Requirements regarding study designs and efficacy thresholds are defined in specific guidelines (e.g. VICH GL19, 2002; VICH GL 20, 2002). For most nematode infections the effectiveness of a product should exceed 90%, however for parasites with public health or animal welfare implications, such as *Echinococcus spp.*, higher effectiveness standards (i.e., up to 100%) are desired. In principle, dose-determination studies are conducted to establish the dosage of the product, followed by studies to confirm the product efficacy against specific parasitic stages of a nematode, e.g. larval or adult stages. Field studies in which the product is tested in a wide range of target animals are necessary to complete the effectiveness package. Those guidelines require a sound statistical analysis and proven methods for effectiveness description, and in the case of anthelmintics for dogs and cats are aligned between e.g. EU, USA and Japan. All currently available anthelmintics for dogs and cats have been used for many years and their efficacy proven in various geographic areas and against various worm isolates (Traversa, 2012).

6. Current knowledge on resistance against anthelmintics (why in livestock and not in pets)

For helminth parasites of livestock, unfortunately, resistance is an established phenomenon. A multitude of literature reports is available including the Health for Animals Position Paper "Anthelmintic Resistance in Small and Large Ruminants and Horses" (Mencke et al., 2015). One approach that can be used to assess the awareness and the knowledge of the distribution of anthelmintic resistance in companion animals and livestock is to evaluate the available scientific information. Searching NCBI's PubMed for "(resistance AND parasite) AND (cattle OR horse OR

sheep OR goat) AND helminth" results in 1245 hits of respective publications, a finding that might be easily increased by more sophisticated search approaches. In contrast, searching for "(resistance AND parasite) AND (dog OR cat) AND helminth NOT *Dirofilaria*" resulted in 34 hits. Inspecting those 34 hits individually in relation to the focus of this position paper decreased the number of relevant publications down to six. Out of those six, four deal with pyrantel resistance of the hookworm *Ancylostoma caninum* in Australia. All four articles are from the same authors, were published in 2007 and 2008, and report and review more or less the same data set and are not followed by any later reports (Kopp et al., 2007, 2008 a-c). The remaining two publications report on field studies suitable to detect anthelmintic resistance in dogs (Schwenckenbecher and Kaplan, 2009; Becker et al., 2012). Giving the amount of pet-parasite related research being conducted (Rehbein et. al. 2017; Boehm et al. 2017;) combined with the impracticality of publishing negative results, these findings indicate the lack of global resistance phenomenon for most common round-, hook-, whip- and tapeworms in pets. Heartworm disease caused by *Dirofilaria* spp. is an exception, which is not a gastrointestinal worm infection and is outside of the scope of this position paper.

This result immediately triggers the question as to why there is an apparent global discrepancy in parasite resistance comparing livestock with pets. The answer is multifactorial but at the same time somewhat simple. In the parasitological frame, the term "refugium" is used for the proportion of worms not exposed to anthelmintics (Besier, 2008). Refugia can be defined as the proportion of a worm population that is not selected by drug treatment. Worms in refugia come from three sources: (i) larvae in the environment (for example on pasture), (ii) untreated animals and (iii) stages of helminths in the host that are not exposed to treatment. For livestock parasites, there is almost no refugium because, usually, at any given time animals are not treated on an individual basis but the whole herd or flock is treated concurrently. In addition, parasites of livestock are almost always host-specific and all parasitic developmental stages on pasture are heavily influenced by respective treatments. Repeating this kind of herd treatment plan over time inevitably leads to resistance as only the resistant parasites can survive the repeated or constant drug pressure.

For pet parasites, however, many wildlife refugia exist. Examples include foxes, wolfs, marten, raccoons, wildcats, lynx and many more. At the same time, pets are not treated in herds but as individual animals or in small groups as they live mostly in single households. In addition, the anthelmintic treatment is not coordinated in a geographic area, nor regarding time or the used

anthelmintic class. Treating a pet at home for intestinal parasites kills the parasite but does not increase the selection pressure towards the whole parasite population in the field.

Another important difference lies in the parasites' life cycles: roundworm and hookworm infections of pets mostly occur in young animals, while later infections lead to a somatic migration of the larvae, i.e. they reach a hypobiotic stage in the tissue and do not enter the intestine. Such metabolically inactive larvae do not undergo the same selection-pressure as developing larvae or adults in the intestine. Furthermore, while gastro-intestinal nematodes in ruminants may reach several generations per season on pasture, the number of generations of nematodes or tapeworms in dogs or cats remains very limited. Even in situations with higher drug pressure and herd-like treatment of dogs in breeding facilities or dog shelters, no cases of anthelmintic resistance have been reported.

7. The risk for humans

Potential risks for humans can be grouped in two categories: the risk of becoming infected with a zoonotic worm species, and the risk of transmission of anthelmintic resistance to other drugs used in humans.

a. The risk of becoming infected with nematodes (roundworms, hookworms, whipworms) or cestodes (tapeworms) is limited to a few parasite species, but it is present (Dantas-Torres and Otranto, 2014). Most worm species are host specific for dogs and cats, and cannot infect humans. However, accidental infections of humans with *Toxocara canis*, *Toxocara cati*, or *Ancylostoma caninum* can cause various "larva migrans" (LM) symptoms (visceral LM, cutaneous LM, and ocular LM). When worm eggs are ingested, mostly by young children, the worms will develop in humans to the 3rd larval stage (L3) and will migrate through various tissues causing minor lesions if any. *Dipylidium caninum i*s one of the tapeworm species which can accidentally infect humans, if humans ingest infected fleas. However, the disease in humans is not very pathogenic. Accidental ingestion of *Echinococcus spp.* eggs (tapeworm) can cause a pathology known as cystic or alveolar echinococcosis in which the eggs develop into metacestodes. The larvae do not reach an infective stage in humans, but they can cause severe health problems due to tumor-like growth. Transmission of parasitic worm from dog or cat to humans occurs in all cases by infected larvae or eggs.

b. There is only a minor risk if any at all, that the trait of anthelmintic resistance is transferred to human pathogenic worms or other parasites. First, there are no resistant zoonotic worm species in dogs and cats known. As outlined above, there is only one anecdotal report of an anthelmintic resistant worm isolate. Secondly, anthelmintics are not used as frequently as other anti-infective drugs like antibiotics. Thus, the drug pressure in pets is not as high or as constant as it is in livestock animals.

Therefore, we confirm the recommendation by the companion animal parasite councils CAPC, and ESCCAP to regularly deworm dogs and cats (basing treatment frequency on the risk of exposure to individual parasites), for the wellbeing of the animal, and also to avoid any risk of infection with a zoonotic worm species, although that risk is low. To the best of our knowledge, there is no risk that anthelmintic resistance will be transferred to other human pathogenic parasites.

*Abbreviations and links:

ESCCAP: European Scientific Counsel Companion Animal Parasites; http://www.esccap.org/

CAPC: Companion Animal Parasite Council; https://www.capcvet.org/

TroCCAP: Tropical Council for Companion Animal Parasites; http://www.troccap.com/

References

Becker AC, Rohen M, Epe C, Schnieder T. (2012). Prevalence of endoparasites in stray and fostered dogs and cats in Northern Germany" Parasitol Res 111(2): 849-857.

Besier RB. (2008). Targeted treatment strategies for sustainable worm control in small ruminants. Trop Biomed. 25(1 Suppl):9-17.

Böhm C, Petry G, Schmidt H, Rue K, Barthes F, Shaper R. (2017). Evaluation of the Persistent Preventive Efficacy of 2.5 % Moxidectin/10 % Imidacloprid Spot-on (Advocate®, Advantage® Multi) in Dogs Experimentally Infected with *Angiostrongylus vasorum*. Parasitol Res. 116, Supplement 1: 1–10

Dantas-Torres F, Otranto D. (2014). Dogs, cats, parasites, and humans in Brazil: opening the black box. Parasit Vectors. 7: 22.

Kopp SR, Kotze AC, McCarthy JS, Coleman GT. (2007). High-level pyrantel resistance in the hookworm *Ancylostoma caninum*. Vet Parasitol 143(3-4): 299-304.

Kopp SR, Kotze AC, McCarthy JS, Traub RJ, Coleman GT. (2008). Pyrantel in small animal medicine: 30 years on. Vet J 178(2): 177-184.

Kopp SR, Coleman GT, McCarthy JS, Kotze AC. (2008). Phenotypic characterization of two *Ancylostoma caninum* isolates with different susceptibilities to the anthelmintic pyrantel. Antimicrob Agents Chemother 52(11): 3980-3986.

Kopp SR, Coleman GT, McCarthy JS, Kotze AC. (2008). Application of in vitro anthelmintic sensitivity assays to canine parasitology: detecting resistance to pyrantel in *Ancylostoma caninum*. Vet Parasitol 152(3-4): 284-293.

Mencke N, Geurden T, Horspool LJ, Rehbein S, Sager H, Durel L, Marchiondo A, Skidmore A, Bhushan C, Welz C, Kaminsky R. (2015). Health for Animals Position Paper: Anthelmintic Resistance in Small and Large Ruminants and Horses.

Prichard RK, Hall CA, Kelly JD, Martin IC, Donald AD. (1980). The problem of anthelmintic resistance in nematodes. Australian Veterinary Journal. 56:239-251.

Rehbein S, Knaus M, Mallouk Y, Breiltgens T, Brianti E, Capári B, Dantas-Torres F, Gau M, Joachim A, Kaulfuß KH, Kirkova Z, Lechner J, Mihalca AD, Mirabito R, Petkevičius S, Rapti D, Shukullari E, Sedeilhan M, Dollhofer D, Kley K, Lebon W, Visser M, Jeannin P. (2017). Efficacy against nematode infections and safety of afoxolaner plus milbemycin oxime chewable tablets in domestic dogs under field conditions in Europe. Parasitol Res. 116(1):259-269.

Schwenkenbecher, J. M. and R. M. Kaplan (2009). "Real-time PCR assays for monitoring benzimidazole resistance-associated mutations in Ancylostoma caninum." Exp Parasitol 122(1): 6-10.

Traversa D. (2012). Pet roundworms and hookworms: A continuing need for global worming. Parasit Vectors. 5: 91.

Guidance for Industry. Effectiveness of Anthelmintics: Specific Recommendations for Canine. VICH GL19.
https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052652.pdf

Guidance for Industry. Effectiveness of Anthelmintics: Specific Recommendations for Feline. VICH GL20.
https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052653.pdf