

## HORMONES IN BOVINE MEAT

### **BACKGROUND AND HISTORY OF WTO DISPUTE**

1. In 1988, the EC introduced a prohibition on the use of hormonal substances for animal growth promotion. This included  $17\beta$  oestradiol, testosterone, progesterone, zeranol, trenbolone acetate, and melengestrol acetate (MGA). The ban applied without discrimination internally and to imports from third countries as from 1 January 1989. As a result, third countries wishing to export bovine meat and meat products to the EC had to either have equivalent legislation or to operate a hormone-free cattle programme.
2. Some third countries, in particular the US and Canada, have been contesting the EC hormones ban and the US, in the absence of a mutually agreed solution, applied measures in the form of 100% *ad valorem* duty on a variety of EC exports at a value of about \$93 million per year since 1989. In May 1996 these retaliatory measures were withdrawn when the EC sought in April 1996 a panel against the unilateral US measures which had clearly no basis in the GATT 47 and WTO law.
3. In March 1996, the US and Canada held formal consultations with the EC in the framework of the WTO dispute settlement mechanism regarding the EC legislation prohibiting the use of the six hormones for animal growth promotion. Following requests from these two countries, two WTO panels were set up to assess the conformity of the EC prohibition with its WTO obligations. The reports of these WTO panels were delivered in August 1997. The EC measures were found to be not in conformity with three provisions of the Sanitary and Phytosanitary (SPS) Agreement. The EC appealed the conclusions of the panels in September 1997. In its report of January 1998, the Appellate Body (AB) reversed two of the three inconsistencies found by the Panels. The AB upheld only the finding that the EC prohibition of imports of meat from hormone-treated animals did not comply with the requirement that such a measure be based on an assessment, as appropriate to the circumstances, of the risks to human health. It also stated that it did not consider the risk assessment presented by the EC as valid ones because "it did not focus specifically enough on residues in meat" for the first five hormones and that for the sixth hormone, MGA, no risk assessment had been performed.
4. The AB further clarified that a WTO Member:
  - has the right to choose the level of health protection it deems appropriate in its territory;
  - is not obliged to assess risk only in quantitatively manner in order to be able to take protective measures;
  - is not obliged to follow majority and mainstream scientific views - minority views can also be taken into account.
5. The AB also overruled the Panel's findings that the EC had not been consistent in the level of protection it had set for hormones used for animal growth promotion, on the one hand, and naturally-occurring hormones and some other chemical substances on the other hand. The AB report also mentioned Article 5.7. of the SPS Agreement, which deals with measures taken when scientific information is insufficient. This Article permits members to take measures, but they must be provisional and be based on relevant scientific information. The SPS Members taking such measures

are however obliged to seek the additional information necessary for a more objective and complete assessment of risk and to review the measures within a reasonable period of time. The AB recommended that the EC bring its measures into conformity with its obligations under the SPS Agreement.

6. In May 1998, a WTO Arbitrator awarded the EC 15 months to implement the WTO Dispute Settlement Body's recommendation, i.e. until 13 May 1999. The EC decided to implement the DSB recommendations by carrying out a complementary risk assessment in accordance with the clarifications and finding provided by the WTO panels and the AB. It should be noted that the *Hormones* dispute was the first case that was decided under the WTO/SPS Agreement and, consequently, it clarified for the first time an important number of issues, including in particular the concepts of risk assessment, appropriate level of protection, the role of international standards laid down by Codex Alimentarius Commission and the precautionary principle. Because the performance of this type of risk assessment and subsequent adoption of risk management measures require a substantial amount of time, the EC could not meet the deadline of 13 May 1999 for implementation. As a result, a WTO Arbitrator awarded the US and Canada nullification and impairment suspension of concessions to the amount of \$ 116,8 mio per year for the US and CN\$ 11,3 mio per year for Canada. Consequently, since August 1999, these two WTO members are authorised to apply retaliation in the form of 100% *ad valorem* duty on imports of a variety of EC products up to the amounts indicated above.

### **1.1. Risk assessment in the light of the WTO outcome**

7. The WTO Appellate Body's ruling provided a series of fundamental clarifications concerning a number of provisions of the SPS Agreement. In particular, the AB found that a sanitary measure may go beyond international norms if it is sufficiently warranted or reasonably supported by a risk assessment that:
  - can be of qualitative or quantitative nature;
  - can take into account risks as they actually exist in the real world, including risks arising from difficulties of control, inspection and enforcement of good veterinary practice;
  - can be based on minority views from qualified and respected scientific sources, and
  - evaluates the possible risks to human health from residues in meat resulting specifically from the administration of hormones for animal growth promotion purposes.

### **1.2. EC response to the WTO rulings**

8. The European Commission launched in early 1998 a series of 17 specific research studies to respond to the findings of the AB report. These specific experimental studies concern *inter alia* toxicological and carcinogenicity aspects, residue analysis, potential abuse and control problems, environmental aspects, etc.
9. In response to the AB's main concern about the need for a comprehensive risk assessment, the relevant independent Scientific Committee, that is the Scientific Committee of Veterinary Measures Relating to Public Health (SCVPH), was charged at the end of 1998 to carry out an assessment of the risk to human health arising from the use of the six hormones as growth promoters, in particular from

residues in meat and meat products from bovine animals to which these hormones are administered for growth promotion purposes.

**OPINION OF THE EC SCIENTIFIC COMMITTEE ON VETERINARY MEASURES RELATING TO PUBLIC HEALTH (SCVPH)**

10. In accordance with its normal procedure, the SCVPH established a working group under the chairmanship of one of its members. The SCVPH identified the fields of expertise it considered necessary to respond to the risk assessment mandate it was given and decided on the composition of the working group. It consisted of 9 specialists, including 4 scientists from the USA, selected on the basis of their scientific expertise in the different scientific areas concerned. This working group met several times and prepared a draft report, which was subsequently presented by the reporter to the SCVPH. The SCVPH discussed the draft report in detail at its plenary session on 29-30 April 1999 and adopted its opinion unanimously.
11. The opinion of the SCVPH of 30 April 1999 constitutes an up-to-date and comprehensive assessment of risks of the six hormones in question, when used for animal growth promotion purposes that respects the specific WTO requirements as to the performance of a risk assessment. Moreover, it answers the criticism of the WTO panels and AB that the EC had not presented a risk assessment focussing on the risk from the presence of residues of these hormones in meat. The SCVPH concluded that a risk to consumers, i.e. possible endocrine, developmental, immunological, neurobiological, immunotoxic, genotoxic and carcinogenic effects, has been identified with differing levels of conclusive evidence for each of the substances, but that the current state of knowledge does not allow a quantitative estimate of the risks. In doing so, the SCVPH reviewed and criticised the assumptions and studies on which JECFA (Joint FAO/WHO Expert Committee on Food Additives) advising Codex Alimentarius and the countries that have authorised the use of these hormones for animal growth promotion based their recommendations and decisions.
12. For  $17\beta$  oestradiol in particular, the SCVPH concluded that there is a substantial body of recent and reliable scientific evidence suggesting that this substance has to be considered as a complete carcinogen (i.e. both tumour initiating and tumour promoting), but it was not possible to quantify this risk. For the hormone MGA, there was no available risk assessment and the SCVPH concluded that the publicly available information is inadequate to carry out a complete assessment, but the available data allowed a non-quantifiable risk for the consumers to be identified. For the other 4 hormones (testosterone, progesterone, trenbolone acetate and zeranol), it was found that the available information is also inadequate to allow a quantitative estimate of the risk but that a risk to the consumers has been identified in qualitative terms. Of particular relevance to the SCVPH's opinion was the finding that, because no safe threshold could be established for any of these hormones, exposure to even small traces in meat carries a risk, and that "of the various susceptible risk groups, pre-pubertal children is the group of greatest concern" because of the extremely low level of endogenous production of hormones by pre-pubertal children.
13. In April 2000, the SCVPH was asked again by the European Commission to consider the latest scientific information that was published after its opinion of 30 April 1999, in particular the reports from the CVMP (Committee on Veterinary Medicinal Products), the report from the VPC (Veterinary Products Committee) from the United Kingdom and the 1999 re-evaluation of some of these hormones by JECFA for Codex

Alimentarius. All this latest information was submitted and examined by the SCVPH carefully, but it did not lead it to revise its previous opinion. Therefore, on 3 May 2000, it reconfirmed unanimously its risk assessment of 30 April 1999 on the six hormones.

#### **COMMISSION PROPOSAL AMENDING DIRECTIVE 96/22/EC CONCERNING THE PROHIBITION ON THE USE IN STOCK-FARMING OF CERTAIN SUBSTANCES HAVING A HORMONAL OR THYROSTATIC ACTION AND BETA-AGONISTS**

14. In the light of the opinions of the SCVPH, the Commission has adopted this proposal 24<sup>th</sup> May 2000 and proposed to the Council and the European Parliament to definitively ban the use of 17 $\beta$  oestradiol and its ester-like derivatives in farm animals and to maintain provisionally the prohibition for growth promotion of all other substances having an oestrogenic, gestagenic or androgenic effect until more complete scientific information becomes available. This will be kept under regular review. A first reading of this proposal took place in the European Parliament who adopted it in their plenary meeting of 1<sup>st</sup> February 2001. The Commission is awaiting the Council's position.

#### **CONTACTS WITH THE USA AUTHORITIES AND SCIENTISTS**

15. In a spirit of co-operation and mutual understanding, an exchange of views took place in Washington in June 1999 between EU and US scientists. The rapporteur of the EC SCVPH committee, accompanied by 3 external independent scientists, presented the SCVPH opinion and findings to a group of US scientists selected by the US authorities, which was subsequently followed by an exchange of views and discussion.
16. It should also be noted that the European Commission requested several times in the course of 1998 and the beginning of 1999 in writing from the US and Canada to provide it with copies of all relevant scientific information and data they had in their possession on these hormones and on which they based their risk assessments and marketing authorisations. The same scientific information and data was requested also from Australia and New Zealand. But to date no information has been received from any of these countries.

#### **ADDITIONAL SCIENTIFIC STUDIES**

17. As already indicated, following the clarifications by the AB, the Commission approved and financed 17 scientific studies in early 1998 with the aim of obtaining as much as possible additional information concerning certain aspects of these hormones, in particular toxicology, abusive use, residue levels in meat, potential adverse human effects from residues in meat and environmental aspects arising specifically from the use of the six hormones as animal growth promoters. The majority of these studies have now been completed and the results of most of them have been presented in international conferences and published in peer-reviewed scientific journals.
18. In particular, two studies have demonstrated that bovine meat and liver imported into the EC from the US under the Hormone Free Cattle Programme (HFCEP) contained residues of hormones in excess of the authorised amounts and also residues of prohibited hormones in the US and, thus, were held not to respect the EC rules for import of bovine meat and meat products. It was these studies in particular that led to the application of specific additional conditions to the import of US beef and offal

into the EC since 1999. Since then the situation in terms of implementation of the HFCEP has improved considerably.

#### **RELATIONSHIP BETWEEN THE 17 SPECIFIC SCIENTIFIC STUDIES AND THE SCVPH RISK ASSESSMENT**

19. The 17 scientific studies were launched before the SCVPH was asked to provide a new risk assessment. Therefore, although the opinion of the SCVPH was elaborated in full knowledge of the studies and their intermediate results, it must be stressed that the SCVPH in no way was involved in their setting up or management. Moreover, as the 17 studies were initiated before the SCVPH began its risk assessment, they were not conceived to respond to the gaps in scientific knowledge which the SCVPH subsequently discovered and identified in its opinion of 30 April 1999. Indeed, while adding substantially to our knowledge on the broad and complex issues concerning these hormones, the 17 scientific studies will not provide answers to all of the numerous remaining scientific questions and gaps in our knowledge that have been identified in the opinion of the SCVPH.

##### **1.1. Status of the 17 scientific studies and availability of their results**

20. It should be pointed out that the European Commission is awaiting the completion of the 17 scientific studies and the publication of their results in peer-reviewed scientific journals before drawing any conclusions. It has also undertaken to keep the SCVPH, the Member States and any interested third countries informed of the scientific developments.

21. As of September 2001, 15 of the 17 studies have been completed. Of the remaining two studies, one is expected to be completed by end September 2001 and the other one by end 2001. One research contract was terminated in its initial phase.

22. Whilst the Commission is committed to full publication of their results, it is important for the credibility of the work that the scientific results undergo scientific review through the normal procedures used for publication in peer-reviewed journals. This inevitably means delays in making the full results available to the public.

23. Results from these scientific studies have already begun to be published in established and well known scientific journals, as can be seen from the attached Annex.

## Annex

### Name of all studies and publications in relation to them.

<b>title of study</b>	<b>publications</b>
Presence of estrogen in meat (delivery of samples)	no publications to be done
Hormones as growth promoters: genotoxicity and mutagenicity of Zeranone & Trenbolone	"Genotoxic potential of xenobiotic growth promoters and their metabolites" ( <i>APMIS 109:89-95, 2001</i> )
Metabolic pathways of estrogens as steroidal growth promoting agents	"Estrogenic activity of estradiol and its metabolites in the ER-CALUX assay with human T47D breast cells" ( <i>APMIS 109: 101-7, 2001</i> )
Metabolites of melengestrol acetate, trenbolone acetate & zeranol in bovine & humans	"Metabolism of melengestrol acetate and trenbolone";( <i>publication foreseen</i> )
Application of anabolic agents to food producing animals- health risks through disregard of requirements of good veterinary practice	1)"Detection of melengestrol acetate residues in plasma and edible tissues of heifers" ( <i>The Veterinary Quarterly,21, 154-158</i> ) 2) "Detection of anabolic residues in misplaced implantation sites in cattle" ( <i>Journal of AOAC International 83(4); 809-819</i> ) 3) "Suppression of testosterone in entire male pigs by anabolic preparations" ( <i>Livestock Production Science - 69 (2001) 139-144</i> ) 4) "A sensitive enzyme immunoassay (EIA) for the determination of Melengestrol acetate (MGA) in adipose and muscle tissues" ( <i>Food Additives and Contaminants -vol.18,no.4,:285-291, 2001</i> ) 5) " Characterisation of the affinity of different anabolics and synthetic hormones to the human androgen receptor, human sex hormone binding globulin and the bovine gestagen receptor" ( <i>APMIS -108, 838-46; 2000</i> ) 6) "Dose dependent effects of melengestrol acetate (MGA) on plasma levels of estradiol, progesterone and luteinizing hormone in cycling heifers and influences on oestrogen residues in edible tissues" ( <i>APMIS 108: 847-854, 2000</i> ) 7) "Hormone contents in peripheral tissue after correct and off-label use of growth promoting hormones in cattle: Effect of the implant preparations Finaplix-H®, Ralgro®, Synovex-H® and Synovex Plus®" ( <i>APMIS -109, 53-65; 2001</i> ) 8) "Tissue-specific expression pattern of estrogen receptors (ER): Quantification of ER $\alpha$ and ER $\beta$ mRNA with real-time RT-PCR" ( <i>APMIS 109: 345-55, 2001</i> )

Analysis of 500 samples for the presence of growth promoters	"Hormones found in meat samples from regular controls within the EU and from US imports" ( <i>Chemical awareness; issue 9, July 5th 2000,</i> )
Analysis of 500 samples for the presence of growth promoters	1)"Ultra trace detection of a wide range of anabolics in meat by gas chromatography coupled to mass spectrometry" ( <i>Journal of Chromatography A, 867(2000) 219-233</i> ) 2)"Le contrôle des anabolisants dans la viande" (The survey of anabolic agents in meat.) ( <i>Annales de Toxicologie Analytique, vol.XII, no.1,2000</i> )
Comparison of assay methods	1)"Frequency and molecular analysis of <i>hprt</i> mutations induced by estradiol in Chinese hamster V79 cells" ( <i>International Journal of Oncology 17; 1141-1149, 2000</i> ) 2)"Estrogens as endogenous genotoxic agents-DNA adducts and mutations" ( <i>Monographs, JNCI, 27, 75-93; 2000</i> ) 3)"Tissue-specific synthesis and oxidative metabolism of estrogens" ( <i>Monographs, JNCI, 27, 95-112; 2000</i> ) 4)"Induction of uterine adenocarcinoma in CD-1 mice by catechol estrogens" ( <i>Cancer Research 60, 235-237, January 15, 2000</i> ) 5)"Genotoxicity of the steroidal estrogens estrone and estradiol: possible mechanism of uterine and mammary cancer development" ( <i>Human Reproduction Update, vol.7,no.3 pp 273-281,2001</i> )
Bioassay of estrogenic/anti-estrogenic compounds	"Assessment of oestrogenic potency of chemicals used as growth promoter by in-vitro methods" ( <i>Human Reproduction- 2001 16: 1030-1036</i> )
Interaction of xenobiotics with sex hormone binding globulin; impact on endogenous steroid transport, bioavailability, mechanism of action	scientist has not yet indicated name of journal and publication date
Reproductive sequelae of developmental exposure of rabbits to trenbolone, zeranol & MGA; emphasis on differential & neoplastic transformation of germ cells	publication foreseen by the end 2001
Long term effects in children to estrogenized meat	"Accidental gynecomastia in children" ( <i>APMIS 109-suppl. 103,pp 203-9, 2001</i> )
Androgen exposures in utero, risk of breast cancer	"A study of opposite-sexed twin pairs" ( <i>Journal of The National Cancer Institute, JNCI, volume 93, issue 1;60-62, 3.1.2001</i> )

Endocrine disrupting activity of anabolic steroids used in cattle	1) " Characterisation of the affinity of different anabolics and synthetic hormones to the human androgen receptor, human sex hormone binding globulin and the bovine gestagen receptor" ( <i>APMIS</i> -108, 838-46; 2000) 2)"The fate of trenbolone acetate and melengestrol acetate after application as growth promotants in cattle - environmental studies" ( <i>Environmental Health Perspectives- in preparation</i> )
Screening water samples for estrogenic & androgenic anabolic chemicals	<i>scientist has not yet indicated name of journal and publication date.</i> some results can be found in <i>APMIS</i> 109-suppl. 103; pp 551-6, 2001 General discussion on " Existing guidelines for the use of meat hormones and other food additives in Europe and USA"
Endocrine disrupting effects of cattle farm effluent on environmental sentinel species	"A reexamination of variation associated with environmentally stressed organism" ( <i>Human Reproduction update, vol.7, no.3 pp.265-272, 2001</i> )
Human cells exposed to the estrogenic compound zeranol	"Oestrogenic potencies of zeranol, estradiol, diethylstilboestrol, Bishphenol-A, and genistein: Implications for exposure assessment of potential endocrine disrupters" ( <i>Human Reproduction- 2001 vol.16: 1037-1045</i> )

APMIS - Acta Pathologica, Microbiologica et Immunologica Scandinavia

AOAC - Scientific Association Dedicated To Analytical Excellence

JNCI - Journal of the National Cancer Institute

**other publications in relation to the subject:**

"Intrauterine exposure to diethylstilbestrol: long-term effects in humans"  
(*APMIS* 108: 793-804, 2000)

"Getting the problem of endocrine disruption into focus: the need for a pause for thought"  
(*APMIS* 108: 805-13, 2000)

"Human exposure to endocrine disrupters: standardisation of a marker of estrogenic exposure in adipose tissue"  
(*APMIS* vol.109:issue 3, 2001)

"Threshold analysis of selected dose-response for endocrine active chemicals"  
(*APMIS* vol.109:issue 3, 2001)

"Biochemistry and physiology of anabolic hormones used for improvement of meat production"  
(*APMIS* 109; 1-8, 2001)

"Possible health impact of phytoestrogens and xenoestrogens in food"

*(APMIS vol.109:161-84; 2001)*

"Possible health impact of animal oestrogens in food"  
*(Human Reproduction Update, vol.7, no.3 pp. 340-355, 2001)*

"Assessment of estradiol and its metabolites in meat"  
*(APMIS 109: 32-8, 2001)*

"Hormones in meat : different approaches in the EU and in the USA"  
*(APMIS 109, suppl. 103, 357-64, 2001)*

"Hormones and Endocrine Disrupters in Food and Water: Possible Impact on Human Health"  
(Forty-three peer-reviewed papers and discussions from an international workshop held at the University Hospital Rigshospitalet, Copenhagen, Denmark, May 27- 30, 2000 (Reprints of APMIS, Supplementum no. 103, vol 109, 2001))