



TRADEMARK

Flubenol

Dewormer for poultry

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The worm problem surfaced again in the poultry sector

One of the main reasons why laying hens were transferred to wire cages years ago was to prevent parasitic infections. In wire cages the contact with faecal material is rare and consequently there is only a limited risk of coccidiosis or worm infections. Today there is a strong trend towards putting laying hens back onto litter, with the inevitable consequences. In the Netherlands (in 1997), the Poultry Health Institute investigated the incidence of worm and lice infestations in layer flocks that were not kept in battery cages. The results show that 68% of the flocks were infested with worms and 50% with lice.

All poultry reared on litter or in free range systems is at risk from worm infections. Only in broiler chickens, when slaughtered before 50 days of age, is the risk small.

Litter provides the worms with a new opportunity. Indeed, worm eggs and their vectors, such as beetles and flies, thrive well on litter and soil. Depending on the worm species, the eggs may survive for months or sometimes for more than a year. Bringing the birds into contact with the litter will cause infection and re-infection.

The concentration of large numbers of poultry on farms has also increased the chances of survival for most worm species.

Once a worm infection is established in a flock, the whole environment will be heavily contaminated with infective worm eggs. Therefore a good prophylactic deworming programme should be a standard management procedure on any poultry farm.

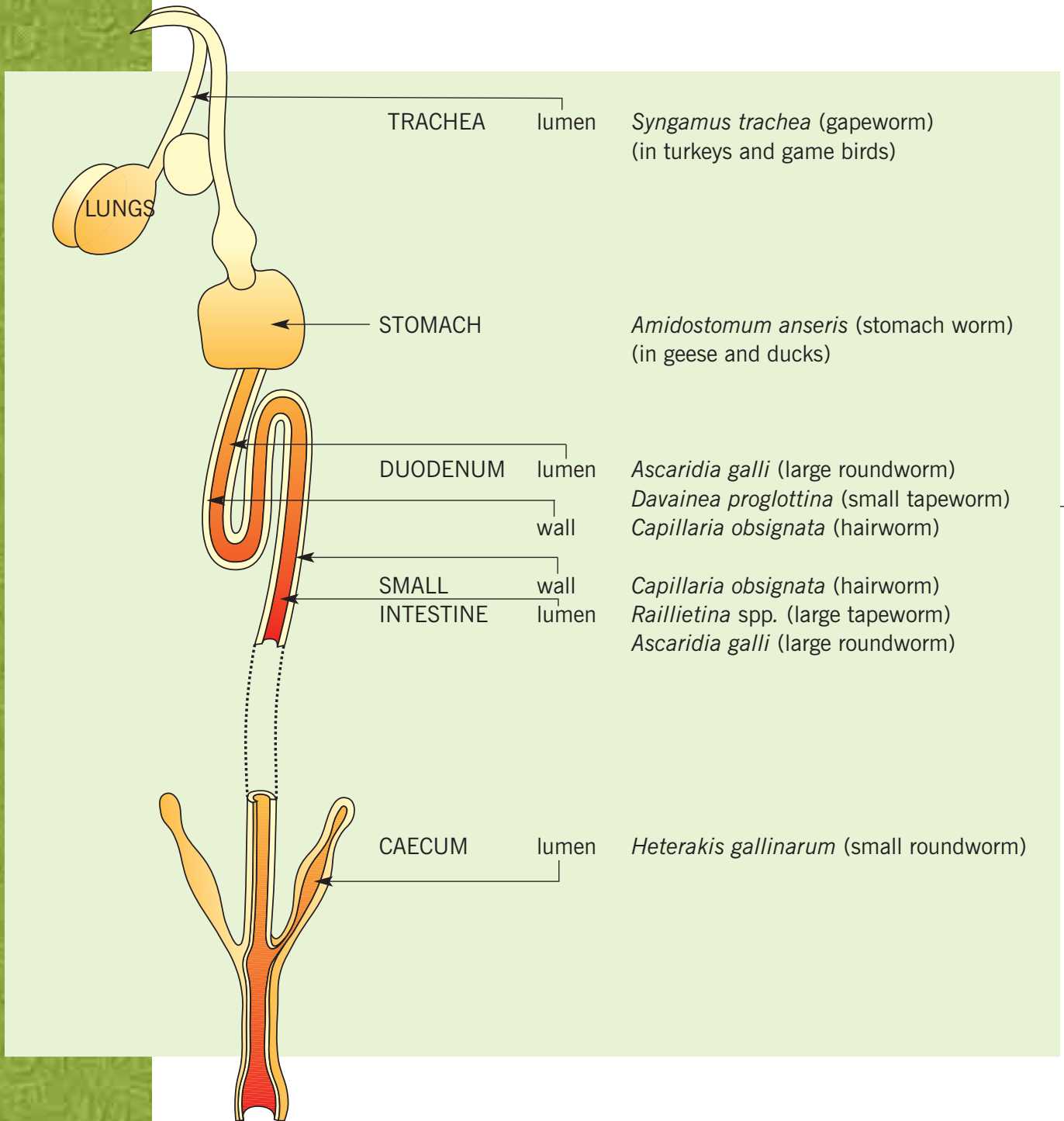


Worm infections cause serious problems, particularly in flocks reared on litter.



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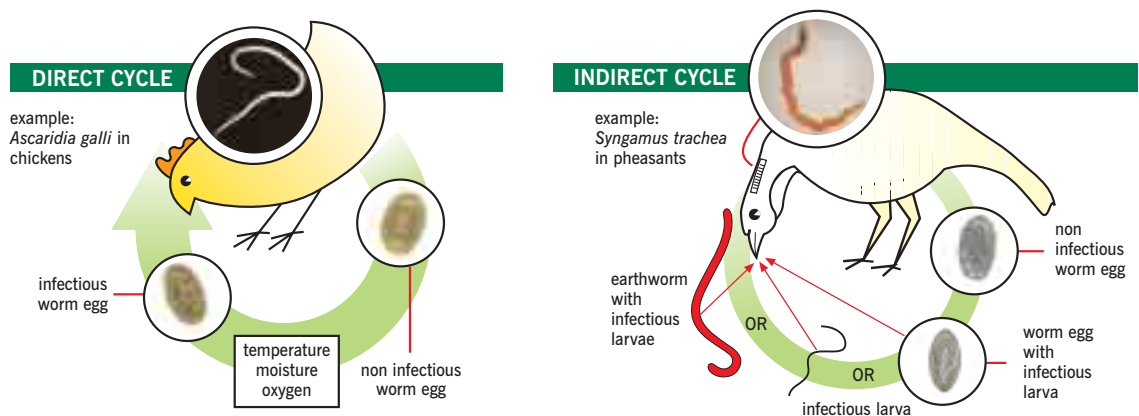
Poultry worms cause damage





Worms lay eggs, too

To make the species survive, worms living in their host have to produce tremendous numbers of eggs. Those eggs are spread with the excreta in the poultry houses, the nests, on the ground, etc. They first have to "mature" or embryonate. That may happen in two ways: in case of a direct life cycle they embryonate in the environment; in case of an indirect life cycle this will happen in an intermediate host. Once matured and after being taken up by a new host, the larvae will be released from the eggs and develop further to become adult adult worms.



Route of infection:

(1) When birds are placed on fresh litter, the worm infection can be brought about by larvae or worm eggs which have been sticking to people, materials, trucks, feed bags, insects, wild birds, cats, dogs, etc. A few grams of dung contaminated with worm eggs are sufficient to re-start a worm infection in a flock.

(2) Once the litter is contaminated with worm eggs, it is difficult to stop the cycle of continuous re-infection of the animals. In the birds the eggs develop into adult egg laying worms that, again, contaminate the litter with massive numbers of eggs.

In the case of tapeworms, the infection is transmitted by an intermediate host such as snail, fly or beetle. Animals that have an outside run will therefore more easily contract an infection than those that are kept inside. However, even when birds are kept in batteries the infection can not be avoided and is often due to flies and small meal worms.

Worm eggs are hard to break

Worm eggs may remain infectious for months and sometimes for more than a year if circumstances in the litter are favourable. The egg wall is thick and most of the disinfectants are ineffective in achieving their destruction. Worm eggs will even survive in, say, 1/10 N sulphuric acid or in 2% formol.



worm eggs cannot "mature" or become infectious

- in a very dry atmosphere;
- at temperatures below 10°C to 15°C ;
- at very high temperatures (above 34°C);
- in the absence of oxygen.

worm eggs are destroyed by:

- drought;
- heat;
- prolonged and deep frost;
- direct sun light.



Diagnosis of worm infection

A. Symptomatical diagnosis is generally very difficult since worm infections are normally of a “chronic” nature and most of the symptoms may also occur with other diseases such as coccidiosis. The occurrence of one or more of the following symptoms should be an inducement to investigate further:

- excessive mortality
- marked variability of the flock
- poor growth
- poor condition of the animals:
rough feather coat, pale head ornaments, anaemic, animals failing to thrive
- reduced laying rates, reduced egg weights
- reduced hatchability results
- loose droppings



Pale and limp head ornaments caused by verminous anaemia



Young turkey in a poor condition due to verminosis

B. Coprological examination: Counting the worm eggs in the faeces provides a good picture of the degree of infection in a poultry house, provided it is based on a representative number of samples from intestinal as well as caecal droppings that is proportionate to the number of birds.

However, one should always bear in mind that during the prepatent phase of the infection, the animals can harbour large amounts of immature worms, without worm eggs being present in the faeces.

Taking a representative number of samples:

When faecal samples are taken, one should see to it that only fresh faeces are collected and that the sample is representative. Thus for chickens the procedure is as follows: in the evening brown paper is laid under the perches (8 leaves of 1 by 0.5 m per 1000 animals) and randomly spread. In the morning little heaps of faeces are collected at random.

From up to 500 animals a minimum of 20 samples of faeces from the small intestine and 20 from the caecum are collected. For each additional 500 chickens that number is increased by 2x10 fresh samples, with a maximum of 2x50. Especially slimy and flat droppings should be taken. If no paper can be spread under the perches, the faecal samples are taken directly from the litter or from the perches. They should be really fresh and not mingled with the litter. When a henhouse is divided into several compartments, samples are taken from each compartment. Pending the microscopical examination, the droppings should be kept in small plastic bags or in specially designed small pots.



C. Post-mortem examination can provide additional information once a worm infection is diagnosed by positive EPG* counts. Again, a representative number of animals from different places on the farm have to be examined. Large and small ascarids and also adult stages of the large tapeworms are easily recognised in the intestines.

Hairworms can be seen by mixing the intestinal scrapings with water in a petri dish. The thin white threads, when put on a dark background, are visible with the naked eye. These scrapings can also be pressed between glass slides and held up to the light for inspection.

*EPG: number of worm Eggs per Gram of Faeces



Damage done by worms

In young chickens (replacement pullets or broilers)

Young chickens are very susceptible to roundworm infections. *Ascaridia* and especially *Capillaria* infections will cause depressed growth and undermine the general health status of the flocks. This in turn can jeopardise the applied vaccination schemes.

The massive impact of ascarids was shown in a study⁶ with broiler chickens artificially infected with 500 ascarid eggs. This single infection caused serious clinical signs 6 weeks later. The chickens showed emaciation, loss of colour of combs and legs and of brightness of plumage, diarrhoea, drooping wings, ruffled feathers and a gradual loss of strength manifested by leg weakness. At autopsy, the small intestine showed external macroscopic lesions of haemorrhage and congestion.

In laying hens and breeder birds



Significant drops in egg production are apparent in infected breeders or layers because of ascarid infections. An extra concern of ascarid infection in laying hens is that occasional ascarids may undergo an aberrant migration and become incorporated into an egg. This will be very unappealing to the consumer.

The large roundworm damage the chicken's intestinal mucosa. Massive ascarid infection may cause intestinal blockage and possible rupture, loss of blood and nutrients.



Tapeworms do not commonly cause severe pathology in poultry, but live in the intestinal tract and compete with the host for the nutrients in the feed.

The small tapeworm sticks its hooks in the folds of the intestinal mucosa. The intestinal mucosa may thereby be severely damaged and body fluids are lost.

A hairworm (*Capillaria*) infection can produce severe clinical signs. Affected birds appear pale and depressed, they become emaciated, develop diarrhoea and may die. Hens with capillariasis may develop a secondary vitamin A deficiency which, on top of the decreased laying rates, will cause reduced hatchability in breeders and pale yolks in layers. Gapeworms (*Syngamus trachea*) are a serious threat to farms with a free range management system. The gapeworm life cycle may involve the earthworm. In the earthworm, infections can persist for many years and over a period of time soil can become heavily infected. Moreover, wild birds will provide reservoirs of infection for domestic birds like turkeys, pheasants and ducks.

Turkeys

Recent studies confirm that worm infections in turkeys are very common and cause considerable losses. The turkey roundworm - *Ascaridia dissimilis* - is a serious threat. Primarily, the larval stages give cause for concern¹⁴.

The intestines of turkeys often contain only few adult worms, whereas larval population is significant. These larvae cause 2 phenomena not known to most turkey breeders.

First they cause a necrotic-like enteritis, most severe in the jejunum, often with additional *E. coli* and/or *C. perfringens* infections, resulting in low market weights¹⁷ or even mortality¹³. Secondly the migrating ascarid larvae^{12, 15, 16} may cause 'white spots' on the liver.

These liver foci cause lots of livers to be rejected at slaughter.

In young turkeys heavy infections with the cecal worm, *Heterakis gallinarum*, may cause serious damage such as thickening of the cecal mucosa and petechial haemorrhages.

This worm is also the transmitter of the flagellate *Histomonas meleagridis*. In the liver and

the caecum it causes infections and diarrhoea resulting in many rejections ("blackhead").

In breeder turkeys the tiny hairworms in the stomach (*Capillaria* spp.) cause a great number of rejections.

Young pheasants are also very susceptible to gapeworm infections (*Syngamus trachea*).



Adult gapeworms frequently obstruct the trachea, so that the bird is literally choked by the worms.

The picture shows a young turkey which has died from syngamosis, in a typical 'choked' pose.

Game birds (pheasants and partridges)

Wild animals are naturally fairly resistant to parasitic infections, but when confined in small areas, they may become severely infected. In particular younger animals are susceptible to a vast number of parasitic infections which cause serious disease and high mortality. *Syngamus trachea* infection needs to be tightly controlled, but *Capillaria* and *Ascaridia* infections are also quite common and can cause significant direct and indirect losses.



Ripped up tracheas of pheasants with gapeworms

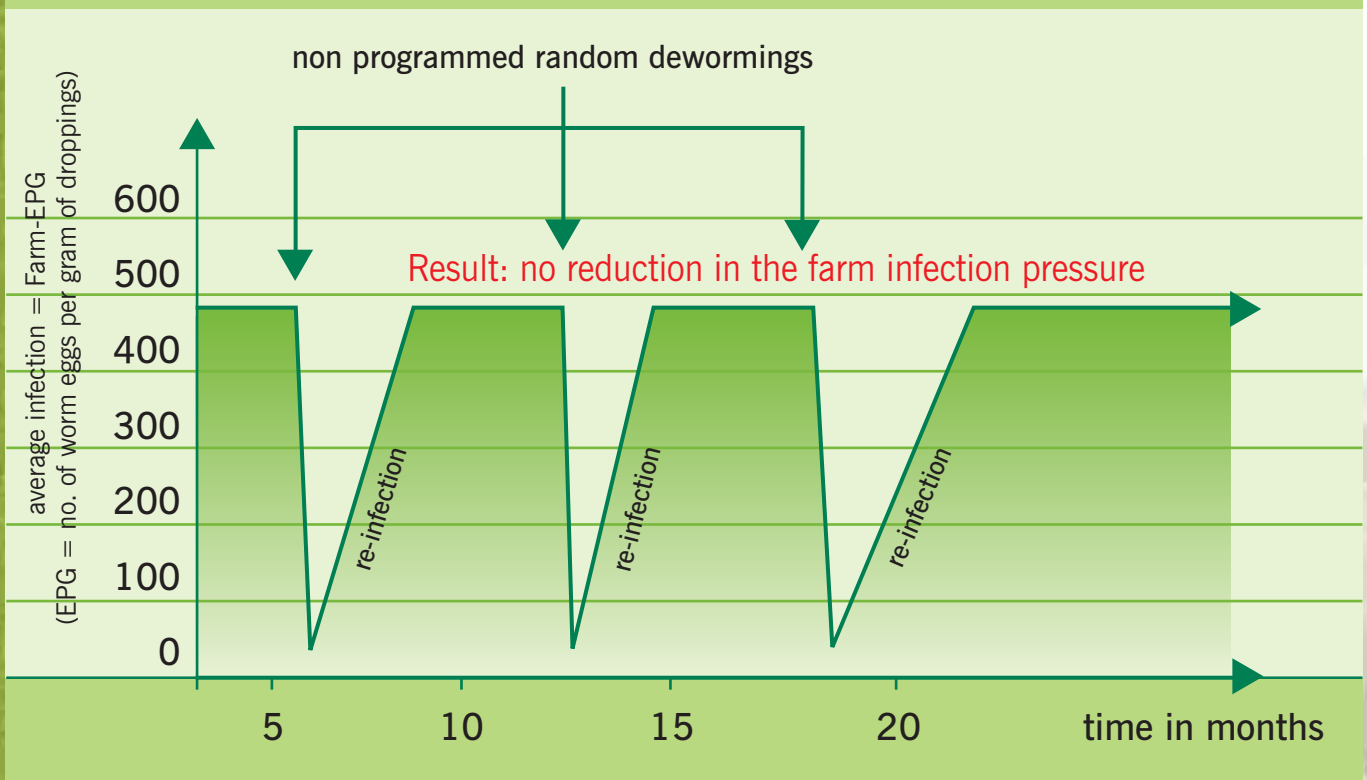


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Prevention rather than treatment

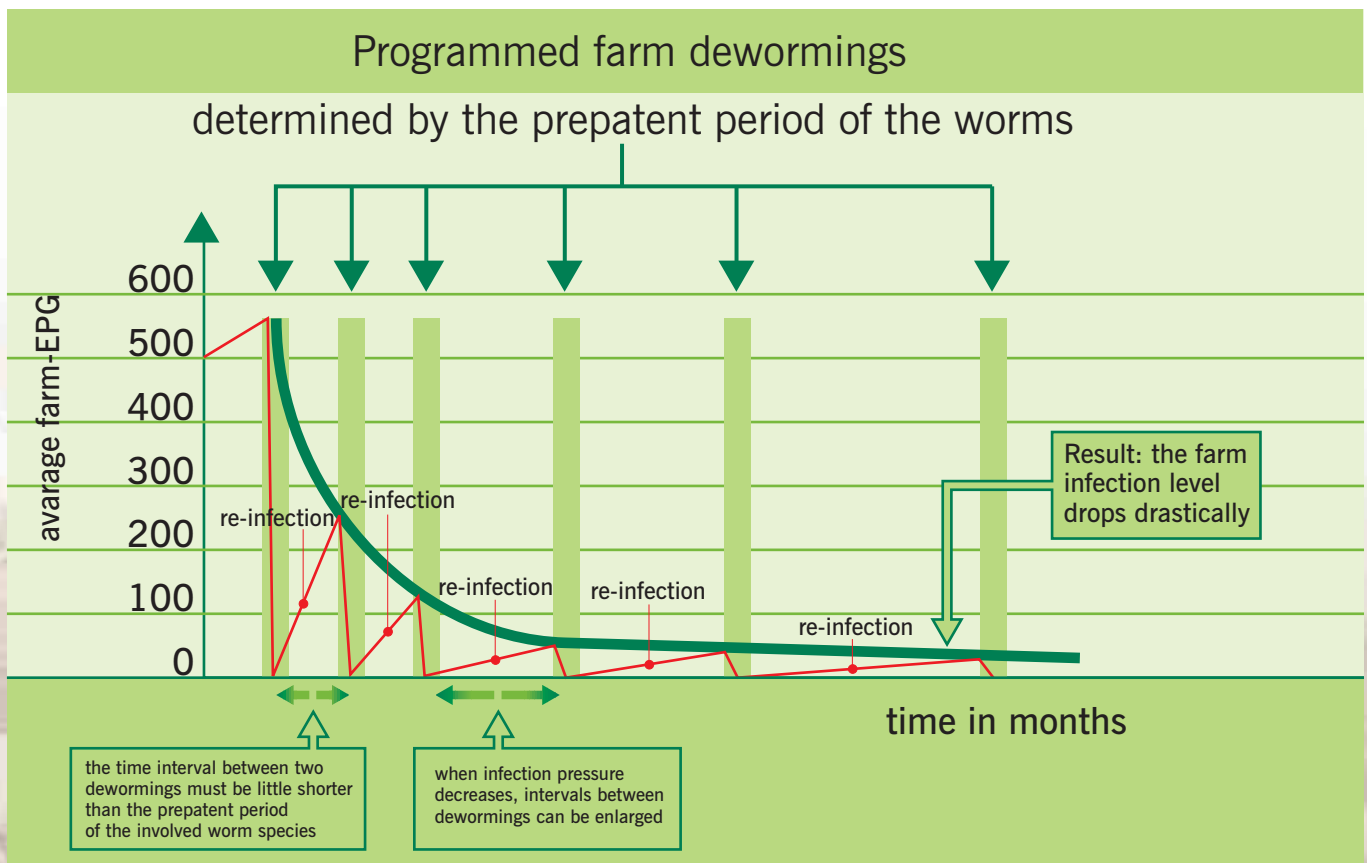
The source of a worm infection is through litter or faecal material contaminated with worm eggs, or through intermediate hosts such as flies, beetles and earthworms. Even after deworming all animals the soil or litter bedding will remain contaminated with high numbers of worm eggs and continuous re-infection of the flock will take place. Occasional deworming treatments are not effective. The use of anthelmintics has to be programmed with the aim of keeping the infection pressure on the farm as low as possible. Such programme will take into account the life cycle of the worms. A potent anthelmintic, fully effective against mature and immature stages of the worms, has to be used. Even if only a few percentages of worms or larvae would remain present in the animal after a treatment, these would continue to produce eggs and re-contaminate the litter.

Conventional deworming of poultry: **not effective**



A strategic deworming programme

A strategic deworming programme has to be targeted at the entire farm. It results in a drastic fall of the farm infection pressure within a limited time. After a number of treatments the farm infection level has lowered to a level that can be maintained with larger intervals between the treatments. The intervals between treatments are determined by the prepatent period of the worm(s) concerned. The objective is to keep all animals free of adult, egg laying worms. When we maintain this for a sufficiently long period, the infection pressure will gradually decrease or, when this was low already, will certainly not have the chance to increase.



THE PREPATENT PERIOD OF THE IMPORTANT POULTRY WORMS

nematodes:

<i>Ascaridia galli</i>	young birds	35-42 days
	adult poultry	50-56 days
<i>Syngamus trachea</i>		18-20 days
<i>Capillaria obsignata</i>		20-26 days
<i>Heterakis gallinarum</i>		24-30 days
<i>Capillaria contorta</i>		30-60 days
<i>Amidostomum anseris</i>	in geese	14-22 days
	in ducks	35-49 days
<i>Trichostrongylus tenuis</i>		08-10 days

cestodes

<i>Raillietina</i> spp.		21 days
<i>Davainea</i> spp.		14-21 days

Limit the chances for re-infection from the environment:

- regularly replace the litter, keep it dry, prevent excess of faecal material;
- never feed on the floor or on the litter;
- develop good hygiene practice and prevent infections from being imported onto the farm;
- combat flies, beetles, snails, earthworms;
- use a deworming programme that prevents excessive shedding of worm eggs.



Efficacy of Flubenol

Flubenol is highly effective against all important roundworms and tapeworms that occur in poultry.

The product has been tested extensively in 48 clinical trials in 10 different countries, using in total 134 069 chickens, 17 957 pheasants, 4921 turkeys, 6249 geese and 1042 partridges. In all clinical studies, the activity of flubendazole was evaluated either by critical tests or by control tests. In the **critical tests**, each animal serves as its own control as the number of parasites expelled after treatment is evaluated against the number of parasites retained after treatment. In the **control tests**, either EPG values before and after treatment are compared (called 'control EPG') or the residual worm burden after treatment is evaluated in a number of randomly selected birds from each treatment group and compared with the worm burden of the untreated group (called 'control worm').

Flubendazole proved to be a highly efficacious anthelmintic against the various parasite species of poultry.

In **chickens**, fed *ad libitum* at 30 ppm for 7 days, it provides a 100% activity against *Ascaridia*, *Heterakis* and *Capillaria* infections. A dose level of 60 ppm for 7 days in the feed is highly effective against immature and mature stages of *Raillietina cesticillus*.

In case of restricted feeding, the flubendazole dose level in the feed should be increased.

In **turkeys**, fed *ad libitum*, 20 ppm flubendazole in the feed for 7 days is completely effective against *Ascaridia*, *Capillaria* and *Syngamus*.

In **geese** fed *ad libitum* 30 ppm flubendazole for 7 days is highly efficacious. Complete efficacy is obtained against *Capillaria*, *Syngamus*, *Trichostrongylus* and the stomach worm *Amidostomum anseris*. In case of a restricted feeding regimen, a dose of 60 ppm for 7 days is required to obtain the same efficacy.

In **pheasants and partridges** the dose of 60 ppm for 7 days provides 100% activity against *Capillaria*, *Syngamus*, *Heterakis* and *Ascaridia* infections.



Summary of the clinical trials with Flubenol in chickens

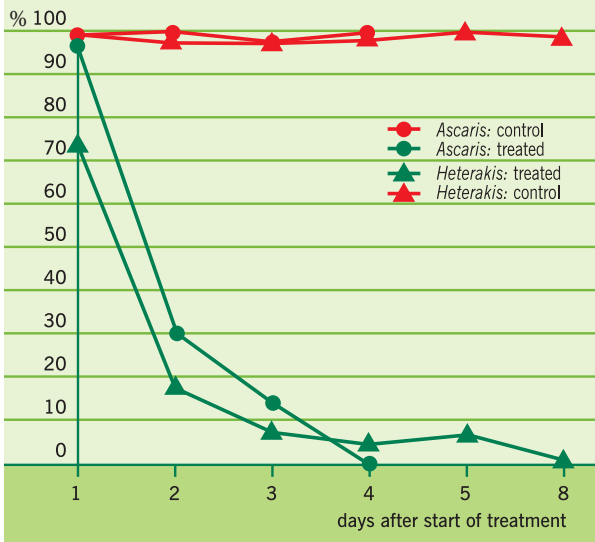
Treatment (ppm)	Number of animals treated	Evaluation	% Efficacy				
			<i>A. galli</i>	<i>H. gallinarum</i>	<i>Capillaria</i> spp.	<i>R. cesticillus</i> adults	<i>R. cesticillus</i> immatures
	18	critical	100	100			
	9	control EPG	100	100			
	12	control worm	100	100	100	92	
	25	control EPG	100	100			
	25	control worm	100	100			
	8	critical	100	100			
	17 141	control EPG	100	100	100		
	2200	control worm	97	97	100		
	360	critical EPG	100				
	22 000	control	100		100		
	12	EPG/worm				88	
	10	control worm				100	93
	100	control worm				100	99.8
	20 (2)	control worm				100	
	12 (2)	control worm	100	100	100	99	
	18	critical	100				
	12 (1)	control worm				100	

(1) 60 ppm for 7 days (2) restricted feeding regimen

Summary of the clinical trials with Flubenol in turkey, goose, pheasant and partridge

Treatment (ppm)	Number treated	Evaluation	% Efficacy						
			<i>A. galli</i>	<i>H. gallinarum</i>	<i>Capillaria</i> spp.	<i>S. trachea</i>	<i>A. anseris</i>	<i>T. tenuis</i>	
Turkey									
20 ppm for 7 days	5	control EPG	100		100				
20 ppm for 7 days	4	control worm				100			
20 ppm for 7 days	10	control worm			100				
Goose									
30 ppm for 7 days	5000	control EPG					99.7	100	
30 ppm for 7 days	1200	control worm			100	100	99.8		
60 ppm for 7 days	49	control EPG	100	100	100		100		
Pheasant									
60 ppm for 7 days	1000	control worm			100	100			
60 ppm for 7 days	12	control worm	100	92	83	100			
60 ppm for 7 days	2500	critical EPG		100	100	100			
60 ppm for 7 days	11 000	critical EPG	100	100	100	100			
60 ppm for 7 days	1515	critical EPG			100	100			
Partridge									
60 ppm for 7 days	1000	control worm				100			
60 ppm for 7 days	12	control worm	100	100	92	100			

Daily percentage of embryonated eggs in the faeces of chickens treated with 30 ppm Flubenol in the feed for 7 consecutive days.



Worm eggs are killed by Flubenol

A number of chickens, artificially infected with *Ascaridia* and *Heterakis*, were divided into 2 groups: one was treated with the therapeutic dose of 30 ppm Flubenol into the feed for 7 consecutive days. The other group remained untreated and served as controls. The treatment resulted in a complete elimination of the worm burden 2 to 3 days after the start of treatment. From the second day of treatment the ovicidal effect of the Flubenol treatment could be observed, because of the strong reduction in embryonation rates.

Activity of Flubenol against tapeworms

Flubenol at the concentration of 60 ppm for 7 consecutive days is highly effective against the adult and the immature stages of the tapeworm *Raillietina cesticillus*. This was confirmed both in broilers and in layers.

Raillietina cysticercoids that are ingested by chickens will develop into adult tapeworms over a period of a minimum 11 to 14 days.

1. In broiler chickens

In a control trial¹¹ artificially infected four-day-old broiler chickens were treated with 60 ppm for 7 consecutive days. The treatment was equal to a drug uptake of around 12 mg flubendazole per kg body weight per day.

- When the treatment was given right after artificial infection (young immatures) this resulted in a 93% reduction in worm burden as compared to the untreated controls.
- When the treatment was initiated 7 days after artificial infection (immatures) this resulted in a 99.8% reduction in worm burden.
- When the treatment was initiated 14 days after artificial infection (adults) this resulted in a 100% reduction in worm burden.

2. In layers

In another trial¹⁸ 24 week-old Isa-Brown layers were used. The birds were artificially infected and fed *ad libitum*. When dewormed with 60 ppm Flubenol in the feed for 7 days, starting 3 weeks after artificial infection, it resulted in a reduction in the worm burden of 98.7%. The birds took up 4 mg flubendazole per kg body weight per day.

Summary of the efficacy spectrum of Flubenol

Poultry species	Worm species	Treatment schedule	Anthelmintic efficacy
Chicken	ascarids, hairworms tapeworms (<i>Ascaridia galli</i> , <i>Heterakis gallinarum</i> , <i>Capillaria</i> spp, <i>Capillaria obsignata</i> , <i>Raillietina cesticillus</i> *)	30 ppm 7 days	97-100%
Turkey	ascarids, hairworms, gapeworms (<i>Ascaridia galli</i> , <i>Capillaria obsignata</i> , <i>Syngamus trachea</i>)	20 ppm 7 days	100%
Goose	hairworms, gapeworms, stomach worms (<i>Capillaria anseris</i> , <i>Syngamus trachea</i> , <i>Trichostrongylus tenuis</i> , <i>Amidostomum anseris</i>)	30 ppm 7 days	99-100%
Pheasant, partridge	ascarids, hairworms, gapeworms (<i>Ascaridia galli</i> , <i>Heterakis gallinarum</i> , <i>Capillaria</i> spp., <i>Syngamus trachea</i>)	60 ppm 7 days	100%

*Against *Raillietina* a concentration of 60 ppm for 7 days is needed for 100% efficacy.

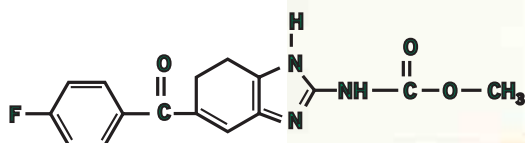




The safety aspect of Flubendazole

Pharmacodynamics of flubendazole

Flubendazole belongs to the chemical group of the benzimidazole carbamates. It has the following chemical structure:



Flubendazole is very poorly soluble in aqueous systems, such as the gastro-intestinal tract, which results in a low dissolution rate and a low absorption. This is reflected by the high faecal excretion of unchanged parent drug. The small fraction absorbed is extensively metabolized by first-pass metabolism in the liver. The biotransformation products are excreted quickly with the bile and the urine.

Flubendazole acts by binding to tubulin, the dimeric subunit protein of the microtubules. It inhibits microtubular assembly in absorptive cells, i.e. of the intestinal cells of nematodes or the tegumental cells of cestodes. Flubendazole also inhibits the microtubule-dependant processes in the embryonation phase of the worm egg (ovicidal effect). Because of its low solubility in aqueous systems, flubendazole has a very good safety profile.

Toxicity profile of flubendazole

Acute toxicity studies

The acute oral toxicity was evaluated in rats, mice, guinea pigs, chickens and guinea fowl. No mortalities occurred and the LD₅₀ values were >10 000 mg/kg in rats and mice, >5000 mg/kg in guinea-pigs, >640 mg/kg in chickens and >400 mg/kg in guinea fowls.

Repeated dose toxicity

The subchronic toxicity of flubendazole has been studied after daily oral administration to rats (up to 160 mg/kg BW) and dogs (up to 40 mg/kg BW) for 3 months. No adverse effects were observed.

Reproduction toxicity

Rats, mice and rabbits received flubendazole in their feed during the period of pregnancy. No drug-induced embryotoxic or teratogenic effects were evidenced at doses up to 60 mg/kg BW.

Mutagenicity

In a series of mutagenicity tests including bacterial, yeast, insect and rodent systems, flubendazole was devoid of any mutagenic potential.

Tolerance in the target animal species

Broilers

Different groups of broiler chickens received doses of 30, 60, 120 and 180 ppm for 7 consecutive days in their feed. Even at the highest dose, no side-effects were observed and body weight gain remained normal.

Laying hens

A single dose of 640 mg/kg body weight did not affect clinical behaviour or body weight. The LD₅₀ in laying hens is > 640 mg/kg.

During a laboratory trial, Hisex layers were treated with doses of 30, 60, 120 and 180 ppm flubendazole for 7 consecutive days. No negative effect was seen on clinical behaviour and egg production. In addition large scale field studies were organised to confirm the safety of Flubenol in laying hens. The first trial comprised 22 000 animals treated for 7 consecutive days at 30 ppm flubendazole. In a second trial 24 000 birds were treated for 5 days at 30 ppm flubendazole. No effects on egg laying rates, egg weight or egg quality were seen.

Breeder hens

A laboratory trial³ was conducted at the R.V.K. Institute in Merelbeke, Belgium. 400 females and 40 males of the Ross 208 breeder strain, 40 weeks old, were treated with 60 ppm flubendazole in either mash or pelleted feed. Laying rates, egg weights, fertility, hatchability, embryonic mortality and chick quality were carefully measured before, during and after treatment. None of these parameters were affected by the Flubenol treatment (see table).

Effect of Flubenol in either meal or pelleted feeds for broiler breeders on laying rates, hatchability and weight of settable eggs.

Week	Feed-Treatment	Lay (%)*	Egg weight (g) (settable) *	% Hatchability
38	meal (control)	68.4 a (± 1.5)	---	-
	pellet (control)	62.6 b (± 0.83)	---	-
39	meal (control)	71.3 a (± 1.4)	60.4 a (± 0.27)	91.5
	pellet (control)	62.8 b (± 1)	59.3 a (± 0.3)	90.7
40	meal (Flubenol)	70.1 a (± 0.71)	60.6 a (± 0.18)	89.2
	pellet (Flubenol)	64.1 a (± 1.17)	59.5 a (± 0.27)	89.7
41	meal (control)	60.60 a (± 1.20)	60.1 a (± 0.42)	89.9
	pellet (control)	63.10 a (± 2.50)	59.4 a (± 0.15)	91.9

*Averages followed by the same letter are not significantly different from each other (> 0.05).

Guinea fowl

Guinea-fowl are a very susceptible poultry species. Single doses up to 1200 mg per bird did not have any negative effect and did not cause changes in behaviour during 5 days after treatment.

Pheasants and pheasant breeders

Flubendazole at 60 mg per kg feed does not adversely affect egg production or hatching results. In a field trial performed with pheasant breeders in France, Flubenol was incorporated in the feed at 60 mg per kg feed and given for 7 days. The parameters studied were percentage of egg lay, fertility and hatchability. There was no negative effect on any of these parameters⁴.

In another field study performed in the United Kingdom, Flubenol was incorporated in a pelleted pheasant feed. The treatment with 60 mg/kg Flubenol did not have any adverse effect on the number of eggs laid, the egg fertility or hatchability⁵.

Turkeys

Several trials have demonstrated that Flubenol at 60 ppm in the feed for 7 days does not cause any side-effects in young growing turkeys.

Field studies confirm the safety of Flubenol

Clinical studies have been performed in chickens and pheasants. In none of these clinical studies there has been any sign of toxicity. All investigators concluded that even at the highest dose levels used, there was no negative impact of the flubendazole administration on the laying performance, the egg quality and the hatching results.

Flubenol has been intensively used to treat all kinds of poultry species in 56 countries for more than 15 years.

Number of birds treated and monitored	Treatment schedule	Observations
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chickens

10 085 Hybro and Ross broiler breeder hens	flubendazole at 4 ppm for 62 days	no negative influence upon reproduction parameters
5093 Hubbard broiler breeder hens	flubendazole at 10 ppm for 7 days	no negative influence on egg-laying performance and hatchability during or after treatment
33 000 hens of various breeds	flubendazole at 30 ppm for 7 days	no side-effects during or after treatment
17 141 Ross broiler breeders	flubendazole at 30 ppm for 7 days	no side-effects during or after treatment
23 500 heavy breeders (breed not specified)	flubendazole at 30 ppm for 7 days repeated every 3 weeks	no negative effects on laying performance and fertility
5950 Hubbard Broiler Breeders	flubendazole at 60 ppm for 7 days	no alterations of egg production & reproductive performance
24 Hisex hens	flubendazole at 30, 60 or 120 ppm for 7 days compared with untreated controls	no adverse effects on body weight, food consumption and egg production; no side-effects
220 Arbor Acres	flubendazole at 60, 120 or 180 ppm for 7 days compared with untreated controls	no drug- or dose-related effects on mortality, clinical behaviour, egg production, egg weight and egg quality, hatching results, offspring performance

pheasants

80	flubendazole at 60 ppm for 7 days	no drug-related effects on egg production or egg hatching; no side-effects
1 100	flubendazole at 60 ppm for 7 days	no side-effects

Safety aspects for the feed mill operator and the poultry farmer



- In the toxicity studies dermal application to or inhalation by laboratory animals did not induce drug related effects.
- A primary eye irritation study conducted in rabbits revealed minimal ocular irritation. This indicated that the commercial Flubenol 5% premix is devoid of irritating potential after accidental exposure of the mucosae.
- Staff are advised to wear protective clothing and a dust mask during the production or handling of Flubenol premix.

Safety for the consumer



In accordance with Council Regulation (EEC) No. 2377/90, the Committee for Veterinary Medicinal Products (CVMP) has examined flubendazole with the aim of establishing Maximum Residue Limits (MRLs). These MRLs indicate the maximum levels of residues that can be present in edible tissues without posing a health risk for the consumer.

The following MRLs for flubendazole are adopted in the Commission Regulation (EC) No. 100/98 of 13 May 1998 (Official Journal of the European Communities):

Marker residue	Animal species	MRLs	Target tissues
Sum of flubendazole and its main metabolites	Porcine, chicken, game birds (*)	50 mg/kg	Muscle
		50 mg/kg	Skin + Fat
		400 mg/kg	Liver
		300 mg/kg	Kidney
Flubendazole	Chicken	400 mg/kg	Eggs

(*) A procedure for the establishment of the MRL in turkeys is pending (Nov. '98).

Poultry species	Withdrawal time in days
Broiler chickens (meat)	3
Laying hens (eggs)	0
Growing turkeys (meat)	1
Game birds (meat)	4

On the basis of residue depletion studies it can be measured how quickly the drug residues are excreted and removed from different parts of the body. These studies allow us to predict how soon after treatment the tissue residues have dropped below the MRL levels as set by the Committee for Veterinary Medicinal Products (CVMP). The following withdrawal periods for flubendazole can be recommended to the local health authorities, in order to comply with the established MRLs in the various poultry species. It is important however to stress that these are only recommended withdrawal periods: local health authorities might decide to implement different withdrawal periods. Please consult the Flubenol insert leaflet for the correct withdrawal periods in your country.

Safe for other animal species

Specific studies have shown that flubendazole is very well tolerated in cats, dogs, pigs, cattle, small ruminants and rabbits. Accidental feeding of Flubenol or Flubenol supplemented feed to any of these animals does not pose any health risk.

Safe for use in combination with other poultry feed additives

Until now no incompatibilities have been reported with other feed additives or therapeutics.

In broilers, the association of flubendazole (60 ppm for 7 days) with diclazuril at 1 ppm had no negative influence on behaviour, general health, weight gain and feed conversion.

In a trial with pheasants, the combination of flubendazole with anticoccidials meticlorpindol and the combination meticlorpindol - methylbenzoquate, with the anti-black-head drug dimetridazole and with the antimicrobial furoxone was shown to be safe.

In partridges, the association of flubendazole at 60 ppm with diclazuril at 4 ppm for 7 days in the feed had no negative influence on behaviour, general health, weight gain or feed conversion ratios. In turkeys, the combination of flubendazole at 20 ppm with diclazuril at 1 ppm for 7 days had no negative influence on body weights, feed consumption or feed conversion. Side-effects were never observed.





9

Flubenol deworming programme



Replacement pullets reared on litter

Treat at week 5, week 10 and week 15 of age. Thoroughly deworm before putting on batteries.

30 ppm Flubenol mixed into the feed for 7 days



Laying hens

On batteries: thoroughly deworm before putting on batteries.

30 ppm Flubenol mixed into the feed for 7 days

On litter bedding: treat with 4 week intervals in case of high infection pressure. Otherwise the intervals can be extended to 6 or 8 weeks

30 ppm Flubenol mixed into the feed for 7 days
60 ppm for 7 days against *Raillietina* sp.



Broiler breeders

Treat with 4 week intervals in case of high infection pressure. Otherwise the intervals can be extended to 6 or 8 weeks.

30 ppm Flubenol mixed into the feed for 7 days



Deworm at week 5, week 10 and week 15 (depending on the slaughter age).

In case of gapeworm infection, the interval between treatments should be reduced to 18 days

20 ppm Flubenol mixed into the feed for 7 days



Deworm at week 3, week 7, week 11 (maximum intervals of 3 weeks between treatments because of gapeworm threat).

pheasants and partridges: 60 ppm Flubenol for 7 days



Deworm regularly (cfr. table page 12: prepatent period of important worm species).

30 ppm Flubenol mixed into the feed for 7 days
60 ppm for 7 days against *Raillietina* sp.



Flubenol: practical data

1/ Composition

Active ingredient : 50 g flubendazole per kg Flubenol 5% premix

Other ingredients :

sodium lauryl sulphate	10 g
titanium dioxide	20 g
lactose	920 g

2/ Product characteristics

Aspect: grey-white to yellowish powder, completely tasteless and odourless.

Bulk density: 1,8 ml/g

Moisture content: less than 1%

Particle size: 90% of particles between 20 μm and 100 μm

Flowability: good

Not hygroscopic/ not corrosive

Melting range: $\pm 202^\circ\text{C}$ (lactose)

3/ Fire and explosion hazard of Flubenol 5%

Fire class 20°C : 3

100°C : 3

Auto-ignition temperature: 370°C

Dust explosion class: 1

Lower explosion limit: <15g/m³

4/ How to mix?

For group treatment, Flubenol 5% should be thoroughly mixed into the feed in order to obtain a homogeneous mixture.

Quantities to be mixed for group treatments:

required concentration of flubendazole in the feed:	quantity of Flubenol 5% premix to be mixed per ton of feed:
20 ppm	400 g Flubenol 5% premix per ton of feed
30 ppm	600 g Flubenol 5% premix per ton of feed
60 ppm	1200 g Flubenol 5% premix per ton of feed

With small numbers of animals, one measuring spoonful (supplied with the product) is mixed into 11 kg of complete feed for pheasants and partridges, into 21,5 kg complete feed for chickens and geese and into 32 kg complete feed for turkeys.

5/ Feed assay procedure

A HPLC method is available²⁰. A detailed description of the assay method can be obtained upon request.

6/ Mixability

Mixability tests^{21, 8} at TNO in the Netherlands and at the German IFF confirm that the mixing uniformity of Flubenol at normal concentrations in animal feed is excellent. With different types of mixers and in various types of feed the coefficient of variation (C.V.) was always below 5%.

7/ Stability

The German Forschungsinstitut Futtermitteltechnik (Braunschweig, Germany) performed tests with complete broiler feed supplemented with Flubenol. After use of a pressure conditioner - at feed temperatures of 116°C at the head of the conditioner - with subsequent pelleting, the Flubenol concentration did not significantly decrease⁸. This value did not deteriorate after a two months storage of the pellets. Mixing uniformity was excellent.

In a stability experiment²¹ performed at the TNO Institute of the Netherlands, Flubenol was mixed and pel-



leted into a representative feed at 15 ppm. It was evident that after pelleting and expanding, with a maximum product temperature of slightly over 100°C, flubendazole remained stable.

Storage stability of Flubenol in pelleted feed proved to be excellent for at least 12 weeks under ambient conditions. Up to 12 weeks the flubendazole quantity recovered from stored feed was over 90% of the initial value.

In a comparative experiment³, done at the Belgian Research Station for Small Stock Husbandry at Merelbeke, the influence of heat during pellet processing upon the flubendazole concentration was evaluated. It was concluded that the steam pelleting process (temperature of 85°C) did not significantly alter the flubendazole content in the pellets when compared to the concentrations in meal.

Analytical tests⁹ showed that the increase of pressure, necessary for the production of pellets, has no effect on the stability of flubendazole.

Up to a temperature of 100°C, flubendazole is completely stable. Flubendazole remained stable after 15 days at 17000 Lux.

Shelf life

In its original packaging under normal storage conditions, Flubenol premix remains stable for 5 years. Flubenol in prepared feeds has a shelf life of 6 months.

Withdrawal periods

The locally registered withdrawal periods should be respected.



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Technical information on Flubenol in poultry

Target species

chickens, turkeys, pheasants, partridges, geese

Indications for use

Flubenol 5% is indicated for the treatment of helminthiasis caused by: *Syngamus trachea*, *Ascaridia galli*, *Heterakis gallinarum*, *Capillaria* spp., *Amidostomum anseris*, *Trichostrongylus tenuis* and *Raillietina* spp.

Contra-indications

It is contra-indicated to administer flubendazole to pigeons and parrots.

Undesirable effects, frequency and seriousness

Flubendazole is well tolerated by the target animal species and has a wide safety margin of at least 5 times. In pigeons and parrots, flubendazole can result in feathering problems.

Special precautions for use

Treatment with Flubenol 5% can only give optimum results when the hygiene of pens and huts is strictly observed at the same time.

Use in layers

Even at 3 times the highest dose (180 ppm flubendazole) for 7 days, no drug-related effects could be observed on egg production, egg quality, egg hatching results, off-spring performance nor on any other clinical symptom.

Interaction with other medicines and other forms of interaction.

None known

Posology and method of administration

Flubenol 5% should be thoroughly mixed into the feed in order to obtain a homogeneous mixture.

a. turkeys: 20 g flubendazole per ton feed (20 ppm) for 7 consecutive days.

b. chickens and geese: 30 g flubendazole per ton feed (30 ppm) for 7 consecutive days. In case of an infection with *Raillietina* sp., 60 g flubendazole per ton feed (60 ppm) for 7 consecutive days.

c. pheasants and partridges: 60 g flubendazole per ton feed (60 ppm) during 7 consecutive days.

Quantities to be mixed for group treatments

-20 g flubendazole per ton corresponds to 1 bag of 12 kg for 30 tons of feed or 1 pot of 600 g for 1.5 tons of feed.

-30 g flubendazole per ton corresponds to 1 bag of 12 kg for 20 tons of feed or 1 pot of 600 g for 1 ton of feed

-60 g flubendazole per ton corresponds to 1 bag of 12 kg for 10 tons of feed or 1 pot of 600 g for 500 kg of feed

-With small numbers of animals, one measuring spoonful is mixed into 11 kg meal for pheasants and partridges, into 21.5 kg meal for chickens and geese and into 32 kg meal for turkeys.

Overdose (symptoms, emergency procedures, antidotes)

Overdosing did not result in adverse effects. In chickens a safety factor of >34 for laying hens (*ad libitum* feeding) and > 65 in reproduction poultry (restricted feeding regime) was witnessed.

Special warnings for each target species

None

Withdrawal periods

The locally registered withdrawal periods should be respected.

Special precautions to be taken by the person administering the product to animals

None known

Incompatibilities

None known

Shelf-life

5 years. Note the expiry date ("exp.") on the package.

Prepared feeds containing flubendazole: 6 months.

Special precautions for storage

Store between 15 and 30° C.

Nature and contents of the container

polyethylene pots of 600 grams with a measuring spoon of 20 ml (equivalent to 13 g Flubenol 5%)

polyethylene bag of 12 kg in drums

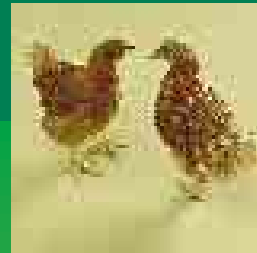
polyethylene bag of 25 kg in drums



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