COMMISSION OF THE EUROPEAN COMMUNITIES

COM (84) 295 final

Brussels, 12 June 1984

COMMUNICATION FROM THE COMMISSION TO THE COUNCIL

concerning the use of certain substances having a hormonal action in animal production

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Proposal for a

COUNCIL DIRECTIVE

amending Directive 81/602/EEC concerning the prohibition of certain substances having a hormonal action and of any substances having a thyrostatic action

COM 285

COMMUNICATION FROM THE COMMISSION TO THE COUNCIL

CONCERNING THE USE OF CERTAIN SUBSTANCES HAVING A HORMONAL ACTION IN ANIMAL PRODUCTION

GENERAL

1. In order to protect the health of the consumer; in October 1980 the Commission proposed (Com (80) 614 Final) to the Council that the use on domestic animals of substances with oestrogenic, androgenic and gestagenic effects should be prohibited, except for the therapeutic use of natural hormonal substances[1].

2. On 31 July 1981 the Council adopted Directive 81/602/EEC concerning the prohibition of certain substances having a hormonal action and of any substances having a thyrostatic action[2]. Subsequently, in February 1983, to take account of this decision, the Council amended Directive 64/433/EEC on health problems affecting intra-Community trade in fresh meat[3] and Directive 72/462/EEC on health and veterinary inspection problems upon importation of bovine animals and swine and fresh meat from Third Countries[4].

   With its first decision, the Council agreed with the general approach of the Commission and decided on the urgent need to prohibit the marketing of stilbenes, stilbene derivatives, their salts and esters and thyrostatic substances for administering to animals of all species.

   However, it did not take a decision concerning the administering to farm animals of Oestradiol 17B, Progesterone, Testosterone, Trenbolone and Zeranol for fattening purposes. The Commission undertook to further consult the competent scientific committees on this question and to make a further proposal to the Council.

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(1) OJ No C 305 of 22.11.1980, p. 2
(2) OJ No L222 of 7.8.1981, p 32
(3) OJ No L 59 of 5.3.1983, p 10
(4) OJ No L 59 of 5.3.1983, p 34

HEALTH ASPECTS

3. To this end the Commission asked the opinions of the Scientific Veterinary Committee, the Scientific Committee for Animal Nutrition and the Scientific Committee for Food. To further this work a Scientific Group on Anabolic Agents in Animal Production studied the matter; their report was the basis for the work of the committees. The result of these consultations is annexed to this communication.

4. The Scientific Committees were in general agreement with the conclusions and recommendations of the Scientific Group, namely:

"The Scientific Working Group is of the opinion that the use of Oestradiol 17B, Testosterone and Progesterone and those derivatives which readily yield the parent compound on hydrolysis after absorption from the site of application, would not present any harmful effects to the health of the consumer when used under the appropriate conditions as growth promoters in farm animals."

Evaluation of the data on "trenbolone" and "zeranol" revealed that some data on the hormonal non-effect level and the toxicology of these compounds and their metabolites are still missing.

The Scientific Working Group considers it necessary that additional information be provided before a final conclusion can be given on trenbolone and zeranol.

Proper programmes to control and monitor the use of anabolic agents are essential.

It is necessary to continue scientific investigations on the relevance of the present use of the "no-hormone effect" level when related to the harmful effects of anabolic agents.

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5. The Commission finds no reason to disagree with with the findings of its Scientific Committees.

   The Commission accepts that the Committees studied the question on the basis of the latest advances in scientific knowledge in the matter of toxicity including the biological aspects. It in particular notes the observations to the effect that as regards the natural hormones (endogenous).

   - humans are daily producing high quantities of natural hormones ;
   - humans are regularly exposed to higher and widely variable levels of natural hormones in food from untreated animals ;
   - the human liver and placenta present effective tissue barriers to the residues of natural hormones which may be present in the tissue of treated animals ;
   - Thus no question of safety arises in relation to the proper use of Oestradiol 17 β, Testosterone and Progesterone in an appropriate form

6. The Commission takes into account the advice of Community Scientific opinion that the use of Oestradiol 17 β, Testosterone and Progesterone and those derivatives which readily yield the parent compound after absorption from the site of application, would not present any harmful effects to the health of the consumer when used under appropriate conditions as growth promoters in farm animals.

7. In addition the Commission accepts the need for the authorisation of any substances to be subject to the establishment of proper conditions of use, including specification of the doses, the type of pharmaceutical preparation, the number and frequency of administrations, the association of anabolic agents, localisation of implant and ablation of the zone treated and the delay period before the animal may be slaughtered. These conditions must be established to supplement the existing criteria in relation to veterinary medicines, and should be established by a Community procedure.

The Commission considers that the basis for the establishment of these criteria is already provided for in the Council Directives 81/851/EEC of 28 September 1981 on the approximation of the laws of the Member States relating to veterinary medical products and 81/852/EEC of 28 September 1981 on the approximation of the laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of veterinary medical products and that any authorisation of substances must be subject to the full implementation in all Member States of the principles established in these Community texts.

8. Scientific opinion in the Community considers it necessary to obtain supplementary information before giving a final conclusion on trenbolone and zeranol. In these circumstances, the Commission may not propose the continued use of these substances in the Community as long as it has not been shown that they are without danger. For the moment it proposes that they are banned. It is evident that it will submit any possible new data on these products or on any new substances, to the advice of the Scientific Veterinary Committee, the Scientific Committee for Animal Nutrition and the Scientific Committee for Food. It will also consult the numerous interested parties on the subject and in particular the consumers within the Veterinary Advisory Committee and will inform the Consumers Advisory Committee.

9. The need for the Community to continue to follow the most modern scientific developments and investigations in this field is clear. The Commission will support such work wherever possible, so that it may make any proposals necessary to take new developments into account.

ECONOMIC ASPECTS

10. The Commission services have studied available information as regards the economic benefit to the producer and consumer that may result from the safe use of authorised anabolic substances.

This information included, in particular, the proceedings of a workshop held in Brussels 5th-6th March 1981 on anabolic agents in beef and veal production, under the auspices of the division for the co-ordination of agricultural research of the European Commission[1]; the joint FAO/WHO expert committee on food additives (JECFA) which was convened in Geneva 23 March - 1 April 1981; and the symposium organised by the International Office of Epizootice (O.I.E.) on anabolics in animal production in Paris 15th-17th February 1983.

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(1) IBSN-0-905442-54-7

The conclusions in all cases agree that there is a significant benefit to be gained by the safe use of anabolic agents. Benefit arising from the clear increases in the daily weight gains of most classes of animals under various systems of fattening; gains in carcase weight, and in particular significant increase in the efficiency of feed conversion into meat. The latter is of particular importance as regards avoiding wastage of feed resources and also preventing escalation of the price of meat to the consumer. If an average benefit of 10% is allowed for, the extra feed needed for food production would be a notable economic burden on the population of those states not taking advantage of this safe aid to animal production.

QUALITY ASPECTS

11. The Commission services at the same time as examining the information available on the economic aspects of the use of anabolics has also examined the quality aspects, in particular as far as the three natural substances are concerned.

Due to the influence it has on the physiological and anatomical development of animals, there is an indication that certain quality factors may be improved; such as the composition of the tissues of the carcase, especially an advantageous proportion between meat, fat and bone.

It appears that other factors in animal production such as feeding systems, and management may still have much more dominant influences on meat quality than use of anabolic substances. Much more detailed studies are needed to increase our knowledge of these questions.

As regards the other aspects of quality there is no indication of adverse effects on meat qualtiy. A number of variations have been recorded but in the studies made none of the changes noted have been demonstrated to be significant.

12. As with all chemical substances in widespread daily use in the modern world, there must be recognised the possibility of misuse of authorised substances and illegal use of banned substances.

The Commission believes that the availability of safe authorised substances will discourage the temptation of the illegal use of banned substances. However, it will always be necessary to establish an efficient Community system of control and monitoring to ensure that any problems may be traced to their source and that appropriate steps are taken to prevent potentially hazardous products from reaching the consumer.

13. The results of the Commission's scientific work were submitted to the Consumers Consultative Committee and the Veterinary Advisory Committee, together with a working document of a draft legislative proposal. On the basis of the scientific work it was proposed that the three natural substances be authorised subject to conditions but that the other two substances should not be authorised for the use in the Community.

The Consumers Consultative Committee was unanimously opposed to this Commission orientation, it does not accept the validity of the scientific reports as it considers that biological effects are insufficiently taken into account, that not enough consideration had been given to quality consequences and that the problem of controls was not solved.

The Veterinary Advisory Committee which has a multiple interest representation including the Consumers was also consulted. In general there was again opposition to the Commission's orientation for different reasons. The consumers' representatives maintained their opposition on quality grounds and in addition maintained that no economic benefits of using the substances under consideration had been demonstrated.

Representatives of the Industry, co-operatives and the producers, generally maintained that a ban on the substances 'trenbolone' and 'zeranol' is premature and that the new information being made available should first be studied. Workers' representatives did not consider that sufficient harmonization was envisaged. The Veterinarians were in general agreement. The representatives of Commerce abstained from taking a position but emphasised the need for controls. All interests shared the view that it is essential to establish appropriate control measures.

The conclusions the Commission has drawn from these consultations are incorporated in the present proposal.

14. The Commission still considers that proper controls are essential. It recognises that recently in February the Council adopted modifications to the "Third Country" veterinary Directive and to the "Intra-Community Fresh Meat" Directive.

With the latter the obligation is now introduced to make sampling examination of animals or meat for residues of substances having a pharmacological action and of the conversion products thereof and for reference methods to be laid down and references laboratories designated by the Standing Veterinary Committee procedure after the Scientific Veterinary Committee has expressed an opinion.

Further steps are, however, proposed. It is not only necessary to have a Community approval of the substances concerned. It is considered necessary that individual products which contain these substances are also subject to approval by means of a Community procedure using the relevant criteria established in the Community directives on veterinary medicines. In this way the further safeguards concerning dosage, administration and period of delay before slaughter will be determined at Community level for all products approved to figure on a Community list. Principles of conditions of use of any approved products must be respected, including restriction to implantation in a part of the animal which is discarded at slaughter, obligation to identify the animal at the time of slaughter and respect of the period of delay laid down for each approved product. Provision must be made for Community establishment of further details of the controls of the respect of the conditions of use which are laid down at the time of product approval.

For the banned substances other controls are provided at all levels to ensure that these substances are not present either in factories or pharmacies, on farms or as residues in meat. The latter control must also be applied in respect of any approved substances as an additional check that the conditions of use are being respected and that residue limits are not exceeded.

The Commission calls upon the Council to take an urgent decision on this matter.

ANNEX

REPORT OF THE SCIENTIFIC VETERINARY COMMITTEE, SCIENTIFIC COMMITTEE FOR ANIMAL NUTRITION AND THE SCIENTIFIC COMMITTEE FOR FOOD ON THE BASIS OF THE REPORT OF THE SCIENTIFIC GROUP ON ANABOLIC AGENTS IN ANIMAL PRODUCTION

REPORT OF THE SCIENTIFIC VETERINARY COMMITTEE, SCIENTIFIC COMMITTEE FOR ANIMAL NUTRITION AND THE SCIENTIFIC COMMITTEE FOR FOOD ON THE BASIS OF THE REPORT OF THE SCIENTIFIC GROUP ON ANABOLIC AGENTS IN ANIMAL PRODUCTION

I. INTRODUCTION

On the 31 July 1981 the Council adopted Directive 81/602/EEC[1] concerning the prohibition of certain substances having a hormonal action and of any substance having a thyrostatic action.

By Article 5 of that Directive the Council decided to take a decision as soon as possible on the administering to farm animals of oestradiol 17β, testosterone, progesterone, trenbolone and zeranol, for fattening purposes. It also noted the Commissions intention to consult the competent Scientific Committees on the matter.

The Commission asked the Scientific Veterinary Committee, the Scientific Committee for Animal Nutrition and the Scientific Committee for Food the question :
"Does the use for fattening purposes in animals of the following substances : oestradiol - 17β, testosterone, progesterone, trenbolone and zeranol present any harmful effect to health."

To facilitate this work a specific Scientific Group was created in which representatives of each of the Scientific Committees participated.

This document contains the report adopted by the Scientific Group as a result of its final meeting of 22.9.1982. This report was made available to the Scientific Committees whose opinion was requested.

The Scientific Veterinary Committee gave its opinion at its meeting on 9.11.1982.

The Scientific Committee on Animal Nutrition gave its opinion at its 33rd meeting on 17.11.1982.

The Scientific Committee for Food gave its opinion at its 39th meeting on 4.02.1983.

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(1) OJ No L 222 of 07.08.1981, p. 32

II. REPORT OF THE SCIENTIFIC GROUP ON ANABOLIC AGENTS IN ANIMAL PRODUCTION

A. COMPOSITION OF THE SCIENTIFIC GROUP

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B. REPORT

1. INTRODUCTION

The Council Directive 81/602/EEC[1] concerning the use of certain substances having a hormonal action and of any substances having a thyrostatic action stipulates in Article 5 that the Council would as soon as possible take a decision on the use of oestradiol-17β , progesterone, testosterone, trenbolone and zeranol for the fattening of farm animals. For this purpose the Commission was required to present to the Council, a report on the collected experience and scientific developments in this field. Consequently a Scientific Working Group was set up to advise the Commission of the European Communities on whether the use of oestradiol-17β , testosterone, progesterone, trenbolone and zeranol as anabolic agents in animal production was a risk to public health.

The Terms of Reference of the Scientific Working Group were as follows: -
"Does the use for fattening purposes in animals of the following substances: oestradiol-17β , testosterone, progesterone, trenbolone and zeranol present any harmful effect to health?"

In framing its advice, the Scientific Working Group considered the guidelines prepared by the Scientific Committee for Food[2], the Scientific Committee for Animal Nutrition[3] and the Council Directives on Veterinary Medicinal Products (81/851/EEC and 81/852/EEC)[4].

The Working Group decided:

a) that the most suitable criteria for assessing the safety of anabolic agents (growth promoters) were those set out in Part 2, Chapter I, Section A-D of the Annex of Directive 81/852/EEC of 28 September 1981 on the approximation of laws of the Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of testing of veterinary medicinal products.

b) that safety is related to the conditions of use of anabolic agents.

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(1) OJ L 222 of 7. 8.1981, p. 32
(2) Reports of the Scientific Committee for Food (EUR 6892) 10th Series
(3) Reports of the Scientific Committee for Animal Nutrition (1980 EUR 6918)
(4) OJ L 317 of 6.11.1981, p. 1 and 16

The Scientific Working Group gave special consideration to a number of general points, such as the need to protect those segments of the population, e.g. prepubertal children, which were most likely to be affected from the toxicological point of view; the distribution of residues in edible tissues; the conditions of use of anabolic agents for growth promotion and improved feed conversion in relation to the general food supply; the need to avoid illegal use; and the importance of providing sensitive and accurate monotoring procedures on which to base enforcement of compliance with regulations.

Enforcement of proper conditions of use is essential for safeguarding the consumer.

In the opinion of the Scientific Group the appropriate conditions of use include

a) the site of application should be discardable,
b) the withholding periods must be observed.

Anabolic sex hormones like oestradiol-17β , testosterone, progesterone, trenbolone and zeranol lead to an increased feed conversion and hence protein deposition in farm animals. The basic mechanisms of action on the molecular level are not completely understood. However, there is increasing evidence that the effects are mediated through the basic hormone-receptor interactions. The food of animals, including man, normally contains natural substances with hormonal activity.

No side effects on animal health have been reported following the recommended use of these materials in growing animals other than those related to their hormonal effects on behavior and the reproductive system. Behavioral problems may occur during the first few weeks following treatment but with careful management these problems are not difficult to overcome. The use of anabolic agents to promote growth in animals intended for breeding is contraindicated because of their adverse effects on the reproductive and endocrine systems.

2. PRESENT SITUATION

Based on previous safety evaluations some EEC member states have accepted the use of trenbolone and zeranol and of oestradiol-17β , progesterone and testosterone.

The conditions of use require the drug to be implanted at a site (ear or base of ear) which is discarded at slaughter. Withholding periods have to be observed and doses applied per animal range from 20-40 mg for oestradiol-17β and zeranol, ca 200 mg for progesterone and testosterone and 140-300 mg for trenbolone in the form of its acetate.

Council Directive 81/602/EEC of 31 July 1981 prohibits the placing on the market of stilbenes, stilbene derivatives, their salts and esters and thyrostatic substances for administering to animals of all species.

The Committee did not consider the consequences on the quality of meat of the use of anabolic substances.

3. ENDOGENEOUS SEX STEROIDS : OESTRADIOL-17β, TESTOSTERONE AND PROGESTERONE

The Scientific Working Group considered that evaluation of the safety-in-use of oestradiol-17β, testosterone and progesterone included consideration of those derivatives which readily yield the parent compound on hydrolysis after absorption from the site of application.

Physiologically the steroidal sex hormones oestradiol-17β and testosterone as well as the gestagen progesterone control the proper function of the sexual physiology and "anabolism" in man and animals. The sex hormones are secreted by the gonads, the adrenals, and the placenta, the level of secretion being controlled by a complex but well established feedback mechanism. Sex steroids exert their hormonal effects at target tissues by binding to highly specific receptor proteins.

Because these compounds occur naturally they have to be considered as inevitable constituents of food from animal origin. Hormone levels in untreated animals vary widely depending on species, sex and physiological state, eg. adult male cattle produce 40-50 mg testosterone/24 h, cattle in late pregnancy several hundred milligrams of oestrogens/day. Thus the highest tissue levels of androgens are found in the mature male animal and of oestrogens in females during the later stages of pregnancy. Oestradiol-17β, testosterone and progesterone also occur normally in milk in varying amounts depending on the physiological state of the animal. In man and animals endogenous sex hormones are rapidly metabolised predominantly in the

liver to compounds exerting only little, if any, biological activity. A large percentage of these metabolites is excreated directly in the bile following conjugation (glucuronide, sulphate). However, because of systemic circulation, metabolites (both free and conjugated) may be found in the tissues, particularly in the kidney and liver.

Because there is a natural endogenous production of oestradiol-17β, progesterone and testosterone in all farm animals, any residues of these steroids are qualitatively indistinguishable from those derived from the use of these same steroids as anabolic agents administered to animals during life. Under appropriate conditions the treatment of animals with exogenous natural steroids results in residues in edible tissues which are orders of magnitude lower than those that can occur naturally in mature males, females and pregnant females. Therefore in practice no quantitative differences have been observed between treated and untreated animals when the recommended conditions of use were observed. Levels in treated and untreated calves are of the order of 0.1 µg testosterone/kg and 0.03 µg natural oestrogens/kg edible tissues.

No problems arise concerning contamination of the environment as a result of the administration of endogenous hormones, given the natural background of these substances and their biodegradability.

Levels and production rates of endogenous natural sex hormones vary in humans with age, state of sexual maturity, menstrual cycle and pregnancy. Daily production of oestrogens in infants ranges from 1-40 µg, in man from 40-130 µg, in women during reproductive life from 50-450 µg, in menopausal women from 5-40 µg. Daily production of testosterone in infants is about 100 µg, in man 4-10 mg, and in women 120-300 µg.

In relation to the endogenous sex steroid production in the human, the actual amount of sex steroids consumed with food of animal origin is toxicologically negligible as these steroidal residues do not reach effective concentrations at the relevant hormone receptor sites in target tissues. Moreover, the low oral bioavailability (less than 15 %) of these steroids and the existing tissue barriers in the liver and placenta effectively prevent any adverse toxicological effects from the ingestion of the minute residues of natural sex steroids which may be present in all edible tissues of animals treated with

anabolic hormones. Thus no questions of safety arise in relation to the proper use of oestradiol-17β , progesterone and testosterone in an appropriate form of preparation.

4. EXOGENOUS ANABOLIC AGENTS

4.1. Trenbolone (17-β hydroxy trenbolone)

Trenbolone is a synthetic steroid with androgenic activity similar to testosterone but with greater anabolic activity. It has several structural features similar to testosterone but unlike testosterone, it has three conjugated double bonds, and is chemically less stable. The material normally in commerce is trenbolone acetate.

Metabolism and Residues

The metabolism of trenbolone acetate has been studied in the rat, calf, heifer, cow and steer. Trenbolone acetate is rapidly hydrolysed to trenbolone, and both trenbolone and its metabolites are rapidly excreted as the glucuronides and sulphates, mostly in the bile. The predominant metabolites identified in the extractable fractions of bile in the rat are trenbolone and a 16-OH and a 17-keto metabolite; while in cattle it is mainly 17α-hydroxy trenbolone with small amounts of trenbolone and other metabolites. Many of the minor metabolites have been identified in both species. The parent compound and its metabolites have low oral activity.

Following the recommended use of trenbolone acetate in cattle and the application of various methods of assay (radioimmunoassay, thin-layer and high performance liquid chromatography) the main metabolite found in muscle has been shown to be trenbolone (<0.5 ppb muscle) and in liver and kidney a conjugated form at 17 hydroxy trenbolone (< 3 ppb). 17α-hydroxy trenbolone has a biological activity at least 10 times less than 17β hydroxy trenbolone.

Similarly following subcutaneous implantation of cattle with trenbolone radiolabelled with tritium, total residues, expressed as trenbolone equivalents, were a few parts per billion (10^{-9}) in muscle and approximately 10 times higher in liver and kidney (5-35 ppb). 5-10 % of the total residues labelled with tritium are extractable from meat, liver or kidney, and have been identified as similar to those found in bile. The identity of the remaining

unextractable residues, labelled with tritium, which are most likely irreversible bound, is not known but some tritium is found in the body water. The bioavailability of these unextractable residues in liver, kidney and muscle, following ingestion in rat feeding studies was found to be < 10 %.

Toxicity studies. Acute toxicity studies in several species showed trenbolone to be of low oral toxicity.

In subchronic toxicity studies trenbolone acetate was administered for 8 weeks in the diet of mice without any significant changes apart from those related to hormonal activity, which were still present at 25 mg/kg diet, the lowest level tested. Similar subchronic studies in normal male and female rats and in castrated male rats, extending from 10 days to 3 months, showed increased size of liver, kidney and spleen at high doses and the expected hormonal changes down to dose levels of 50 µg/kg bodyweight. A 14 weeks oral feeding study in pigs produced increased liver weight and liver cell size in females at levels of 2 and 20 mg/kg diet. At the lowest dose level of 100 µg trenbolone acetate/kg diet tested there was no clear absence of a lack of a hormonal effect.

A life-span feeding study in the mouse (dose range 0.5-100 mg/kg diet) extended over about 100 weeks. There was some increase in kidney weight at the highest dose levels in females sacrificed at 13 weeks, an effect typical of androgenic activity. At terminal sacrifice no organ weights were recorded, but there was an increased incidence of liver nodular hyperplasia and tumours in males of all dose groups which reached significance at the two highest dose levels and for females at the highest dose level tested. The control mice also had a high incidence of liver tumours.

Female rats were administered with trenbolone acetate during pregnancy and the pups used in a 112 week feeding study, using doses of 0.5-50 mg/kg diet. A number of mild toxic changes were seen at the highest dose level. A clear cut no-effect level for hormonal activity could not be determined. However, the data indicated that (since the lowest dose group showed no significant changes in all parameters examined compared to controls) a concentration of 0.5 ppm in the diet (25 µg/kg B.W.) is the probable "no-hormonal effect level" for the rat. This result requires confirmation. An increased (though not statistically significant) incidence of pancreatic islet cell tumours

was seen at the highest dose level (50 mg/kg diet). A one-generation reproduction study in rats, using 0.5-16 mg/kg diet in males and 0.5-50 mg/kg diet in females showed a dose related effect on pregnancy rate and litter parameters. No teratogenic effect was seen in two feeding studies in rats. A relay toxicity study has shown that meat from cattle treated at doses 10-25 times greater than the normal doses for 17β oestradiol and trenbolone acetate showed no effects in rats.

Because of the irreversible binding of some residues to macromolecules, which may indicate a genotoxic potential, special attention was given to mutagenicity tests with trenbolone.

Genotoxicity was examined by mutagenicity tests and by the capacity for DNA binding. Neither β-Trenbolone nor α-Trenbolone showed any mutagenic activity in prokaryotic systems nor in any in vivo test for bone marrow and germ cell cytogenetics. Clastogenic activity in vitro against human lumphocytes in culture were negative but tests against cells (L 5178 mouse lymphoma) were slightly positive, but to the same degree shown by testosterone and oestradiol. Concerning DNA binding in vivo in rats covalent binding indices were very low and equivalent for trenbolone and testosterone and less than for oestradiol. The data available to the group do not indicate any genotoxic activity. The question of binding to macromolecules other than DNA is a general problem which the group consider worthy of further study.

The findings of the carcinogenicity studies in rodents are difficult to interpret because of the interference by the hormonal activity of the dose levels employed and the comparatively high incidence of liver tumours in the controls used in the mouse study. The results of the mutagenicity tests do not indicate genotoxic activity. Hence the increased tumour incidence observed at high dose levels is probably due to epigenetic mechanisms related to the modulating effect of the hormonal activity on the mechanism of tumour production.

The present information on the average daily consumption of muscle tissues and offals within the EEC suggest that the consumer would probably be exposed to similar amounts of 17α and 17β-hydroxy trenbolone through his food. Therefore more toxicological information

particularly the determination of the no hormone effect level of 17α-hydroxy trenbolone is desirable. In summary for trenbolone, establishment of the no hormonal effect level of 17-β and 17-α trenbolone is required. Clarification is required of carcinogenicity data of 17β trenbolone particularly from the chronic toxicity study by taking into account the mutagenicity studies already completed.

4.2. Zeranol

This substance is structurally not a steroid and does not itself occur in nature although the parent substance zearalenonde is a natural substance elaborated by Gibberella Zea. It has oestrogenic and anabolic activity.

Metabolism

The metabolism has been studied in a number of species including cattle and sheep. Most of the orally administered substance is absorbed and eliminated in the faeces and urine. The proportions of urinary and faecal elimination is species dependent.

Zeranol is excreted both as free and conjugated substance and as free and conjugated zeralanone. The same metabolites appear in the bile. Most of orally administered zeranol has practically disappeared from the tissues within 24 hours except for the liver and kidney, however, no thorough identification of the possible metabolites has been made in the relevant species.

The oestrogenic properties were studied in many species using comparatively high doses but a no-hormonal effect level has not been determined, activity still being detectable at levels of 30-50 µg/animal/day in rats and mice. However, in vitro assays point to zeranol having about 20 % of the oestrogenic activity of oestradiol.

Toxicity

Zeranol has a low acute oral toxicity in most species. Subchronic feeding studies for 13 weeks in the rat showed hepatotoxicity in both sexes and none of the doses was free from hormonal activity (lowest dose tested 0.25 mg/kg bodyweight). Feeding studies in dogs ranging from 6-104 weeks and over a wide range of doses showed some haematological effects at high dose levels andevidence of gross hormonal

effects at all levels tested. A no-hormonal effect level was not determined.

A life span feeding study in rats over 2 years at dose levels from 0.8-20 mg/kg bodyweight/day showed hormonal effects in males and females at all dose levels. Some haematological effects at the highest dose levels as well as microscopically detected hapatotoxicity at all levels were noted. No carcinogenic effects were seen.

A seven year study in female beagles showed variable toxic effects at the high dose level on the haemopoietic system with increased weights of liver, kidney and adrenals at all levels but also significant effects due to hormonal activities on all reproductive organs at both dose levels. Female beagles were hysterectomised. Although not specially designed for this purpose, no carcinogenic effects were seen.

A ten year feeding study in female rhesus monkeys using a dose range of 15 and 75 mg/kg bodyweight showed some haematological changes at the highest dose level and alteration in hepatic function at both dose levels tested with increased liver weight at termination. Both dose levels showed significant hormonal effects on the reproductive system, hence a no-hormonal effect level was not determined. Although not specially designed for this purpose, no evidence of carcinogenicity was found.

A three-generation reproduction study in rats combined with a teratology study showed no adverse effects at all levels up to 200 µg/kg diet. Another teratology study in rats showed inhibition of implantation at the lowest dose tested (1 mg/animal/day during 1 to 4 of gestation). A similar study in mice gave no effects on pregnancy and litter parameters at doses below 100 µg/kg bodyweight without showing any teratogenic effects.

Mutagenicity was studied in prokaryotic systems but the toxicity of zeranol for the indicator organism made the study difficult to interpret. Low level exposures in these systems produced no mutagenic effects.

In summary, although a large number of studies have been performed with zeranol, there are insufficient data on the nature of the metabolites, on the quantity and nature of the residues in the

edible tissues of animals and on mutagenicity to interpret the available information in terms of the safety or otherwise of zeranol. A sufficiently sensitive method for determining unlabelled zeranol in edible tissues is not available, although a satisfactory method is available for urine of cattle and sheep. There is not sufficient information about the chemical impurities of the commercial product. None of the experiments permit the establishment of a no-hormonal effect level necessary for the interpretation of the toxicological significance of any residues found in edible tissues of treated animals.

5. Conclusions and recommendations

5.1.
The Scientific Working Group is of the opinion that the use of oestradiol-17β , testosterone and progesterone and those derivatives which readily yield the parent compound on hydrolysis after absorption from the site of application, would not present any harmful effects to the health of the consumer when used under the appropriate conditions as growth promoters in farm animals.

5.2.
Evaluation of the data on "trenbolone" and "zeranol" revealed that some data on the hormonal non-effect-level and the toxicology of these compounds and their metabolites are still missing.

5.3.
The Scientific Working Group considers it necessary that additional information be provided before a final conclusion can be given on trenbolone and zeranol.

5.4.
Proper programmes to control and monitor the use of anabolic agents are essential.

5.5.
It is necessary to continue scientific investigations on the relevance of the present use of the "no-hormone effect" level related to the harmful effects of anabolic agents.

ANNEX

REFERENCES

Endogenous steroid sex hormone preparations

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III. OPINION OF THE SCIENTIFIC COMMITTEES

A. SCIENTIFIC VETERINARY COMMITTEE

1. COMMITTEE MEMBERS :

a) Section I : Animal Health

P.H. BOOL	D.J. O'REILLY
M.K. ESKILDSEN	O. PAPADOPOULOS
R. FARINE	V. PAPPARELLA
J. LEUNEN	W. PLOWRIGHT
B. LIESS	GH. SCHLIESSER
J.B. McFERRAN	B. TOMA
C. MEURIER	

b) Section II : Public Health

G. CUMONT	CH. LABIE
M. DEBACKERE	G.E. LAMMING
F. KENNY	A. MANDIS
P.S. ELIAS	F. PANEBIANCO
R.J. GILBERT	C. RING
D. GROSSKLAUS	N.P. SKOVGAARD
E.H. KAMPELMACHER	R. VIVIANI

2. OPINION

"The Committee unanimously agreed that it fully supports the conclusions and recommendations of the report of the Commission Scientific Group.

However, the Committee attracted the attention of the Commission to the urgent need for further discussion and action to establish :

(a) the conditions of use,

(b) methods of analysis,

(c) monitoring programmes,

as regards these substances."

B. SCIENTIFIC COMMITTEE ON ANIMAL NUTRITION

1. COMMITTEE MEMBERS :

D.G. ARMSTRONG
G. BALLARINI
G. BORIES
P. DORN
V. ELEZOGLOU
P.S. ELIAS
R. FERRANDO
G. GEDEK
H. HEIGENER
S. MALETTO
B. BREST NEILSEN
M.M. McALEESE
M. VANBELLE
G.J. VAN ESCH
M. WOODBINE

2. OPINION

"The Committee has examined the report by the Commission's scientific working group on anabolic agents used in livestock production and has approved its conclusions and recommendations.

The Committee, however, wishes to draw the Commission's attention to the need to lay down certain essential provisions, in particular as regards the following :

a) Instructions for use
   1. Specification of the doses, the type of pharmaceutical preparation, the number and frequency of administrations.
   2. Association of anabolic agents.
   3. Localization of implant and ablation of zone treated.
   4. Withdrawal period before slaughter.
   5. Identification of animals treated, with indication of the period of treatment.

b) Surveillance programme and analysis methods
   1. Control of production and trade in anabolic agents.
   2. Veterinary control of authorized uses.
   3. Means and methods of control."

C. SCIENTIFIC COMMITTEE FOR FOOD

1. COMMITTEE MEMBERS :

P.S. ELIAS
A. HILDEBRANDT
F. HILL
A.W. HUPBARD
A. LAFONTAINE
B. MAcGIBBON
A. MARIANI
K.J. NETTER
A. POLYCHRONOPOULOU-TRICHOPOULOU
E. POULSEN
J. REY
V. SILANO
R. TRUHAUT
G.J. VAN ESCH
R. WENNIG

2. The Committee gave its opinion at its meeting of the 4 February 1983.

Terms of Reference

To give an opinion on whether the use for fattening purposes in animals of the following substances : oestradiol -17β, testosterone, progesterone, trenbolone and zeranol present any harmful effect to health.

Background

On the 31 July 1981 the Council adopted Directive 81/602/EEC(1) concerning the prohibition of certain substances having a hormonal action and of any substance having a thyrostatic action.

By Article 5 of that Directive the Council decided to take a decision as soon as possible on the administering to farm animals of oestradiol -17β, testosterone, progesterone, trenbolone and zeranol, for fattening purposes. It also noted the Commission's intention to consult the competent Scientific Committees on the matter.

The Commission asked the Scientific Veterinary Committee, the Scientific Committee for Animal Nutrition and the Scientific Committee for Food the same question, recognizing that the three committees would lay emphasis in their separate reports on the aspects of the question which fell within their terms of reference.

The three Committees established a joint working group composed of members of the committees with special knowledge of the subject.

A number of eminent specialists in the field joined the working group which met several times under the auspices of the Commission Services as a "scientific working group on anabolic agents in animal production".

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(1) OJ No L 222 of 07.08.1981, p. 32

The Scientific Committee for Food, together with the Scientific Committee for Animal Nutrition and Scientific Veterinary Committee, was requested to consider the report of the Scientific Working Group and to comment on its conclusions and recommendations during the Committee's own review.

The committee has been informed that the Commission intends to make public the report of the Scientific Working Group. The Committee also notes that the Scientific Veterinary Committee and the Scientific Committee for Animal Nutrition have both already made recommendations to the Commission on the proper use of these anabolic agents.

Current Review

The Committee is impressed by the thoroughness with which the report of the joint working group has been prepared. There appears no reason in the present report to reherse all the reasoning included therein, particularly in view of its imminent publication.

The conclusions of the Scientific Working Group were as follows :

1. The Scientific Working Group is of the opinion that the use of oestradiol -17β, testosterone and progesterone, and those derivatives which readily yield the parent compound on hydrolysis after absorption from the site of application, would not present any harmful effects to the health of the consumer when used under the appropriate conditions as growth promoters in farm animals.
2. Evaluation of the data on "trenbolone" and "zeranol" revealed that some data on the hormonal no-effect level and the toxicology of these compounds and their metabolites are still missing.
3. The Scientific Working Group considers it necessary that additional information be provided before a final conclusion can be given on trenbolone and zeranol.
4. Proper programmes to control and monitor the use of anabolic agents are essential.
5. It is necessary to continue scientific investigations on the relevance of the present use of the "no-hormone effect" level when related to the harmful effects of anabolic agents.

Conclusions and Recommendations

In general, the Scientific Committee for Food agrees with the conclusions and recommendations of the Scientific Working Group. It also wishes to put forward the following comments for consideration by the Commission :

i) In relation to Recommendation 2 it would be of interest to generate data on the threshold values for the toxic and hormonal activities of trenbolone and zeranol.

ii) The Committee endorses the Recommendation 4 on the importance of implementing programmes for control and monitoring of anabolic agents. It emphasizes that proposals should be made by the Commission for implementation. In connection with this aim it would be necessary to encourage the development and standardisation of appropriate analytical methods.

iii) The Committee recognises that the possible misuse of naturally occurring hormones or their derivatives, which easily yield the original hormone, may be difficult to detect analytically. Information is therefore needed on the levels of naturally occurring hormones likely to engender a health hazard. It is an important public health consideration to prevent the illegal use of banned products and the misuse of authorised products by efficient monitoring and proper controls.

Proposal for a

COUNCIL DIRECTIVE

amending Directive 81/602/EEC concerning the prohibition of certain substances having a hormonal action and of any substances having a thyrostatic action

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Proposal for a

COUNCIL DIRECTIVE

amending Directive 81/602/EEC concerning the prohibition of certain substances having a hormonal action and of any substances having a thyrostatic action

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THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 43 thereof,

Having regard to 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[1], and in particular Articles 5 and 7 thereof,

Having regard to Council Directive 64/433/EEC of 26 June 1964 on health problems affecting intra-Community trade in fresh meat[2], as last amended by Directive 83/90/EEC[3], and in particular Article 4(2) thereof,

Having regard to the proposal from the Commission,

Having regard to the opinion of the European Parliament,

Having regard to the opinion of the Economic and Social Committee,

Whereas the adoption of Community provisions concerning the absorption by farm animals of substances having a hormonal action or thyrostatic action have the object, in the interest of consumers, of protecting human health and of removing barriers to intra-Community trade of animals, meat and meat products resulting from differences between the health requirements of Member States;

Whereas it is, therefore, necessary to supplement the provisions already laid down on the matter by the aforementioned Directive 64/433/EEC and Council Directive 71/118/EEC of 15 February 1971, concerning health problems of trade in fresh poultrymeat[4], as last amended by Directive [5], and by the aforementioned Directive 81/602/EEC;

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(1) OJ No L222, 7. 8.1981, p 32
(2) OJ No 121, 29. 7.1964, p 2012/64
(3) OJ No L 59, 5. 3.1983, p 10
(4) OJ No L 55, 8. 3.1971, p 23
(5) OJ No L . .19 , p

Whereas, in accordance with Article 5 of Directive 81/602/EEC, it is necessary to take a decision as soon as possible on the administering to farm animals of Oestradiol 17β, Progesterone, Testosterone, Trenbolone and Zeranol for fattening purposes;

Whereas it is important to authorise only substances which have a favourable effect on farm animal production and whose administration will neither present harmful effects on human health nor harm the consumer by altering the characteristics of meat;

Whereas the Scientific Veterinary Committee, the Scientific Committee for Animal Nutrition and the Scientific Committee for Food have studied this problem on the basis of a report of a Commission scientific group on anabolic agents in animal production, and whereas the Commission has declared its intention to continue to consult these Committees and the numerous interested parties in particular the consumers on these questions.

Whereas it appears that some data necessary on the toxicology of Trenbolone and Zeranol and their metabolites are still lacking; whereas, in consequence, their use for fattening purposes must in the present circumstances be prohibited:

Whereas, on scientific grounds, it appears that the use of Oestradiol 17β, Testosterone and Progesterone and those derivatives which readily yield the parent compound on hydrolysis after absorption from the site of application would not present any harmful effects to the health of the consumer nor harm the consumer by altering the characteristics of meat when used under the appropriate conditions as growth promoters in farm animals; whereas, in consequence, Member States may authorise their use for fattening purposes;

Whereas approval of products containing authorised substances must comply with the relevant principles and criteria set out in Council Directive 81/851/EEC of 28 September 1981 on the approximation of the laws of the Member States relating to veterinary medicinal products(6), and Council Directive 81/852/EEC OF 28 September 1981 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of veterinary medicinal products(7);

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(6) OJ No L317, 6.11.1981, p 1
(7) OJ No L317, 6.11.1981, p 16

whereas additional requirements as regards carrier substances, conditions of use and withdrawal periods must also be complied with; whereas a Community procedure within the Standing Veterinary Committee, set up by Council Decision of 15 October 1968[8], should be used to establish a list of products which may be approved and the conditions of their use, as well as to modify the list of authorised substances in the light of progress in scientific and technical knowledge;

Whereas Member States may choose not to allow in their territory the marketing and administration to farm animals, for fattening purposes, of substances and products which may be authorised under the present Community rules, but must not raise any obstacle for human health reasons to the importation of animals, meat and meat products from other Member States where such substances and products have been authorised in accordance with Community rules;

Whereas it is suitable to prescribe, in accordance with Article 7 of Directive 81/602/EEC and Article 4(2) of Directive 64/433/EEC, the measures necessary for the control of farm animals, of meat and meat products in relation to the use of substances having a hormonal action or thyrostatic action, as well as tolerances for these substances and the frequency of sampling; and that these measures must also facilitate the cooperation between Member States in the application of these controls and, where necessary, provide for the adoption, in accordance with procedure of the Standing Veterinary Committee, of measures necessary to ensure the coordination and uniform application of these controls;

HAS ADOPTED THIS DIRECTIVE:

Article 1

Directive 81/602/EEC is hereby amended as follows:

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(8) OJ No L255, 18.10.1968, p 23

1. Article 5 is replaced by the following:

"Article 5

1. By way of derogation from Article 2, Member States may authorise the administering to farm animals, for fattening purposes, of Oestradiol 17β, Testosterone and Progesterone and those derivatives which readily yield the parent compound on hydrolysis after absorption from the site of application.

2. Member States shall ensure that the aforementioned substances are:

- only administered to farm animals by implantation which is located in a part of the animal which must be discarded at slaughter
- only administered to animals which are identified at the time of implantation and that these animals are not slaughtered before the expiry of the delay period laid down in application of subparagraph 3a)
- administered by a veterinarian.

3. a) Before 1 April 1986 in accordance with the procedure laid down in Article 16 and following the relevant principles and criteria of Directives 81/851/EEC and 81/852/EEC there shall be established:

- a list of products containing as active substances the substances referred to in paragraph 1 which may be approved for marketing and use in the Community
- the conditions of use of products contained in the abovementioned list in application of paragraph 2, in particular the delay period necessary and detailed provisions concerning the control of these conditions of use
- the means of identification of animals.

b) Member States shall ensure that the products mentioned under subparagraph a) are subject to the rules of Articles 24 to 50 of Directive 81/851/EEC except for those rules which relate to the national authorisation for marketing.

4. In order to take account of scientific and technical progress, the list of substances referred to in paragraph 1 which may be administered to animals for fattening purposes, may be completed or amended in accordance with the procedure laid down in Article 16.

   Any substance which may be authorised:
   - must have a favourable effect on farm animal production
   - must not endanger human or animal health nor harm the consumer by altering the characteristics of farm animal products
   - must comply with the relevant principles and criteria of Directives 81/851/EEC and 85/852/EEC.

5. However, any decision concerning the possible inclusion of Trenbolone or Zeranol on the list shall be made by the Council, acting by a qualified majority on a proposal from the Commission, and in conformity with the other conditions laid down in paragraph 4."

2. Article 7 is replaced by the following Articles:

"Article 7

Without prejudice to the provisions of Directive 64/433/EEC, Member States shall ensure that checks on compliance with the prohitions as laid down in Articles 2 and 3, checks on farm animals, the meat of such animals, the meat products obtained therefrom for the presence of residues of hormonal substances referred to in Article 2(a) and checks on compliance with the conditions of use of products provided for in Article 5 are carried out in their territory in accordance with the provisions of this Directive.

Article 8

Member States shall ensure that on-the-spot random checks for the presence of prohibited substances as referred to in Articles 2 and 3 are made officially at the levels of manufacturing, handling, storage, transport, distribution and sale.

Article 9

1. Member States shall ensure that on-the-spot random checks are made officially for the presence of prohibited substances as referred to in Articles 2 and 3 at agriculture holdings where animals are reared, held or fattened for slaughter.

2. The checks shall include taking random samples from animals for examination for the presence of residues.

Article 10

1. Member States shall ensure that random checks are taken officially from animals and meat, including meat destined for the production of meat products, at the slaughterhouse of production for examination for the presence of residues of substances mentioned in Article 2(a).

2. In particular, random samples shall be taken of animals and meat from holdings submitting regularly calves and fattened bovine animals for slaughter.

Article 11

1. The samples referred to in Article 9 (2) and Article 10 shall be taken officially and examined by an authorised laboratory for the presence of residues.

2. The examination for residues referred to in paragraph 1 must be carried out in accordance with proven methods which are scientifically recognised, in particular those laid down by Community provisions.

   It must be possible to assess the examination for residues using the reference methods established in accordance with Article 4(1)(b) of Directive 64/433/EEC.

3. All positive findings shall be confirmed by an official laboratory using the reference method referred to above in paragraph 2.

Article 12

1. Where examination as referred to in Article 11(3) has confirmed the presence of prohibited substances or of residues exceeding the maximum natural physiological levels of authorised substances, the competent authorities shall be informed without delay of:

   a) all information needed to identify the origin of the animals

   b) the result of the examination.

2. The competent authorities shall thereupon ensure that:

   a) an investigation is made at the farm of origin to determine the reason for the presence of residues

   b) an investigation of the source or sources of the substance concerned is made as necessary at the levels of distribution, sale, transport, handling, storage and manufacture.

3. The competent authorities shall also ensure that:

   a) the herd or animals at the farm of origin and herds which, as a result of the investigations referred to in paragraph 2 may be assumed to contain the residue in question, are provided with official marking and subject to appropriate examinations

   b) if the examination reveals the presence of prohibited substances, the animals shall be confiscated or destroyed

   c) if the examination reveals the presence of residues of authorised substances above the limits mentioned in paragraph 1, the slaughter of the animals concerned for human consumption shall be prohibited until it can be ensured that the amount of residue no longer exceeds the permitted levels. This period may in no case be shorter than the delay period fixed for the substance in application of Article 5 (3)(a), However, where it is ascertained that the conditions of use laid down have not been complied with, the animals concerned shall be confiscated or destroyed

   d) during the period of examination, the animals must not be disposed of to other parties.

4. By way of derogation from paragraph 3(c), animals whose slaughter is prohibited may be slaughtered before the end of the prohibition period if the competent authority is informed at least one week before the proposed slaughter date, stating the place of slaughter. The officially marked animals must be accompanied to the place of slaughter by an official veterinary certificate containing the information required under paragraph 1(a).

   The carcase of each animal whose slaughter is notified pursuant to the above subparagraph shall be officially examined for the residue concerned and shall be detained until the result of the examination is known.

Article 13

Where the checks and investigations referred to in Articles 8 to 12 disclose the presence of prohibited substances referred to in Articles 2 and 3, Member States shall ensure that the substances concerned are placed under official control until the necessary sanctions are taken.

Article 14

1. Where the findings in one Member State indicate the need for investigation in one or more other Member States, the Member State concerned shall inform the other Member States and the Commission thereof.

2. In accordance with the procedure of Article 17, measures may be taken to ensure the coordination of the investigations necessary in relation to the presence of prohibited substances.

Article 15

1. Member States shall inform the Commission annually of the details of the result of sampling, examinations and investigations made for the presence of residues of substances referred to in Article 2(a).

2. On the basis of this information, the Commission shall report to the Member States meeting in the Standing Veterinary Committee set up by the Council Decision of 15 October 1968 (hereinafter called the Committee); if necessary, in accordance with the procedure laid down in Article 16, measures may be taken to ensure the uniform application of the controls laid down by this Directive.

Article 16

1. Where the procedure laid down in this Article is to be used, matters shall, without delay, be referred by the chairman, either on his initiative or at the request of a Member State, to the Committee.

2. Within the Committee, the votes of Member States shall be weighted as provided in Article 148 of the Treaty. The chairman shall not vote.

3. The representative of the Commission shall submit a draft of the measures to be adopted. The Committee shall deliver its opinion on such measures within a period be determined by the chairman in keeping with the urgency of the question submitted for examination. Opinions shall be delivered by a majority of 45 votes.

4. The Commission shall adopt the measures and implement them immediately where they are in accordance with the opinion of the Committee. Where they are not in accordance with the opinion of the Committee or if no opinion is delivered, the Commission shall, without delay, propose to the Council the measures to be adopted. The Council shall adopt the measures by a qualified majority.

If, within three months from the date on which a matter was referred to it the Council has not adopted any measures, the Commission shall adopt the proposed measures and implement them immediately, save where the Council has decided against these measures by a simple majority.

Article 17

1. Where the procedure laid down in this Article is to be followed, the chairman shall, without delay, refer the matter, either on his own initiative or at the request of a Member State, to the Committee.

2. Within the Committee, the votes of Member States shall be weighted as provided in Article 148 of the Treaty. The chairman shall not vote.

3. The Commission representative shall submit a draft of the measures to be adopted. The Committee shall deliver its opinion on such measures within a period of two days. Opinions shall be delivered by a majority of 45 votes.

4. The Commission shall adopt the measures and shall apply them immediately where they are in accordance with the opinion of the Committee. Where they are not in accordance with the opinion of the Committee or if no opinion is delivered, the Commission shall, without delay, propose to the Council the measures to be adopted. The Council shall adopt the measures by a qualified majority.

   If, within 15 working days from the date on which the proposal was submitted to it, the Council has not adopted any measures, the Commission shall adopt the proposed measures and apply them immediately, save where the Council has decided against these measures by a simple majority."

3. Articles 8, 9 and 10 shall become Articles 18, 19 and 20.

Article 2

Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive

- not later than 1 July 1985 as regards the prohibition of the administration of Trenbolone and Zeranol to farm animals for fattening purposes, in application of Articles 2 and 5 of Directive 81/602/EEC, as amended by Article 1(1) of this Directive;
- not later than 1 July 1986 for the remaining provisions. They shall forthwith inform the Commission thereof.

Article 3

This Directive is addressed to the Member States.

Done at Brussels,

For the Council

The President