FEED ADDITIVES: DO THEY ADD TO ANIMAL WELFARE? AN EVALUATION

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Abstract *Animal Welfare 1998, 7:* 397-414

The welfare of farm animals is strongly influenced by the man-made environment. Welfare problems also arise from reduced homeostatic capacities in animals. Feed additives, used to promote growth or to prevent diseases can alter the animals' self-regulating capacities thus affecting their welfare. The EU regulates the use of these additives within specified groups of Directive 70/524/EEC. Although these feed additives can be regarded as prescription-free veterinary drugs, critical remarks on their desired and adverse effects have received little attention.

A survey of the available literature shows that about one-third of licensed feed additives alter adrenal function in vitro. Reports of the adverse effects of anticoccidial additives in vivo suggest they can be classified under three headings: (i) substances with a very narrow safety margin (the difference between the permitted dose and the dose with adverse effects) and often irreversible effects on growth and feed conversion; (ii) substances with a narrow safety margin and largely reversible effects; (iii) substances with an adequate safety margin. The growth promoters (including antibiotic growth promoters) can – on the basis of their adverse effects – be classified into two groups: (i) substances with a very narrow safety margin; and (ii) substances with an adequate safety margin.

On the one hand, animal welfare considerations require use of disease-preventing additives, but on the other hand, they also demand discontinuation of current practices. Judicious use of additives can add to animal welfare. However, their unlimited use to obscure defects in husbandry is detrimental to animal welfare. A major obstacle to the judicious use of feed additives, is the lack of published, unbiased information on their efficacy and safety for farm animals.

Keywords: *animal welfare, antimicrobials, cattle, coccidiostats, growth promoters, pigs, poultry*

Introduction

Animal welfare is concerned with the interaction between animals and their environment, since difficulties in an animal's ability to cope with its environment may lead to chronic stress or disease. However, nutrition and animal welfare have not, as yet, been extensively

interconnected. Animal feeds may contain compounds to prevent diseases or to increase performance. These compounds are sometimes also licensed as veterinary medicines, albeit at higher dosages or in other formulations. Therefore, these feed additives can also be regarded as prescription-free medicines. Their use has received little or no attention from those involved in animal welfare research (with the notable exception of Leeson [1991]). Although the use of pharmaceuticals in human and veterinary medicine is strictly regulated, feed additives are regulated separately and differently. Toxicological considerations in the licensing of feed additives mostly concern consumer safety and, more recently, also environmental safety; target animal safety (and in particular animal welfare) are minor issues in this regard (Anonymous 1987).

All animals live in a precarious balance with the parasites in their environment. Husbandry in man-made environments can alter this balance, creating the need for preventive or curative action. In retrospect one can ask whether the availability of prescription-free medicines as feed additives furthered the development of intensive husbandry, or whether intensive rearing systems in themselves necessitated the use of medicinal compounds as feed additives.

Recently, one of the prerequisites for animal welfare was defined in terms of the animal's unhampered, species-specific capacity to function as a self-regulating entity in harmony with its environment (Rutgers *et al* 1996). For farm animals this environment is defined by 'Good Agricultural Practice' rules (Council of Europe 1976). A prime question is thus, whether an animal's homeostatic capacity is temporarily or permanently changed by feed additives. Some effects of the additives may be reversible and only require physiological compensation; other effects, however, may result in an irreversible pathophysiological status. In the latter situation, animals may become dependent on these substances, or there may be interactions with other therapeutics. It is also possible, that these feed additives contribute to pushing the animals up to, or even over, their homeostatic limit, exceeding their abilities to adapt adequately to the environment.

This paper aims to draw attention to the use of growth-promoting and disease-preventing feed additives and their possible adverse effects on animal welfare, where effects on the self-regulating capacities of the animals are used as yardstick of animal welfare. First, the groups, the use and the supposed mode of action of the feed additives currently permitted in the EU will be reviewed. Then a systematic and critical analysis of adverse effects on target animals, based on data in the 'open' literature, will be given. Discussion will be limited to the effects of doses in feed at levels up to twice those allowed under Directive 70/524/EEC (since such overdosing is an easily and frequently made error in compounding feed). No attention will be paid to adverse effects observed in non-target animals. Finally we will discuss the benefits and risks of the use of feed additives, promoting growth and preventing disease as a prerequisite for animal welfare.

Feed additives: general characteristics

The components used to prepare compounded feed or feed concentrates in western Europe are either agricultural products such as feed-grade grains, tapioca, fish, etc; or by-products from industrial processes – such as the production of vegetable oil, beer, and chips – or mere recirculation of material of animal origin. Their use in feeds is governed by price and nutritional value.

Feed additives are used to compensate for possible nutritional deficiencies, to ensure optimal utilization of nutrients, for technological purposes, to promote growth, or to prevent disease. Since 1970, the European Union has regulated the use of feed additives under Directive 70/524/EEC, which recognizes 14 distinct groups of additives: antibiotic growth promoters (group A), antioxidants (group B), flavour enhancers (group C), anticoccidials (group D), stabilizers (group E), pigments (group F), conserving agents (group G), vitamins (group H), trace elements (group I), binding agents (group J), growth promoters (group K), pH controlling agents (group L), enzymes (group M), and probiotics (group N). A large majority of these additives (in groups other than A, D, K, and N) are also allowed in human food.

The addition to animal feed of drugs which are antibiotic growth promoters, anticoccidials, and growth promoters (groups A, D and K respectively; Table 1), is based on the influence these substances have on the performance of the animals. These drug-type feed additives may, however, cause side-effects when administered at the levels necessary for achieving their desired effects.

The A group (antibiotic-type) substances are claimed to have prophylactic action against intestinal pathogens, with the added bonus of causing favourable changes in the gastrointestinal flora so that they also act as growth promoters (Jukes 1977). While the K group (growth promoter) feed additives are claimed to be growth promoters, unlike the A and D group substances their mode of action is undefined in the EU directives. However, the compounds currently licensed in group K have the bonus that they can prevent colonization of the gastrointestinal tract by anaerobic pathogens that enter the animal orally. Therefore we will count the A and K feed additives as growth promoters. The D group substances are claimed to prevent coccidiosis and histomoniasis.

The licensing of drugs as – prescription-free – feed additives is based, as with both human and veterinary medicines, on the triad of composition, efficacy and safety. A prime prerequisite in the procedure for allowing feed additives on to the European market is their safety for man. While the principle is nicely formulated, the real situation is not so reassuring. This is partly due to the initial set-up of Directive 70/524/EEC, which allowed generic substances, without specifications about the formulation, onto the market as additives for an indefinite period. Although substances in groups A, D and K must now be re-evaluated every 10 years, and only formulated substances instead of generic substances are to be licensed, some 'old' substances remain. These have not, therefore, been tested with the current protocols and tests, nor with current breeds of farm animals, feeds or husbandry systems. This might imply that some old feed additives are no longer effective. Ignoring the influence that pharmaceutical quality and formulation has on the bioavailability of active compounds is a serious risk (eg Rogers *et al* 1983). Thus, 'old' additives that might be still active, have an unspecified formulation and uncertain efficacy. Furthermore, the safety of feed additives for farm animals is quite often weighed against their (assumed) efficacy against certain diseases (Jager & Vroomen 1990).

The influence of the A, D and K additives on the physiology of farm animals, implies that their actions have to be evaluated both in terms of external parameters (eg milk/egg production, feed conversion, behaviour) and internal parameters (eg hormones, histological alterations). Any physiological reaction can be a 'normal' (often reversible) physiological compensation mechanism or an 'abnormal' (often irreversible) pathophysiological reaction.

Table 1 **Medicinal compounds licensed as feed additives. (Group letters indicate to which group defined in EU Directive 70/524/EEC a compound belongs: A – antibiotic growth promoters; D – anticoccidials and K – growth promoters. Target animals are indicated by the highest permitted dose in mg kg^{-1} in the finished feed.)**

Medicine	Group	Chicken	Turkey	Other poultry	Pigs	Cattle	Sheep	Goats	Rabbits	Fur animals
Amprolium	D	125	125	125						
Ardacin	A	7								
Arprinocid	D	60								
Avilamycin	A	10			40					
Avoparcin [1]	A	15	20		40	40	20			
Carbadox	K				50					
Decoquinate	D	40								
Diclazuril	D	1	1							
Dimetridazole	D		200	150						
Dinitolmide	D	125	125	125						
Efrotomycin	A				8					
Ethopabate	D	8	8	8						
Flavophospholipol	A	20	20		25	16			4	4
Halofuginone	D	3	3							
Ipronidazole	D		85							
Lasalocid	D	125	125							
Maduramicin	D	5								
Methyl benzoquaat	D	10	10						20	
Meticlorpindol	D	125	100						200	
Monensin	A					40				
	D	125	100							
Narasin	D	70								
Nicarbazin	D	125								
Nifursol	D		75							
Olaquindox	K				100					
Robenidine	D	36	36						66	
Ronidazole	D		90							
Salinomycin	A				60					
	D	70							25	
Spiramycin	A	20	20		80	80	80	80		20
Tylosin	A				40					
Virginiamycin	A	20	20		50	80				
Zinc bacitracin	A	100	50	50	80	80	80	80		20

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The use of feed additives

Anticoccidials

In the Netherlands, all broiler feeds for the starter and grower phase currently contain a coccdiostat. The feed in the finisher phase does not contain anticoccidials, because of the legally required withdrawal times. The same principle holds for prophylactics in feed for meat turkeys and rabbits. Young layer chickens up to 14 weeks old generally receive feed with a coccidiostat.

Antibacterial growth promoters

The extent of use of growth promoters in feeds by Dutch farmers is harder to estimate. Feeds and feed concentrates for meat-producing animals generally contain antibiotic growth promoters, while in feeds for laying hens the assumed inclusion rate lies around 10%; for sow feed the estimated inclusion rate is 25%, while concentrates for milking cows are not supplemented with these substances (J de Jong personal communication; Produktschap voor Veevoeder 1996). The K group additives (carbadox and olaquindox) are only allowed, under Directive 70/524/EEC, for pigs up to 16 weeks of age. Carbadox is not used at present, while, in the Netherlands, olaquindox is included in nearly all pig feeds for animals up to 12 weeks of age.

Desired effects of feed additives.

Anticoccidials

Coccidia divide their life cycle between two places: the animal and its manure. The most effective preventive action against these parasites would be a complete separation between the animal and the faeces it produces. Flock-management systems separating the animals from their manure are, however, notoriously detrimental to the animals' welfare (Moss 1980). Flocks in confinement on litter and not receiving a coccidiostat will develop clinical coccidiosis resulting in considerable mortality and morbidity. In-feed administration of a coccidiostat to young animals will prevent the development of clinical coccidiosis, but it does not prevent infection. The resulting subclinical coccidiosis enables young animals (eg replacement hens) to develop a lifelong immunity against coccidia, and makes further treatment against coccidiosis after the first 10–12 weeks unnecessary. However, as the lifespan of broiler chickens is only 5–7 weeks, these animals will not acquire immunity.

Coccidiosis in turkeys follows a similar pattern. Meat-type turkeys, however, have lifespans of 13 weeks (hens) to 20 weeks (toms), which is long enough to profit from an acquired immunity against coccidiosis. In rabbits the story is more complicated as these animals practise coprophagy to meet certain nutritional needs. Thus, separation between animals and their faeces to prevent clinical coccidiosis is not possible and in-feed administration of a coccidiostat is necessary. Young rabbits will, however, develop immunity against coccidia after a subclinical infection.

Thus, the desired effect of in-feed administration of coccidiostats to young poultry and rabbits is the prevention of acute clinical coccidiosis, whilst enabling the animals to acquire immunity which will protect them against future infections.

Blackhead or histomoniasis is an infectious disease caused by a group of protozoan parasites, which mainly affect turkeys. The parasites are transmitted via earthworms and gastrointestinal worms. In contrast to the case with coccidia, exposed animals, do not develop immunity against these parasites, but their susceptibility decreases slightly with age. Besides adequate sanitation, in-feed administration of an anti-blackhead drug is necessary to control this disease in large flocks of turkeys or pheasants.

Antibacterial growth promoters

Gastrointestinal disorders affect not only farm animal welfare, but also seriously decrease the animals' productivity. Two sources of pathogens can be identified: i) housing and ii) feed. Adequate and hygienic housing systems can prevent infections with pathogens. Unhygienic production and/or contamination of feed can be masked by the A and K group additives. Although feed formulation complies with the nutrient requirements of the animal for most of the time, it does not necessarily meet its physiological requirements for a normal digestion process. A disturbed digestion process will cause an unbalanced intestinal microflora and creates opportunities for pathogens: eg an overgrowth of *Lactobacillus* spp. in the gastrointestinal microflora turns this (normally useful) organism into a 'pathogen'. Addition of low, subtherapeutic dosages of antibacterial drugs to the feed may exert a selection pressure nudging the microflora towards a more balanced composition and restoring normal circumstances. Supplementing 'beneficial' micro-organisms (probiotics, N group additives) is an alternative method of maintaining a wholesome intestinal microflora.

Good hygienic conditions cannot prevent stressful events such as transport occurring, and relocation is known to enhance susceptibility to opportunistic pathogens. Most gastrointestinal pathogens enter the animal via the mouth. Thus, administering a protective concentration of an antibacterial drug in the first part of the gut before, during, and just after a stressful period seems sensible (de Graaf *et al* 1988). An alternative might be to avoid stressful conditions as much as possible, eg as in the farrow-to-finish housing of pigs (Ekkel 1996).

The desired effect of these feed additives is thus to ensure the maximum performance of food producing animals under the given circumstances.

Unwanted or side-effects of feed additives

With very few exceptions, no biologically active substance used as a medicine acts only at the intended site or sites: either the same mode of action also influences other cells or systems, or the drug has more than one mode of action. For instance: an aching pain can be muffled with Aspirin, which at the same time stifles the repair of the gastric wall; and Aspirin is also an anticoagulant.

The effects of feed additives on farm animals, as published in the literature, are summarized in Tables 2 and 3. The rows of Tables 2 and 3 list the compounds permitted in the EU under Directive 70/524/EEC. These rows are subdivided according to the animal species for which a drug is licensed, except for those drugs and animal species for which no information could be found. The numbered columns of Table 3 are largely defined by the gross 'organ systems' studied in pathological and clinical studies. Columns 1 and 2 (feed conversion, growth,) are the main criteria considered when marketing permission is granted (by the EU), and used by the farmer, and can easily be checked in practical situations. Broom (1991) lists growth, feed conversion, life expectancy and immune responsiveness among the major indicators of animal welfare. Adverse effects on growth and feed conversion must be caused by adverse effects on (one of) the organ systems listed in columns 3–15 of Table 3. Unfortunately this supportive information is often not available. The many remaining question marks therefore do *not* imply, that these organ systems are probably (un)affected by the additive

Almost one-third of the drugs mentioned in Table 1 have the potency to alter (in vitro) steroid biogenesis in pig adrenals (Table 2). Elevated blood levels of corticosterone are regarded as prepathological indicators of stress (Broom 1991; Wiepkema & Koolhaas 1993). Thus, the alterations in steroid biogenesis caused by feed additives might prevent the use of steroid levels in blood as indicators of animal welfare. We speculate that the growth-promoting effects of some

some feed additives might be due to the altered hormonal balances. Similar changes are sought by administration of growth 'promoting' exogenous hormones (steroids, somatotropins), which are allowed in the USA but banned in the EU.

Table 2 **In vitro tests in tissues from farm animals on drugs licensed as feed additives.**

Additive	animal	Effects observed	References
Amprolium	pig	Adrenocortical cells: aldosterone release not altered	Jager *et al* 1994
Avilamycin	pig	Adrenocortical cells: non-significant reduction of aldosterone release	Jager *et al* 1994
Carbadox	pig	Adrenocortical cells: steroidogenesis is altered by inhibition of C21-hydroxylation and C18-oxidation resulting in lower output of aldosterone, corticosterone, cortisol and deoxycortisol and enhanced output of progesterones.	Jager *et al* 1996
Dimetridazole	pig	Adrenocortical cells: reduction of aldosterone release	Jager *et al* 1994
Halofuginone	chicken	Fibroblasts: inhibits collagen type I synthesis	Granot *et al* 1993
Lasalocid	pig	Adrenocortical cells: reduction of aldosterone release	Jager *et al* 1994
Maduramicin	pig	Adrenocortical cells: reduction of aldosterone release	Jager *et al* 1994
	chicken	Intestinal wall: decreased transport of monosaccharides	Vinardell & Gonzalez 1992
Monensin	pig	Adrenocortical cells: reduction of aldosterone release	Jager *et al* 1994
	chicken	Intestinal wall: decreased transport of monosaccharides	Vinardell & Gonzalez 1992
	chicken	Muscle cells: disturbed Ca homeostasis, enhanced Na entry, cell death	Mitchell & Sandercock 1994
	cattle	Neutrophils: increased chemotactic activity	Stephenson *et al* 1996
Narasin	pig	Adrenocortical cells: reduction of aldosterone release	Jager *et al* 1994
Nifursol	pig	Adrenocortical cells: non-significant reduction of aldosterone release	Jager *et al* 1994
Olaquindox	pig	Adrenocortical cells: steroidogenesis is altered by inhibition of C18-oxidation resulting in a reduced output of aldosterone	Jager *et al* 1994
Ronidazole	pig	Adrenocortical cells: reduction of aldosterone release	Jager *et al* 1994
Salinomycin	pig	Adrenocortical cells: reduction of aldosterone release	Jager *et al* 1994
Semduramicin[1]	pig	Adrenocortical cells: non-significant reduction of aldosterone release	Jager *et al* 1994

[1] Permission to include this as a group D feed additive under Directive 70/524/EEC has been applied for.

Table 3 Effects in farm animals of drugs licensed as feed additives observed in vivo [1]

Medicine	Animal	Adverse effects observed on function [2]															References
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Amprolium	chicken	0	0	?	?	?	?	?	X	?	?	?	?	?	?	0	Anderson & Garry 1973; Keshavarz & McDougald 1982
	turkey	X	X	?	?	?	?	?	?	?	?	?	?	?	?	?	Spencer & Waldroup 1985
Ardacin	chicken	0	0	?	?	?	?	?	?	?	?	?	?	?	?	?	Rogers *et al* 1993
Arprinocid	chicken	0	X	?	?	?	?	?	?	?	?	?	?	?	?	0	Anonymous 1979; Stephenson *et al* 1985; Bartov 1992a; Keshavarz & McDougald 1982
Avilamycin	pigs	0	0	?	?	?	?	?	?	?	?	?	?	?	?	?	SCAN 1988
	chicken	0	0	?	?	?	?	?	?	?	?	?	?	?	?	?	Jamroz *et al* 1995
Avoparcin	chicken	0	0	?	?	?	?	?	?	?	?	?	?	?	?	X	Decuypere *et al* 1989
	turkey	0	0	?	?	?	?	?	?	?	?	?	?	?	?	?	Richter & Ranft 1991; Bartov 1992a
Carbadox	pigs	X	X	X	X	0	X	X	X	0	0	0	0	0	0	X	van der Molen *et al* 1986; Nabuurs *et al* 1990
Decoquinate	chicken	0	0	?	0	?	?	?	?	?	?	?	?	?	?	?	Kingston 1977; Helder & Versteegh 1976
Diclazuril	chicken	0	0	?	?	?	?	?	?	?	?	?	?	?	?	?	Page 1990
Dimetridazole	turkey	0	0	?	?	?	?	?	?	?	?	?	?	?	0	?	Jongenburger 1983; Condren *et al* 1963; Scholtyssek 1983
Dinitolmide	poultry	?	X	?	?	?	?	?	?	?	?	?	?	?	?	?	Stavrou 1966
Flavophospholipol	turkey	0	?	?	?	?	?	?	?	?	?	?	?	?	?	?	Caston & Leeson 1992
Bambermycins	chicken	0	0	?	?	?	?	?	?	?	?	?	?	?	?	?	Dost 1985
	cattle	0	0	?	?	0	?	0	?	0	0	?	?	?	?	?	NADA 044-759
	rabbits	0	0	?	?	?	?	?	?	?	?	?	?	?	?	?	Bombeke *et al* 1986
Halofuginone	turkey	0	0	?	?	?	?	?	?	?	?	?	?	?	?	?	Waibel *et al* 1991
	chicken	X	X	?	X	?	?	?	?	?	?	?	?	?	?	0	Casey *et al* 1992; Elwinger *et al* 1994; McDougald 1980; Granot *et al* 1991; Keshavarz & McDougald 1982; Morrison *et al* 1979
Ipronidazole	turkey	0	0	?	?	?	?	?	?	?	?	?	?	?	?	?	Harms & Buresh 1987a
Lasalocid	turkey	0	X	?	?	?	X	X	?	?	?	?	?	X	?	?	Lodge *et al* 1988; Czarnecki 1990
	chicken	0	X	?	?	?	?	0	?	?	0	?	?	0	?	0	Perelman *et al* 1986; Broz & Frigg 1987; Smith & Teeter 1987b; Keshavarz & McDougald 1982
Maduramicin	chicken	X	X	?	?	?	?	0	?	0	X	X	?	?	?	?	Laczay *et al* 1989; Badiola *et al* 1994; NADA 139-075

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Medicine	Animal	Adverse effects observed on function [2]															References
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Meticlorpindol	chicken	0	0	?	?	?	?	?	?	?	?	?	?	?	?	0	Vogt 1980; Keshavarz & McDougald 1981
Clopidol	rabbits	0	0	?	?	?	?	?	?	?	?	?	?	?	X	?	Varewyck *et al* 1984
Monensin	cattle	?	?	?	?	?	?	X	?			?	?	?	?	?	Pressman & Fahim 1982
	chicken	X	X	?	?	?	X	X	?	0	X	?	?	X	?	?	Wagner *et al* 1983; Riley *et al* 1986; Smith & Teeter 1987a; Hanrahan *et al* 1981; Howell *et al* 1980; Sandercock & Mitchell 1996
	turkey	X	X	?	?	X	?	X	?	?	?	?	?	X	?	?	Scholtyssek 1983; Stuart 1978; NADA P-130-736
Narasin	chicken	X	X	?	?	?	X	X	?	?	?	?	?	?	?	0	Riley *et al* 1986; Watkins *et al* 1991
Nicarbazin	chicken	X	X	?	?	?	?	?	?	X	X	?	?	?	?	X	Newberne & Buck 1957; Beers *et al* 1989; Chapman 1994
Olaquindox	pigs	X	X	X	X	0	X	X	X	0	X	0	0	X	0	?	Nabuurs *et al* 1990; Waldmann *et al* 1989
Robenidine	chicken	0	0	?	?	?	?	?	?	?	?	?	?	?	?	?	Helder & Versteegh 1976
	rabbits	0	X	?	?	?	?	?	?	?	?	?	?	?	X	?	de Jonge *et al* 1994; Varewyck *et al* 1984
Ronidazole	turkey	0	0	?	?	?	?	?	?	?	?	?	?	?	?	?	Olson *et al* 1970
Salinomycin	pigs	?	?	?	?	?	?	X	?	?	?	?	?	?	?	?	Szancer 1989; Pressman & Fahim 1982
	chicken	X	X	?	X	?	0	X	?	?	?	?	?	?	?	?	Harms & Buresh 1987b; Hoshino *et al* 1992; NADA 128-686
	rabbits	X	X	?	?	?	?	X	?	?	?	?	?	?	X	?	Anonymous 1983; Okerman & Moermans 1980
Spiramycin	chicken	0	0	?	?	?	?	?	?	?	?	?	?	?	?	?	Anonymous 1984; Combs & Bossard 1963
Virginiamycin	chicken	0	0	?	?	?	0	?	?	?	0	?	?	?	0	0	Miles et al 1984, 1987; Bartov 1992b; Belay & Teeter 1996
	turkey	0	0	?	?	?	?	?	?	?	?	?	?	?	?	?	Harms & Miles 1983
	cattle	0	0	?	?	?	?	X	?	?	?	?	?	?	?	?	NADA 140-998
Zinc bacitracin	chicken	0	0	?	?	?	X	?	?	?	?	?	?	?	0	0	Lee *et al* 1993; Stutz *et al* 1983; Franti *et al* 1973
	turkey	0	0	?	?	?	?	?	?	?	?	?	?	?	?	?	Potter *et al* 1974; Daghighian & Waibel 1982

[1] The maximal dosage considered is twice the highest dosage (mg kg^{-1} feed) permitted under Directive 70/524/EEC for the animal species indicated.

[2] Effects are classified as: ? - not studied; 0 - studied, no adverse effect observed; X - studied, adverse, negative effect observed.Localization of observed effects: 1 – feed conversion; 2 - growth; 3 - behaviour; 4 - skin/feathers/hair; 5 - lungs / airsacks; 6 - gastro-intestinal tract/digestion; 7 - heart & circulation; 8 - endocrine organs/hormones; 9 - liver; 10 - kidneys and body fluids; 11 - immune system; 12 - bones & joints; 13 - skeletal muscle/ motor coordination; 14 - reproductive system; 15 - thermoregulation.

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Anticoccidials

Vahl (1983) showed that most coccidiostats induced growth retardation in broiler flocks without subclinical coccidiosis. Since then, however, permitted compounds and/or their dosages, period and duration of administration have changed considerably. The evidence from the literature (see Table 3) suggests a classification into three categories: i) a group that will always affect the host animals within the permitted dose range; ii) a group that may affect the host animals within the permitted dose range; and iii) a group with no known effects on the host within the permitted dose range.

Among those substances that always impair animal performance, are the ionophore coccidiostats. Ionophores, such as monensin, narasin and salinomycin, alter the permeability of membranes to ions, both in coccidial cells and those of the host animal. Ionophores are usually large molecules that are slowly absorbed and rapidly metabolized in the liver of birds and rabbits, so large systemic effects are not very likely. Nevertheless, doubling the permitted dose can result in a 40 per cent reduction in growth rate. Susceptible organs are those with excitable membranes, such as heart, nerve and muscle; ionophores will cause irreversible effects and ultimately cell death in these organs. Ionophores are often rapidly lethal in high dosages (Pressman & Fahim 1982). The effects of these compounds are generally irreversible, and although the animals can resume growth after cessation of administration, total body weights remain lower and efficiency is lastingly impaired in affected tissues.

The second group is formed by drugs that, each in a different way, can affect the host, but usually do not impair growth and feed conversion. Nicarbazin, for instance, reduces the heat stress tolerance of broilers (eg Beers *et al* 1989). This reduction of the animal's homeostatic capacity manifests itself only during elevated temperatures, eg above 30°C for 5-week-old chickens. Halofuginone impairs the biosynthesis of collagen type I (Granot *et al* 1993) and thus reduces the strength of the skin, as measured post-mortem. The alterations induced by these feed additives are mostly reversible after cessation of administration.

Amprolium and diclazuril are examples of probably harmless coccidiostats.

Antibacterial growth promoters

The A and K group additives can probably be classified (see Table 3) into two groups: i) a group of substances which will always negatively affect the treated animals within the usual dose range; and ii) a group of compounds for which negative effects have not been reported.

The first group is made up by the ionophore growth promoters (monensin, salinomycin; these are also D group additives) and the quinoxalines (carbadox and olaquindox). Adverse effects of the ionophores have been outlined in the previous paragraph. Quinoxalines do not increase the growth rate of healthy pigs. On the contrary, several adverse effects (dry faeces, urine drinking, irritability, and pathological alterations in the glomerular zone of the adrenals) have been observed in vivo, indicating hypoaldosteronism (van der Molen *et al* 1985; Baars *et al* 1988). These in vivo effects can be attributed to an impaired homeostasis of water and salt. In vitro, the quinoxalines and several other antibiotic growth promoters (as well as some anticoccidials) alter the biogenesis of steroids (namely aldosterone) in an adrenocortical cell culture (Jager *et al* 1994;1996). The adrenal alterations induced in vitro by quinoxalines explain the observed in vivo effects (van der Molen *et al* 1989).

Classical antibacterial-type growth promoters including zinc bacitracin, virginiamycin and the bambermycins, but also newer compounds like avilamycin, form the second group. The oral toxicity of these additives is low: their estimated oral LD_{50} is in the range of *grams* per kg body weight, while the permitted dose range for feed additives is in *milligrams* per kg body weight.

These additives do not generally pass through the gastrointestinal wall. However, if the intestinal wall has become more permeable, as happens during regeneration after a rotavirus infection, these compounds can enter the body and cause damage.

Combinations of drugs

A major limitation of our present approach is that we only review single substances. There are several known toxic interactions between feed additives and medicines, which can be explained in terms of limits to physiological compensation. The alterations in an animal's physiology induced by both carbadox and furazolidone each seem reversible, as growth and feed conversion hardly change after treatment. However, the combination is lethal when given together or shortly (up to 1 week) after each other (van de Kerk *et al* 1985). Thus, the compensatory mechanisms in the animal's physiology are stretched to the limit by one treatment, and addition of the second gives an irreversible reaction. Similarly, Litjens *et al* (1965) showed that the coccidiostat dinitolmide alone has no observable influence on young broilers, but together with a therapeutic dose of furazolidone, dose-related abnormalities in posture were observed. Amprolium, a coccidiostat also licensed as feed additive, did not show this interaction with furazolidone.

We therefore conclude that a feed additive can change the physiology of an animal so that it can no longer react 'normally' towards a therapeutic treatment. Under these circumstances, the ability of the animal to cope with its environment in its broadest sense has been impaired.

Homeostasis or the limits to growth

Any well-functioning organism shows a dynamic internal equilibrium or homeostasis. All homeostatic processes and reactions are reversible and of a physiological nature. Only when the organism can no longer cope with the internal and external demands and cannot maintain homeostasis, do irreversible processes occur. However, the distinction between reversible and irreversible processes or between physiological and pharmacological effects in the (living) animal is not easy to make.

The limits to growth are often first met by the fastest-growing animals. Crossing these limits may result in problems (eg ascites or sudden death with broilers, or leg weakness with pigs). Similarly, feed additives may also diminish an animal's ability to cope with changes in management, such as relocation or changes in temperature, food or humidity. Administration of feed additives to achieve maximal performance, might therefore also increase the number of animals approaching/exceeding their physiological limits and experiencing health and welfare problems.

Pros and cons

Residues of feed additives in animal products are not seen as a threat to human consumers (Waltner-Toews & McEwen 1994). Most feed additives are not used in human medicine and thus the risk of selecting for resistant micro-organisms does not reduce the scope of drug type to be used there (Corpet 1996). However, the recent discussions on whether the use of avoparcin in animal feed was the possible source of vancomycin resistance in human isolates of pathogens shows the complexity of additive use (SCAN 1996).

The lasting efficacy of the coccidiostat, nicarbazin, shows that the development of resistance in coccidia can be delayed by selective and restricted use of feed additives (Chapman 1994). Another way to delay the onset of resistance is regularly rotating or shuttling the coccidiostats. This requires the availability of different types of coccidiostats as feed additives. Not all coccidiostats presently permitted as feed additives are required in such a system, as changes

should be made between drugs with different modes of action. Thus, a switch between ionophores from, eg monensin to salinomycin is probably ineffective, whereas the change from monensin to meticlorpindol is likely to be effective.

Tylosin is licensed both as a veterinary medicine and as a feed additive. An outbreak of swine dysentery might, therefore, be due to a tylosin-resistant strain (in 1988 in The Netherlands all 35 field isolates of *Serpulina [Treponema] hyodysenteriae* were tylosin-insensitive [Vijfhuizen *et al* 1988]). The veterinarian, often unaware of its preventive use, might choose tylosin as an (ineffective) treatment. Licensing a compound as prophylactic feed additive, creates a fair chance of selecting for resistant pathogen strains. Therefore, only compounds which do not belong to a group in use in (veterinary or human) medicine should be licensed as feed additives.

In intensive husbandry the 'need' for the use of D or A and K additives often becomes manifest, when infections (endoparasitic or microbial) become a major – economic – threat to the animals and the farmer. Prevention of clinical coccidiosis in young animals by D group additives is essential. But a cost-benefit analysis of the treatment of subclinical coccidiosis in young broilers does not favour a curative strategy (van der Stroom-Kruyswijk 1992).

The use of antibiotic growth promoters in feeds is much more controversial, and the extent of their use is quite hard to estimate. Arguments in favour of the use of these antimicrobials are that they suppress intestinal infections (like swine dysentery or necrotic enteritis in broilers) and improve dietary nutrient utilization. Counter arguments include their unproven efficacy in many circumstances and the possible selection of antibiotic-resistant micro-organisms. An umbrella of prophylactic feed additives, vaccines, mass-medication, and very strict sanitary conditions (specified pathogen free (SPF), gnotobiotic environments) removes the incentive for development or conservation of genetic resistance in farm animals against pathogens. Hence, continuous prophylaxis will mask not only defects of the system, in which the animals are kept, but also genetic defects bred into in the animals.

The counter arguments led to the 1986 ban on the use of antibiotics and growth promoters in Swedish feeds (Best 1996; Björnerot *et al* 1996). The use of antibiotic growth promoters in feeds is the result of an economic cost-benefit calculation, whether made implicitly or explicitly (for a recent review see Richter *et al* 1996). The Swedish example shows that farm animal husbandry without these additives is possible, albeit that the inclusion of zinc into Swedish feed has now reached levels that renders the manure an environmental liability. (Ten years ago agricultural ministers had to act to reduce the copper content of feeds for pig[-lets] in the EU, because the manure endangered the existence of earthworms and other soil [micro-]organisms.)

The missing rows and the many question marks in Table 3 show that, although these medicines can be used freely, little is known about their effects on animal physiology as a whole. The low number of 'open' follow-up studies might suggest that only a few intoxications and accidents with these drugs have occurred, but, with so much of the literature 'closed' we doubt this interpretation. Our extensive in vivo studies with carbadox and olaquindox, covering most of the organ systems of the pig were, however, curiosity driven. We also suggest that other, supposedly harmless, feed additives may well affect many organ systems in animals, because if effects are not intentionally investigated, then they may remain unobserved. In the course of our search of the literature databases for effects to be reported in Table 2, we were surprised to find that no feed additive screening, comparable to our studies with the in vitro adrenal model, has been reported with other in vitro models. Although an extensive review was published in 1982 (Pressman & Fahim 1982), showing the potential danger that ionophore feed additives constituted for animal (and human) welfare due to their cardiovascular activity, no systematic

study on their (in vitro) effects has since been published. Systematic studies with these feed additives on target animal safety (toxicity and welfare) ought to be performed and their results made public.

To use or not to use...

Farm animals are kept by man to 'harvest' their milk, meat, or eggs. To thrive and to grow they need an adequate supply of air, water, space and food. The use of A, D, and K group additives might be regarded as favourable in terms of the prevention of animal health problems, of more economical production of meat and eggs, of excretion of less manure, and of less usage of feed ingredients also suitable for human nutrition.

The possible adverse effects are: i) toxicity to the target animal as the margin between effectiveness and toxicity is often quite small; ii) obscuring defects in quality or hygiene in animal management, making animal production structurally dependent on these substances; iii) possible interactions with veterinary drugs; iv) pushing the animal over its 'limits to growth'; and v) reducing an animal's capacity to cope with its environment.

The judicious use of anti-parasitic feed additives (group D) for young animals is beneficial to their well-being in the current husbandry systems. The same applies to the prophylactic use of some antibacterial feed additives (groups A and K) around stressful episodes. The long-term use of these additives as growth promoters probably does not add to animal welfare. Instead, it can be regarded as an insurance premium against avoidable bad conditions. However, if medicines do not help, they may harm. Both of these aspects of additive use can be regarded as detrimental to the welfare of farm animals.

Animal welfare implications

The long-term use of feed additives as growth promoters probably does not add to animal welfare. Additives have no effect when animal performance is maximal, although inducing maximal performance in an animal at, or over, its physiological limit may prove detrimental to its well-being. As submaximal performance is often caused by poor hygiene (which is avoidable), additive use in these circumstances risks becoming an insurance against occasional mishaps – or even a replacement for good animal practices. As medicines have both desired effects and unwanted, adverse, side-effects, there is also a risk of adverse effects prevailing when the intended effect is not achieved – and compromising Good Agricultural Practice.

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