# Anabolics: the approach taken in the USA

Tm Farber

*Ann Rech Vet* (1991) 22, 295-298



# Anabolics: the approach taken in the USA

TM Farber

*Toxicology Advisory Services, 706 Small Wood Road, Rockville, MD 20850, USA*

(27–28 March 1990: International Meeting on Anabolics, Toulouse, France)

**Summary** — In the United States, the Food and Drug Administration has developed a scientifically sound and rational approach to assure human safety from both naturally occurring and synthetically-derived hormones used in animal production. On this basis, estradiol, progesterone, androsterone, zeranol and trenbolone have been registered. For trenbolone a maximal residue limit of 50 ppb for meat has been accepted.

**Food and Drug Administration / hormone / trenbolone**

**Résumé — Anabolisants : l'approche adoptée aux USA.** *Aux États-Unis, la Food and Drug Administration a enregistré comme anabolisants 3 hormones naturelles (l'œstradiol, la testostérone et la progestérone) en se fondant sur le fait que les quantités de ces produits apportées par l'alimentation, représentent une très faible fraction des quantités biosynthétisées journellement par les individus.*

*En ce qui concerne la trenbolone, stéroïde semi-synthétique androgénique, l'analyse des résultats scientifiques a montré que ce composé n'était pas mutagène et que dans ces conditions, son évaluation toxicologique pouvait se faire sur la base d'une dose sans effet hormonal. Une limite maximale de résidus de 50 ppb pour la viande a donc été retenue pour ce composé. Une approche analogue a été appliquée au zéranol.*

***Food and Drug Administration / hormone / trenbolone***

As many of you are aware, the European Economic Community (EEC) has banned the use of anabolic hormones for growth promotion in food-producing animals and has effectively banned US meat abroad. This has occurred in spite of the fact that the US Food and Drug Administration (FDA) has developed a scientifically sound and rational approach to assure human safety from both naturally-occurring and synthetically-derived hormones used in animal production. We well know that the consumer is exposed throughout his lifetime to large amounts of estradiol, testosterone and progesterone as a consequence of their own daily *de novo* synthesis of these hormones and to much lesser quantities of these hormones from the consumption of meat and milk containing naturally-produced animal hormones.

Analysis of meat from cattle treated with hormones for growth promotion contain 15 000 times less estradiol than the average daily amount produced by a human male and several million times less that the amount produced by a pregnant woman. This is also the case for progesterone and testosterone. Thus, the FDA feels that the risk is negligible compared to the consumer's own daily production.

The hormone levels the FDA considers to be safe in muscle are 120 ppt for es-

tradiol, 3 ppb for progesterone and 600 ppb for testosterone. These levels were established on the basis that no physiological effect could be expected from consuming meat containing added hormone equal to 1% or less of the amount produced daily by prepubertal children. In actuality, analysis has demonstrated that human exposure falls far below these calculated safe levels. The FDA has concluded that it is unnecessary to monitor these hormones in meat because these levels could not reach a concentration deemed to be unsafe even in cases of misuse. The FDA has also recognized the impossibility of banning these agents because analytical methodologies cannot distinguish between naturally-occurring hormones and hormones found in meat as a consequence of administration for growth promotion purposes.

The FDA believes that the approach for the regulation of natural and synthetic hormones is rational, logical and scientifically sound. The FDA also believes that a proper forum for the discussion of the safety of these hormonal agents should be at the level of the joint expert committee on veterinary drugs in food. Such a meeting was held in June, 1987 when 11 experts from 7 different countries met at the request of the codex committee to evaluate 5 hormonal agents. This joint expert committee found that residues resulting from the use of these compounds (naturally-occurring hormones) as growth promoters are unlikely to pose a hazard to human health. The committee also agreed that, with proper use, zeranol and trenbolone acetate posed no safety concerns to consumers.

You are well aware that a scientific working group appointed by the EEC to look into the safety of these agents agreed with the conclusions of the US FDA regarding the safety of these agents. This EEC committee, chaired by Professor GE Lamming of the United Kingdom and composed of 15 additional European scientists, has recently presented its findings to the British Veterinary Association. The committee concluded that the use of either naturally-occurring or synthetic hormones as growth promoters in cattle does not present any harmful effects to the health of the consumer.

Much discussion has occurred today about trenbolone. Please allow me to spend some time discussing the FDA's approach in regulating hormones and to describe to you in summary form the important studies performed on trenbolone which were the basis of approval of this agent.

An extensive series of toxicologic studies has been performed on trenbolone acetate. By virtue of its hormonal activity, trenbolone acetate produced certain endocrinologic effects in the rat which were not surprising. These effects are the following: impairment of reproductive performance in rats; female rats had coarse male-like fur, perineal hair loss, prominent pudendum, small ovaries and non-palpable cervix; male rats receiving high doses had an increased incidence of small adrenals, small pituitaries and lower prostate, testes and kidney weights; in rhesus monkeys trenbolone acetate inhibited gonadotrophin secretion and ovarian function.

An increase in pancreatic tumors was seen in the rat only at the highest dose tested (50 ppm) in a chronic bioassay (males 20.8% *vs* 8% in the controls, $P = 0.063$ ; females 12.2% *vs* 0% in the controls, $P = 0.014$). The incidence at 0.5, 1.0, 4.0 and 16.0 ppm was 4.0, 4.1, 6.8 and 4.1% respectively, indicating the absence of a dose-related increase. It was concluded by the FDA and the World Health Organization (WHO) that the increase in pancreatic islet cell tumors observed in the rat

**Table I.** Mutagenicity studies on 17 β-trenbolone.

| *Tests* | *Effects* [a] |
|---|---|
| *Microbial tests* | |
| *Salmonella typhimurum* | – |
| *Escherichia coli* (SOS test) | – |
| *Bacillus subtilis* (REC-assay) | – |
| *Mammalian cell tests* | |
| Chinese hamster (CHO, V79) | – |
| Mouse lymphoma (L5178Y-TK locus) | ± |
| UDS (HeLa, Syrian hamster embryo) | – |
| Sister chromatid exchange (V79) | – |
| *In vitro* DNA binding | – |
| *In vivo* DNA binding | + [b] |
| Micronucleus (CHO, human lymphocytes, bone marrow) | – |
| Chromosomal aberrations (mouse and rat marrow, spermatogonia) | – |
| *In vitro* transformation (C3H10T1/2) | – |
| (baby hamster kidney, hamster embryo cells) | + |
| Solt-Farber assay) | – |

[a] : + positive effect; – negative effect; ± equivocal effect. [b] : but very low levels of binding.

study was not the result of a carcinogenic effect of trenbolone acetate.

In a chronic bioassay, male mice showed an increase in total hepatic tumors at all treatment levels. This increased incidence was statistically significant only at the 100 ppm dose. The females once showed an increase in the incidence of liver tumors in the 100 ppm group. However, the effect was less remarkable than in the males. The FDA felt that these tumors were a manifestation of the hormonal effect of some naturally-occurring and synthetic anabolic steroids in a recognized target tissue. As seen in tables I and II a battery of mutagenicity studies have been performed on 17-β and 17-α trenbolone. No genotoxic activity has been observed.

The FDA believes that 3 types of hormonal agents can be clearly distinguished and regulated on the following bases : i), If the compound is not genotoxic and not tumorogenic, it can be regulated on the basis of hormonal no-effect level; ii), if the

**Table II.** Mutagenicity studies on 17-α trenbolone.

| *Tests* | *Effects* |
|---|---|
| *Microbial tests* | |
| *Salmonella typhimurum* | – |
| *Mammalian cell tests* | |
| Chinese hamster (HGRT) | – |
| Mouse lymphoma (L5178Y) | ± |
| UDS (HeLa) | – |
| Chromosomal aberrations (human lymphocytes, rat marrow, spermatogonia) | – |

compound is not genotoxic but is positive, to some extent, in chronic toxicity studies and there are specific effects on tissues known to be hormone dependent, then the compound can be presumed to be tumorogenic by a non-genotoxic mechanism and can be regulated on a hormonal no-effect level basis; iii), if the compound is genotoxic and tumorogenic then it can be regulated on the basis of a virtually safe level under the sensitivity of method procedure. Clearly, trenbolone acetate falls into the second category.

Based on the FDA's evaluation of the toxicologic data on trenbolone acetate, a safe concentration of total residues of trenbolone acetate was established based upon the application of traditional safety factors to the hormonal no-effect-level seen in the female rhesus monkey. This level in meat was set at 50 ppb, a level that the FDA is fully confident in.