FEED ADDITIVES WITH PARTICULAR REFERENCE TO GROWTH PROMOTION

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SUMMARY

The widespread use of feed additives in intensive livestock husbandry practices is noted and reference made to aspects of legislation on feed additives in the UK and the EEC.

Feed additives in growth promotion in pigs include antibacterials, carbadox, copper, an orally administered hormone and an oral vaccine preparation. Brief mention only is made to the antibacterials as growth promoting feed additives. for broilers. With ruminants reference is made to antibiotics, various rumen modifiers and the anabolics; of the last mentioned the majority are administered as implants and consideration has to be given to ensuring that they are used correctly and that no residues remain in the meat products.

INTRODUCTION

During the last 15 - 20 years there has been a very considerable expansion of intensive livestock production, particularly of cattle, pigs and poultry in many countries in the world, which has led to greatly increased production of animal protein.

Feed additives have become an accepted and integral part of these systems and can be considered as fulfilling 2 major roles: Firstly, to improve animal performance in terms of growth rate and/or feed conversion efficiency, in clinically and nutritionally normal animals, Such feed additives are said to be growth promoters and are therefore substarices other than a normal dietary nutrient that increase growth rate and/or feed efficiency in animals fed a nutritionally adequate, balanced diet. A second role fulfilled by some feed additives is to maintain health in the face of the environmental stress and challenges that are an inevitable consequence of modern systems of intensive livestock production. Collectively therefore, feed additives are essentially involved in the enhancement of animal performance and disease prevention (prophylaxis). A few products that meet one or both of the above criteria can also be effective in the treatment of disease, as distinct from its prevention and these products thus become associated with veterinary therapy. An example of such a product is dimetridazole, which not only has growth promoting propertiesin healthy pigs but is also used in the treatment as well as control of swine dysentery. The therapeutic use of such products is a matter for the concern of the veterinary profession. In this paper attention will be focussed primarily on products exhibiting growth promoting properties.

A leading U.K. pharmaceutical firm has estimated the value of the feed additive market on a world wide basis to be of the order of $ (US) 1690 x 10^{6} of which some 27 percent is associated with growth promoters, the great majority of which are antibacterials, 53 percent nutritional feed additives (vitamins, trace elements), 11 percent coccidiostats and the remaining 9 percent unspecified. Table 1 lists for certain countries the value of animal product sales of total feed additves and of growth promoters.

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With reference to Table 1, it will be appreciated that the high figures for the USA and to a lesser extent countries of Europe, but reflect the widespread existence of intensive livestock practises in these' countries. The low values for Australia not only reflect relative differences in the size of the animal industry of that country but also the fact that the predominant system of beef production is extensive. For New Zealand,, despite the very large size of the sheep meat industry and the fact that lamb meat production is essentially an intensive one based on grass, all growth promoters are banned; it is considered that their use adversely affects carcass quality and constitutes a potential hazard to human health.

TABLE 1 Estimates of the value of product sales of total feed additives and of growth promoters in various countries of the world. [$ (us) x 10^6] .

Country	Total Feed Additives	Growth Promoters
USA	808	151
West Germany	71	20
Japan	63	30
U.K.	44	12
Australia	6	2
New Zealand	4	1

LEGISLATION ON FEED ADDITIVES IN THE U.K. AND E.E.C.

Not surprisingly, the very marked increase in number of additives becoming available during the last two decades has aroused concern at the implications for human health of their use. An early manifestation of such concern were the fears expressed in the U.K. over the widespread use of antibiotics of great therapeutic value in human medicine, as feed, additives in meat-producing animals and the risk of development of antibiotic resistance. Thus' in the U.K. recognition 'of the phenomenon of transferable drug resistance was reflected in the appointment by the Goverpment of the Swan Committee, whose report in 1969 led to the banning in the U.K. from 1971 of therapeutically valuable antibiotics for routine, low level use as feed additives.

Within the context of the E.E.C. feed additives are regulated by E.E.C. Directive 70/524 the annexes of which list the permitted additives for growth promotion; feed additives that are acceptable to all members of the Community are listed in Annex I while those permitted only in some are listed in Annex II. Products in the latter annex eventually must become acceptable to all Member States (and hence be transferred to Annex I) or are permanently banned from use. It is noteworthy that the substances listed as feed additives in Annexes I and II are essentially growth promoters with the specific exception of coccidiostats for use in poultry which are also included; this exception is an acknowledgement by the E.E.C. of the great value of prophylaxis against coccidiosis in poultry. Therapeutic substances are of course available to the farming, industry as ethical products under veterinary control and prescription.

The E.E.C. is 'advised by a Scientific Committee for Animal Nutrition whose reports on feed additives and matters concerning animal nutrition are published (see reference list for details). The second report of the above Committee published in 1980 contains "guide lines" for the assessment of additives in feeding stuffs; these include identity and physico-chemical properties, of the additive, evidence for effectiveness of the product, the biological consequences of its use, including its fate in the target animal, toxicity, teratogenicity and mutagenicity and finally consideration of the possible consequences to the environment that may result from its presence in excreta. The 'guide lines' are intended for guidance of the pharmaceutical and other industries concerned with the development of a feed additive in indicating the nature and extent of the information required by the E.E.C. for assessment of a proposed new product with a view to its being allowed into Annex I or II.

The Member States are individually responsible for enacting the appropriate legislation relating to a feed additive. In the UK all products claiming medicinal (including growth promoting) properties must, under the Medicines Act 1968, be approved and licensed by the Veterinary Products Committee (VPC) of the Medicines Commission. The VPC will only grant a license when it is satisfied that the manufacturers of the product being presented can substantiate the claims being made for it and that its use is safe for the target animal, operators handling the product and the end consumer of the animal product. Feed additives fall into two classes; those available without prescription i.e. 'Permitted Merchants List' (PML) and those available for inclusion in feeds on veterinary prescription 'Prescription Only Medicines (POM). PML products are all growth promoters, have little or no therapeutic activity and may be supplied to farmers in feed or in special containers, for home mixing through the normal channels of agricultural distribution.

FEED ADDITIVES FOR PIGS

By far the largest group of feed additives concerned with growth promotion in pigs are those classed as antibacterials (Stoker 1980). In addition to this group there is copper supplied most frequently as copper sulphate, an oral hormone preparation sold under the name Maxymin and comprising methyltestosterone and stilboestrol (in the U.K. this product has a POM classification and is thus only available on prescription), and an "oral" vaccine intagen.

The antibacterials

Table 2 lists the six such products currently in use in the U.K. for pigs up to 6 months of age. The first four are essentially antibiotic products of the fermentation industry, while the remaining two are non-antiobiotic growth promoters. As already mentioned diemtridazole 'is also used in the control of swine dysentery, It is the only product listed in Table 2 for which there is a withdrawal period, viz.6 days. All the products are growth promoters enhancing daily growth and improving feed conversion efficiency in clinically healthy animals. As Stoker (1980) points out, use of one of the compounds may also exert a beneficial effect on herd health but 'disease control is 'not the primary objective in their use. The average response is about 5 percent in growth rate and in improvement in feed efficiency (Stoker 1980) although actual levels of response depend upon environment, length of time the additive is used and growth performance of the pigs not given the supplement. Stoker, (1980) notes that since, in the U.K. some 4 million tonnes of feed are used annually to finish some 15 million pigs, a 5 percent saving in feed represents an annual saving of some 200,000 tonnes of feed.

The mode of action of this group of antibacterials in enhancing animal performance is not readily understood and is liable to be a resultant of a number of interrelating factors. Visek (1978) considers that a factor of likely importance is thereduction in ammonia levels in the lower gut due to suppression of urease activity consequent upon bacterial inhibition within the small intestine:. He also notes that products 'of hydrolysis produced from bile acids by bacterial enzymes are also harmful products, whose formation may be suppressed.

TABLE 2 Antibacterials used as growth promoters for pigs in the U.K.

Name (Trade name)	Nature	Active against	Inclusion level of antibacterial	Withdrawal period
Avoparcin (Avotan)	Glyopeptide antibiotic produced from fermentation of Streptomyces candidus.	Gram + ve	under 10 weeks 10-40g tonne 10 weeks - 6mths 5-20g/tonne	None
Virginiamycin (Eskalin)	mixture of two antiobiotics a polypeptide + a macrocyclic lactone.	Gram + ve	weaning to 6mths up to	None
Zinc Bacitracin	Polypeptide antibiotic from strain of Bacillus subtilis.	primarily Gram + ve	up to 4mths 5-50g/tonne 4-6mths 5-20g/ tonne	None
Bambermycin (Flavomycin)	Glycolipid antibiotic from fermentation of mixture of streptomyces.	Gram + ve	sow milk replacer 10g/ tonne creep feed 6g/tonne grower/ finisher 2.5g/ tonne	None
Dimetridazole (Emtryl)	Imidazole compound.	broad spectrum including antiprotozoal activity	100-200g/tonne	6 days before slaughter
Nitrovin (Payzone)	Guanidine derivative	broad antibiotic spectrum	up to 26 weeks 10g/tonne	None

There is certainly evidence of considerable changes in the microflora of the small intestine due to the presence of antibiotics (Vervaeke et al. 1979) most of which act by suppressing bacterial protein synthesis, although each at one of a number of different sites (Biot 1979). However as Vervaeke et al. (1979) comment, it would be premature to conclude that the Gram-positive microflora are growth depressants.

It would appear that bacteria may be affected in one or all of the following ways:

(i) suppression of species which compete with the host animal for growth factors;

(ii) a selective stimulation of those species which synthesise growth factors from which the host animal benefits;

(iii) suppression or elimination of those bacteria which produce an exotoxin or toxic metabolite harmful to the host animal or;

(iv) by alteration of the metabolic activities of bacteria which lead to the effects referred to in i, ii and iii above; in this last mentioned case there may be no major change in bacterial species or numbers.

Carbadox' Another effective growth promoter in pig feeding is the product Carbadox (Mecadox) (methyl-3(2-quinoxalinylmethylene) - carbazate - N,N' - dioxide) which although currently allowed in certain countries is not permitted for use in the U.K. The Scientific Committee on Animal Nutrition (1980) has commented favourably on allowing the product to be used for. growth promotion in pigs up to 4 months of age,. at 50g/tonne feed, with the stipulation of a 4 week withdrawal period before slaughter. Although carbadox has antibacterial properties it modifies only slightly the intestinal flora of animals; indeed the beneficial effects of the product on feed utilization have been demonstrated both in normal and in specific, pathogen-free animals. Carbadox at 50 ppm (but not 20 ppm) induces a significant increase in protein digestibility and N retention in the pig, appearing to extert its maximum effect with rations suboptimal in protein and lysine levels.

Within the body it is rapidly metabolised to quinoxaline - 2 carboxylic acid and methyl carbazate, but with the intermediary formation of desoxycarbadox (methyl - 3 - (2 - quinoxaline - methylene) carbazate which, together with carbodox is suspected of being carcinogeneic. The. Committee were satisfied that, with an adequate withdrawal period there was no danger from residues in meat for the consumer. The problem however, is really one of safety for the personnel involved in the handling of the product in bulk, and in the prepation of medicated feeds, and the matter is currently being reconsidered by the Committee.

Copper One of the most widely used additives in pig feeds is copper (Cu) added as copper sulphate to feeds to give 250 ppm added Cu in the feed (UK), or to give 200 ppm added Cu in the feed (Netherlands). This addition is over and above the Cu naturally present in feeds an approximate value for which is 20 ppm (UKASTA 1979).

In a review of experiments between 1955-65, Braude (1967) reported an average improvement for live weight gain of 8.1 percent and for feed conversion ratio of 5.4 percent over a weight range of 15-90 kg resulting from a supplement of 250 mg Cu/kg diet; the comparable figures for the period 1965-75 (Braude 1975) were 9.1 and 7.4 percent. In a recent world wide survey of the literature by UKASTA (1979), it was concluded that the optimal level of added Cu for maximum rate of growth (the improvement in rate of live weight gain was 6.5 percent over the weight range 4 - 90 kg) was 224 mg added Cu/kg pig diet. (The value was obtained from the overall regression equation forced through the origin); added Cu levels ranging from 188-260 mg/kg gave only marginally smaller responses (X.7 percent of maximum)- The UKASTA (1979) survey indicated that at 1978-79 prices the cost of including 224 mg added Cu/kg pig diet (£0.07/pig) yielded a benefit in the order of £2.75/bacon pig.

Dietary Cu is poorly absorbed and for pigs receiving dietary copper sulphate the range has been found to be 2 - 10 percent. Only the liver stores appreciable amounts of Cu (see Table 3) although Cunha (1977) suggests that growing/finishing pigs receiving levels of 250 ppm Cu in feed should be given levels of 130 ppm zinc and 150 ppm iron in the diet to-protect against Cu toxicity; an adequate level of protein should also be fed and an excess of calcium should be avoided since it increases Zn needs.

TABLE 3 Relationship between levels of copper in diet of pigs and the copper content of their livers. (data of Meyer & Kroger 1973).

Copper in diet mgCu/kg diet	Copper in liver mgCu/kgDM	
	Average	Range
60	36	5 - 170
125	171	22 - 821
250	768	24 - 2672
500	2452	up to 4668

The future of Cu as a feed additive in the E.E.C. is very much in debate at the present time. Essentially certain Member States want to ban its use completely or at least restrict the maximum authorised level to be 125 ppm total Cu in feed, on the grounds that the accumulation of the element in soils during subsequent dispersal of waste results in a build up in Cu-status of the soil which, if allowed to continue would eventually lead to levels toxic to at least certain plant growth. Those in favour of its continued use point out that, as made clear in the. UKASTA survey, the beneficial effect of 125 ppm is so reduced as to make questionable the value of continuing to use it at such a level, and maintain that direct evidence of a build up of Cu levels in soils to toxic levels through waste disposal on land is lacking.

In October, 1980, at Bordeaux, France, the E.E.C. held a 'workshop' to examine the use of Cu as a growth promoter for pigs and the consequences to the environment of the resulting slurry containing enhanced. levles of Cu. The workshop participants concluded that there was no scientific basis to recommend changing the existing directive on the use of Cu as a feed additive for pigs (200 ppm total Cu); restriction to 125 ppm could not be justi'fied, but they stressed the need for more research into the long-term environmental effects of Cu-rich slurry disposal, and emphasised the desirability of finding an alternative growth promoter which would substitute for Cu and have no environmental impact.

Oral hormone administration

A mixture of methyl testosterone and diethylstilbeostrol (DES) (Maxymin) is available on prescription in the U.K. to improve carcase quality, decrease subcutaneous fat thickness and increase carcase lean content. It is fed to growing/fattening stock (only those for slaughter, not animals intended for breeding) from 18 kg live weight to 72 h prior to slaughter at the rate of 2.2 - 4.4 g of each hormone (equal quantities of each) /tonne of feed. Reference will be made later to the fact that use of DES is increasingly being. discouraged as are all oral anabolic products, and it would seem likely that in the near future E.E.C. regulations will prevent its use in countries of the E.E.C.

'Oral' vaccine preparation

A heat-treated, formalinised bacterial preparation from seven specific serotypes of *E. coli*, all known porcine enteropathogens, marketed under the name 'Intagen' and given orally to healthy young piglets up to ten weeks of age has been shown to improve weight gain and feed conversion efficiency (Porter *et al*. 1973). It acts by stimulating the cells on the surface of the intestinal villi to produce specific IgA antibodies to the seven serotypes of *E. coli* used in its preparation. A feature of the secretory immune system is that it is not long lasting unlike normal, blood borne, immunity in which a simple course of vaccination will provide protection for a considerable period of time. In the U.K. the product has a POM classification.

Intagen is also proposed for use in sows to enhance immunological. action of the colostrum; they are fed the oral intagen from six weeks, prefarrowing and given a single, parenteral injection of a specifically prepared form of the product - 'Intagen injectable' - three weeks prior to farrowing (Porter & Allen 1978).

FEED ADDITIVES FOR POULTRY

The feed additives used for growth promotion and improved feed conversion efficiency in poultry are shown in Table 4. Essentially the products, all antibacterials, are those which are listed in Table 2 as antibacterials for growth promotion in pigs. Lucas (1972) has reviewed much of the literature relating to the efficiency of a number of these products. More recently Foster (1978) reexamined the effectiveness for broiler chickens of virginiamycin, bambermycin, nitrovin and zinc bacitracin. Of these, only virginiamycin, nitrovin and zinc bacitracin (the last mentioned at 100g/tonne but not at 10 or 50g/tonne) gave significant increases in growth rate; none'induced feed conversion efficiencies significantly different from control values. However, Foster (1978) does emphasise that levels of additive in feed, when tested did not always reach the levels intended and this was certainly true of bambermycin. He also states that improvements in gross margins were not statistically significant but were economically so in several instances.

FEED ADDITIVES FOR RUMINANT LIVESTOCK

It is convenient to subdivide growth-promoting additives for ruminants into three categories; antibiotics, rumen modifiers and anabolics. With the last mentioned group the oral route of administration is much less significant than the direct implant of the product into body tissue; in this paper licence will be taken to include consideration of such products. It will be recognised that, of the three broad groups referred to above, those in the first two groups act within the digestive system whereas for the anabolics the resulting affects occur within the body itself.

Antibiotics

Not surprisingly there is only limited use of such products in ruminating livestock since indiscriminate use would seriously affect the ability of the animal to maintain the vigorous microbial flora and fauna essential to efficient digestion. One such product that is receiving considerable attention at the present time is the antibiotic Avoparcin, In studies with feed lot cattle (Johnson et al. 1979) dietary supplements of Avoparcin at 33 and 66 ppm in the diet increased gain and improved feed conversion efficiency (Table 5). The mechanism of action of Avoparcin is not known but in vivo and in vitro studies haveshown that its presence in ruminant feed induces a decrease in the ratio of acetate to propionate. (Ingle et al, 1978).

TABLE 4 Antibacterials used as growth promoters for poultry in the U.K.

Name	As feed additive for:	Inclusion Level	Withdrawal period
Avoparcin (Avotan)	Broiler chickens	7.5-15g/tonne	None
Virginiamycin (Eskalin)	Poultry, day old to slaughter (max. 16 wks. of age).	5g/tonne	None
	Broiler chickens, to max. age of 9 weeks.	up to 20g/tonne	None
Zinc Bacitracin	Broilers Turkeys	5-10g/tonne 20-30g/tonne	None
Bambermycin (Flavomycin)	Broilers Layers) Turkeys)	1-3g/tonne 2-5g/tonne	None
Dimetridazole (Emtryl)	Chickens growth promotion and control of Blackhead.	75g/tonne	None
	Turkeys, growth promotion and control of Blackhead.	125-150g/tonne	None
Nutrovin (Payzone)	Broiler chickens) Turkeys up to 26 wks.) Replacement pullets) up to 16 wks.)	10g/tonne	None

TABLE 5 Effect of avoparcin on performance in feed-lot steers. . (data of Johnson et al. 1979)

	Avoparcin (ppm in feed) 33	66
	as percent of controls	
Intake	98	95
Gain	104	106
Intake/Gain	94	90

Rumen modifiers

A great deal of effort is currently being expended in the discovery of chemical. agents that will modulate rumen fermentation in such a way'as to enhance growth and/or feed conversion efficiency in growing/fattening ruminant livestock, and the subject has recently been excellently reviewed by Chalupa (1979). A rumen modifier is defined as a chemical substance which so alters rumen fermentation as to ensure an increased supply of nutrients to the host animal. Evidence suggests that such alterations may be reflected in at least three ways; a reduction in methane energy , loss, but with the energy so spared being effectively captured in some substrate useful to the host animal, a change in the molar proportions of individual volatile fatty acids within the rumen such that the ratio of acetate and butyrate to propionate is narrowed and finally a sparing of feed protein degradation and/or N recycling within the rumen such that energy losses are reduced and/or more amino acid N is made available to the host animal. At the present time the outstandingly successful commercial product in this class is monensin.

Monensin sodium This product, marketed as Romensin in the U.K. and as Rumensin in the USA and rest of Europe is a polyether ionophore synthesised by Streptomyces cinnamonensis from which it derives its name. An ionophore (ion-bearing) is a lipophilic compound which renders cations lipid soluble by binding the cations to it. Monensin has a special affinity for sodium (Na) and facilitates its entry into'the cell as well as altering the activity of the sodium-potassium pump in the pericytoplasmic membrane (Austic & Smith 1980).

Originally marketed as a coccidiostat, the product was subsequently shown to enhance growth performance in adult ruminants by 5 - 10 percent. In some instances the improvement is due to a decrease in intake with no change in liveweight (Byers 1980), in others an increase in gain with no change in intake (Dinius et al. 1978) or to higher gains with lower intakes (Steen et al. 1978). Table 6 gives the results of growth performance monitored% 35 trials carried out in nine European countries (Hawkridge 1980). In a recently conducted trial with growing bulls (Daenicke et al. 1981) observed no change in feed intake but an increase of 4.8 percent in daily gain associated with 5.1 percent better feed conversion efficiency. Carcass composition studies showed that the bulls receiving the additive had a 15.3 percent increase in fat content with no change in protein content and that energy retention was some 15.9 percent higher than in the controls. Increases in fat content with no change in protein content would be expected to improve efficiency of energy retention since the cost of fat synthesis is appreciably higher than that of protein synthesis. (Pullar & Webster 1974).

A full understanding of how these results are achieved must await further study but researches have shown that in rumen fluid, the presence of the additive increases the proportion of propionate at the expense of both acetate and butyrate (Mowat et al. 1977; Prange et a1.1978; Daenicke et al.1981) and, as would be expected methane production is reduced by 30 - 40 percent (Allen, Harrison and Armstrong unpublished observations) with no production of hydrogen. In studies with lambs Toyner et al.(1979) observed an increase in digestibility of energy and an increased energy retention when monensin was included in the feed. Microbial protein in the rumen is decreased as is the degradability of the feed protein (Allen & Harrison 1978) .

TABLE 6 The combined results of 34 trials carried out on monensin used as a feed additive to beef cattle under European conditions, (data of Hawkridge 1980). The values in parentheses show percent change from control.

Monensin (ppm)	No. of replicates	Average daily gain (kg)	Average daily feed (kg)	Feed conversion ratio
0	94	1.153	7.45	6.59
10 - 13	11	1.206(4.60)	7.28(-2.28)	6.16(-6.53)
16 - 21	14	1.196(3.73)	7.19(-3.76)	6.05(-8.19)
25 - 33	77	1.213(5.20)	7.15(-4.03)	6.02(-8.65)
37 - 40	16	1.208(4.77)	6.95(-6.71)	5.91(-10.32)

Other ionophores which are also effective coccidiostats and which are already marketed or about to be marketed are Lasalocid and Narasin.

Halogenated compounds Halogenated compounds such as chloroform, amichloral (a hemiacetal of chloral hydrate and starch) and trichloroethyl adipate are effective inhibitors of methane production, at least in the short term. Many suffer the disadvantage that they are too volatile. Also there is evidence of gradual adaptation of the rumen microflora to their continued presence and thus a gradual return of methane levels to those seen in animals not fed the additive. In addition it is the experience of the author that most of these. compounds although effectively inhibiting methane production initially give rise to appreciable levels of hydrogen production.

Diaryliodonium compounds Such products as diphenyliodonium chloride have been shown to improve the N economy and performance of ruminant livestock by suppressing ruminal degradation of amino acids but again have been little exploited commercially as feed additives. The reader is directed to Chalupa (1980) for further information on these and the previously mentioned products.

Anabolics These are substances which increase N retention and protein deposition in animals. The Products used in farm livestock are related to the sex hormones and can be conveniently subdivided into androgens, oestrogens and progesterones. Each of these three categories has natural and synthetic products (see Table 7).

TABLE 7 Some naturally occurring and synthetic anabolics.

Androgens	(i)	Natural	testosterone, testosterone esters	
	(ii)	Synthetic	Trenbolone acetate, methyl testosterone	
Oestrogens	(i)	Natural	17B oestradiol, 17B oestradiol esters	
	(ii)	Synthetic	zeranol	
			hexoestrol)	stilbene derivatives
			diethylstilboestrol)	
			dienoestrol)	
Progestines	(i)	Natural	progesterone	
	(ii)	Synthetic	melengestrol	

In the U.K. the only oral preparation marketed is diethylstiboestrol plus methyltestosterone marketed as Maxymin and used to increase lean tissue growth in pigs; as already mentioned it has a POM classification. The products that can be used as implants in the U.K. are 17-B oestradiol, zeranol (trade name Ralgro), trenbolone acetate (trade name Finaplix) and mixtures of oestradiol plus testosterone and of oestradiol plus progesterone. Of these only zeranol has a PML certificate; the rest carry a POM classification. In the U.S.A. melengestrol is used as an oral oestrogen with finishing cattle.

In many species including rat, mouse, horse and poultry anabolic responses appear to occur only with androgens but not oestrogens, whereas in cattle and sheep anabolic responses are obtained with either androgens or oestrogens or both together. Maximum effect is achieved by using an androgen for heifers and cows, an androgen plus oestrogen for castrates and an oestrogen for bulls. Table 8 lists some data relating to dose rates used for the implants and the delay time required after implant before slaughter.

TABLE 8 Anabolic agents used in ruminant meat production.

Type of implant	Animal	Dose for cattle (mg)	Time after implant before slaughter (days)
(1) Androgens			
Trenbolone acetate (Finaplix)	heifer, cow	300	60
(2) Oestrogens			
Hexoestrol	steers, wethers, veal calves	45 - 60	90
Zeranol (Ralgro)	" " " " " "	36mg cattle 12mg sheep & lambs	70
(3) Androgen + Oestrogen			
Trenbolone acetate/ oestradiol	steers, wethers, veal calves	140/20	60
" "/hexoestrol	steers, veal calves	300/30-45	90
""/zeranol	" " "	300/36	65
Testosterone/oestradiol	" , heifers, "	200/20	90
(4) Progesterone + oestrogen			
Progesterone/oestradiol	steers	200/20	90

There are very considerable sets of data in the literature which consistently show the large responses in liveweight gain that result from the proper use of the anabolics. Table 9 gives some data relating to trials carried out in the U.K. by the Meat & Livestock Commission (MLC) (Stollard et al. 1977) -and the Agricultural Advisory and Development Service (ADAS), (Scott 1978). In both these trials involving 1557 and 790 steers respectively it can be seen that the use of a combined implant resulted in 26 to 33 percent increases in liveweight gain. The type of ration fed has little effect on the growth stimulating powers of these hormone implants. In the ADAS trial with cattle fed barley-based diets the net return/head at 1979 prices was calculated to be £16-50 while animals on the barn-dried hay diet gave a net return of £16-10. Responses occur in pasture fattened animals and thus can be used in hoggets. At a recent farming conference held in U.K. (Livestock Farming, April 1981) many farmers claimed that under the practical conditions of commerical farming, weight gains of 25 0 50 kg over control groups were being achieved as a result of implants and that for an outlay of £5 for the implants returns were in the order of £40/animal greater, due to faster growth and more efficient feed conversion:

TABLE 9 Average percentage responses in liveweight gain to anabolic implants observed in trials carried out in the U.K.

	MLC Trial (1557 steers)	ADAS Trial (790 steers)
Trenbolone acetate	9	11
Hexoestrol	25	22
Zeranol	15	17
Trenbolone acetate + hexoestrol	33	26

The exact mode of action of anabolic agents is still in doubt (Heitzman 1979), although the common action of all of them is to increase N-retention. It is considered that androgens may act differently from oestrogens. Androgens but not oestrogens are known to displace corticosteriods, which are potent catabolic agents, from their receptor sites, and thus androgens may act by substituting at receptor sites for corticosteriods (Heitzman 1979). The androgens may also act indirectly by regulating the circulating levels of thyroxine. Androgens induce marked falls in total circulating levels of thyroxine in both sheep and cattle (Heitzman 1979) and the consequence may be a decreased turnover of protein in muscle cell.

The primary effect of oestrogens is thought to be on factors controlling growth hormone secretion from the pituitary, (Davis et al. 1977). The increased production of growth hormone may stimulare mitosis of the satellite cells that lie between the basement membrane of the plasmalemma of muscle cells, and fusion of one or both daughter cells with the growing muscle fibre, thereby increasing the numbers' of nuclei and hence desoxyribonucleic acid present in the muscle fibre (Trenkle 1980).

The carcinogenicity of anabolic agents has been reviewed (IRAC monograph 1975) and it is known that at very high dose levels anabolics such as diethylstilboestrol, testosterone and'oestradiol are carcinogenic (Roe 1976); uncertainty remains concerning trenbolone acetate, zearanol and melengesterol acetate. A great deal of attention is being given to the detection of levels of anabolic residues in animal tissues (Hoffman 1981; Heitzman et al.1981). Suffice it to say that if implants are used as prescribed, are implanted in the base of the ear and that the delay after' time of implant, before slaughter is correctly observed then the -evidence available indicates that residues in meat from naturally occurring anabolic products are not in excess of those occurring naturally in non-implanted animals.

Very recently the European Commission was stimulated by the Italian Government into proposing a complete ban on the use of anabolics throughout the E.E.C. This action followed evidence of excessive levels of hormones in veal sold in Italy - in part home-produced and in part imported from Belgium. The anabolics were never intended for use in veal production and it is a further irony that Italy and Belgium, along with the Netherlands and Denmark ban the use of hormone-active substances for growth and fattening purposes in livestock.

In the U.K. with its beef production largely based on castrate animals grazing pastures, the use of anabolics to overcome the setback in lean meat production following castration is an important consideration. It is hoped that the difficulty can be resolved by banning the use of orally administered anabolics, and those based on a stilbene structure (hexoestrol, diethylstiboestrol and dienoestrol) and ens'uring, through an adequate monitoring system that the others are used in the prescribed manner.

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