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Steroid Hormones in Food Producing Animals: Regulatory Situation in Europe

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1. Introduction

Hormones are chemicals produced by animals to co-ordinate their physiological activities. They act as messengers, produced in and released from one kind of tissue to gradually stimulate or inhibit some process in a different tissue over a long period.

Steroid hormones fulfill an important role at different stages of mammalian development comprising prenatal development, growth, reproduction and sexual and social behavior.

The importance of individual hormones varies between sexes and age and a disruption of the endocrine equilibrium may result in multiple biological effects.

One hormone can have multiple actions, e.g. the male hormone testosterone controls many processes from the development of the foetus, to libido in the adult. Alternatively, one function may be controlled by multiple hormones, e.g. the menstrual cycle involves oestradiol, progesterone, follicle-stimulating hormone and luteinising hormone.

Hormones produced by the bodies of humans and animals are called endogenous or natural hormones. Compounds chemically synthesised to mimic the effect of natural hormones are called synthetic or xenobiotic hormones.

Hormones are vital in normal development, maturation and physiological functioning of many vital organs and processes in the body. However, like any other chemicals of natural or synthetic origin, hormones may be toxic to living organisms under certain circumstances. The toxicity may be due to an excess of its normal ('physiological') action. This may be the result of excessive exposure to the substance, for example following absorption of a large dose, or because the physicochemical nature of the substance gives it greater or more prolonged activity of the same type, or because the hormonal action occurs at an abnormal time during development or adult life, or is an action on an organism of the inappropriate sex. Hormones, like other chemicals, may also exert direct toxic actions not related to their endocrine ('physiological') effects.

Due to the obvious ability to improve weight gain and feed efficiency in meat producing animals, natural hormones and/or the synthetic surrogates have been used in agricultural practice for several decades (table 1).

Substances	Form	Main use - Animals
Oestrogens alone:		
DES	Feed additive	Steers, heifers
DES	Implant	Steers
DES	Oil solution	Veal calves
Hexoestrol	Implant	Steers, sheep, calves, poultry
Zeranol	Implant	Steers, sheep
Gestagens alone:		
Melengestrol acetate		Heifers
Androgens alone:		
TBA	Implant	Heifers, culled cows
Combined preparations:		
DES and Testosterone	Implant	Calves
DES and Methyl-testosterone	Feed additive	Swine
Hexoestrol and TBA	Implant	Steers
Zeranol and TBA	Implant	Steers
Oestradiol-17 β and TBA	Implant	Bulls, steers, calves, sheep
Oestradiol-17 β benzoate and testosterone propionate	Implant	Heifers, calves
Oestradiol-17 β benzoate and progesterone	Implant	Steers

Table 1. Hormonally-active substance used in animal production (by <http://www.fao.org/DOCREP/004/X6533E/X6533E01.htm>, modified)

Implanting hormonal growth promoters is currently widespread in the beef cattle industry of many non-EU countries for the better performance in growth and improvement of feed efficiency. These hormonal implants may enhance growth during suckling, growing and finishing stages of production (Mader, 1997; Platter *et al.*, 2003).

Growth hormones are implanted under the skin (usually behind the ear) of the animal in the form of depot capsules, where they release a specific dose of hormones over a fixed period of time.

The five hormone types most widely used in meat production include three natural hormones, oestradiol 17- β , testosterone, and progesterone, and two synthetic substances, trenbolone and zeranol.

Oestradiol 17- β has oestrogenic action (i.e. responsible for female characteristics); testosterone has androgenic action (i.e. responsible for male characteristics); and progesterone has gestagenic action (i.e. responsible for maintaining pregnancy). The other two hormones, as aforesaid, mimic the biological activity of the natural hormones: trenbolone mimics the action of testosterone, and zeranol mimics oestradiol 17- β .

1.1 Hormonally active substances

1.1.1 Oestradiol 17- β

Oestradiol 17- β is the most active of the female sex hormones synthesized and secreted mainly by the ovary, the adrenals and the testis.

Oestradiol is synthesized and secreted in early stages of embryogenesis and has an active role in the normal development of the female sex accessories during the lifetime of females.

It has been used to induce parturition (birth) especially in sheep, a species in which an associated oestradiol-induced increase in mothering ability has also been recorded (Poindron, 2005).

In non-pregnant animals, oestradiol has been used clinically to increase uterine contractions and cervical softening for the expulsion of unwanted uterine contents in the absence of a corpus luteum (i.e. to remove a dead fetus or infected material especially in cattle) (Elmore, 1992; Pepper & Dobson, 1987; Sheldon & Noakes, 1998).

Oestradiol has been used in the past in turkeys and other poultry to castrate young birds. Implants would be placed subcutaneously at 5-6 weeks of age, or in slightly older birds, but certainly 4 weeks before killing. Alternatively, preparations were available as feed-additives. This approach is not now used in Europe although it was used in slower growing Spanish breeds. There are very few reproductive problems in rabbits.

Fetal mummifications and macerations occur, as do endometritis and pyometra but treatment with oestradiol has not been reported (Flecknell, 2000).

In fish, administration of oestradiol at first-fry feeding (approximately 40-70 days of age depending on species) will induce ovarian development and female characteristics in salmonids, flat-fish and eels (Shepherd & Bromage, 1988). Sex-control in this way depresses or inhibits maturation to ensure that metabolism is channelled into body growth (i.e., more saleable flesh). However, this approach is no longer commercially adopted.

Another use of very low doses of oestradiol is as a growth promoter via appetite stimulating and increased food-conversion properties. Occasionally in the past, this approach has been taken to advance the onset of puberty and thus alleviate potential gynaecological problems in slower maturing species. However, as use of hormonal growth promoters is prohibited within the European Union¹.

1.1.2 Testosterone

Testosterone and its more active metabolite, 5 α -dihydrotestosterone (DHT), are the main sex hormones secreted by males. Testosterone is responsible for the early development, and the appearance and maintenance of male secondary sex accessory organs (prostate, secretory glands, penis size, etc.) during adulthood. Testosterone secretion is also affected by the complex interaction among all endocrine glands, especially with those in the brain.

Testosterone is metabolized and as a result, metabolites of different activity are generated. Some of these metabolites play a more active role in certain organs than in others.

The actions of both testosterone and DHT are mediated through their high affinity and high specificity binding and activation of an intracellular protein, the androgen receptor (AR). This AR protein is a member of the steroid hormone superfamily. The ligand-activated androgen receptor mediates its effects on cell growth and differentiation through the

¹ See the following paragraph: Background of the European Union legislation

activation and/or suppression of specific gene transcription in target organs. Androgen receptors are detected in tissues of females, as well as males. The presence of this receptor in organs such as the ovary indicates significant activity of androgens in both sexes. Furthermore, the androgen receptor is thought to be involved in ovarian tumorigenesis, as it has been detected in 67 percent of ovarian tumors. Although current information indicates the presence of only a single androgen receptor, it is known that different subsets of genes may be activated by either testosterone or DHT (Chang *et al.*, 1995).

In animals, testosterone or testosterone propionate, alone or in combination with other hormonally active substances, is used primarily to improve the rate of weight gain and feed efficiency. This effect is most likely a consequence of the anabolic action of androgens.

1.1.3 Progesterone

Progesterone is synthesized and secreted mainly by the corpus luteum in the ovary of cycling females, and, during pregnancy, by the placenta.

As all hormones, progesterone synthesis and secretion is regulated by a series of positive and negative feedback mechanisms in which polypeptidic hormones secreted by the brain (hypothalamus, pituitary) affect circulating progesterone levels.

Progesterone and synthetic progestins are used pharmacologically in women in conjunction with ovulation stimulation drugs as well as during early pregnancy in cases of luteal phase dysfunction. Although results have been conflicting, some studies find an association between pregnancy-related intake of progestins and increased risk of hypospadias (congenital malformation of the urethral opening on the penis) in the male offspring (Carmichael *et al.*, 2005). It should however be noted that this was observed in relation to pharmacological doses of progestins, and as progesterone levels are normally high during pregnancy, minor additional exogenous progestagenic activity would presumably be without significant effects in the presence of a high endogenous activity, unless the synthetic progestins act at different sites and by different mechanisms. In contrast, serum levels of progestins in children and postmenopausal women are very low. Data on effects of progesterone in the prepubertal child are scarce and no new data have been identified. Likewise, no animal studies on the effects of progesterone during the postnatal development have been published recently.

It is well established that progesterone not only serves as the precursor of all the major steroid hormones (androgens, oestrogens, corticosteroids) in the gonads and adrenals, but also is converted into one or more metabolites by most tissues in the body (Wiebe, 2006).

1.1.4 Trenbolone acetate

Trenbolone acetate (TBA) is a synthetic steroid with an anabolic potency that may exceed that of testosterone. It is a prodrug that converts into its active form 17 β -trenbolone, which isomerises into 17 α -trenbolone.

17 β -trenbolone is the major form occurring in muscle tissue, whereas the 17 α -epimer is the major metabolite occurring in liver and in the excreta including bile. It is assumed to exert

its anabolic action via interaction with androgen and glucocorticoid receptors (Danhaive and Rousseau, 1986, 1988). Experiments with cattle tissues have shown that 17 β -trenbolone binds to the androgen receptor with similar affinity as dihydrotestosterone. It also binds to the progesterone receptor with an affinity that exceeds that of progesterone. The other metabolites of TBA, including 17 α -trenbolone (17 α -hydroxy-estra-4,9,11-trien-3-one) and TBO (estra-4,9,11-triene-3,17-dione) show a significantly lower binding affinity to both types of receptors (Bauer *et al.*, 2000).

Reports regarding the (mis)use of TBA as an anabolic agent in sports people describe several adverse effects, including liver cell injury with an increase in liver-specific enzymes in serum, cholestatic jaundice, peliosis hepatitis and various neoplastic lesions. Moreover, decreased endogenous testosterone production and spermatogenesis, oligospermia and testicular atrophy may be associated with the repeated use of TBA as anabolic (Bahrke and Yesalis, 2004; Maravelias *et al.*, 2005).

1.1.5 Zeranol

Zeranol is derived from the naturally occurring mycoestrogen zearalenone, and is a potent oestrogen receptor agonist *in vivo* and *in vitro* (Leffers *et al.*, 2001; Le Guevel and Pakdel, 2001; Takemura *et al.*, 2007; Yuri *et al.*, 2006). Its actions resemble those of oestradiol. (Leffers *et al.*, 2001).

Zeranol stimulates the proliferation of ER-dependent cell proliferation in MCF-7 human breast cancer cells (which are widely used in the assessment of estrogenic activity) and in transfected cells (Leffers *et al.*, 2001; Le Guevel and Pakdel, 2001; Liu and Ling, 2004).

It is used alone or in combination with TBA as a hormonal growth promoter in various products.

2. Background of the European Union legislation

The use of hormonal growth promoters in food-producing animals has been a sensitive issue of debate in the EU and elsewhere for several decades.

Prior to 1981, the EC had no universal policy on the use of growth promoting hormones in meat animals.

The use of hormones had been banned in Italy since 1961, in Denmark since 1963, and in Germany since 1977. Belgium and Greece had never permitted the use of hormones for fattening purposes. However, Spain, the United Kingdom, France and Netherlands permitted the use of most hormones for speeding growth in beef cattle².

The move to impose a Europe wide ban was spurred by the worrying discovery in 1977 of breast enlargement in girls and boys attending a school in Milan (Italy) (Scaglioni *et al.*, 1978). Although oestrogen contamination was not detected when samples of school meals were tested, an uncontrolled supply of poultry and beef was hypothesized as being the cause of this outbreak (Fara *et al.*, 1979).

² See <http://www.fao.org/DOCREP/004/X6533E/X6533E03.htm#refeestr> Accessed August 19, 2011.

In 1980 the discovery of 30,000 jars of baby food containing dethylstilboestrol, commonly known as DES, contaminated French veal was reported. European consumer organizations called for a boycott of veal, and the market for veal was severely affected. On September 20, 1980, the EC Council of Agriculture Ministers adopted a declaration in favor of a ban on the use of oestrogen and endorsed the principle of greater harmonization of legislation on veterinary medicines and of greater control on animal rearing, both at the production and slaughtering stages.

On October 31, 1980, the EC Commission proposed even more rigorous legislation that would ban the use of all hormone products in meat production, except for therapeutic purposes³. This proposal was expanded later by documents COM(80)920 and COM(80)922, presented on 6 January 1981. These allowed for the controlled use for therapeutic and zootechnical purposes of three natural hormone products, and introduced a number of control measures on the production and handling of such products, together with proposals on the testing of animals. Discussions in the European Parliament revealed that three EC member States (Belgium, Ireland and the United Kingdom) favored the use of some hormones to promote growth in meat animals, and Ireland and the United Kingdom also argued for the retention of the synthetic hormones, trenbolone and zeranol. Third countries, including The United States, Argentina, Australia, Canada, New Zealand and South Africa raised concerns concerning the potential impact of a ban on their exports to European Communities⁴.

Subsequently, the European Council adopted its first directive on the hormones issues in July 1981 (Directive 81/602/EEC)⁵.

Directive 81/602/EEC prohibits the administering to farm animals of substances having a *thyrostatic action* or substances having an *oestrogenic, androgenic or gestagenic* action; the placing on the market or slaughtering of farm animals to which these substances have been administered; the placing on the market of meat from such animals; the processing of meat from such animals and the placing on the market of meat products prepared from or with such meat. The Directive provides two exceptions to the prohibition: one exception is provided for substances with an oestrogenic, androgenic or gestagenic action when they are used for therapeutic or zootechnical purposes and administered by a veterinarian or under a veterinarian's responsibility. The other exception was for oestradiol-17 β , progesterone, testosterone, TBA and zeranol - when they were used for growth promotion purposes and their use was governed according to the individual regulatory schemes maintained by EC member States. This exception was made pending an examination of the effects of these hormones on the health of consumers and the adoption of an EC rule. EC member States are obliged to apply their regulatory schemes to imports from third countries in a manner not more favorable than that applied to intra-EC trade.

³ Commission of the European Communities 1980. Proposal for a Council Regulation (EEC) Concerning the Uses of Substances with a Hormonal Action and those having a Thyrostatic Action in Domestic Animals. COM (80) 614, 31 October, Brussels: Commission of the European Communities.

⁴ WTO, 1997. EC measures concerning meat and meat products (hormones), complaint by the United States. Report of the WTO Panel, WT/DS26/R/USA, August 18, 1997, 2: 26-28. Available at <http://www.sice.oas.org/dispute/wto/horm-us.asp>, Accessed August 20, 2011.

⁵ Council Directive 81/602/EEC of 31 July 1981 concerning the prohibition of certain substances having a hormonal action and of any substances having a thyrostatic action. Official Journal of the European Communities, L Series, No. 222, pp. 32-33.

The relevant international organizations - FAO, WHO, OIE and Codex - started to seriously examine the safety of these hormones in meat production only during the 1980s.

The first substantive scientific report had been published by OIE in 1983. The Joint FAO/WHO Expert Committee on Food Additives (JECFA)⁶ had discussed and issued a scientific report on these hormones only in 1988⁷.

There were two other international reports comprising collective scientific work: the 1984 Scientific Report published by the European Commission (based on the Lamming Report⁸) and the Proceedings of the 1995 EC Scientific Conference⁹.

⁶ It is an independent expert group which deals with specific commodity issues or general health and safety matters related to food. The JECFA focuses on the scientific evaluation of a veterinary drug and does not consider government policies and politics.

⁷ The JECFA Report, on which the Codex standard for zeranol is based, noted that zeranol was a weak oestrogen which mimicked the action of oestradiol-17 β . The report concluded that the toxic (*in casu* tumorigenic) effect of zeranol is associated with its hormonal (i.e. oestrogenic) properties and that an ADI could thus be established on the basis of a no-hormonal-effect level. Adopting what it considered to be a conservative approach by using as a basis studies on ovariectomized female cynomolgus monkeys (highly sensitive to oestrogenic substances) and using a safety factor of 100, JECFA set an ADI for human beings of 0-0.5 $\mu\text{g}/\text{kg}$ of body weight. For a 70 kg person consuming 500 g of meat daily over an entire lifetime, the maximum permissible or safe level of zeranol residues in meat would then, according to JECFA, be 70 $\mu\text{g}/\text{kg}$ of edible tissue. However, the report noted that when zeranol is administered to cattle according to good animal husbandry practice, the maximum mean residue levels did not exceed 0.2 $\mu\text{g}/\text{kg}$ in muscle, 10 $\mu\text{g}/\text{kg}$ in liver, 2 $\mu\text{g}/\text{kg}$ in kidney, and 0.3 $\mu\text{g}/\text{kg}$ in fat at any time after implantation. These residue levels obtained on the basis of good animal husbandry practice are thus below the maximum permissible level of 70 $\mu\text{g}/\text{kg}$. However, in order to set a level which is detectable by routine residue analysis methods, the Codex MRL was increased to 2 $\mu\text{g}/\text{kg}$ in muscle and set at 10 $\mu\text{g}/\text{kg}$ in liver.

With respect to trenbolone acetate (TBA), the Report concluded that its potential toxic effects only arise as a consequence of its hormonal activity. The report further concluded that, therefore, an ADI could be established on the basis of a no-hormonal-effect level. Adopting what it considered to be a conservative approach by using as a basis studies on castrated male rhesus macaque monkeys (which are highly sensitive to compounds with antigonadotropic activity) and pigs (which are a sensitive model for assessing hormonal effects of TBA) and using a safety factor of 100, JECFA later set an ADI for human beings of 0-0.02 $\mu\text{g}/\text{kg}$ of body weight (34th JECFA Report of 1989). The maximum ADI for a 60 kg person would thus be 1.2 μg of TBA residues. JECFA then set MRL's for -trenbolone in muscle and -trenbolone in liver of 2 $\mu\text{g}/\text{kg}$ and 10 $\mu\text{g}/\text{kg}$, respectively, based on average residue levels in heifers at 15-30 days after implantation of 300 mg TBA, noting that concentrations would be even lower at proposed GPVD. According to JECFA, the MRL's thus obtained on the basis of conservative estimates should not exceed the Codex ADI or safe level at any time after implantation of the drug, that is, irrespective of the withdrawal period used.

⁸ The Lamming Group's interim report, issued in September 1982, found that the three natural hormones (oestradiol-17 β , testosterone and progesterone) "would not present any harmful effects to the health of the consumer when used under the appropriate conditions as growth promoters in farm animals".

For the findings of the scientific working group, see Lamming, G.E., Ballarini, G., Baulieu, E.E. *et al.*, (1987). Scientific Report on Anabolic Agents in Animal Production. *The Veterinary Record*, 121, at 389-392.

⁹ The 1995 EC Scientific Conference on Growth Promotion in Meat Production concluded that: "At present, there is no evidence for possible health risks to the consumer due to the use of natural sex hormones for growth promotion, since: Residue levels of these substances measured in meat of treated animals fall within the physiological range observed in meat of comparable untreated animals. The daily production of sex hormones by humans is much higher than the amounts possibly consumed from meat, even in the most sensitive humans (prepubertal children and menopausal women).

The European Communities stressed, however, that these reports did not constitute the entire body of scientific knowledge on the issue of safe use of these hormones for growth promotion. There were also important studies made by individual scientists, and other specialized institutions like the International Agency for Research on Cancer (IARC).

The EC Scientific Veterinary Committee gave its reaction to the Lamming Report on November 9, 1982, followed by the EC Scientific Committee for Animal Nutrition on November 17, 1982 and by the EC Scientific Committee for Food on February 4, 1983. These Committees supported the conclusions and recommendations of the Lamming Report, but stressed the need to lay down provisions regarding the establishment of proper programmes to control and monitor the use of anabolic agents with regard, in particular, to instructions for use, surveillance programmes and analysis methods. In January 1984, the Commission asked a group of experts within the EC Scientific Committee on Anabolic Agents to review the information on trenbolone and zeranol. On June 12, 1984, the Commission published a proposal (COM(84)295 final) for a Council Directive amending Directive 81/602/EEC, which envisaged the controlled use of the three natural hormones for growth promotion purposes and proposed re-examining the ban on the two synthetic hormones after their scientific evaluation had been completed. However, the European Parliament, the EC Economic and Social Committee and the EC Council of Ministers rejected the Commission's proposal.

The EC Commission amended its proposal accordingly and on December 31, 1985 the EC Council adopted Directive 85/649/EEC¹⁰. This Directive banned the use of all the substances concerned for growth promotion purposes and established more detailed provisions concerning authorized therapeutic uses. Its preamble began by emphasizing that differing rules on hormone use in different member countries had distorted trade in the European market and that "[...] these distortions of competition and barriers to trade must therefore be removed [...]".

The Directive was challenged in the European Court of Justice, which annulled it on procedural grounds. The proposals were re-introduced by the EC Commission and re-adopted by the EC Council as Council Directive 88/146/EEC on March 7, 1988¹¹. This Directive extends the prohibition imposed by Directive 81/602/EEC to the administration to farm animals of trenbolone acetate and zeranol for any purpose, and oestradiol-17 β ,

Due to an extensive first-pass metabolism, the bioavailability of ingested hormones is low, thus providing a further safety margin".

With regard to the synthetic hormones, zeranol and trenbolone, the 1995 EC Scientific Conference concluded that: "At the doses needed for growth promotion, residue levels [of trenbolone and zeranol] are well below the levels regarded as safe (the MRLs). There are, at present, no indications of a possible human health risk from the low levels of covalently-bound residues of trenbolone".

See Assessment of Health Risk - Working Group II", in 1995 EC Scientific Conference Proceedings, pp. 20-21.

¹⁰ Council Directive 85/649/EEC of 31 December 1985 prohibiting the use in livestock farming of certain substances having hormonal action. *Official Journal of the European Communities*, L Series, No. 382, pp. 228-231.

¹¹ Council Directive 88/146/EEC of 7 March 1988 prohibiting the use in livestock farming of certain substances having a hormonal action. *Official Journal of the European Union*, L Series, No. 70, pp. 16-18.

testosterone and progesterone for fattening purposes. However, the Directive maintains the permission to administer these three natural hormones to animals for therapeutic and zootechnical purposes under prescribed conditions; in particular, therapeutic treatment is defined to mean the administering to an individual animal of any of the substances which are authorized to treat a fertility problem diagnosed on examination by a veterinarian. The products which are used for therapeutic treatment may be administered only by a veterinarian, in the form of an injection (to the exclusion of implantation) to farm animals which have been clearly identified. Such treatment must be registered by the veterinarian and these animals may not be slaughtered before expiry of the period fixed. In the case of animals at the end of their reproductive career, the treatments are prohibited from being administered during the fattening period following the end of their breeding life. Article 4 of Directive 88/146/EEC explicitly requires that undertakings in the EC member States producing the prohibited hormones, those companies authorized to market these hormones for whatever purposes and undertakings producing pharmaceutical and veterinary products based on those substances, must keep a detailed register recording (in chronological order) the quantities produced or acquired and those sold or used for the production of pharmaceutical and veterinary products. The importation from third countries of animals and meat from animals to which have been administered substances with thyrostatic, oestrogenic, androgenic or gestagenic action is prohibited. However, under certain conditions, Article 7 of Directive 88/146/EEC allows trade in those animals and meat from those animals treated for therapeutic or zootechnical purposes, including imports from third countries.

Directive 88/299/EEC¹² lays down the conditions for applying the derogations, provided for in Article 7 of Directive 88/146/EEC, from the prohibition on trade in certain categories of animals and their meat. The first derogation of the Directive requires EC member States to authorize trade in animals intended for reproduction and reproductive animals at the end of their career (and of meat of such animals) which, during their reproductive career, have undergone one of two categories of treatments. The first category is therapeutic treatment with one of the following substances: oestradiol-17 β , testosterone and progesterone; and those derivatives which readily yield the parent compound on hydrolysis after absorption at the site of application which appear in a list of approved products. The second category is the administration of substances having an oestrogenic, androgenic or gestagenic action for synchronization of oestrus, termination of unwanted gestation, the improvement of fertility and the preparation of donors and recipients for the implantation of embryos, provided that the products in which they are contained appear on a list of approved products and with the respect of strict conditions of use concerning, in particular, the respect of the withdrawal period, the monitoring of those conditions of use and of the means of identification of the animals. In addition, Articles 3 and 4 of this Directive provide that trade between the EC member States of the European Communities in animals intended for reproduction and reproductive animals and meat from such animals is allowed only if all the conditions laid down in the Directive are respected, in particular as regards the waiting period and the requirement that animals have not received any of the above treatments with any of the

¹² Council Directive 88/299/EEC of 17 May 1988 on trade in animals treated with certain substances having a hormonal action and their meat, as referred to in Article 7 of Directive 88/146/EEC. *Official Journal of the European Union*, Series L, No. 87, pp. 36-38.

above substances during the fattening period following the end of their breeding life. The EC stamp may be affixed to the meat only if the waiting time ended before the animals are slaughtered. The second derogation in Directive 88/299/EEC allows imports from third countries of treated animals and meat of such animals under guarantees equivalent to those for domestic animals and meat.

Following reports of significant use of illegal growth-promoting hormonal substances in a number of EC member States, on September 26, 1988 the European Parliament established a Committee of Enquiry into the Problem of Quality in the Meat Sector. The conclusions of this Committee were published in a document known as the "Pimenta Report", which recognized the ban on the use of hormones¹³. On March 29, 1989, the European Parliament adopted its recommendations to maintain and expand the ban.

The European Parliament adopted another report on the issue of use of hormones for animal growth promotion, the "Collins Report" of February 7, 1989¹⁴. This report argued that: "Current licensing systems for the regulation of veterinary medicines (including at present, growth promoting products) require that a new product satisfy three criteria: safety, quality and efficacy. These criteria may well be satisfactory for therapeutic drugs. They are by no means sufficient for growth promoting products. For the latter it is proposed here that the Community's veterinary medicine licensing system be adapted to include a "fourth hurdle", entailing an objective socio-economic and environmental impact assessment". In the Commission's July 1988 draft proposals for the reform of veterinary medicine licensing in the Community this idea was accepted in principle. The final version of the proposals (December 1988) does not include this concept. It is clear, however, that the social, agricultural and environmental implications of the use of growth and yield promoting pharmaceuticals require a licensing system somewhat different from that which exists for these products when used for therapeutic purposes.

Directive 96/22/EC¹⁵ replaces Directives 81/602/EEC, 88/146/EEC and 88/299/EEC. It maintains the prohibition on the use of these hormones for growth promotion purposes; extends the prohibition on the use of beta-agonists; restricts the use of the hormones at issue for therapeutic or zootechnical purposes, reinforcing in particular the role of the

¹³ The scientific conclusions regarding the use of natural hormones rested upon strict conditions of use which it believed could not in reality be attained. The Committee was of the opinion that use of the natural/nature-identical hormones carries the risk of inexperienced application, incorrect dosage and unsupervised injection which could pose a risk to the animal and the consumer, and also noted doubts with regard to long-term cumulative and interactive potential carcinogenicity. In addition, the Committee believed that proven necessity and socio-economic desirability should be criteria of acceptability for the use of (bio)chemical growth promoters in animal-rearing. In brief, the essential findings of the Pimenta Report were that the prohibition of hormonal substances for non-therapeutic (i.e. growth-promoting) purposes must be maintained and expanded.

¹⁴ European Parliament, Committee on the Environment, Public Health and Consumer Protection, Report on "The USA's Refusal to comply with Community legislation on slaughterhouses and hormones and the consequences of this refusal", EP 128 381/B, 7 February 1989, named after its reporter Mr. Collins, MEP.

¹⁵ Council Directive 96/22/EC of 29 April 1996 concerning the prohibition on the use in stockfarming of certain substances having a hormonal or thyrostatic action and of beta-agonists, and repealing Directives 81/609/EEC, 88/146/ECC and 88/299/EEC. Official Journal of the European Union, L Series, No. 125, pp. 5-9.

veterinarian; and reinforces the provisions on control and testing. Penalties and sanctions in case of violations are to be increased where checks detect the presence of prohibited substances or products or residues of substances administered illegally.

In Directive 96/23/EC measures are specified to control the ban¹⁶ (Passantino *et al.*, 2001). The control should be performed by special, dedicated institutes. Analysis of the samples taken is performed by routine or field laboratories (RFLs). In each member state the RFLs are coordinated and controlled by at least one national reference laboratory (NRL) designated by the national government.

Finally, the NRLs are supported, advised and controlled by four community reference laboratories (CRLs), which were designated in 1991 by the EU and implemented in 1993 (Stephany *et al.*, 1994). Annually a residue monitoring programme must be made in which the results of the controls of the previous year and the targets for control in the new year are given. People working on the farms and veterinarians are made co-responsible for the control of the ban. Samples can be taken at production plants for banned substances and animal feeds, and at farms, slaughterhouses and butchers. There should be at least one national reference laboratory for every banned substance. Indications should be available for sampling and analysis. The main sanction on the use of banned substances is the destruction of the positive animals. The farmer has to pay for the additional controls that are performed. When meat is imported from third countries, it must also be controlled. When the products give a positive result the European Commission should be informed and additional controls are indicated. Eventually this could lead to a ban on the import from a certain country.

It is important underlines that the Opinion of the Scientific Committee on Veterinary Measures relating to Public Health (SCVPH)¹⁷ of 30 April 1999 on potential adverse effects to human

¹⁶ A principal objective of Council Directive 96/23/EC is to detect illegal use of substances in animal production as well as detecting the misuse of authorized veterinary medicinal products. The Directive lays down measures requiring European Member States to monitor the substances and their residues in both live animals and animal products, listed in Annex I to the Directive.

In particular, this directive describes guidelines for residue control and divides all pharmacologically active substances into two groups:

- Group A compounds, which comprise prohibited substances (listed in the Directive 96/22/EC and in Annex IV of the Regulation 2377/90/EC);
- Group B compounds, which comprise substances with final and provisional MRLs (listed in Annexes I and III of the Regulation 2377/90/EC). See, Council Directive 96/23/EC of 29 April 1996 on measures to monitor certain substances and residues thereof in live animals and animal products and repealing Directives 85/358/EEC and 86/469/EEC and Decisions 89/187/EEC and 91/664/EEC. Official Journal of the European Union, L Series, No. 125, pp. 10-32.

¹⁷ The United States and Canada contested the prohibition imposed by the European Communities on the import from third countries of treated animals with the hormones and, in 1997, a panel of the World Trade Organisation (WTO) ruled that the measure was not in line with the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS). The EU appealed against this ruling and, in 1998, the WTO Appellate Body reversed most of the findings of the panel. The WTO Appellate Body only upheld the finding that prohibition of imports of meat from hormone-treated animals to the EU did not comply with the requirement that such a measure should be based on a relevant assessment of the risks to human health. In reaction to these findings, the EU carried out a complementary risk assessment and mandated the Scientific Committee on Veterinary measures relating to Public Health (SCVPH) to evaluate the risks to human health from hormone residues in bovine meat and meat products treated with six hormones for growth promotion.

health from hormone residues in bovine meat and meat products (which was reviewed on 3 May 2000 and confirmed on 10 April 2002¹⁸) established that there is a substantial body of recent evidence suggesting that oestradiol 17 β has to be considered as a complete carcinogen, as it exerts both tumour-initiating and tumour-promoting effects, and that the data currently available do not make it possible to give a quantitative estimate of the risk to human health¹⁹.

In the light of the conclusions of the 1999, 2000, and 2002 Opinions, the European Communities adopted Directive 2003/74/EC²⁰, which amends Directive 96/22/EC in relation to the prohibition permanently of the use of hormones in stockfarming.

Directive 2003/74/EC maintains the permanent prohibition of the placing on the market of meat and meat products from animals treated with oestradiol-17 β for growth-promotion purposes originally contained in Directive 96/22/EC²¹.

¹⁸ The EU Scientific Committee confirmed that the use of hormones as growth promoters for cattle poses a potential health risk to consumers, following a review of 17 studies and other recent scientific data.

Subsequent to the adoption of the 1999 Opinion, additional scientific information was made available to the European Commission in the form of scientific studies conducted by: (i) the United Kingdom's Veterinary Products Committee sub-group on the 1999 Opinion (October 1999); (ii) the Committee for Veterinary Medicinal Products ("CVMP") of the European Union (a subcommittee of the European Medicines Agency (EMA)) (December 1999); and (iii) the Joint FAO/WHO Expert Committee on Food Additives ("JECFA") (February 2000). At the request of the European Commission, the SCVPH examined this scientific information and, on 3 May 2000, issued a review of its 1999 Opinion in which it declined to alter the conclusions contained therein (the "2000 Opinion").

On 10 April 2002, a second review of the 1999 Opinion was issued by the SCVPH (the "2002 Opinion") on the basis of more recent scientific data collected since the previous review. The scientific data reviewed by the SCVPH included the final results of all 17 studies that had been commissioned by the European Commission. Publishing its third opinion on the risks to human health from hormone residues in beef products, the SCVPH found no reason to change its previous opinions of 1999 and 2000.

See, Opinion of the Scientific Committee on Veterinary Measures relating to Public Health on "Assessment of potential risks to human health from hormone residues in bovine meat and meat products, adopted on 30 April 1999. Available at http://ec.europa.eu/food/fs/sc/scv/out21_en.pdf Accessed August 19, 2011.

See also Opinion of the Scientific Committee on Veterinary Measures relating to Public Health on "Review of specific documents relating to the SCVPH opinion of 30 April 1999 on the potential risks to human health from hormone residues in bovine meat and meat products", adopted on 3 May 2000, and on "Review of specific documents relating to the SCVPH opinion of 30 April 1999 and 3 May 2000 on the potential risks to human health from hormone residues in bovine meat and meat products", adopted on 10 April 2002. Available at http://ec.europa.eu/food/fs/sc/scv/out50_en.pdf Accessed August 19, 2011.

¹⁹ In this context, it is important underlines that Article 168 of the Treaty establishing the European Union (EU) states that a high level of human health protection shall be ensured in the definition and implementation of all EU policies and activities. A comprehensive body of EU legislation has been put in place to achieve this objective. All of this legislation is publicly available at <http://eur-lex.europa.eu/en/index.htm> Accessed August 23, 2011.

²⁰ Directive 2003/74/EC of the European Parliament and of the Council of 22 September 2003 amending Council Directive 96/22/EC concerning the prohibition on the use in stockfarming of certain substances having a hormonal or thyrostatic action and of beta-agonists. Official Journal of the European Union, L Series, No. 262, pp. 17-21.

In relation to the five other hormones (testosterone, progesterone, TBA, zeranol, and MGA) Directive 2003/74/EC continues to apply the prohibition contained in Directive 96/22/EC, but on a provisional basis²².

This Directive specifies that, even though the scientific information available showed the existence of risks associated with these substances, "the current state of knowledge does not make it possible to give a quantitative estimate of the risk to consumers"²³. Accordingly, the prohibition of these five hormones should apply "while the Community seeks more complete scientific information from any source, which could shed light and clarify the gaps in the present state of knowledge of these substances"²⁴.

On 27 October 2003, the European Communities notified the Dispute Settlement Body (DSB) of the adoption, publication, and entry into force of Directive 2003/74/EC, as well as the 1999, 2000, and 2002 Opinions, which it considered to be risk assessments that sufficiently justified the permanent and provisional import prohibitions under the *SPS Agreement* (Agreement on the Application of Sanitary and Phytosanitary Measures)²⁵.

The latter use has to be phased out by until 14 October 2006 and for the rest of the uses the Commission was to present a report in October 2005.

The report was presented on 11 October 2005 to Council and Parliament. It comes to the conclusion that the use of the alternative substances such as prostaglandins is already common.

Veterinarians predict an insignificant impact of future unavailability of oestradiol 17 β and its ester like derivatives on farmers and on animal welfare. It was moreover observed that the unavailability of oestradiol and its ester like derivatives would have minimal economic effect. This is because the incidence of fetal mummification and fetal maceration is low, and although the incidence of pyometra is higher, methods of prevention not involving use of oestradiol do exist and would be preferable.

Article 11a of Council Directive 96/22/EC as amended by Council Directive 2003/74/EC requires the presentation of a report on the necessity of the use of the hormone oestradiol 17 β in food animal production. A report concerning the availability of alternative veterinary medicinal products to those containing oestradiol 17 β or its ester-like derivatives for the treatment of fetal maceration or mummification in cattle, and for the treatment of pyometra prepared (later addressed as the Report) by an independent scientist has been presented by the Commission in October 2006²⁶. The Report concludes that oestradiol 17 β is not essential in food animal production.

²¹ Directive 2003/74/EC, *supra*, footnote 20, Recital 10 and Article 1 (amending Articles 2 and 3 of Directive 96/22/EC).

²² *Ibid.*

²³ Directive 2003/74/EC, *supra*, footnote 20, Recital 7.

²⁴ *Ibid.*, Recital 10.

²⁵ European Communities – Measures concerning meat and meat products (hormones), Communication from the European Communities, WT/DS26/22, WT/DS48/20, 28 October 2003. Available at http://trade.ec.europa.eu/doclib/docs/2003/november/tradoc_114641.pdf Accessed August 23, 2011.

²⁶ See, Report concerning the availability of alternative veterinary medicinal products to those containing oestradiol 17 β or its ester-like derivatives for the treatment of fetal maceration or

3. Situation in other countries

Whereas the EU has banned the use of all hormones, other countries do allow the use of steroid hormones and hormone-like substances in various combinations with the aim to improve weight gain and feed efficiency in livestock farming. Recommended application occurs in the form of small implants or devices, containing the active hormones, into the subcutaneous tissue of the ears. Both ears are completely discharged at slaughter²⁷ (Galbraith, 2002). Pharmaceutically, these implants represent slow-release devices, containing relatively large quantities of hormones, which are fractionally released over a period of several months.

In the United States²⁸, Canada, Australia, New Zealand and in some countries in South America, Asia and Africa the natural hormones - testosterone, 17 β -oestradiol and progesterone - and the (semi-) synthetic hormones trenbolone, zeranol and melengestrol acetate can be used to promote growth.

In particular, in the USA²⁹ five hormones are authorized as the active component of solid ear implants (17 β -estradiol - as such or as benzoate, testosterone - as such or as propionate,

mummification in cattle, and for the treatment of pyometra. Commission of the European Communities - SEC(2005) 1303 of 11.10.2005.

²⁷ See European Commission, 1999. Scientific Committee on Veterinary Measures relating to Public Health (SCVPH). Assessment of potential risks to human health from hormone residues in bovine meat and meat products. Available at http://europa.eu/comm/food/fs/sc/scv/out21_en.html Accessed August 23, 2011.

²⁸ The U.S. Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA) cooperate in regulating growth promotants for livestock. Both of these agencies maintain that hormones in beef from an implanted animal have no physiological significance for humans. All animal drug products are approved for safety and effectiveness under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.). Information on approved hormone products are at 21 CFR Parts 522, 556, and 558. FDA requirements for the review and approval of new animal drug applications is at <http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm123821.htm> Accessed August 26, 2011.

²⁹ The United States continues to maintain that U.S. beef from cattle treated with certain approved growth hormones pose no public health risk. Overall, the official U.S. position is that "there is a clear world-wide scientific consensus supporting the safety of these approved and licensed hormones when used according to good veterinary practice".

The United States claims that this position is supported by "scientific reviews of the six hormones, international standards pertaining to their use, and a longstanding history of administering the six hormones to cattle for growth promotion purposes". Accordingly, the United States claims that the use of these hormones as growth promoters in beef production is safe, when applied in accordance with good veterinary practices.

The United States has criticized the EU's scientific opinions for focusing on only one growth promotant, estradiol-17 β , and on its potential genotoxicity, while directing relatively little attention toward the other natural and synthetic hormones. The United States also claims that the "EU failed to use solid evaluative methods in their studies and completely disregarded the large body of evidence from epidemiological studies that indicate that estradiol does not contribute to any increased cancer risk and that meat from animals tested with estradiol is safe for consumers".

Regarding the EU's more recent reviews, the United States claims they fail to provide any new evidence that would call into question the findings and conclusions of other authoritative reviews.

More broadly, the United States also disputes whether the EU's scientific reviews serve as a risk assessment. The United States claims: "There has been no new risk assessment based on scientific information and reasoning presented by the EU," further claiming that the "17 studies" funded by the Commission beginning in 1998 were "not intended as a to serve as a risk assessment, but instead were

progesterone, trenbolone acetate and zeranol) and two hormones as feed additives: melengestrol acetate (MGA) for feedlot heifers³⁰ (Berende & Ruitenbergh, 1983; Meissonnier & Mitchell-Vigneron, 1983) and ractopamine for swine (Marchant Forde *et al.*, 2003).

As aforementioned, the hormone ban of the EU is currently the cause of a dispute between the EU and these third countries, led by the United States and Canada. The reason for this dispute is that those countries want to export meat to EU nations from animals treated with in their view acceptable hormones. In their opinion the EU blocks international trade on improper grounds and against international law.

The National Cattlemen's Beef Association (NCBA), the largest national group of cattle producers, has long opposed the EU's ban on imports of U.S. hormone-treated beef, claiming that the ban is scientifically unjustified and fails to satisfy the EU's WTO requirements under the SPS. Similar concerns have been expressed by other U.S. farm groups, including American Farm Bureau Federation (AFBF), the Animal Health Institute (AHI), and the American Meat Institute (AMI)³¹. Many trade analysts believe that the United States has a strong case against the hormone ban under WTO rules that require SPS restrictions to be based on risk assessment and to have a scientific justification. These various interest groups have continued to exert pressure on U.S. trade policy officials to hold to their position regarding the EU's meat hormone ban.

Recently, On May 13, 2009, following a series of negotiations, the United States and the EU signed a memorandum of understanding (MOU) implementing an agreement that could resolve this long standing dispute³². On July 13, 2009, the EC adopted regulations opening a tariff quota for imports of High Quality Beef, effective August 1, 2009³³

4. Existing community legislation

Currently Council Directive 2008/97/EC³⁴ has been published amending Council Directive 96/22/EC concerning the prohibition on the use in stock farming of certain substances

to fill in the gaps". Accordingly, the United States claims, the EU's 2003 update to its hormone ban is not in compliance with its WTO obligations and should be discontinued.

For more detailed discussion see USDA, Foreign Agriculture Service, Historic Overview and Chronology of EU's Hormone Ban, GAIN Report E23206, Nov. 7, 2003, available at <http://www.fas.usda.gov/gainfiles/200311/145986773.pdf> Accessed August 26, 2011; USDA, FAS, EU Presentation on Hormone Ban Directive (2003/74/EC), GAIN Report E23217, Nov. 13, 2003, available at <http://www.fas.usda.gov/gainfiles/200311/145986807.pdf> Accessed August 26, 2011.

³⁰ <http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm055436.htm> Accessed August 23, 2011.

³¹ See, "Coalition Statement on EU's Latest Pronouncement on Hormones," May 14, 2002 by AFBF, AHI, AMI, and NCBA, Available at <http://www.meatami.com/ht/d/sp/i/1482/pid/1482> Accessed August 23, 2011.

³² For other information, see WTO, European Communities – Measures Concerning Meat And Meat Products (Hormones), Joint Communication from the European Communities and the United States, WT/DS26/28, September 30, 2009; 74 Federal Register 40864, August 13, 2009; 74 Federal Register 48808, September 24, 2009; and USTR press releases.

³³ Council Regulations (EC) No 617/2009 of 13 July 2009 opening an autonomous tariff quota for imports of high-quality beef. Official Journal of the European Union, L series, No. 182, 1..

³⁴ Directive 2008/97/EC of the European Parliament and of the Council of 19 November 2008 amending Council Directive 96/22/EC concerning the prohibition on the use in stockfarming of certain substances

having a hormonal or thyreostatic action and of β -agonists, to exclude companion animals from the prohibition.

In fact, experience gained in particular with national residue plans submitted under Directive 96/23/EC has shown that the misuse of product presentations intended for pet animals does not play a role as a source of abuse or misuse. That is partly because it is economically unattractive to use presentations intended for pet animals for growth promotion in food-producing animals.

It was considered therefore appropriate to limit the scope of Directive 96/22/EC only to food-producing animals and withdraw the prohibition for pet animals, as well as to adjust the definition of therapeutic treatment.

5. Conclusions

The EU continues to maintain that “there is a lack of data on the type and amount of [growthpromoting hormone] residues in meat on which to make a quantitative exposure assessment” that would change the EU’s understanding of the “possible risks to human health” associated with hormone-treated meat and meat products. It claims that this position is supported by a series of commissioned research studies and scientific reviews conducted by the EU, although there has been no conclusive testing on the issue.

The most recent review, conducted in 2007 by the European Food Safety Authority (EFSA), cites evidence supporting that estradiol-17 β be considered as a carcinogen, and states that all six hormones may pose endocrine, developmental, immunological, neurobiological, immunotoxic, genotoxic, and carcinogenic effects, particularly for susceptible risk groups (such as prepubertal children). The toxicological and epidemiological data reviewed by the Commission panels do not allow a quantitative estimate of the risk, leading to the panel’s conclusions that no threshold levels can be defined for any of the six hormones

Based on this series of reviews, the Commission maintains that these reviews “reaffirmed public health concerns about the large scale use of hormones administered to cattle for growth promoting purposes,” and therefore “provided the scientific basis for community legislation not allowing the use of hormones for growth promoting purposes in the EU”.³⁵

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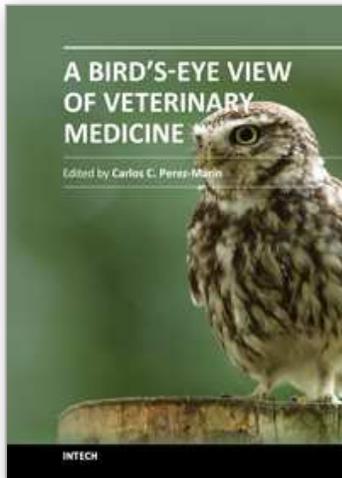
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³⁵ EFSA, “EFSA Concludes Review of New Scientific Data on Potential Risks to Human Health from Certain Hormone Residues in Beef,” Press Release dated July 18, 2007, Available at http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1178622723847.htm. Accessed August 26, 2011.

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Veterinary medicine is advancing at a very rapid pace, particularly given the breadth of the discipline. This book examines new developments covering a wide range of issues from health and welfare in livestock, pets, and wild animals to public health supervision and biomedical research. As well as containing reviews offering fresh insight into specific issues, this book includes a selection of scientific articles which help to chart the advance of this science. The book is divided into several sections. The opening chapters cover the veterinary profession and veterinary science in general, while later chapters look at specific aspects of applied veterinary medicine in pets and in livestock. Finally, research papers are grouped by specialisms with a view to exploring progress in areas such as organ transplantation, therapeutic use of natural substances, and the use of new diagnostic techniques for disease control. This book was produced during World Veterinary Year 2011, which marked the 250th anniversary of the veterinary profession. It provides a fittingly concise and enjoyable overview of the whole science of veterinary medicine.

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