EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate B - Scientific Health Opinions
Unit B3 - Management of scientific committees II

REVIEW OF SPECIFIC DOCUMENTS RELATING TO THE SCVPH OPINION OF 30 APRIL 99 ON THE POTENTIAL RISKS TO HUMAN HEALTH FROM HORMONE RESIDUES IN BOVINE MEAT AND MEAT PRODUCTS

(adopted on 03 May 2000)

1. TERMS OF REFERENCES

To advise the Commission whether any recent scientific information and, in particular, the following reports provide any new information or interpretations which would lead the SCVPH to revise its opinion on potential risks to human health from hormone residues in bovine meat and meat products of 30 April 1999.

- The December 99 Committee on Veterinary Medicinal Products' opinions and summary reports on 17β-oestradiol and progesterone for zootechnical and therapeutic purposes.

- The October 99 report of the UK's Veterinary Products Committee sub-group on the SCVPH opinion of 30/04/99

The Committee is asked to either confirm that there is no recent scientific information that would lead it to revise its previous opinion or, to revise the relevant parts of the opinion as necessary.

The Committee is asked to give its advice as soon as is reasonably possible, preferably at its plenary meeting foreseen for the 11/12 April 2000.

2. OPINION OF THE COMMITTEE

2.1. Documents

The scientific working group reviewed and discussed the documents provided as well as relevant new literature.

The UK's Veterinary Products Committee sub group's document addresses numerous items included in the SCVPH opinion of 30 April 1999 in a point by point approach.

The Committee on Veterinary Medicinal Products' reports are directed to the assessment of various hormones for therapeutical and/or zootechnical use in individual animals or individual herds, including 17β-oestradiol and progesterone, under the objectives of the Council Regulation (EEC) n° 2377/90 laying down the Community procedure to establish MRL-values of veterinary medicinal products. As stated in the CVMP report on the safety evaluation of steroidal sex hormones, in the past few years, CVMP had evaluated MRL applications for 17β-oestradiol, progesterone and three different synthetic hormones.

2.2. Comments

The advisory working group as well as SCVPH reviewed the above mentioned documents thoroughly and discussed all comments submitted. However, re-consideration of the previous opinion (SCVPH 1999) in light of these documents, leads the Committee to state again its concerns.

Briefly, these concerns were that an increased exposure to hormones can be associated with an increased risk of cancer and detrimental effects in development. Most of these effects have been demonstrated following high dose exposure in experimental animals, as well as human beings, at different stages of development (including adulthood). However, particularly in regards to the subject of estrogenic effects during development, there is no compelling evidence suggesting that these effects do not also occur at low doses. More importantly, if endogenous levels of hormones are associated with life-time risk of disease, for example, human breast cancer, then continuous additional exposure, even at low doses, is likely to add to this risk, but, as yet, cannot be quantified.

The SCVPH Committee's report of April 1999 identified several important considerations, linked to the use of hormones for growth promoting purposes in food producing animals. These include:

- the possible consequences of continuous daily exposure – even to low levels of hormones - to all segments of the human population, including at the most susceptible periods (*in utero* and prepubertal).

- the risk to the consumer posed by the use of synthetic hormones in implants, although the data base for a comprehensive evaluation of these synthetic compounds is obviously incomplete.

- the risk posed by higher hormone doses that might be present in meat, when hormonal implants are inappropriately used. These implant residues may end up in the diet of either the population at large or an individual consumer.

The SCVPH opinion stated that hormones exert their effects differently, at different stages of life. Concerns have been expressed that the current state of the art does not allow a reliable quantitative risk assessment to be made with respect to the impact of hormones, and particularly 17β-oestradiol, the most abundantly used hormone for growth promoting purposes. All segments of the human population, including the developing embryo, foetus and prepubertal children, are susceptible. New published data argue for low doses of natural and synthetic estrogens having a deleterious effect on the normal development of secondary sex organs in experimental settings.

Data from epidemiological and experimental studies provided strong evidence that 17β-oestradiol exposure is the most consistent risk factor in breast cancer. Consequently, any added exposure through exogenous hormones is likely to increase the lifetime risk for these cancers, but as yet cannot be quantified.

Adequate exposure assessment requires: firstly, an inventory of the physiological variation in hormone production during the entire human life span – bearing in mind that these physiological levels have been associated with hormone-dependent cancers, and secondly, the knowledge of hormone concentrations in food commodities. Recently, novel techniques in chemical analysis[1] allow for quantification of very low hormone levels, even below those levels considered at present to be physiological. It is anticipated that these more sensitive methods will be applied to thoroughly measure endogenous and environmental estrogens (including dietary ones) in different human populations. Therefore, additional time will be required to validate and apply this methodology in a reliable, accepted fashion before a re-evaluation of this issue can be conducted

A large number of investigations have focussed on elucidating the mechanisms by which hormones cause cancer. A relatively recent and unique aspect of this research concerns the genotoxic potential of these compounds, in particular 17β-oestradiol. Studies showing a lack of correlation between the estrogenic and carcinogenic potencies of certain estrogens (and their metabolites) have led to the hypothesis that besides oestrogen-receptor mediated effects, DNA damage effects may contribute to carcinogenicity.

Whilst 17β-oestradiol failed to show any direct and indirect effects in conventional mutagenicity assays, evidence is accumulating that 17β-oestradiol and/or its metabolites are capable of directly damaging DNA. Considering these more recent data, the Joint FAO/WHO Expert Committee on Food Additives, which very recently published its toxicological evaluation

[1] Results of "hormone" residue analyses of bovine meat and liver imported into the EU and originating from the USA "Hormone Free Cattle Program" analysis - First interim report, May 1999. R.W. Stephany and F. André *(rapporteurs).*

of the natural hormones 17β-oestradiol, progesterone and testosterone in animal production (WHO Food Additive Series, 43/2000), also concluded that oestradiol has a genotoxic potential. Concerning progesterone and testosterone, the data presented with this evaluation did not identify essentially new information.

Any disparities between the various evaluation reports are based on the different interpretation of individual research data. Some authors argue that the dietary exposure to residual amounts of oestradiol, progesterone and testosterone comprises an acceptable risk for the consumer, as these natural hormones (but not the synthetic hormones) occur naturally in meat. Others stress the fact that the new scientific evidence suggests an increased life-time risk for certain forms of cancers and the possibility of detrimental developmental effects even at low dose of added dietary exposure. Thus, although the evaluation reports show a high degree of consensus, the degree of acceptance of the risk related to the use of hormones in animals is modulated by their intended use *i.e.* defined medicinal applications *vs* abundant use for growth promotion purposes, taking into account the resultant consumer exposure.

2.3. Conclusion

The reports of the UK's Veterinary Products Committee subgroup and of the Committee on Veterinary Medicinal Products presented for review to the Scientific Committee, as well as recent scientific information, did not provide convincing data and arguments demanding revision of the conclusions drawn in the opinion of the SCVPH of April, 30th, 1999 on the potential risks to human health from hormone residues in bovine meat and meat products.

The SCVPH discussed again the obvious gaps in the present knowledge on target animal metabolism and residue disposition of the hormones under consideration, including the synthetic hormones. The SCVPH expects that the ongoing EU research programs will provide additional data on both topics.