HORMONES IN BEEF

POST 127
note
May 1999

Growth promoting hormones have been at the centre of a long running trade dispute between the EU and US. The problem arises because of an EU ban on imports of meat from cattle treated with such hormones. Beef producers in the US, Canada and elsewhere commonly treat their cattle with hormone growth promoters; EU policy thus prevents such beef being sold on the European market. While the EU maintains that the policy is based on scientific evidence regarding possible health concerns, the US complained to the World Trade Organisation (WTO) that the EU ban was no more than a trade barrier disguised as health measures.

In February 1998, a WTO Dispute Settlement Body ruled that the EU ban violated international trade rules. The EU now has until 13 May 1999 to comply with its WTO obligations. This POSTnote looks at the scientific basis of the EU policy and examines the options open to the EU in the light of the WTO ruling.

HORMONE GROWTH PROMOTERS

Hormones are chemical messengers that are secreted into the blood to control various processes within the body including growth. They may be given to cattle for a number of therapeutic or other veterinary reasons and are also used in the US and some other countries to boost the growth rate of cattle reared for beef production.

To date, six different hormones have been approved for such use in cattle in the US (**Box 1**). They include three naturally occurring hormones as well as three synthetic substances that mimic the action of these hormones. US Food and Drug Administration (FDA) regulations allow five of these substances to be used as implants; pellets containing specified doses of a hormone (or hormones) are implanted into the ear of a treated animal (see Box 1). The exception is melengestrol acetate (MGA), which is licensed for use as an additive to animal feed (Box 1).

Use of growth promoting hormones increases the efficiency with which treated animals convert their feed into weight gain. The animals put on more weight for the same amount of feed eaten, resulting in faster growth rates (rises in average daily weight gains of up to 20% are claimed). This means that farmers spend less money on feed and get their animals to market weight more quickly. Hormone treatment can also improve the flavour and tenderness of the meat produced.

BOX 1 FDA APPROVED HORMONE GROWTH PROMOTERS

Implants

Implants are pellets containing specified doses of one or (more usually) two hormones. They are inserted in the fleshy part of an animal's ear using a special implant gun; the implants do not enter the human food chain as ears are discarded at slaughter. The hormones are gradually released over a period of 50 days or so, to ensure a relatively constant and slightly elevated level in the animal's blood. Five hormone growth promoters are licensed for use in this way at specified dose levels (doses vary depending on whether the implants are intended for steers [castrated bulls] or heifers [suckling beef cows]):

- **Oestradiol-17b** - a naturally occurring female sex hormone (often given as the benzoate form in implants). It is typically given as the minor component (usually ~20-30mg) in combination with another hormone.
- **Progesterone** - another naturally occurring female sex hormone often given as the major component (up to ~200mg) of dual combination implants.
- **Testosterone** - the main (naturally occurring) male sex hormone, often used (as the propionate form) as the major component (up to ~200mg) of dual combination implants.
- **Trenbolone acetate** (TA**)** - a synthetic hormone that mimics the action of testosterone. It may be given as the major component (up to ~140mg) of dual combination implants.
- **Zeranol** - a synthetic hormone that mimics the action of oestradiol. It is often given as the sole component of implants at doses up to ~72mg.

Feed Additives

The sixth hormone approved for use by the FDA as a growth promoter is **melengestrol acetate** (MGA). Unlike the five growth promoters above, MGA is not given as an implant but is rather administered as an additive to animal feed. It is sold as a premix, added to animal feed to give a dosage of between 0.25 to 0.5 mg per head per day.

THE EU BAN

Concerns over the use of hormone implants first surfaced during the late 1970s and early 1980s when a number of incidents linked hormone residues in meat with various conditions in children (e.g. premature sexual development, ovarian cysts) and adult women (e.g. uterine and ovarian cancers). Such episodes generally involved abuse of good veterinary practice (e.g. direct injection of growth hormones) or hormones that have since been banned (such as diethylstilbene). Nevertheless, they created a climate of consumer concern that prompted a series of EU Directives through the 1980s **(Box 2**), culminating in a ban on:

- the use of growth promoting hormones within the EU except for therapeutic or other veterinary purposes;
- the import or intra-EU trade in meat from animals treated with growth promoting hormones.

BOX 2 DIRECTIVES ON HORMONE GROWTH PROMOTERS

Directive (**81/602/EEC**) banned the use of substances having hormonal action (except for therapeutic purposes) and the sale of meat from animals so-treated. But it did not apply to the use of oestradiol-17β, progesterone, testosterone, TA or zeranol; these substances continued to be subject to existing national regulations pending further study. After further research, the EU decided to extend its ban to include these five hormones. Directive **88/146/EEC** prohibited the use within the EU of synthetic hormone growth promoters for any purpose and the use of the three naturally occurring hormones for growth promotion, while **88/299/EEC** prohibited import and intra-EU trade in meat from animals so-treated. These Directives came into force from January 1st 1989; they have since been supplanted by **96/22/EC**. This effectively maintains the ban, both on the use of hormones as growth promoters within the EU, and on the import and trade of meat derived from animals so-treated.

JUSTIFICATION FOR THE BAN

The EU has sought to justify its ban on hormone growth promoters on two main grounds: that there is sufficient scientific evidence that sex hormones can increase the risk of cancer to warrant a ban on precautionary grounds; and that the ban is consistent with its responsibilities under WTO rules.

Scientific Evidence on Health Effects

The EU has consistently argued that its ban is justified on scientific grounds, citing evidence from bodies such as the IARC and JECFA[1] linking exposure to higher levels of **naturally occurring hormones** to increased risk of various types of cancer. For instance:

- Oestrogens in general (including oestradiol-17β) have been linked with increased risk of endometrial and breast cancers in women and to reproductive disorders in men; they have also been shown to be carcinogenic in animal tests.
- Progesterone increases the incidence of ovarian, uterine and mammary tumours in experiments in laboratory animals.
- Testosterone may be carcinogenic in humans, having been linked with prostatic tumours in men; it has also been shown to be carcinogenic in animal tests.

Other EU concerns focus on the safety of the **synthetic hormones**, since these are not normally found in humans, mammals or foods. Each of these has been shown to cause a variety of adverse health effects (including cancer and reproductive effects) in toxicity tests in laboratory animals; the concern is that they or the substances they are broken down into (metabolites) might have the potential to cause similar effects in humans.

[1] **IARC is the International Agency for Research on Cancer; JECFA is the UN/WHO Joint Expert Committee on Food Additives.**

BOX 3 THE US FDA's REGULATORY APPROACH

Naturally Occurring Hormones - the FDA accepts that persistent over-stimulation of hormonal systems by naturally occurring hormones may play a role in the development of certain types of cancer. It thus sets **incremental limits**, specifying permitted levels by which hormone residues in meat from treated cattle may exceed those normally found in meat from untreated cattle. These limits are set on the basis that the 'extra' residues present in meat should be no more than 1% of the level of hormone produced each day in humans. The calculation for each hormone uses the daily production levels typical of the segment of the population producing least of that hormone (e.g. pre-pubertal boys and girls for oestradiol and testosterone respectively). Calculations based on the relative consumption rates of other tissues compared with meat (muscle), are then used to set incremental limits (in parts per billion - ppb) for fat, kidney and liver (see **Table** below).

Synthetic hormones - TA, MGA and zeranol are not normally found in humans or cattle; FDA thus requires full-scale toxicity studies for these substances. Such studies confirm that the main toxicological concern is their hormonal activity; the regulatory approach is thus to determine **safe limits** below which no hormonal effects occur. Calculated safe limits for zeranol and TA are given in the Table for different tissues. For MGA the safe limit (25ppb) is close to the sensitivity limit for detection. FDA thus set a tolerance of 25ppb in all tissues (no MGA should be detectable using a method sensitive to 25ppb).

	Incremental levels / safe limits (ppb)			
Hormone	**Muscle**	**Fat**	**Kidney**	**Liver**
Oestradiol-17β	0.12	0.48	0.36	0.24
Testosterone	0.64	2.6	1.9	1.3
Progesterone	3	12	9	6
TA	50	200	150	100
Zeranol	150	600	450	300

While few question the academic credentials of the evidence cited by the EU, much of it refers to levels of exposure many times higher than those likely to be encountered via hormone residues in meat. The key question is whether similar effects occur at these lower levels of exposure. Here the EU's position on the risks posed by hormone residues in meat seems somewhat out of line with the views of other national and international bodies. For instance:

- In the US, the FDA point out that people are exposed to the naturally occurring hormones anyway, through synthesis in their own bodies, meat from untreated cattle and other foods. The regulations require (**Box 3**) levels of the 'extra' hormones present in meat from treated cattle to be many times lower than those normally found in the body. For synthetic hormones, FDA regulations require levels in meat and other tissues to be below the level at which no hormonal effects will occur in humans.
- The Codex Alimentarius Commission (CAC), the international body that recommends food safety standards recognised by the WTO (see later), saw no need to set limits for the three naturally occurring

BOX 4 THE SPS AGREEMENT

The SPS Agreement lays down the basic rules for setting food safety and animal and plant health standards. It allows countries to set their own standards, provided these are based on science and are applied only to the extent necessary to protect human, animal or plant health. Countries are encouraged to use international standards, guidelines and recommendations where these exist; relevant bodies include any international organisations/agreements open to all WTO members, although the Agreement names:

- the FAO/WHO[2] Codex Alimentarius Commission for food;
- the International Office of Epizootics for animal health;
- the FAO's Secretariat of the International Plant Protection Convention for plant health.

WTO members may set higher standards than those agreed by such bodies if there is a scientific justification for doing so, or if the standards are based on appropriate assessment of the risks (so long as the approach is consistent). The Agreement also includes provisions on approval, control and inspection procedures.

BOX 5 RECENT HISTORY OF THE DISPUTED EU BAN

1/1/1989 - EU ban comes into effect.
1/1/1995 - the SPS Agreement comes into force.
29/4/1996 - the Agriculture Council adopts Directive 96/22/EC confirming the existing ban on hormone growth promoters.
20/5/1996 - following complaints about the EU ban from the US, Canada (which also pursued its own complaint), Australia and New Zealand, the WTO Disputes Settlement Body set up a formal Disputes Panel.
2/7/1996 - the composition and terms of reference of the WTO Disputes Panel is agreed by the two sides.
30/6/1997 - the Disputes Panel rule that the EU ban violates three rules of the SPS Agreement (see text for details).
24/9/1997 - the EU notifies the WTO that it intends to appeal.
16/1/1998 - the WTO Appellate Body reverses two of the three Panel findings. But it upholds the finding that the ban was not based on an assessment of the risks to human health.
13/2/1998 - WTO Disputes Settlement Body adopts the Disputes Panel and Appellate Body reports.
13/3/1998 - EU agrees to comply with the Appellate Board's ruling, but requests more time to conduct additional risk assessments. Canada and the US insist on a firm deadline for compliance; because the parties cannot agree on a 'reasonable period of time' for implementation, the EU requests binding arbitration.
29/5/1998 - arbitrator decides EU must comply within 15 months.
13/5/1999 - deadline for EU compliance with WTO rulings.

hormones in any tissue in 1987. In each case CAC noted that "*residues resulting from the use of this substance as a growth promoter in accordance with good animal husbandry practice are unlikely to pose a hazard to human health*". However CAC did set limits for the maximum permitted levels of residues of zeranol and TA in muscle and liver.

- The UK originally opposed the ban on the grounds that there was no scientific evidence to justify its imposition (but has since implemented it along with all other Member States).
- A 1995 Scientific Conference on Growth Promotion in Meat Production convened by the EU examined the available evidence, and raised concerns over some aspects of hormone use (e.g. the potential for misuse, possible effects of using hormones in combination). However, it concluded that the "*daily production of sex hormones by humans is much higher than the amounts possibly consumed from meat, even in the most sensitive humans (pre-pubertal children and menopausal women*)" and that the limitations on use established by the US and CAC "*are a reasonable safeguard of public health*".

The EU Ban and the WTO

The EU has also maintained that the ban was consistent with its responsibilities under international trade rules. The key regulations are found in the Sanitary and Phytosanitary Measures (SPS, see **Box 4**) Agreement[3] that covers food safety and plant and animal health. This encourages WTO member countries to use international standards (such as those set by the CAC) in their regulations. But they also permit countries to set higher standards if there is a scientific justification, or if these are based on a risk assessment.

Following the EU's decision to adopt Directive 96/22/EC (which effectively confirmed the ban) in April 1996, Australia, Canada, New Zealand and the US issued a joint challenge in the WTO to the ban on the **import** of meat from cattle treated with hormone growth promoters. These countries claimed that the ban violated various EU obligations under the SPS Agreement; the challenge prompted the sequence of events outlined in **Box 5**. In June 1997, a WTO Disputes Panel ruled that the EU's ban violated three rules of the SPS Agreement:

- it was not based on a risk assessment;
- it was inconsistent (resulting in different levels of sanitary protection being adopted for different substances posing the same health risks to humans);
- it was not based on international (CAC) standards.

Following the EU's appeal, an Appellate Board upheld just one of these Dispute Panel rulings; the EU measures were not based on an appropriate assessment of the risks. It found the evidence submitted by the EU constituted "*general studies which do indeed show the existence of a general risk of cancer*" but that while relevant, such studies "*do not appear to be sufficiently specific to the case at hand*". The EU was thus found to be in violation of its obligations under the SPS Agreement and given until May 13 1999 to comply with the WTO rulings.

[2] **FAO - the United Nations Food and Agriculture Organisation. WHO - the World Health Organisation.**

[3] **The SPS Agreement was reached in 1994 as part of the GATT (General Agreement on Tariffs and Trade) Uruguay Round settlement.**

ISSUES

Following the Appellate Board's decision, the European Commission (EC) now has to decide how to balance its duty to ensure a high level of consumer health protection with its obligations to respect international trade rules. It published a Communication in February 1999 setting out its options, and these are discussed below.

Scientific Uncertainties

The Communication makes it clear that the EC still has a number of concerns about the potential adverse health effects of hormone residues in meat. It has thus initiated a series of 17 new research projects, details of which are given in **Box 6**. This represents the EC's latest attempt at a risk assessment that would be acceptable under the terms of the SPS Agreement. The current risk assessment addresses many of the comments made by the Appellate Board about the previous research programme; it deals with each of the 6 hormones individually and focuses on the potential for adverse health effects at the levels of these substances likely to occur in meat. The EC is thus confident that any measures taken as a result of the current studies could be defended in the WTO.

A major focus of the current EC concerns is the **potential for the misuse of hormones**. Farmers may seek to maximise weight gain by implanting the pellets directly into the muscle rather than in the ear; this could lead to sufficiently high levels of hormone residues around the injection site to pose a risk to consumers. The FDA claim that farmers have nothing to gain by such practices, since the implant dosage is optimised to produce the maximum economic return. However the EC is unconvinced, and several of the new research projects (Box 6) aim to assess the extent of such practices and their implications for human health. One of these projects has detected growth hormones in beef imported from the US under the Hormone Free Cattle (HFC) programme. In one case, it found evidence of a hormone being used in a way that is not approved by the FDA; residues of one or more of the 6 FDA-approved hormones were also found in some 12% of the beef sampled. These results have led the Commission to announce a ban on all beef imported from the US under the HFC programme from June 15th 1999 unless the US implements safeguards to ensure that such beef is free from growth promoting hormones.

Options Open to the EU

The EC has asked its Scientific Committee on Veterinary Matters relating to Public Health (SCVPH) to deliver an opinion on the potential adverse health effects of each of the 6 hormones. SCVPH published an interim report in April 1999 reiterating many of the concerns over the safety of the 6 hormones, as well as raising new worries over their ability to cause cancer (carcinogenicity) and their effects on DNA (genotoxicity). However, it is unlikely to deliver a final opinion until the end of 1999, when the full results of the new research are due. This means that the EC is unlikely to meet the deadline for WTO compliance (13th May 1999); the EU is currently considering three options to deal with this eventuality:

- Maintain the ban on imports and pay compensation to the US and Canada through trade concessions. This would buy the EC the time it needs to complete its latest risk assessment, and may (providing the settlement is negotiated) allow the EU influence over the trade sectors affected.
- Transform the ban into a provisional one. This is allowed on the basis of "*available pertinent evidence*" under the terms of the SPS Agreement, but any such move is likely to be contested by the US and Canada.
- Lift the ban on imports and introduce a labeling scheme to allow consumer choice. This would avoid the issue of compensation, but may expose consumers to risks. It may also be difficult to devise a labeling scheme that is acceptable to all parties.

The Council and the European Parliament are currently considering these options as a matter of urgency. Action taken by the EU on this issue may influence attitudes towards a number of other forthcoming trade issues, such as the EU's stance on bovine growth hormone for milk production and the labeling of GM foods.

BOX 6 THE EUROPEAN COMMISSION'S NEW RESEARCH

In the run up to the publication of the WTO rulings, the European Commission initiated 17 new studies on the potential adverse health effects to humans of the 6 hormones used as growth promoters in cattle. Intermediate results from some of these studies are currently available, but final results are not expected until the end of 1999 or later. The main areas of study include:

- Analysis of the potential genotoxicity of a metabolite of oestradiol-17β and evaluation of its potential health risks.
- Analysis of the potential genotoxicity and mutagenicity of TA and zeranol and their metabolites, and assessment of the implications to human health.
- A collaborative project assessing the potential risks to consumers arising from the misuse of oestradiol-17β.
- An assessment of the carcinogenicity of MGA, TA & zeranol and their metabolites, and the implications for human health.
- A study investigating the effects of low levels of zeranol on gene expression.

In addition to these studies, other projects will assess: the implications for human health arising from misuse of each of the 6 hormones; the direct and indirect effects of the hormones on the environment and wildlife; the potential adverse endocrine effects of the hormones to the population (via an epidemiological study).