Veterinary Medicines Directorate

Coccidiostats

Current Legislation and Future Challenges

Presented by: Fraser Broadfoot BVetMed MRCVS

Date: 14th March 2018

Presentation

- **Legislation for ionophores:**
  - Currently under evaluation

- **Future challenges:**
  - Resistance - links to AMR?
  - Antibiotic free labelling

Feed Additives Legislation

- **Feed additives legislation:**
  - 1970 – Directive - 70/524/EEC
  - 2013 – Reviewed – 1831/2003
- **Key parts of legislation:**
  - European Food Safety Authority (EFSA) – scientific evaluation:
    - Efficacy
    - Safety – human health/ environment
  - Maximum dosage allowance and Maximum Residue Limits
  - Valid for period of 10 years before renewal

Feed Additives Legislation

- **Key parts of legislation:**
  - No prescription, clinical examination or diagnosis needed
  - Licensed for specific species
  - Withdrawal periods
  - Linked to authorisation holder – post marketing monitoring/ traceability
  - Post marketing monitoring required by MA holder
- **Regulation 183/2005:**
  - Farmers can only receive Ready To Use feedstuffs by approved feed compounders
  - Registration and approval of establishments handling coccidiostats

Toxic to humans?

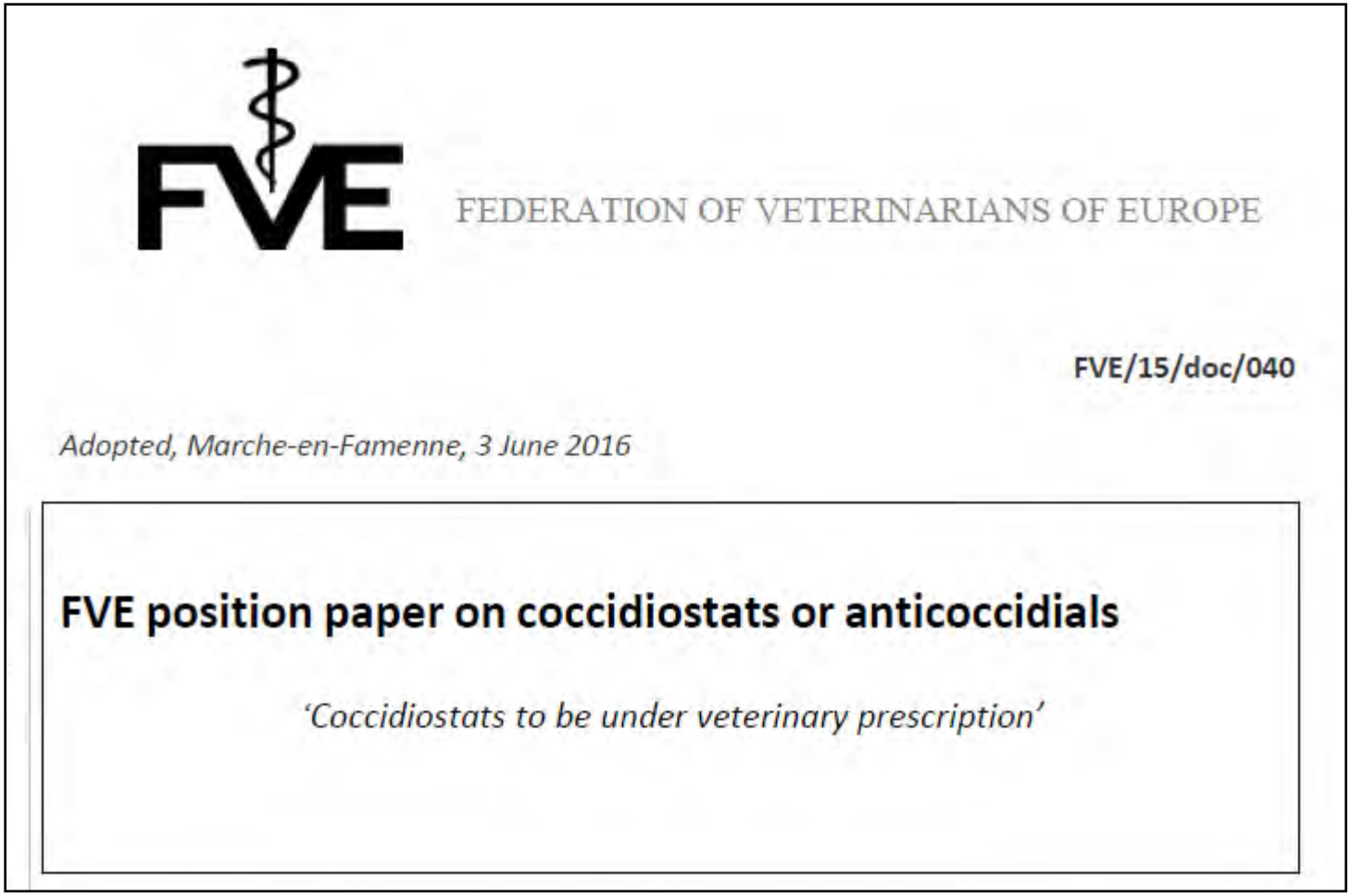
- Tolerance highly species specific
  - Sudden death and coronary artery dilation in some species
  - Horses – depression, ataxia, paresis, paralysis, anorexia and death
- People – headache, nausea, nose bleed, skin rash, dizziness:
  - Precautions – ““Wear suitable protective clothing, gloves and eye/face protection. In case of insufficient ventilation in the premises, wear suitable respiratory equipment”
- If withdrawal periods followed, no risk from food from animals treated with ionophores
  - European commission residue report (2013 data) – non- compliant results for poultry of lasalocid (0.4%), monensin (0.8%), narasin (0.5%) and salinomycin (0.3%)

Legislation Review

- Currently being revised by EC
- Looking into how 1831/2003 has performed in delivering objectives:
  - Difficulties identified and experiences gained
  - Possible burdens, overlaps, inconsistencies, obsolete measures and gaps
  - “Problems such as antimicrobial resistance become more prominent to which novels solutions need to be found which may not necessarily fit within the current quite prescriptive system of feed additive authorisations”
- Public consultation up to 3rd April 2019 with adoption planned Q4 2019[1]

1 – https://ec.europa.eu/info/law/better-regulation/initiatives/ares-2017-4196253_en

Legislation Review



FEDERATION OF VETERINARIANS OF EUROPE

FVE/15/doc/040

Adopted, Marche-en-Famenne, 3 June 2016

FVE position paper on coccidiostats or anticoccidials

'Coccidiostats to be under veterinary prescription'

FVE Concerns

- Development of resistance threatens products efficacy and animal health/welfare
- Some coccidiostats have antimicrobial activity
- Can interact with other drugs and cause adverse events
- Non adherence of withdrawal time or feed cross-contamination can lead to residues being found in food from animal origin, which can cause safety concerns

FVE Concerns

- Important to safeguard availabilility
- All coccidiostats should be under veterinary prescription following clinical examination and diagnosis:
  - Vet choose the best strategy to extend life and, if possible, phase out in the long-term
  - Better monitoring of adverse events, including lack of efficacy
  - Ensure withdrawal periods respected
  - Monitoring through ESVAC

Increasing Use

- In EU – 84% broiler starter, grower and finisher feed contains a coccidiostat[1]
- Upwards sales trend in UK: 2013-2017:
  - Poultry production = +12%
  - Ionophore sales = +34%
  - (Antibiotic sales = -85%)
- Why have ionophore sales increase?
  - Move towards full ionophore programmes
  - Many birds treated throughout life-cycle

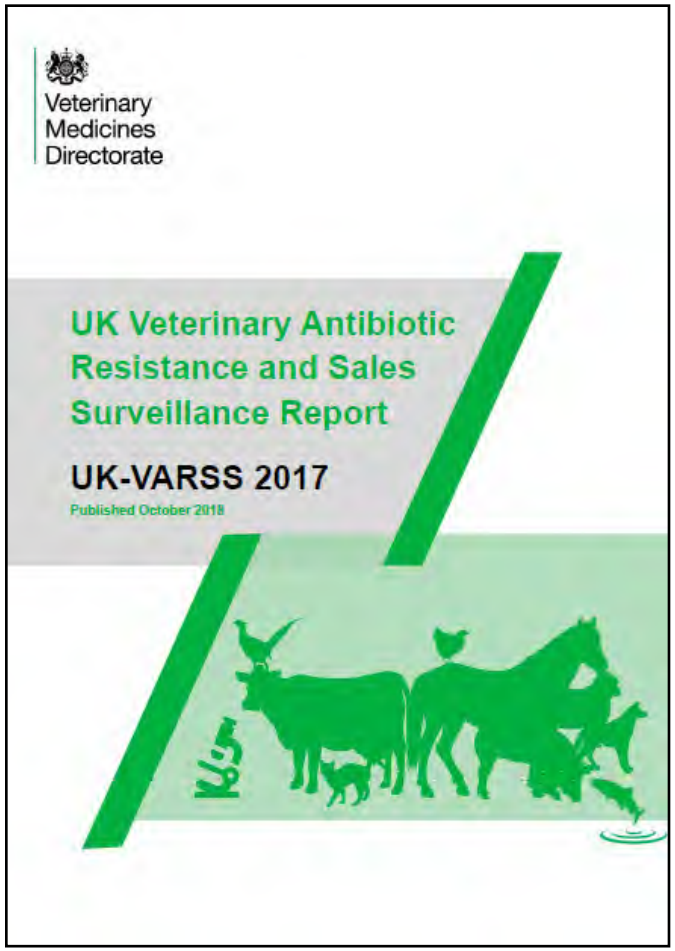
1 - Chapman HD, Jeffers TK, Williams RB. Forty years of monensin for the control of coccidiosis in poultry. *Poultry Sci* 2010; **89** : 1788-1801.

Growth Promotion?

- Well understood in cattle – increase feed efficiency, energy metabolism, rumen fermentation
- Not clearly established in poultry:
  - Effective against C. Perfringens (necrotic enteritis)
  - Sub-acute – intestinal damage, reduced absorption, weight loss
  - Intestinal damage by coccidia predisposing factor for necrotic enteritis

Ionophore Classifications

- EU – not regulated as antibiotics:



Ionophore Classifications

- **WHO: Critically important antimicrobials for human medicine, 5th revision**

Annex 2

Antimicrobial classes currently not used in humans[1]

Antimicrobial Class	Example of drug products used in food animals
Aminocoumarins	novobiocin
Orthosomycins	avilamycin[2]
Phosphoglycolipids	bambermycin (=flavomycin)
Polyethers/Ionophores	lasalocid, monensin, narasin, salinomycin
Quinoxalines	carbadox, olaquindox

1 - https://www.who.int/foodsafety/publications/antimicrobials-fifth/en/

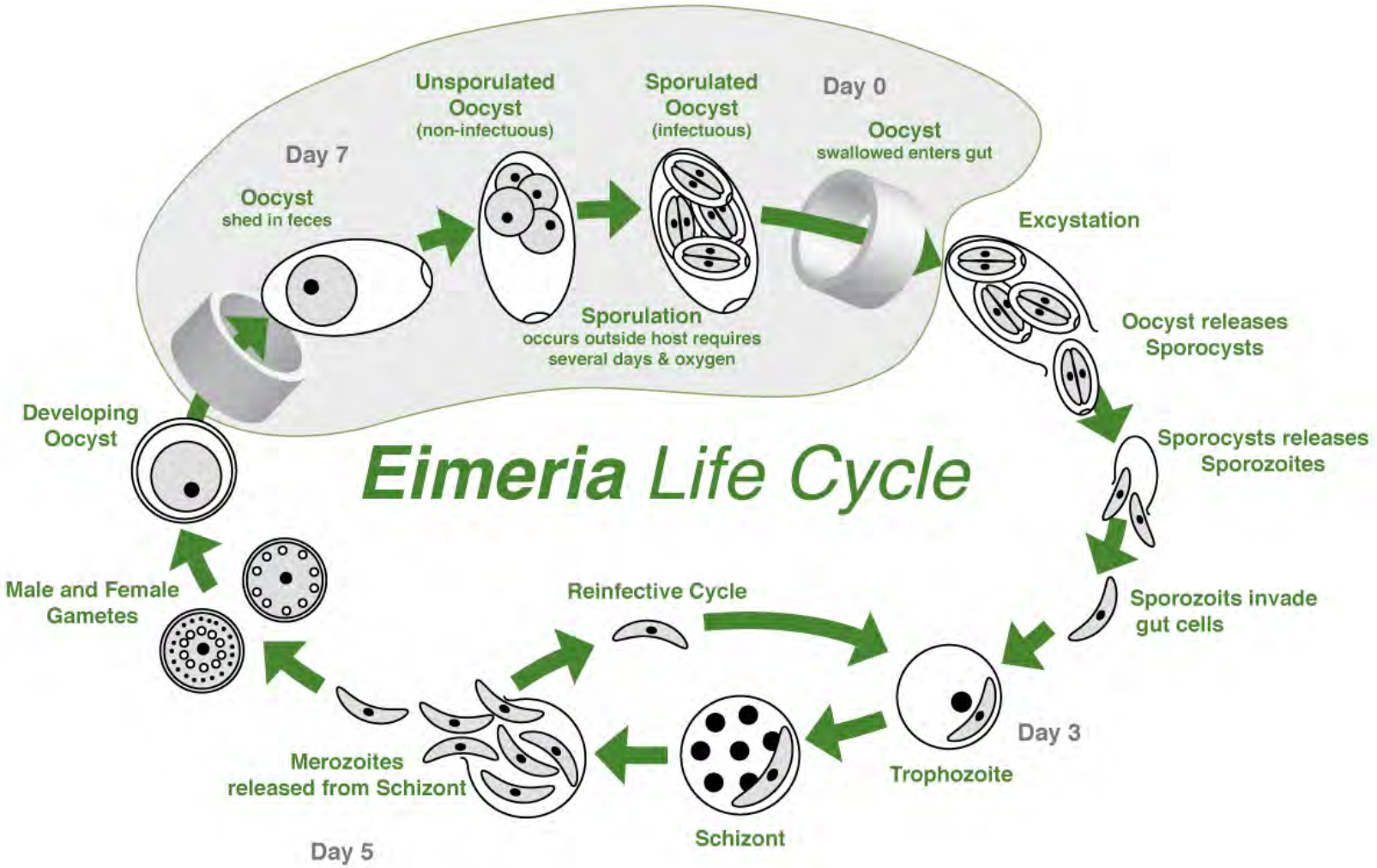
Ionophore Classifications

- **Non-medically important antimicrobials**

> **4. Category IV: Low Importance**
>
> Antimicrobials in this category are currently not used in human medicine. Examples include:
>
> 4.1 Flavophospholipols
> 4.2 Ionophores

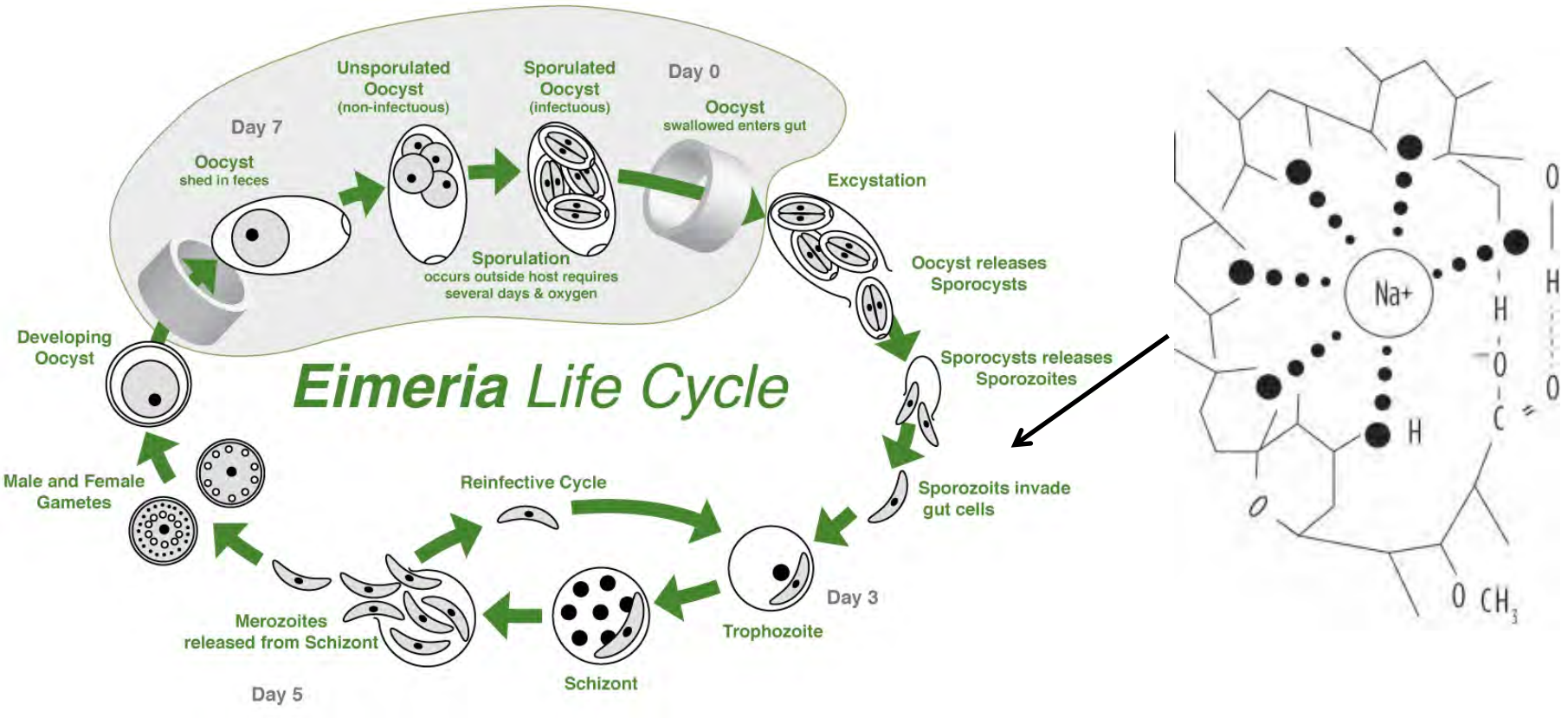
1 - https://www.canada.ca/en/health-canada/services/drugs-health-products/veterinary-drugs/antimicrobial-resistance/categorization-antimicrobial-drugs-based-importance-human-medicine.html

Eimeria Life Cycle



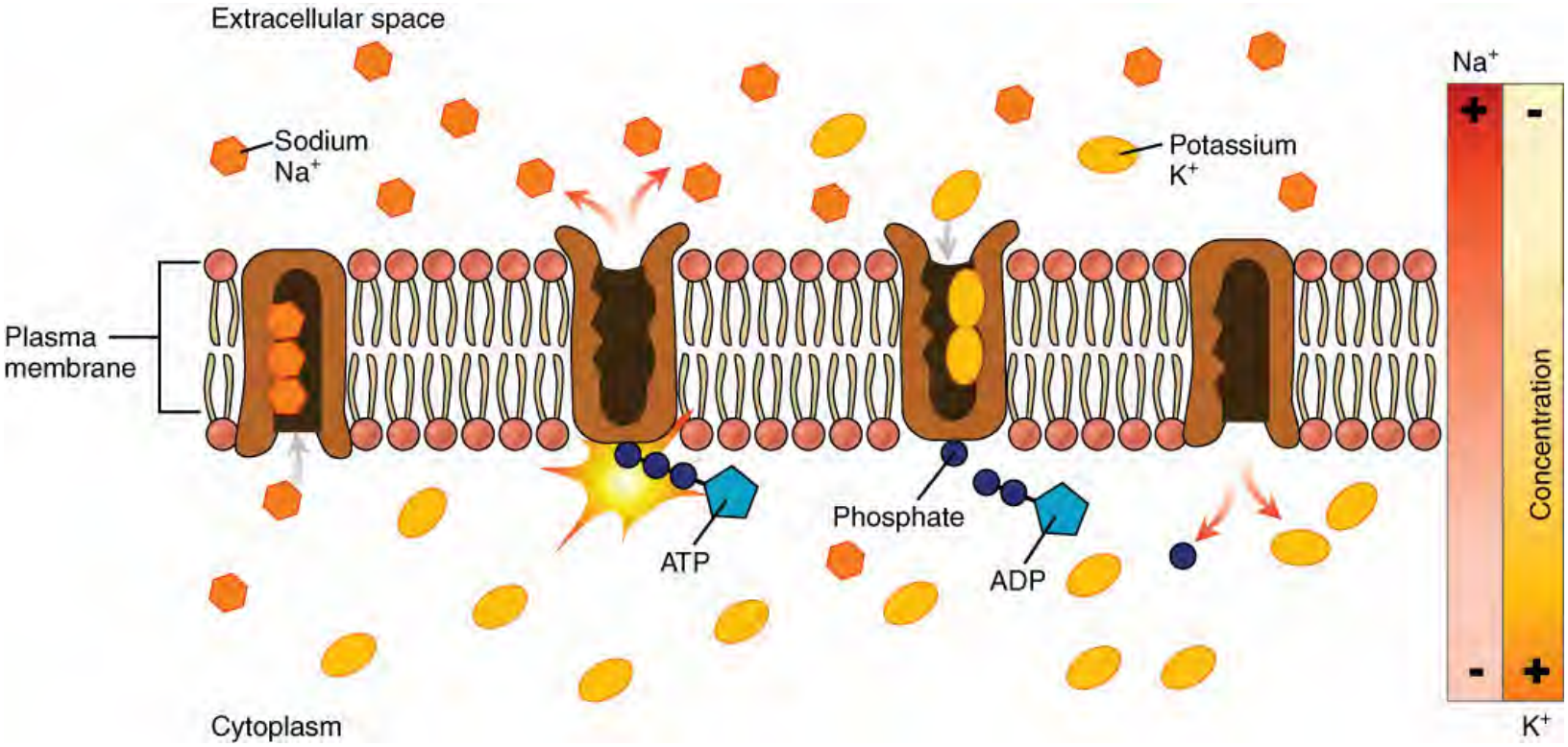
Reference - https://poultryhealthtoday.com/ionophores-control-coccidiosis/

How Do Ionophores Work?

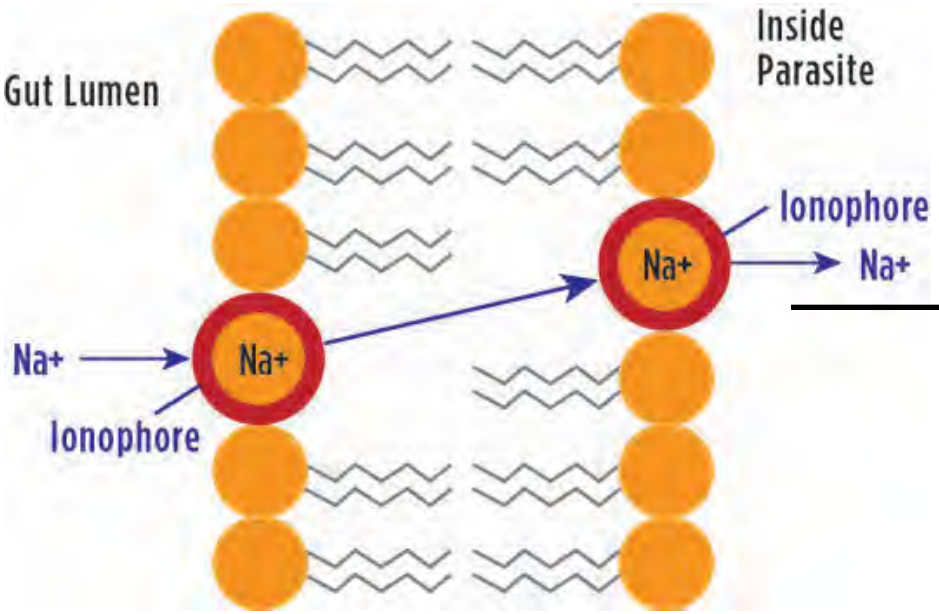


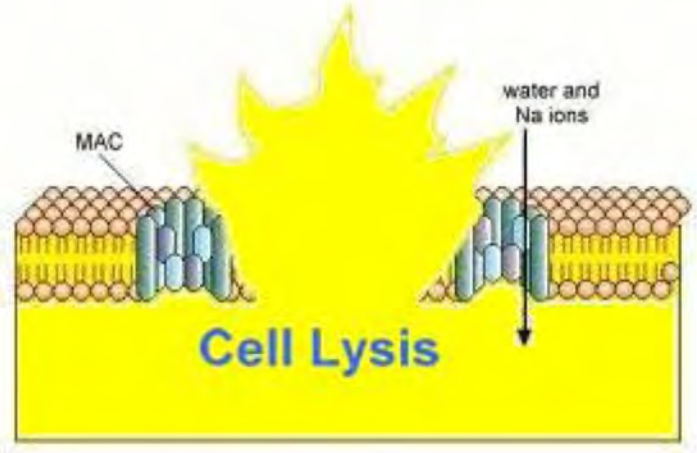
Reference - https://poultryhealthtoday.com/ionophores-control-coccidiosis/

How Do Ionophores Work?



How Do Ionophores Work?





Reference - https://poultryhealthtoday.com/ionophores-control-coccidiosis/

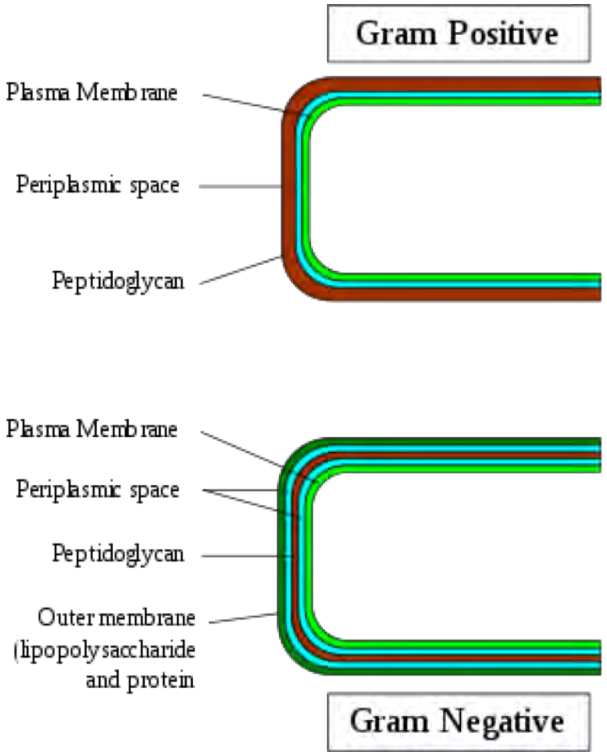
Drug Tolerance/ Resistance

- Sensitivity can be determined by anti-coccidial sensitivity test (AST)
- Resistance has been demonstrated – reduced susceptibility after long term use[1]
- Cross resistance has been reported[2]
- Mechanism – poorly understood; efflux[3]
- Minimised by drug rotation and shuttle programmes[1]

1 - Kant V, Sing P, Verma PK, Bais I, Parmar MS, Gopal A, Gupta V. Anticoccidial drugs used in the poulty: An overview. *Sci Intl* 2013; **1** : 261-265., 2 - Van Veen HW, Margolles A, Muller M, Higgins CF, Konings WN. The homodimeric ATP-binding cassette transporter LmrA mediates multidrug transport by an alternative two-site (two cylinder engine) mechanism. *EMBO J*; **19** : 2503-2514. 3 - Raether, W., and D. Paeffgen. 1989. Drug sensitivity of coccidia recently selected from broiler farms in Europe. Pages 309–312 in Coccidia and Intestinal Coccidiomorphs, Proc. Vth Int. Coccidiosis Conf., Tours, France. INRA Publications, Versailles, France.

Effect Against Bacteria

- **Gram +ve** – "porous"
  - Some allow ionophore through and kill bacteria



- **Gram –ve** –
  - Doesn't allow ionophore through

Bacterial Ionophore Resistance

- Experimental studies: rumen cultures
- Rapid and often reversible adaptation
- Sweden – 100% Enterococci resistant to narasin
- Mechanism – thickend outer membrane/ glycocalyx/ active efflux by ABC transporters[1,2]

1 - Manson JM, Keis S, Smith JMB, Cook GM. Acquired bacitracin resistance in *Enterococcus faecalis* is mediated by an ABC transporter and a novel regulatory protein, BcrR. *Antimicrob Agents Chemother* 2004; **48** : 3743-3748. Mathers JJ, Clark SR, Hausmann D, Tillman P, Benning VR, Gordon SK. Inhibition of resistance plasmid transfer in Escherichia coli by ionophores , 2 - Simjee S, Heffron A-L, Pridmore A, Shryock TR. Reversible monensin adaptation in *Enterococcus faecium*, *Enterococcus faecalis* and *Clostridium perfringens* of cattle origin: potential impact on human food safety. *J Antimicrob Chemother* 2012; **67** : 2388-2395.

Do Ionophores Cause AMR?

- VMD have commissioned independent review
- One study looking at Clostridium aminophilum F adapted to monensin and cross resistant to lasalocid[1]

Table 1. MICs for non-adapted, monensin-resistant and lasalocid-resistant *C. aminophilum* F cultures. All values are given in mg/L

Antibiotic	Target	Non-adapted	Monensin-resistant	Lasalocid-resistant
Penicillin G	cell wall	1	1	1
Ampicillin	cell wall	0.063	0.063	0.063
Cephalosporin C	cell wall	11	8	8
Vancomycin	cell wall	1	1	1
Carbenicillin	cell wall	0.5	0.5	0.5
Bacitracin	cell wall	4	128[a]	128[a]
Tetracycline	protein synthesis	9.33	8	8
Chloramphenicol	protein synthesis	0.167	0.125	0.125
Erythromycin	protein synthesis	0.031	0.031	0.031
Streptomycin	protein synthesis	128	128	128
Lincomycin	protein synthesis	0.016	0.016	0.016
Kanamycin	protein synthesis	128	128	128
Rifampicin	nucleic acid synthesis	0.008	0.008	0.008
Trimethoprim	nucleic acid synthesis	128	128	128
Novobiocin	nucleic acid synthesis	0.008	0.008	0.008
Polymyxin B	cell membrane	128	128	128

[a]Statistically significant ($P < 0.05$).

1 – Houlihan AJ, Russell JB. The susceptibility of ionophore-resistant *Clostridium aminophilum* F to other antibiotics. *J Antimicrob Chemother* 2003; **52** : 623-628.,

Do Ionophores Cause AMR?

- Fibrobacter succinogenes S85, Prevotella ruminicola M384 and Veillonela parvula L59 strains with resistance to monensin and tetronasin also had cross resistance to antibiotics avoparcin[1]
- Banned for animal use in 1997 to prevent selection of vancomycin resistant enterococci (VRE)
- Possible mechanism = active efflux by ABC transporters

1- Newbold CJ, Wallace RJ, Walker ND. The effect of tetronasin and monensin on fermentation, microbial numbers and the development of ionophore-resistant bacteria in the rumen. *J Appl Bacteriol* 1993; **75** : 129-134.,

Can ionophores cause vancomycin resistance?

- VanA gene – spread on plasmid from animal to human Enterococci
- Sweden - vanyomycin resistance persisted after vancomycin ban
- Low prevalence of VRE (<1%) but high use of narasin
- Most VRE isolates also resistant to narasin
- Plasma conjugation studies – transferable resistance to narasin and vancomycin on same plasmid
- Does narasin play a role in co-selection of VanA?

1 – Nilsson O, Greko C, Bengtsson B, Englund S. Genetic diversity among VRE isolates from Swedish broilers with the coincidental finding of transferrable decreased susceptibility to narasin. *J Appl Microbiol* 2012; **112** : 716-722., 2-Nilsson O, Myrenas M, Agren J. Transferable genes putatively conferring elevated minimum inhibitory concentrations of narasin in *Enterococcus faecium* from Swedish broilers. *Vet Microbiol* 2016; **184** : 80-83.

Can ionophores cause vancomycin resistance?

- HOWEVER:

- Decreased susceptibility common in VRE and VSE
- Role in persistence of VanA has not been clearly established

1 – Nilsson O, Greko C, Bengtsson B, Englund S. Genetic diversity among VRE isolates from Swedish broilers with the coincidental finding of transferrable decreased susceptibility to narasin. *J Appl Microbiol* 2012; **112** : 716-722., 2-Nilsson O, Myrenas M, Agren J. Transferable genes putatively conferring elevated minimum inhibitory concentrations of narasin in *Enterococcus faecium* from Swedish broilers. *Vet Microbiol* 2016; **184** : 80-83.

Clinical Signs of Eimeria

- Poor performance
- Gut inflammation
- Decreased intestinal integrity
- Wet litter – pododermatitis
- Secondary bacterial infections
- Hemorrhagic diarrhoea and death

Reference - https://poultryhealthtoday.com/ionophores-control-coccidiosis/

Alternatives to Ionophores

- Chemical coccidiostats
- Vaccines
- Biosecurity
- Herbal products
- Management changes e.g. nutrition, hygiene and housing

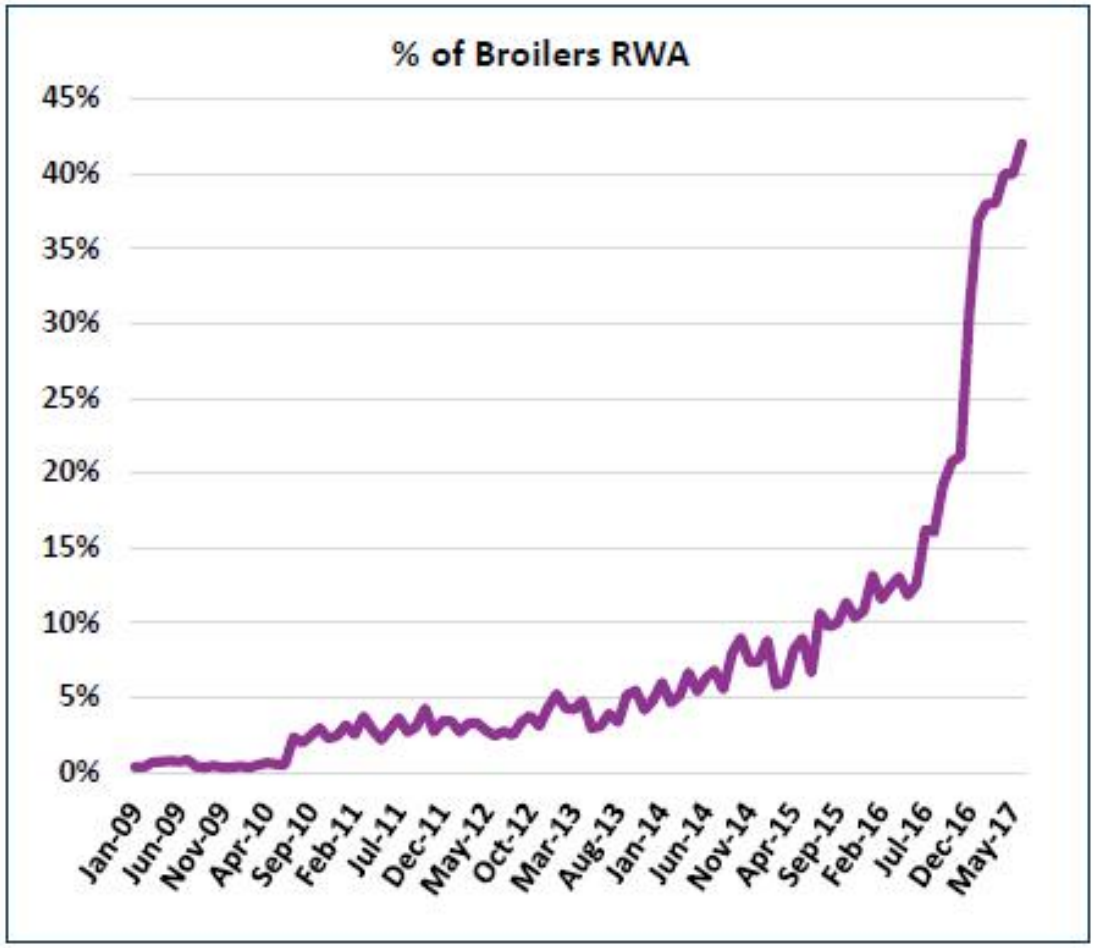
Reference – Nilsson et al. 2012, 2016

Antibiotic Free Debate

Raised Without Antibiotics – Livestock/Red Meat
To use this claim, source animals cannot have been given antibiotics in their feed, water or by injections. This includes ionophores which are recognized as antibiotics by FSIS.

Reference – https://www.fsis.usda.gov/wps/wcm/connect/6fe3cd56-6809-4239-b7a2-bccb82a30588/RaisingClaims.pdf?MOD=AJPERES

Antibiotic Free Debate



Reference – https://www.hhs.gov/sites/default/files/salois-paccarb.pdf

Raised Without Antibiotics

- Data from USDA, industry sources and expert knowledge:

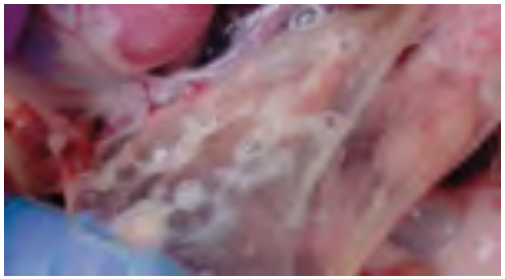
	RWA	Conventional
Mortality (%)	5.03	1.41
Grow out time (days)	47.96	46.30
Bird density (sq foot/ bird)	0.95	0.88
Cycle downtime	18.45	15.29

Reference – Salois, M.J. & Cady, R.A. & Heskett, E.A., 2016. "**The Environmental and Economic Impact of Withdrawing Antibiotics from US Broiler Production**," Journal of Food Distribution Research, Food Distribution Research Society, vol. 47(1), pages 1-2, March., http://www.favamember.org/wp-content/uploads/2017/04/07_Economic-animal-welfare-and-sustainability-impact-of-eliminating-antibiotics-from-USA-broiler-production.pdf

Raised Without Antibiotics

- Data from Elanco Health Track System
- Looked at conditions associated with poor gut health and in RWA group:
  - **Eye burns** – 3.6 times more common
  - **Footpad lesions** – 1.3 times more common
  - **Airsacculitis** – 1.6 * more common





Reference – Salois, M.J. & Cady, R.A. & Heskett, E.A., 2016. "**The Environmental and Economic Impact of Withdrawing Antibiotics from US Broiler Production**," Journal of Food Distribution Research, Food Distribution Research Society, vol. 47(1), pages 1-2, March., http://www.favamember.org/wp-content/uploads/2017/04/07_Economic-animal-welfare-and-sustainability-impact-of-eliminating-antibiotics-from-USA-broiler-production.pdf

VMD Position On Antibiotic Free

- Support responsible use and driving down unnecessary use:
  - Eliminating use = risks to health and welfare

- Support good farm management, biosecurity and animal husbandry to minimise disease:
  - Do not support use to compensate for poor animal husbandry practices

Conclusion

- Ionophores licensed as Feed Additives – not regulated as antibiotics in EU
- Ionophores have antibiotic effects largely against gram positive bacteria
- Limited antibiotic cross-resistance and co-resistance demonstrated
- Controlling coccidiosis is vital in maintaining bird health and welfare
- Key focus for antibiotics and anti-coccidials should be responsible use and reducing unnecessary use rather than eliminating use

Thank you.

Any questions?