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Application of Hormones on Food Animal to Enhance their Production Potential and its Limitation: A Review

Yasin Beriso*

Ethiopian Institute of Agricultural Research, DebreZeit Agricultural Research Center, P.O. Box: 32, Bishoftu, Ethiopia

**Corresponding author*

Abstract

Growth promoters including hormonal substances and antibiotics are used legally and illegally in food producing animals for the growth promotion of livestock animals. Hormonal substances still under debate in terms of their human health impacts are estradiol-17β, progesterone, testosterone, zeranol, trenbolone, and melengestrol acetate (MGA).Hormone increase the animals' growth rate and the efficiency by which they convert the feed they eat into meat. All approved steroid implant products have a zero day withdrawal. This means that the meat from the animal is safe for humans to eat at any time after the animal is treated. Estradiol, progesterone and testosterone are hormones present in plant and animal products. These naturally occurring hormones are endogenous (coming from inside the system). In animals, they travel through the bloodstream to synchronize body functions and influence reproduction, growth and development. Hormones such as androgens and estrogens are exogenous (coming from outside the system). They are given to growing cattle to promote growth and they cooperate with the endogenous hormones. Growth promoting hormones improve feed efficiency, protein deposition and growth rate of cattle.

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Introduction

Food and Drug Administration (FDA) has approved a number of steroid hormone drugs for use in all types of livestock, including natural estrogen, progesterone, rbst, testosterone, and their synthetic versions. These drugs increase the animals' growth rate and the efficiency by which they convert the feed they eat into meat. Hormones play also role in differentiation between sexes of animal used for animal food. It has also been known that growth rate and FCE (feed conversion efficiency) are higher in intact males than in castrates. It was natural, then, that the availability of hormones and other natural or synthetic substances displaying hormonal activity led to experiments aiming at their use to increase production. Beginning in the mid-1950s, DES (diethylstilbestrol) and hexoestrol were administered to cattle increasingly in the US and the UK respectively, either as feed additives or as implants, and other types of substances also gradually became available. In general, such treatment has resulted in 10–15% increases in daily gains, similar improvements in FCE and improvement of carcass quality (increased lean/fat ratio). Thus there has been a substantial reduction in the amount of energy required per unit weight of protein produced (1, 2), and the economic implications of this have been great.

While the use of hormonally active substances in animal production rose, opposition to their use also increased, because of the theoretical possibility that residues in edible tissues might endanger consumers. The factors leading to the ban on DES in the US, first imposed in 1973, have been described (3).

Several reports confirm that DES endangers the health of animals and man, when repeatedly used in large doses (4, 5). However, as regards risks due to the presence of residues in meat produced according to regulations, no documented deleterious effects have ever been reported in man, either from DES or any other substance with hormonal activity.

A distinction should be made between the hormones as such, for which the metabolism in the body is relatively well known, and synthetic or other substances for whose metabolic inactivation the body may not possess the enzymes necessary.

When natural hormones are used in animal production, claims of zero-tolerance residue levels are not meaningful, since these compounds occur in detectable and highly variable concentrations in body fluids as well as in the tissues of all animals, treated or not (6,7). For other substances with hormonal activity the situation is different. However, when residue levels are extremely low, it seems reasonable to weigh the potential risks against the undisputed positive effects some of these compounds have in animal protein production.

Hormones coming from inside the system

These are the "classical" steroid sex hormones, oestradiol-17β, testosterone and progesterone. The first two hormones are used either in the free form or as esters, mainly those of propionic or benzoic acid. Esterification generally causes prolongation of the half-life of the compounds in the body by 40 to 50%. The natural hormones having low bioavailability when administered orally, owing to rapid conjugation and metabolic transformation in the liver, they are therefore administered by subcutaneous implantation.

Hormones coming from outside the system

Of the *oestrogens*, the stilbene derivatives diethylstilboestrol (DES) and hexoestrol possess high biological activity and have been used most widely. They are active orally as well as by implantation. Other orally active oestrogens include ethynyl-oestradiol, a more slowly metabolized derivative of the true hormone, with higher activity. An oestrogen with an entirely different structure is zeranol, a derivative of a resorcylic acid lactone occurring in the fungus *Giberellazeae*. The *synthetic androgens* comprise a large number of substances, most of which are steroids. Of these, trenbolone acetate (TBA) possesses strong anabolic properties and has received much attention during recent years, used alone or in combination with an oestrogen.

Another anabolic steroid is methyl-testosterone. Of *synthetic gestagens*, only one will be mentioned here: melengestrol acetate, which stimulates growth in heifers but not in steers, and which can also be used for the suppression of oestrus. Numerous other gestagens also exist, but at present few other than progesterone and melengestrol acetate are used to stimulate growth.

In addition to these substances, numerous others exist, and some of them are used more or less frequently in clinical veterinary medicine. However, clinical applications of hormones are not considered to be of consequence to the consumer, since such treatment is much less frequent than the use of hormones to promote growth.

Hormone preparations in current use as growth stimulants are listed in Table 1, which also shows modes of application, dosages, etc. It will be noted that almost all preparations currently in use are based on implantation, the site usually being the base of the ear, or less frequently, the dewlap.

Bovine somatotropin (bST)

Bovine somatotropin (bST) is a metabolic protein hormone used to increase milk production in dairy cows. In the 1930s, it was discovered that injecting bST into lactating (milk-producing) cows significantly increased milk production. It was approved for commercial use in the U.S by the Food and Drug Administration (FDA) on November 5, 1993**.** The word bovine refers to cattle, and the word somatotropin refers to the name of the hormone. Hormones are chemicals that are secreted by glands within the body. They are natural substances that affect the way the body operates. Bovine somatotropin, abbreviated as bST, is a protein hormone produced in cattle by the pituitary gland located at the base of the animal brain. A hormone similar to bST is produced in all species of animals. This hormone is important for growth, development, and other bodily functions of all animals.

Recommended application range for hormones in food animal

In *cattle* the use of hormones is limited to veal calves and beef cattle. *Veal calves* are produced mainly in continental Europe, to an extent of about 8 million per year. Research has demonstrated that hormone treatment improves growth rate, nitrogen retention and FCE during the five- to six-week period before slaughter (9, 10). *Beef cattle*, including steers as well as heifers, were treated in large numbers, especially in the USA and the UK, with DES or hexoestrol, administered orally, until the use of these compounds was restricted. During the last several years, practice has changed dramatically in the direction of increased use of implants of natural steroids, synthetic anabolic steroids and the phyto-oestrogenzeranol.

In *sheep*, especially in wither lambs, some increase in gain has been reported (11), but results are somewhat ambiguous.

In *swine*, hormone treatment may increase growth rate, FCE and lean/fat ratio of the carcass in male castrates.

Poultry generally do not appear to respond to oestrogens by increased gain but by changes in lipid deposition. In male and female turkeys, androgens have recently been reported to increase growth rate as well as FCE (13).

How to apply on Animal

When DES was used as a feed additive, a usual procedure was to start treatment of steers at a body weight of 360 kg and continue administration for 120 to 170 days. Since restrictions on its use were imposed, most preparations have been administered as implants, whose effect is usually limited to 80 to 100 days. Practice varies with management systems. Animals may be implanted at live weights from 270 to 450 kg. Depending upon the age and weight at the time of implantation, the animals are either slaughtered at the end of this first period, or fed for an additional period, either without further treatment or after a second implant to act for another 80 to 100 days. Most types of implants in use are not removable, but removable types have recently been tested and their effects described (114).

When tested in steers, no reduction in performance was recorded when the implants were withdrawn 32 and 39 days before slaughter. Implantation is subcutaneous, usually at the base of the ear, thus eliminating the risk that residues of the implantation site will be present in edible tissue. FDA approved anrbST (rBGH) product in 1993 with the brand name “Posilac®” (sometribove zinc suspension) after determining that its use would be safe and effective. Posilac® is approved for over-the-counter use in dairy cows starting at around 2 months after the cow has a calf until the end of the lactation period. During this time, cows are injected with Posilac® subcutaneously (under the skin) every 14 days. A cow’s typical lactation period is approximately 10 months long, starting right after she has a calf. Thus, treated dairy cows are typically given Posilac® for about 8 months of the year. After the 10 month lactation period, the producer stops milking the cow to allow a 2-month period for her mammary gland to rest and regenerate before she has a calf and starts the next lactation period.

Effects of hormones

Dairy cattle

Official estimates of the yield response to BST administration have varied from 10-25% (AHI, 1987) to 10-15% (CAST, 1993). However, responses can be variable and may depend on management factors to achieve a maximal response. Indeed, independent studies suggest that a third of treated herds will have less than a 10% increase(e.g. Chilliard, 1988), while there isat least one full report in which BST administration produced no significant yield increase(Kim *et al.,* 1991)

A higher response is seen when treatment is started after the cow has been producing milk for 101 days, rather than when treatment is started on days 57-100 after calving. The response of cows treated in early lactation is less (15). Cows that have had more than one calf show a greater increase in milk production than do first lactation heifers (5). Milk yield gradually increases for the first few days after rbST treatment begins. A maximum increase is seen in about six days. To meet the needs for this increased milk production, treated cows consume from 10 to 20 percent more grain and forage (8)

Normally, cows reach their peak milk production 7-9 weeks after lactation begins. Milk quantity then slowly declines throughout the remainder of lactation. The ability of cows to maintain relatively high levels of milk production throughout lactation is called "persistency." The major response of cows treated with rbST is a significant improvement in persistency. The normal decrease in milk yield as lactation progresses is markedly reduced. Quality of management, including health programs, milking practices, nutrition, cow condition, and environmental conditions will be major factors in the response to rbST (10).

Veal calves

In veal calves, hormone treatment may begin at a body weight of about 65 kg, the animals being slaughtered at about 170 kg. Implants of 20 mg oestradiol-17β + 200 mg progesterone in males and 20 mg oestradiol-17β + 200 mg testosterone in females resulted in a 20% increase in daily gain and 21% higher nitrogen retention in the period studied (14). In other studies, improvements of 10 to 12% in gain and 10% in FCE have been reported (15, 16, 17, and 18).

Nitrogen retention is about 70% in the very young veal calf, but decreases gradually to below 40% at the age of about 15 weeks. For ages of 10 to 15 weeks, the average conversion of feed protein to body protein is about 40%; this rate can be increased to about 60% by hormone treatment. The effective preparations were DES, oestradiol-17β, and the combination of TBA + oestradiol-17β (9).

More recently, positive effects have been reported (19, 99) for zeranol alone (36 mg) and for zeranol (36 mg) + TBA (140 mg), with increases in nitrogen retention of the same order as for DES and E2 + TBA. When zeranol + TBA was implanted at the age of 56 days, the growth rate up to day 106 increased by 18% (19).

Steers

The most extensive studies of the effects of hormones on growth and FCE have been carried out on steers, under strictly controlled conditions as well as in the field. Since 1975, most studies have involved implants of oestrogens alone, androgens alone, or combined oestrogen/androgen preparations, although many trials have also been based on oestrogen/progesterone combinations during recent years.

Oestrogen implants have included DES, hexoestrol, oestradiol-17β and zeranol. *DES implants* have, as in previous studies, resulted in an increase of about 12% in gain and in improvement in FCE of the order of 10% (20, 21, and 22). *Hexoestrol implants*, usually in doses of 30 to 60 mg, have been shown in numerous experiments to lead to considerable improvement in growth rate and FCE (23, 27, 28, and 29). In 19 trials carried out over the years on experimental husbandry farms in the UK, the overall average increase in gain produced by 45 or 60 mg hexoestrol implants was 0.16 kg a day, and in only 2 of the trials was it less than half that figure (2). *Oestradiol - 17β implants* alone (30 mg) have resulted in a 24% increase in gain and a 13% improvement in FCE (30). *Zeranol implants*, usually at 36 mg, have consistently improved gain as well as FCE (20, 40, and 41). In a series of 21 UK trials over several years, the average response to zeranol implants alone was an increase in daily gain of 0.15 kg. Only in one trial was there no response (23). Similar results have been obtained in Ireland (*cit. 2*). Positive effects on gain in steers have been observed under a variety of experimental conditions, under controlled feeding, on *ad lib* feeding of standardized rations, and on pasture.

TBA implants administered alone at a dose of 300 mg have also had positive effects on growth (23, 24, 25), even if combination with an oestrogen has yielded better responses (*vide infra*). In a series of 8 trials in the UK, the average additional daily gain amounted to 0.09 kg, with considerable variation among trials (23). Similar results have been reported from Ireland (*cit.*2).

Combined preparations

A number of trials have been carried out with implants containing two hormones. The combination of an oestrogen with an anabolic steroid, or with progesterone, has met with the greatest responses. *Synovex-S* has consistently increased gain as well as FCE, with responses averaging about 20% and 17% respectively (44, 45, 46, 47, and 48). *Hexoestrol + TBA* (usually 30 or 45 mg hexoestrol + 300 mg TBA) has resulted in marked increases in gain (24, 52, 53), of the order of 30% and in FCE (51, 53) of the order of 20%. *Oestradiol-17β + TBA* (20/140 mg) has given similar results (27), as has *Zeranol + TBA* (36/300 mg), also recently tested (27, 37).

Hormone preparations have also been tested in combination with substances such as monensin, which increase FCE by promoting propionic acid formation in the rumen. Results have varied from no effect (38, 52) to marked additional gain (43).

Re implantation, tested under various forms of management with varying results (25 and 58), has not gained general acceptance. Lamming (45) has stated that "repeat implantation of hormone is not likely to produce the benefits obtained from its initial use, since a second dramatic change in the endocrine balance of the animal is not likely to occur. In addition, double implantation increases the possibility of exceeding the optimum dose rate and the chance of deleterious side effects occurring." The evidence for highly significant positive effects on the growth rate and FCE of steers is thus beyond dispute, the most marked effects being provoked by implants combining an oestrogen with an androgen of high anabolic activity.

Bulls

Since the entire male animal produces its own anabolic androgen, testosterone, an effect of additional hormones similar to that for steers is not to be expected. The number of trials with bulls is also limited. Positive effects on gain have been reported using DES alone (2, 58, 59) and combined oestrogen/TBA implants (60); in other studies, no effect on gain has been recorded (49, 61), while a certain increase in the deposition of fat in the carcass has been observed (61).

Heifers

Recent trials with beef-producing heifers have mostly been based on the use of an androgen, although oestrogens have been tested, alone or in combination. Thus, zeranol has been reported to increase gain (62, 63), while in other trials no response has been observed (37, 62).

TBA administered alone (300 mg) has led to increases in weight gain and FCE of the order of 36% and 25% respectively (24, 27, 37). In other trials, combinations of an oestrogen with TBA (68) or testosterone (62) have yielded significant growth responses. In general, it appears that the effect of TBA alone in heifers corresponds closely to the effect of combined oestrogen/TBA implants in steers.

Sheep

Trials have mainly concerned wither lambs, and positive effects of hormonal treatment have been reported using DES (69), hexoestrol (71) and zeranol (72, 73), although other reports have indicated that zeranol yields no significant effects (74, 75). Wether lambs implanted with TBA + oestradiol-17β has shown increases in gain, carcass weight and FCE (11, 69). In general, however, the results obtained in sheep thus far do not warrant the same clear-cut conclusions as for steers and heifers.

Swine and poultry

There is little evidence that existing hormonal preparations influence the growth rate and FCE to an extent that would be interesting from a practical point of view. The lean/fat ratio in male castrate and female pig carcasses may be increased by the use of oestrogen/androgen combinations (76). In poultry, redistribution of fat in the body is a known effect of oestrogens. Recent research indicates improved growth rate and FCE using androgens in young male and female turkeys (13, *cit.* 27).

Undesirable side effects in treated animals

Reported side effects of hormone treatment for growth stimulation are few and generally concern the use of oestrogens in steers. Changes in body conformation such as feminization and raised tail-heads were described as early as 1958 (18). Similarly, bulling has occurred with increased frequency (57, 18, and 11); although in most animals it is limited to the first few days after implantation (46). However, it has been reported from Kansas that 2.2% of all steers fed in pens have to be removed, at an estimated loss of $23 per head (19). In a study of the effect of reimplantation of oestrogens in steers, all animals were given a 30 mg DES implant at a live weight of 260 kg, and then reimplanted 91 days later, with either 30 mg DES or Synovex S. Following the second implant, the frequency of the steer-buller syndrome was 1.65% for the DES-DES group, and 3.36% for the DES-Synovex S group. The economic advantage of using DES + DES was estimated at $1.15 per head (57). The steer-buller syndrome is a special problem in feedlots.

The physiological effects of rbST treatment on dairy cattle are the same as those seen in any high-producing cow (80). Nutrition, health programs, environment, and milking technique must be appropriate for the use of rbST or results will be disappointing. On many farms, the management changes instituted by producers as they are preparing to use rbST will probably cause a greater increase in milk production, efficiency, and profitability than actual use of rbST. In the initial stages of use, producers will be encouraged to use rbST on cows that have been in lactation for at least 100 days, are in good physical condition, pregnant, and are free from health problems such as mastitis or infertility (100).

Concern has been expressed regarding the effect of rbST on reproduction. The optimum calving interval of 12-13 months may lengthen because rbST can extend the time that cows efficiently produce milk. Dairy Herd Improvement Association (DHIA) records show that higher milk-producing herds have lower conception rates than lower producing herds (Ferguson and Skidmore). This negative effect on reproduction is seen in cows treated with rbST and is associated with increased milk production. However, some people believe that a longer calving interval could benefit the health of rbST- treated cows, since many health problems of dairy cows are associated with calving and rebreeding. The ability of a cow to reproduce is affected by her physical condition, nutrition, health, and level of milk production.

Few research studies have investigated the physiological effects of rbST on the functioning of the ovaries and pituitary gland (80). Cows receiving dosages of rbST far beyond what will be used in practice have shown an adverse effect on estrous activity (the time when an animal is capable of being bred).

This effect is not seen when cows receive low to average dosages of rbST (80). High dosages of rbST are reported to increase the death rate of calf embryos, so starting a cow on rbST during early pregnancy should probably be avoided (Ferguson and Skidmore). This effect is not seen at recommended dosages. The effect of rbST on reproduction will have to be monitored closely in individual herds (77).

Mechanism of action of hormones

No reliable explanation of how the growth-promoting hormones act has yet been furnished. Some observations indicate an indirect influence through changes in the balance of endogenous hormones. Thus there have been reports of DES and TBA increasing the levels of growth hormone and/or of insulin in plasma (51, 63); these hormones are known to stimulate amino acid transport across the cell membrane.

However, others have found no such effect (49, 60, 67, 77, 82). Bulls fed DES (10 mg/day) over two years had significantly higher plasma testosterone levels than controls (78); those levels are positively correlated with growth (78, 79, 80). Recent experiments indicate that DES reduces the rate of muscle catabolism in steers (81).

As regards the anabolic androgens, evidence exists indicating competition with glucocorticoids for receptor sites on the muscle cell membrane. Since glucocorticoids have a catabolic effect on tissues, their displacement from muscle cells would reduce catabolism. TBA alone, and even more when combined with oestradiol-17β, causes a marked decrease in the concentration of total thyroxin in plasma of steers (82). In another study, combined oestradiol-17β-progesterone implants (20 + 200 mg) in steers caused a uniform but slight increase in thyroxine binding capacity (44). The significance of these findings is not yet clear.

To affect a cows' milk production, rbST must be injected into the animal on a regular basis, similar to the way insulin must be regularly injected into people who have certain types of diabetes. Feeding rbST to cows will not work. Amino acids and peptides are the building blocks of proteins.

The hormone rbST is a complex protein that is immediately broken down into small, inactive amino acids and peptides and rendered ineffective when it enters a cows' digestive system. How often a cow must be injected with rbST will depend on whether arbST product can be developed that releases the hormone gradually over a long period of time.

The exact details of how rbST increases milk production are not known, but it is thought that blood flow to the cows' mammary (milk-producing) gland is increased. The blood carries an increased amount of nutrients available for milk production. More nutrients are extracted from the blood by the mammary gland, which improves efficiency of milk production. Feed efficiency (pounds of milk produced per pound of feed consumed) is improved because more milk is produced and the proportion of feed used for body maintenance is decreased. The actual amount of feed consumed by rbST-treated cow' increases and helping the cow meet the increased nutrient demands.

Levels of endogenous hormones in body fluids and tissues

Any discussion of possible health hazards connected with the use of hormones in animal production must take into account the normal occurrence of hormones and their metabolites in body fluids and tissues, and the fact that the levels of these hormones vary greatly, according to the physiological state of the animal.

Thus, oestrogen levels in the blood of female farm animals may vary from a few pg up to 5–6 000pg per ml plasma (6). As to males, the plasma of stallions and entire male pigs contains high levels of oestrogens, although mainly in the conjugated form. Milk also contains oestrogens in very high concentrations in the first drawings after parturition; in non-pregnant animals, levels in the range of 80–100 pg/ml have been reported

(6, 84). More recently, reliable data have also become available concerning concentrations in edible tissues; some of these are presented in Table 3. For the sake of comparison, levels of oestrogen activity normally present in products of plant origin widely used in human nutrition are included.

Metabolism, routes and rates of elimination

The general patterns of metabolism and elimination of endogenous hormones in farm animals have been outlined (90). In ruminants, testosterone and oestradiol-17β are rapidly converted to their epimers, biologically much less active, epitestosterone and oestradiol-17α. Progesterone is partially converted to androgens before excretion.

In the pig, epimerization of testosterone and oestradiol-17β does not appear to take place to a significant degree. The fecal route of elimination dominates in ruminants, while in the pig urinary excretion is more important.

Progesterone

After repeated injections of progesterone to cows and steers over 2 to 3 weeks followed by ^{14}C-progesterone for 2 to 5 days, the animals were slaughtered 2 to 3 hours after the last injections. Activity levels were 2 to 7 times higher in the fat, 3 times higher in the kidneys, and 13 times higher in the liver than in the muscle. Excretion of radioactivity amounted to 50% and 12% in faeces and 2.0% and 1.2% in urine in cows and steers respectively. About 50% of the activity in muscle and milk was associated with unchanged progesterone, most of the remaining activity being associated with a mono-hydroxy compound. Cooking or frozen storage did not affect the nature or quantity of metabolites (91).

Oestradiol-17β

Following daily injections of 1 mg oestradiol-17β or its benzoate to heifers and steers for 11 days, followed by the ^{14}C-compounds on days 12, 13 and 14, the animals were slaughtered 3 hours after the last injections, when residual levels were maximal. In muscle extracts, oestradiol-17β represented the major fraction of extracted activity (38 to 71%), followed by oestrone (17 to 45%). Levels in muscle were 161 to 225pg/g and 40 to 86pg/g for oestradiol-17β and oestrone respectively. In fat, the levels were 3 to 5 times higher. Thus we can conclude that residual levels are extremely low when these hormones are administered as growth stimulants to growing/finishing cattle (92).

Glucosides of the 17β- and the 17α- epimers, and the glucoronide of the 17α- epimer are the major metabolites in cattle (25). When oestradiol-17β was administered orally to swine, plasma concentrations were very high 7 min after administration. Oestradiol was completely conjugated during absorption and its first passage through the liver. Some conversion to oestrone took place (93).

Des

The metabolism of DES in food-producing animals has been reviewed recently (94). The substance seems to be eliminated to a large extent in unaltered form. After oral administration of ^{14}C-DES to beef cattle, 99.5% of the radioactivity was excreted within 5 days after withdrawal. In liver extracts, radioactivity associated with DES-conjugate and free DES was found to be 75% and 25% respectively. Higher than background levels of activity were observed after withdrawal in kidney, liver, bile and urine/faeces for up to 5, 7, 9 and 11 to 12 days respectively (95). The fate of 24-mg DES implants containing ^{14}C-DES and implanted in the dewlap of calves was studied over 98 days. Free radioactivity was almost completely associated with unchanged DES. At the time of slaughter, levels were less than 0.1 ppb in muscle and fat, and 1 to 1.5 ppb in liver and kidney (96).

In a study in steers implanted with ^{14}C-DES, on day 120 after implantation radioactivity in muscle was not distinguishable from background. It was above background in spleen, lung, adrenal glands and kidney, but less than levels corresponding to 0.5 ppb. In a similar study on steers, 120 days after implantation, levels in liver, kidney, lungs and salivary glands were in the range of 0.07 to 0.13 ppb of DES equivalent (98). In a recent study of DES metabolism in rhesus monkeys and chimpanzees, most of the substance was excreted with the urine. Extracts in the organic and aqueous phase mostly contained unchanged DES in the free and conjugated form respectively (21). Current evidence indicates that the oxidative metabolism of DES leads to at least three compounds that may have cytotoxic or mutagenic activity (21), but these have not been identified as DES metabolites in ruminants, but in the mouse.

Table.1 Hormonally-active substances used in animal production

Substances	Dose levels	Form	Main use – Animals	Trade name
Oestrogens alone:				
DES	10–20 mg/day	feed additive	steers, heifers	
DES	30–60 mg/day	Implant	Steers	
DES		oil solution	veal calves	
Hexoestrol	12–60 mg	Implant	steers, sheep, calves, poultry	
Zeranol	12–36 mg	Implant	steers, sheep	Ralgro
Gestagens alone:				
Melengestrol acetate	0.25–0.50 mg/day	Heifers		
Androgens alone:				
TBA	300 mg	Implant	heifers, culled cows	Finaplix
Combined preparations:				
DES + **Testosterone**	25 mg 120 mg	implant	calves	Rapigain
DES + Methyl-testosterone		feed additive	Swine	Maxymin
Hexoestrol + **TBA**	30–45 mg 300 mg	implant	steers	
Zeranol + **TBA**	36 mg 300 mg	implant	steers	
Oestradiol-17β + **TBA**	20 mg 140 mg	implant	bulls, steers calves, sheep	Revalor
Oestradiol-17β benzoate + **Testosterone propionate**	20 mg 200 mg	implant	heifers, calves	(Synovex H (Implix BF
Oestradiol-17β benzoate + **Progesterone**	20 mg 200 mg	implant	steers	(Synovex S (Implix BM

Table.2 Increases in milk production and feed efficiency of rbST-treated cows (10)

Location	Increase in Milk Yield (%)	Increase in Feed Efficiency (%)
Arizona	8.3	2.7
Cornell University	11.5	5.3
Missouri/Monsanto	21.8	8.2
Utah/Utah State U.	14.6	5.3
France	17.8	9.3
Germany	16.6	4.9
Netherlands	18.5	7.1
United Kingdom	19.2	5.4

Table.3 Concentrations of endogenous hormones in edible tissues of farm animals

Animal/tissues	Oestrone pg/ml	Oestradiol-17β pg/ml	Testosterone pg/g	Progesterone pg/g
Veal calf				6
muscle		<100	70	
liver		<100	47	
kidney		<100	685	
fat		< 100	340	
Bull				
muscle			335	
liver			749	
kidney			2783	
fat			10 950	
Heifer	20–40			16
muscle		12–13	92	
liver		38–71	193	
kidney		40–71	595	
fat		6	250	
Cow, pregnant				336
muscle		370–860		
		2 500–5 500		
fat	3 870			
Steers				
muscle	6	14		
liver	20	14		
fat	23	10		
Wheat germ oil	4 000 pg/g DES equivalent			
Soy-bean oil	2 000 000 pg/g DES equivalent			

Table.4 Hormones in certain dairy foods

	Oestrogens (pg/ml)	Progesterone (ng/ml)
Milk, from non-pregnant cows	80	9.5
Milk, from pregnant cows	126	
Cream		73
Butter		133

Table.5 Relative contribution of meat from hormone-treated steers to total hormone intake via food (per cent)

	Oestrogens	Progesterone
Child under 1 year	0.22	0.014
Child 6 to 8 years	1.56	0.1
Adult male	7.69	0.5

Table.6 Contribution of hormones from hormone-treated steers relative to total daily hormone production in man (per cent)

	Oestrogens	Progesterone	Testosterone
Prepuberal girls	0.00636	0.00078	0.005
Prepuberal boys	0.00826	0.00130	0.00244
Women			
Follicular phase	0.00018	0.00047	
Luteal phase	0.00007	0.01	0.0004
Men	0.00025	0.00048	0.00003

Zeranol

Using a gas chromatographic method with a sensitivity limit of 20 ppb, no residues of zeranol could be detected in edible tissue from cattle slaughtered 65 days following implantation of 36 mg, or from lambs 40 days following implantation of 12 mg (101). In another study, tritiatedzeranol was implanted in cattle as part of 36-mg doses. Skeletal muscle obtained 10, 30 and 50 days following implantation contained no detectable residual activity (99). This confirms previous results based on the use of ^{14}C-labelled zeranol (100).

Trenbolone acetate (TBA)

Trenbolone is a 17β-OH steroid esterified in the 17 position with acetic acid. Upon release in the organism the ester is rapidly hydrolyzed to the free compound TB-17β-OH and acetate. In cattle the 17β-OH compound is rapidly transformed to its 17α-OH epimer, in the same manner as oestradiol-17β in this species. The 17α epimer possesses only about 5% of the biological activity of the 17β epimer.

Another metabolite of TBA in cattle is the 17-keto compound, analogous to oestrone; quantitatively it appears to be of very little importance. Following intravenous injection of TBA, levels of TB-17β-OH and TB-17α-OH of 0.05 and 0.005, 0.10 and 1.0, 0 and 191 ppb have been recorded for muscle, liver and bile respectively. Other metabolites occurred in extremely small quantities in cattle (102, 101).

Similar findings have been reported in studies based on the use of implants (*cit.* 102). The major route of excretion is by faeces. Metabolism studies of TBA thus clearly show that the substance is rapidly subjected to biological inactivation in cattle, mainly by epimerization of the free steroid to the 17α-compound, and that the major route of excretion is via the bile.

Hormones in food: meat from hormone-treated animals versus other sources

According to the Agricultural Research Service, United States Department of Agriculture (ARS), the average per caput consumption of beef is 157 g per day in the US (102).

Calculations show that 157 g of beef from an animal implanted 61 days before slaughter with a combined implant containing 20 mg oestradiol-17β + 200 mg progesterone or testosterone will contain 3.43 ngoestrogen and 19.5 ng progesterone or 16 ng testosterone. Table 4, which provides data on normal levels of these hormones in certain dairy foods, shows that some foods represent hormone sources vastly richer than meat from hormone treated animals.

Based on these values, and averages for consumption of various foods, the relative contribution of meat from hormone-treated animals to the total consumption of hormones has been calculated on the assumption of proper use of the hormones (see Table 5).

It is clear that in most cases the contribution from meat of treated animals is insignificant when hormones have been properly used, and must be considered to be biologically without impact. This becomes even more evident when seen in relation to normal endogenous hormone production in man, as illustrated in Table 6.

It will be seen that even for oestrogens, the hormones considered the greatest risk; the maximal contribution from meat (assuming proper use of the hormones) is less than 0.01% in the prepubertal boy who represents the lowest endogenous oestrogen production.

The figures represent effective fractions (i.e. 10% of real fractions), to take into account the low bio-availability of the hormones absorbed orally.

Limitation or drawbacks of some hormones used on food animal

Consumer advocates and others have expressed concern about the safety of milk from rbST-treated cows. All milk contains natural bST that is produced by the cow. Milk from rbST-treated cows also contains the same amounts of injected rbST and no differences can be measured compared to untreated cows.

There are four forms of natural bST, and each has a chain of either 190 or 191 amino acids. The recombinant bST that is injected into cows has 191 amino acids. The biological activity of commercial rbST is identical to naturally produced bST.

Studies indicate that both natural bST produced by the cow and bST produced by recombinant DNA techniques are immediately broken down into inactive amino acids and peptides in the digestive tract when they are consumed by humans. In contrast, steroid hormones such as estrogens, progesterones, and anabolic steroids are smaller, ring-like structures that are absorbed from the digestive tract and are biologically active in humans. This is not the case with bST in milk, whether it is produced naturally by the cow or by recombinant DNA technology (Barbano and Lynch).

Studies show that bovine somatotropin is inactive in humans. During the 1950s, natural bST produced by cows was injected into children with growth defects in an attempt to encourage growth. There was no effect, probably because the bovine somatotropin protein molecule differs from human somatotropin (human growth hormone) by about 30 percent of the amino acid sequences.

Milk composition from bST-treated cows has been thoroughly investigated (Barbano and Lynch). The characteristics of milk from bST-treated cows are within the normal range of variation of milk from untreated cows. During the first 28 days of treatment, milk fat increases and milk protein decreases slightly. After longer treatment, cows adjust their nutrient intake and the normal balance is re-established. An increase in non-protein nitrogen and whey protein and a decrease in casein have been observed aft er long-term bST administration. This difference is not always significant, and the effect on cheese yield would probably be minor, if any. One study showed a slight increase in unsaturated compared to saturated fat. The difference was small, but suggested a healthier product from bST treatment (88). No differences in free fatty acids have been observed. Cholesterol levels are in the range of normal milk composition. Insulin-like growth factor I increases by up to two-fold in milk from treated cows, but it is still well within the range for both bovine and human milk. No differences in flavor have been found (99).

The potential economic effect of bST on the family dairy farm has generated heated debate. The Animal Health Institute, an organization of drug and vaccine manufacturers, maintains that the use of bST will be of equal value to any size farm (Milligan). They contend that use of the product will favor the good dairy manager, regardless of farm size.

Estimates of the effect of bST on dairy production have probably been exaggerated. The United States Department of Agriculture estimates that the use of bST could lead to a 2 to 5 percent increase in national milk production within five years, or about the increase seen yearly without the use of bST (98). This increase would be in addition to the normal milk production increase per cow.

In most dairy herds, bST will not be used in cows until they have been in lactation for about 100 days. It will not be used in cows with chronic health or fertility problems. It is expected that bST will be used less in heifers than in adult cows. If 50 percent of farmers adopt the use of bST, and it is used in 60 percent of the lactation days per user herd, milk production will increase about 3.5 percent (assuming an average per cow production increase of 15 percent).

Many well-managed dairy herds increase per cow production more than this on an annual basis by using improved management and genetics. For most herds, a farmer who requests a thorough herd analysis by a competent nutritionist and veterinarian and then follows their recommendations will achieve a larger increase in milk production than by using bST alone (102) Generally these are some limitation it has on the health of cow itself among others evidence of welfare problems in dairy cows, for instance more than 50 cases of foot disorders and more than 40 cases of mastitis per 100 dairy cows can typically occur in Europe per year. Some of these animals and others in the herd may have reproductive disorders and other production related diseases (100). There is clear evidence from several countries of significant positive associations between milk yield and mastitis, foot disorders, reproductive disorders and other production related diseases.

Residues in edible tissues of hormone-treated animals

Much work has been devoted to the development of sensitive methods of detecting hormone residues in meat from hormone-treated animals. As regards compounds given orally, it should in principle be possible to realize claims of zero-tolerance residue levels, by selecting the proper withdrawal time. During recent years, the use of implants has, however, gained in importance. While removable implants have been tested in steers, with no decrease in performance when withdrawn 32 and 39 days before slaughter (99), the wide use of non-removable implants makes residue studies important. Determination of normal levels of endogenously produced natural hormones is also important, to enable risk evaluation to be carried out in realistic terms.

Several residue studies have been made of synthetic as well as natural compounds, mainly in cattle. When regulations governing dose, sites of implantation and timing in relation to slaughter are adhered to, residue levels of DES (88, 95, 96, 97, and 98), hexoestrol (100) and oestradiol-17β (102, 101) in edible tissues have generally been in the lower ppb to the ppt range, i.e. from a few ng/g down to some hundred pg/g of tissue. In the latter case there was almost complete overlap between values for untreated and treated steers after 105 days (107). Zeranol implants have so far not left detectable residues in edible tissue (99, 100, and 101).

Most studies of androgens have concentrated on TBA. The ester being rapidly hydrolyzed, measurements of residues have been limited to the free compound and/or its major metabolite. Results based on radio-immunoassay of extracts or on radioactivity measurements (88, 102, 13, 16, 10, 101, and 22) have indicated levels in edible tissue of the order of 1 ppb or below. In a recent study using implants containing tritiated TBA in heifers, it was found that when slaughter took place 60 days after implantation, the major proportion of tritium-containing residues was not extractable with organic solvents.

In muscle, 95.5%, in liver 94.4%, in kidney 98.8% and in fat 59.1% of the radioactivity remained in the aqueous phase, not quantifiable by radio-immunoassay. This suggests that the major part of the residues after TBA implantation occurs in a non-extractable, possible covalently bound form in tissues (23). Residue levels of gestagens have been also measured, in connection with their use as growth stimulants. Residues of melengestrol acetate used as a feed additive in daily doses of 0.25 to 0.50 mg per head have consistently been below the sensitivity levels of the methods used (i.e., below 10 ppb in fat, liver, muscle and kidney), whether or not the compound was withdrawn 48 hrs before slaughter (24).

Recommendation

Hormones are chemicals that are produced naturally in the bodies of all animals, including humans. They are chemical messages released into the blood by hormone producing organs that travel to and affect different parts of the body. Hormones may be produced in small amounts, but they control important body functions such as growth, development and reproduction. Hormones can have different chemistry. They can be steroids or proteins. Steroid hormones are active in the body when eaten.

For example, birth control pills are steroid hormones and can be taken orally. In contrast, protein hormones are broken down in the stomach, and lose their ability to act in the body when eaten. Therefore, ordinarily, protein hormones need to be injected into the body to have an effect. For example, insulin is a protein hormone. Diabetic patients need to be injected with insulin for treatment. Certain hormones can make young animals gain weight faster. They help reduce the waiting time and the amount of feed eaten by an animal before slaughter in meat industries. In dairy cows, hormones can be used to increase milk production. Thus, hormones can increase the profitability of the meat and dairy industries. There are six different kinds of steroid hormones that are currently approved by FDA for use in food production in the US: estradiol, progesterone, testosterone, zeranol, trenbolone acetate, and melengestrol acetate. Estradiol and progesterone are natural female sex hormones; testosterone is the natural male sex hormone; zeranol, trenbolone acetate and melengesterol acetate are synthetic growth promoters (hormone-like chemicals that can make animals grow faster). Currently, federal regulations allow these hormones to be used on growing cattle and sheep, but not on poultry (chickens, turkeys, and ducks) or hogs (pigs).

The above hormones are not as useful in increasing weight gain of poultry or hogs. As mentioned earlier, FDA allows the use of the protein hormone rbGH to increase milk production in dairy cattle. This protein hormone is not used on beef cattle. Dairy cattle may be injected under the skin with rbGH. This hormone is available in packages of single dose injections to reduce chances of accidental overdose.

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