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# FVE position paper on coccidia control in poultry

*'Coccidiostats use requires veterinary supervision'*

**A FVE REVISED POSITION PAPER IN LIGHT OF THE NEW VMP REGULATION**

**Summary**

Coccidiosis is a parasitic disease, which is ubiquitously prevalent in all poultry production systems worldwide. Even where the sanitary and management standards are high coccidial infections can occur with a serious potential impact on animal health and welfare. Therefore, effective long-term management of coccidia is indispensable, through a combination of holistic flock health management, optimised stocking density, litter management, feeding and drinking regime as well as nutraceuticals, accompanied by appropriate biosecurity measures, vaccination and coccidiostats, where indicated.

In European legislation, coccidiostats or anticoccidials are categorised either as feed additives or as veterinary medicinal products, depending on their pharmacologically active substance, mode of action, pharmaceutical form, target species and route of application. Challenges in coccidia control are due to parasitic and bacterial drug (cross-)resistance. Coccidiostats also interact with other veterinary medicinal products and have a secondary residual activity against gram-positive bacteria. Regular monitoring of performance and parasitic burden at flock level has been a fundamental part of developing rotational and alternative strategies which have helped to maintain the effectiveness of these medicinal products in the field. A standard procedure/ guideline for such monitoring should be developed by e.g. EFSA, to enable rapid and low-cost national and regional monitoring. Especially quantitative tests would be beneficial for ongoing surveillance and monitoring purposes.

Though there is no legislative requirement for veterinary supervision of in-feed coccidiostats, FVE strongly believes that it is of paramount importance to improve veterinary oversight of coccidiostat use in poultry production to further strengthen the prudent and responsible use of coccidiostats. FVE recommends that monitoring of polyether ionophores coccidiostats sales and potentially use should be included in the ESVAC system. However, the in-feed or in-water use of coccidiostats or anticoccidial medicinal products remains for the time being a necessary option for rearing of short-living birds such as broiler chickens in the EU due to their short grow out and for turkeys due to the unavailability of an EU-licensed vaccine. Feed containing coccidiostats must always be labelled in a clear and comprehensive manner, including for hobby farmers, to allow for immediate identification of the pharmacologically active ingredient, its concentration and withdrawal period.

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**FVE recommends that:**

- Decisions on the most appropriate, efficacious and safest coccidiosis control options should be elaborated between the supervising veterinarian and the poultry farmer formulating a medium to long-term strategy
    - based on comprehensive and continuous on-farm surveillance of excretion levels in each flock
    - by using firstly all appropriate strategies in the toolbox for coccidiosis control including flock health management, appropriate biosecurity measures, vaccines, nutraceuticals, as well as coccidiostats and anticoccidials prudently and responsibly, only where indicated.
    - based on veterinary examination, diagnosis and/or supervision prior to use of a feed additive by the veterinarian in charge who can check interactions with other medications and liaise - if necessary - with the feed mill prior to the supply of feeds containing coccidiostats.
    - In production units where in-feed coccidiostats are the norm rather than the exception and a relevant vaccine can be provided, it is highly advisable to vaccinate against coccidiosis.

- Moreover,
    - The development of rapid, low-cost and especially quantitative diagnostic tests for ongoing surveillance and monitoring purposes should be promoted.
    - an EU-licensed anticoccidial vaccine for other poultry species than chicken, most importantly turkey, should be marketed. Monitoring of polyether ionophores coccidiostats sales should be included in the ESVAC (European Surveillance of Veterinary Antimicrobial) system.
    - Feed containing coccidiostats must always be labelled in a clear and comprehensive manner, including for hobby farmers, to allow for immediate identification of the pharmacologically active ingredient, its concentration and withdrawal period.

**Introduction**

FVE published its first position paper on coccidiostats in 2016. In 2022, this position was revised based on new published scientific research and the new legislative framework which came into force.

**Background**

Coccidiosis is a universally seen parasitic disease in modern livestock husbandry and without doubt the most important parasitic disease in poultry. It is also of major importance in other species such as rabbits, ruminants and pigs. The infection of the intestinal tract is caused by a family of single celled obligate intracellular parasites, and affects all livestock species as well as wildlife and companion animals. The most common genera affecting livestock are *Eimeria spp*., which are highly host-specific and has a specific site of development in the intestine [1,2]. *E. necatrix* and *E. tenella* are the most pathogenic in chickens, *E. adenoides* and *E. meleagrimitis* are considered most pathogenic in turkeys [3].

After ingestion of infective oocysts, the parasite penetrates the intestinal mucosa or epithelial cells of the host and starts to multiply within 4-7 days, during which damage develops to the (sub)mucosal tissues of the intestine. Oocysts develop and are discharged in the faeces. The extent of the intestinal damage is a consequence of the coccidial species infecting the host, the host immunity system and the level of exposure. Clinical signs of coccidiosis develop due to the intestinal damage. Clinical coccidiosis is most prevalent after ingestion of relatively large numbers of sporulated oocysts under imperfect sanitary conditions, e.g., contaminated environment, and stressors such as high stocking density [3]. In addition, mucosal damage caused by coccidia predispose to the development of necrotic enteritis in chicken. Mortality concurrently infected with *Eimeria* species was 25% higher than in those affected by necrotic enteritis alone [4].

**Diagnosis**

The clinical signs of coccidiosis may or may not be accompanied by large numbers of oocysts being shed in the faeces. Currently the most commonly used diagnostic methods are oocyst counts and lesion scoring of freshly dead carcasses, but rapid alternative methods have been developed as well [5–7]. More rapid, low-cost and especially quantitative diagnostics tests such as rt-qPCRs would be beneficial for ongoing surveillance and monitoring purposes. Anticoccidial sensitivity testing is available, and is beneficial to monitor sensitivity levels of field and vaccine strains as well as efficacy testing of drug for regulatory purposes. It has however it limitations as it requires laborious in-vivo experimental inoculation in the target species and consequently necropsies [8–10]. Therefore, routine testing for sensitivity in field isolates has only begun in recent years [11,12].

**Coccidiosis control measures**

Coccidiosis control is of paramount importance and based on limiting the intake of sporulated oocysts by susceptible individuals so that a subclinical infection is established to induce immunity but not clinical signs. Best feeding and watering practices and good flock health management, including temperature, light, litter, air, stocking density and disease control for immunosuppressive diseases such as Marek's, contribute to this goal. Whilst there is no specific requirement under feed additives legislation for a veterinary examination and/or oversight prior to use of a feed additive in poultry production, it is best practice for the supervising veterinarian to liaise with the poultry farmer and feed mill to develop a coccidiostat programme prior to the supply of feeds containing in-feed coccidiostats. Decisions on the most appropriate, efficacious and safest coccidiosis control strategy should be elaborated between the supervising veterinarian and the poultry farmer formulating a medium to long-term strategy based on comprehensive and continuous on-farm surveillance of excretion levels in each flock, implementing firstly all strategies in the toolbox for coccidiosis control including flock health management, appropriate biosecurity measures, vaccines, nutraceuticals, as well as prudent and responsible use of coccidiostats and anticoccidials, where indicated.

**Nutraceuticals and sanitation:**

Recent approaches focused on new nutraceutical compounds such as phytochemicals (e.g., plant extracts), and probiotics due to their capacity to diminish oocyst burden and improving intestinal integrity [13,14]. When applied in the proper feeding period, probiotics, natural herbal extracts with bioactive molecules (i.e., saponins, artemisin, and curcumin) and short chain fatty acid (SCFA) such as coated butyrate, and threonine (an essential amino acid) were shown to support chicken resilience during coccidiosis infection [15]. Results of nutritional interventions like medium chained fatty acid

additives and sophorolipids were promising to decrease intestinal lesions and improve feed conversion rates (FCR) in combination with coccidiosis vaccines [16,17]. It was shown that supplementation of organic acids significantly increased body weight gain, improved feed conversion ratio (FCR), reduced lesion scores and oocyst shedding[18]. Many phytochemicals that contain natural active compounds are now commercially available to assist coccidia control [19,20]. Nonetheless, and even where hygiene and management standards are high, coccidiosis can occur with a serious potential impact on animal health and welfare and potentially high mortality rates as protozoal oocysts are highly resistant in the environment. Therefore, proper sanitation and disinfection protocols are essential to lower the oocyst burden. Ammonium hydroxide as cleaning agent and sanitizer inactivates coccidial oocysts which are resistant to most standard chemical disinfectants. Halogens as strong oxidising agents in high concentrations, ozone and halogenated phenols are efficient as well [21].

**Vaccination:**

Alternative preventive ways such as vaccination are available for some species, especially for chicken. Current commercial vaccines consist of live, sporulated oocysts of the various coccidial species administered at low doses to stimulate the development of immunity [2]. Modern anticoccidial vaccines are intended for day-old chicks and can be applied to chicks either via semi-automatic applicators which delivers coarse sprays or gel drops onto the chicks in the crate or box to ensure uniform application. Manual application as well as application via feed or drinking water are also possible but harbour a higher risk for non-uniform application and may result in a sub optimal immune response by the flock. An indicator (food grade dye or milk) should be added to the vaccine solution to allow for vaccine uptake monitoring and increased preening [22]. Live vaccines serve to introduce a low dose of fully susceptible oocysts and chickens are re-exposed to the vaccine strain through their excretion, further stimulating increasing their level of immunity [23]. Depending on the strain, two to three cycles of re-ingestion are necessary to achieve the best possible immunity. During this period, it is important to limit possible stressors, avoid antibiotics with a residual activity against *Eimeria* and any anticoccidials and feed containing anticoccidials. This highlights the importance of veterinary oversight and education in relation to implementation and monitoring of vaccination programmes. Feed containing coccidiostats must always be labelled in a clear and comprehensive manner, including for hobby farmers, to allow for immediate identification of the pharmacologically active ingredient, its concentration and withdrawal period. Monitoring the development of the immunity should be done by determining oocyst burden per gram of faeces during the first 4 weeks post-vaccination. Although anticoccidial drugs have been preferred for protection of poultry for many years, vaccination programmes are gaining popularity, especially in long-living poultry such as breeding stocks and layers and in organic farming [23,24]. Although experience from organic farming and form certain conventional farming in certain countries, i.e. Norway demonstrates the possibility to manage vaccination programmes in broiler chickens, the short grow out of broiler chickens hampers vaccine use [25] . Better administration techniques, formulations, higher concentration, and tailored choice of *Eimeria* strains must be considered to improve the feasibility of vaccination in broiler chickens in the future. In addition, the importance of the cell-mediated immunity against coccidiosis has to be considered [26,27]. For example, novel *in ovo* vaccines delivered promising results to pass maternal antibodies to their offspring [28–30]. Though marketed in other regions in the world, there is no EU-licensed vaccine for turkey which is a major drawback. Multiepitope antigen proteins are the most recent potential vaccine candidates [31].

**Coccidiostats:**

Coccidiostats or anticoccidial drugs act at specific times during the life cycle of the parasite, or exert their effects at several phases. Coccidiostats can act on extracellular stages (sporozoites and merozoites) to prevent penetration of cells or on the intracellular stages to stop or inhibit development, and a few anticoccidials affect the sporulation of oocysts after they are excreted. All coccidiostats inhibit reproduction and do not fully eliminate the parasite from the intestine of the animal. Administration of in-feed coccidiostats is recommended when animals even under best management regimens can be predictably expected to develop clinical coccidiosis and other measures are unable to limit clinical signs but should never be the norm. Coccidiostats can be grouped into two major classes, namely ***polyether ionophores*** (i.e. monensin, lasalocid sodium, maduramicin, narasin, salinomycin, semduramicin) and the ***synthetic products not of an ionophoric nature*** (decoquinate, robenidine hydrochloride, amprolium, halofuginone, diclazuril, toltrazuril, nicarbazin and sulfonamides) as well as ***combinations*** of different classes (i.e. narasin and nicarbazin, sulfonamides with trimethoprim, ormetoprim or pyrimethamine) and act on different stages of the lifecycle.

Polyether ionophores are by far the most widely used coccidiostats. They have some residual antimicrobial activity against gram-positive bacteria, and aid in controlling simultaneously pathogens such as *Clostridium perfingens* [32]. Recently, targeted studies are divided on how in-feed coccidiostat use contributes to economically sustainable animal production, particularly on the long term [12,33,34]. In Norway, narasin was gradually phased out as an in-feed coccidiostat for broilers by 2016 and various measures, such as nutraceuticals and vaccination, were successfully employed in order to prevent increased occurrence of clinical coccidiosis and necrotic enteritis (NE) [35].

They are not currently used in human medicine and therefore not classified as medically important antimicrobials by WHO [36]. Nonetheless, some pharmacologically active substances (i.e. monensin, salinomycin) are being studied such as possible bioactive molecules for future cancer therapy drugs, but to date none have been licenced for this purpose [37–39].

**Legislative framework**

FVE published its first position paper on coccidiostats in 2016. In 2022, this position was revised based on new research and the new legislative frameworks which came into force. The current legislative background for coccidiostats in the European Union (EU) considers them as feed additives for poultry (category of coccidiostats and histomonostats). The legal basis for additives for use in animal nutrition is laid down in Regulation (EC) No. 1831/2003. Several coccidiostats containing polyether ionophore antibiotics or chemical anticoccidial agents for use in chickens, turkeys and rabbits are included in the list of feed additives. Coccidiostats for poultry are usually fed via a premixture. This guarantees good mixing and homogeneity, and no over/under dosing or ´off label´ use is allowed [40]. On top of the legal requirement, almost all feed manufacturers in the EU are also certified by voluntary quality system with additional safety requirements. An immediate change in the legislative status of coccidiostats from the feed additive legislation towards the VMP Regulation has the danger that manufacturers would be unable or unwilling to update an existing dossier or compile a new dossier because of insufficient data and hamper their use [41]. The Regulation (EU) 2018/848 bans the use of coccidiostats in organic farming [24].

**Drug residues of coccidiostats**

A critical factor in the medication of all food-producing animals is the mandatory withdrawal period to avoid residues in products of animal origin. Historically anticoccidial residues were one of the most frequently veterinary drug residues. However, the most recent EFSA report for 2020 on the results from the monitoring of veterinary medicinal product residues and other substances in live animals and animal products, found only 0.07% of the samples analysed to be non-compliant (0.05% in 2019) of which pigs (0.01%), poultry (0.06%) and eggs (0.35%) [42]. From 2009 to 2019, an overall important decrease has been observed in the frequency of non-compliant samples for anticoccidials in poultry. This decrease is most likely the result of the awareness and the measures that followed the implementation of the Commission Directive 2009/8/EC setting up maximum levels (ML) of unavoidable carry-over of coccidiostats in non-target feed. In summary, residues are nowadays well managed, occur rarely and technical cross-contamination of animal feeds would not be expected to adversely affect the health of consumers [43]. In addition, authorisation and prerequisites for their use are defined for individual products (brand names) following review by the European Food Safety Authority (EFSA). Feed additives are subject to post-market monitoring plans, regular revised safety, efficacy and vigilance environmental risk assessments to ensure a responsible handling and low risk of adverse events.

**Resistance to coccidiostats**

***Parasitic resistance***

An early recognised problem associated with the control of coccidiosis is the development of resistance by the coccidia to coccidiostats [44]. A number of strategies have been developed to extend the useful life of coccidiostats, while still controlling coccidiosis; such as through 'shuttle use' or 'rotational use'. Rotational use involves changing the in-feed coccidiostats used every 4–6 months with combinations of anticoccidials comprising drugs with different modes of action [45,46]. 'Shuttle use' employs two or more products most suited to each phase of the grow out, i.e. one medicine for the starter period, one for grower and another for the finisher phase [3]. However, it increases the useful life of the drug but does not fully avoid the acquisition of resistance [47,48]. Resistance to coccidiostats is generally thought to be stable, nevertheless, relaxation of selection pressure through vaccination for 2 or 3 consecutive cycles can be advantageous in rotational programmes to re-colonise broiler chicken houses with fully susceptible strains and is employed for example in Spain, France and Italy [49]. Consequently, strategies have to be employ all tools for control of coccidiosis, including vaccination, to mitigate resistance development [50].

Cross-resistance to combinations of polyether ionophore and chemical coccidiostats class was already shown more than 30 years ago and is still evident today [10,51]. The loss in sensitivity was attributed more recently to the polyether ionophore component of the combination [52]. Cross-resistance between polyether ionophores can also occur, although strain differences in response to specific polyether ionophores have been demonstrated. In general, resistance to a monovalent polyether ionophore confer some cross-resistance to other monovalent polyether ionophores (salinomycin, monensin, narasin, maduramicin, and semduramicin, but susceptibility to monovalent and divalent polyether ionophores (lasalocid) may be retained [53,54].

***Bacterial resistance***

In the last decades, bacterial resistances to polyether ionophores were discovered. Aarestrup et al. found up to 6% *Staphylococcus hyicus* and *Enterococcus* spp. in Danish pigs with reduced monensin sensitivity through official monitoring 25 years ago [55]. Nilsson et al. (2012) described a reduced susceptibility in a large proportion of *Enterococcus faecium* from Swedish broiler chickens to the polyether ionophore narasin and discovered a plasmid-borne narasin resistance transferred together with vancomycin resistance [56,57]. However, sequencing of the plasmids has shown that the responsible genes are not located next to each other on the same plasmid and weakened the hypothesis of the narasin influence on persistence of vancomycin resistant enterococci in Swedish broiler chickens [58]. Preliminary research data showed a plasmid-borne resistance gene against salinomycin together with resistance genes towards different antibiotics in Dutch broiler chicken [59]. Currently, the prevalence of phenotypical polyether ionophore resistance is however difficult to assess since there are no clinical breakpoint values for resistance. It is acknowledged that the use of polyether ionophores still carries risks owing to the possibility of cross-resistance or co-selection as shown before for antibiotics [60,61]. More research data will be required to systematically investigate the contribution of polyether ionophores to the burden of antimicrobial resistance [50]such as the ICONIC project investigating Ionophore coccidiostats and therisk of CO-selectioN of antImicrobial resistance. FVE monitors the situation carefully in order to adapt recommendations when indicated in line with EMA recommendations [62].

**Interactions of polyether ionophores with antibiotics**

Studies have reported interactions between macrolide antibiotics and/or pleuromutilin derivative (tiamulin) administered concurrently with several compounds including polyether ionophore coccidiostats (monensin, salinomycin) which have metabolism partly or entirely dependent on the cytochrome P450 drug metabolising system of the liver [63]. Moreover, toxic interactions between polyether ionophores (mainly monensin) and sulphonamides, erythromycin, and enrofloxacin have been observed [64,65]. All these other active ingredients are already subject to prescription when used in veterinary medicine. Veterinarians prescribing and dispensing antibiotics or other veterinary medicinal products should, as part of their due diligence and judicious use of medicines, check with the farmer if any polyether ionophore coccidiostats are being administered in feed prior to the dispensing of any medication which may result in these adverse interactions. Furthermore, the requirements for feed mills to adhere to good manufacturing practice (GMP) should minimise any adverse reactions associated with inaccurate dosing or carryover in the feed mill.

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