Beef Cattle Growth Promoting Products are Safe When Used as Approved — Carcinogenic Aspect

J.W. Lauderdale
October 2007

Summary

Regulatory authorities of the U.S. Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM) and Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA) concluded that:

1) consuming meat from cattle produced with growth promoting products containing estradiol, testosterone and progesterone creates no carcinogenic potential;
2) the growth promoting products containing trenbolone acetate (TBA), zeranol or melengestrol acetate (MGA) can be regulated through tolerances and acceptable daily intakes (ADI) without concern for carcinogenicity.

Introduction

The Food and Drug Administration Center for Veterinary Medicine is responsible for ensuring that food from animals treated with animal health products is safe for human consumption. Concerns have been expressed in news media and through some publications that beef cattle growth promoting products might be associated with cancer in humans. Such concern is not founded since each approved product has undergone extensive investigation under the supervision of and review by scientists at FDA/CVM to ensure animal products from treated animals are safe for human consumption.

Natural Hormones: Estradiol-17β, Progesterone and Testosterone

Estradiol-17β, progesterone and testosterone are steroid hormones used in beef cattle growth promoting products. Each of these hormones occurs naturally and each is produced in significant quantities throughout the lifetime of every man, woman and child. These hormones are essential for the proper physiological functioning and maturation of all mammals.

FDA/CVM Regulatory Decisions

Scientific studies demonstrated that, when the products containing these hormones are used in accordance with their label, concentrations of the hormones in edible tissues remain within the normal physiological range established for edible tissue from untreated animals of the same sex and age. Consumers are not at risk from eating food from animals treated with these products because the amount of added hormone is negligible compared to the amount normally found in the edible tissues of untreated animals and the amount that is naturally produced by the consumer's own body.[1]

The physiology, pharmacology and toxicology of these hormones are well established. The accumulated evidence supports a role for estradiol in the development of certain types of cancer seen in humans and animals under certain extreme circumstances. Experiments in which very high (superphysiologic) doses of estradiol were administered to animals demonstrate that estradiol has the potential to cause toxic effects, including carcinogenic effects. The evidence also indicates that estradiol is not genotoxic, thus does not initiate cancer *per se*.[4] FDA scientists have concluded, however, that unless there is persistent over-stimulation of the hormonal system by residues remaining in the tissues of treated animals, individuals will not be subjected to an unacceptable increased risk of cancer from estradiol or testosterone. FDA scientists concluded that there is no persistent over-stimulation of the hormonal system by residues remaining in the tissues of treated animals. Because these compounds are naturally occurring in people and in food-producing animals, an individual is exposed to large quantities of these compounds throughout his/her lifetime by his/her own daily synthesis and to much lesser quantities from untreated food-producing animals.

FDA/CVM regulates natural hormones through the Allowable Incremental Increase approach.[5] FDA scientists have concluded that no harmful effects will occur in individuals chronically ingesting beef that contains an incremental increase of endogenous steroid equal to 1 percent or less of the amount produced daily by the segment of the population with the lowest daily production. For example, prepubertal boys synthesize the least estradiol (6,000 ng/24 hours) and the least progesterone

(150,000 ng/24 hours); prepubertal girls synthesize the least testosterone (32,000 ng/24 hours).[17] Daily consumption rates of 300 g of muscle, 50 g of fat, 100 g of liver and 50 g of kidney tissue were established by worldwide regulatory organizations. The FDA/CVM permitted incremental increase of 120 ppt of estradiol and 0.64 ppb of testosterone in beef muscle above the amount naturally present in untreated animals. Based upon relative consumption of other tissues rather than muscle, safe incremental levels of 480 ppt and 2.6 ppb for estradiol and testosterone, respectively, are established for fat; 350 ppt and 1.9 ppb for kidney tissue; and 240 ppt and 1.3 ppb for liver.[6,7] The acceptable increment for progesterone is 3 ppb in muscle and 12 ppb in fat.[8]

Therefore, no carcinogenic potential exists as a result of natural hormones from consumption of meat from either treated or untreated cattle.

Food and Agriculture Organization/World Health Organization Regulatory Decisions

The Thirty-second Report of the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 1988) concluded that:

1) none of these hormones are mutagenic;
2) the carcinogenic response was related to the hormonal activity at levels considerably higher than those required for a physiological response.

The committee concluded that the amount of estradiol-17β, progesterone and testosterone ingested by eating beef from treated cattle would be incapable of exerting a hormonal effect, and, therefore, incapable of exerting any toxic/carcinogenic effect in human subjects.[2] JECFA re-addressed use of the natural hormones for growth promotion during the Fifty-second JECFA (2000) Meeting and established ADIs for each hormone of 0.05 μg/kg (50 ppt) for estradiol, 30 μg/kg (30 ppb) for progesterone and 2 μg/kg (2 ppb) for testosterone per kg of body weight.[13] These ADIs reinforced JECFA's previous decisions that these hormones, as used in cattle production, do not pose a human food hazard.

Synthetic Hormones: Trenbolone Acetate, Zeranol and Melengestrol Acetate

TBA and testosterone have an androgenic biologic activity as an androgen; zeranol has biologic activity as a weak estrogen; and MGA and progesterone have biologic activity as a progestogen. These molecules are used in beef cattle growth promoting products.

FDA/CVM Regulatory Decisions

Trenbolone Acetate

After extensive dose-response carcinogenetic studies in mice and rats, the Cancer Assessment Committee of the CVM concluded that TBA is not a carcinogen. After extensive studies, the CVM also concluded that TBA and both the 17α-OH-trenbolone and 17β-OH trenbolone metabolites are not mutagenic.[9, 10]

FDA/CVM determined, based on extensive dose-response animal feeding studies (mouse, rat, monkey), that the principle effects of trenbolone acetate are associated with its hormonal activity. Therefore, trenbolone acetate is regulated based on the Hormonal No Observed Effect Level (HNOEL).

Zeranol

Human food safety was established by the data in the parent NADA 38-233. These data documented zeranol is neither a carcinogen nor mutagen. Zeranol is a non-steroidal, anabolic agent, determined to be a weak estrogen. Based on the negative findings for carcinogenicity and mutagenicity in extensive animal studies, the CVM allowed zeranol to be regulated as a hormone through the HNOEL. An ADI was established at 1.25 μg per kilogram of body weight per day.[11]

During the past 10 years, concerns about *in vitro* studies with zeranol and estradiol-17β have been reported in some published scientific papers and abstracts, in newsprint and on TV. The concerns are that these estrogenic substances consumed by humans may contribute to breast cancer and other estrogen-dependent human disorders. The long-term

studies with rats (an estrogen-sensitive animal) to investigate the potential for both human and animal health estrogen-containing products to cause cancer found that zeranol is not a carcinogen. Zeranol binds to the estrogen receptor with low affinity, which is the understood mechanism by which it is able to elicit an estrogenic biologic response. All biologic responses are dose-dependent. Long-term animal dose-response studies investigated the long-term effect of zeranol at doses covering the range of "very small" to "very large" doses. These animal studies provide the valid data upon which regulatory agencies worldwide make defendable decisions that an animal health product is or is not safe for use without compromising human food safety.[12]

The concerns and assumptions that beef might produce cancer that were published in papers, abstracts and in the media were based on *in vitro* studies and are not consistent with the FDA/CVM conclusion that meat and meat products derived from cattle implanted with zeranol are safe for human consumption. The FDA/CVM relies on animal (*in vivo)* studies, not cell culture (*in vitro*) studies, to provide the valid data upon which regulatory agencies worldwide make defendable decisions that an animal health product is or is not safe for human consumption. FDA/CVM conclusions are the correct conclusion, not the implications derived from *in vitro* studies. Zeranol is used consistent with its label in cattle growth promoting products and does not pose a human health hazard.[12]

Melengestrol Acetate

The human food safety studies defining the toxicity of MGA are contained in NADA 34-254 and NADA 39-402, and a detailed summary of these studies has been published (Lauderdale et al., 1977. *J. Toxicol. & Environ. Health* 3:5-33). The data referenced in Freedom of Information (FOI) documented that MGA is neither a mutagen nor carcinogen. The endpoint of toxicological concern is hormonal activity; therefore, MGA is regulated as a hormone with a tolerance of 25 ppb in fat. It was concluded that residues of parent MGA at or below 25 ppb in edible tissues of treated animals will not elicit a hormonal response. For monitoring purposes, fat is the target tissue.[14]

Food and Agriculture Organization/World Health Organization Regulatory Decisions (JECFA)

Trenbolone Acetate

The Twenty-seventh Report of JECFA (1983) concluded that trenbolone is not carcinogenic, is a hormone that could induce lesions at elevated doses and duration of treatment, and can be regulated as a hormone with an ADI based on an HNOEL.[16]

Zeranol

The Thirty-second Report of JECFA (1988) concluded that zeranol is not carcinogenic, is not genotoxic, is not mutagenic, and is not teratogenic. Zeranol is a non-steroidal anabolic agent, and was determined to be a weak estrogen. Zeranol is regulated as a hormone with an ADI based on an HNOEL.[2]

Melengestrol Acetate

The Fifty-fourth Report of JECFA (2001) concluded that MGA is neither carcinogenic nor genotoxic and can be regulated as a hormone with an ADI based on a HNOEL[15].

European Community (EC) Studies Relative to Human Food Safety of Beef Produced with the Aid of the Natural Hormones Estradiol-17β, Progesterone and Testosterone and the Synthetic Hormones Trenbolone Acetate, Zeranol and Melengestrol Acetate

The EC banned importation of beef produced with the aid of growth promoting products. The U.S., Canada and Australia sued the EC in the World Trade Organization (WTO) to lift the beef import ban since all evidence documented that beef is safe for human consumption. The WTO Appellate Body, in their January 1998 decision, allowed the EC to fund studies to obtain information relative to the human food safety of beef produced using FDA-approved growth promoting hormone containing products. The EC "17 Studies" were funded to investigate further the 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 in cattle growth promoting products. The six hormones are the natural steroids estradiol, progesterone and testosterone and the

synthetic hormones or hormonally active chemicals zeranol, melengestrol acetate and trenbolone acetate.

The data derived from the EC "17 Studies" were reviewed relative to the extensive scientific publications existing from studies completed over the past 50 years. The EC-funded studies that have been published have not identified any human health hazard from consuming beef produced with use of the FDA/CVM approved growth promoting products. Residue concentrations were based on the most modern assay technology. Modern assay sensitivity is more exquisite than earlier assays and with limits of detection well below those of earlier assays. The data from the EC-funded studies reaffirmed that residues present in beef produced using the approved dose of the growth promoting products are below the FDA/CVM allowed levels. The reviewed EC papers reaffirm that residues may be/will be detected in cattle when the products are used illegally, such as implantation in sites other than the ear and quantities of product administered to the animal that are greater than the label allows.

Conclusion

Human food safety from consuming beef produced with the aid of growth promoting hormonal products is assured because 1) the FDA/CVM approval procedure requires adequate data from scientifically justified studies that ensures there is no human safety concern, and 2) label use of cattle growth promoting products is both monitored and enforced by the U.S. Department of Agriculture Food Safety Inspection Service (FSIS) and illegal use is minimized/prevented through monetary fines and imprisonment. Additionally, there is no producer economic incentive to use greater than label number of implants or dose of MGA.[3]

References

[1] FDA Veterinarian, Center for Veterinary Medicine, September/October 2002, Vol. XVII, No. V.

[2] Evaluation of Certain Veterinary Drug Residues in Food, Thirty-second Report of the Joint FAO/WHO Expert Committee on Food Additives, World Health Organization Technical Report Series 763, World Health Organization, Geneva, 1988.

[3] Lauderdale, J. W. Review of the Publications Derived from the European Commission (EC) Funded "17 Studies" Commissioned to Investigate Further the 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, Animal Health Institute, February 2002.
[4] FDA/CVM Freedom of Information, NADA 118-123.
[5] 21 Code of Federal Regulations (CFR) 556.240.
[6] FDA/CVM Freedom of Information, NADA 011-427.
[7] FDA/CVM Freedom of Information, NADA 141-040.
[8] FDA/CVM Freedom of Information, NADA 110-315.
[9] FDA/CVM Freedom of Information, NADA 138-612.
[10] FDA/CVM Freedom of Information, NADA 141-043.
[11] 21 CFR 556.760.
[12] Lauderdale, J.W. Public Safety Is Assured for Beef Produced with Approved Growth Promoting Implants, NCBA/GET IT, 23 March 2006.
[13] Evaluation of Certain Veterinary Drug Residues in Food, Fifty-second Report of the Joint FAO/WHO Expert Committee on Food Additives, World Health Organization Technical Report Series 893, World Health Organization, Geneva, 2000.
[14] FDA/CVM Freedom of Information, NADA 034-254 and NADA 039-402.
[15] Evaluation of Certain Veterinary Drug Residues in Food, Fifty-fourth Report of the Joint FAO/WHO Expert Committee on Food Additives, World Health Organization Technical Report Series 900, World Health Organization, Geneva, 2001.
[16] Evaluation of Certain Veterinary Drug Residues in Food, Twenty-seventh Report of the Joint FAO/WHO Expert Committee on Food Additives, World Health Organization Technical Report Series 696, World Health Organization, Geneva, 1983.
[17] Fagatz, G.E. and E. Gurpide. In *Handbook of Physiology*, Greep & Astwood, eds. Section 7, Vol. 11 (1):603, 1973; cited by T.M. Farber & M. Arcos in Regulatory Approach to the Use of Anabolic Agents, in *Anabolics in Animal Production: Public Health Aspects, Analytical Methods and Regulation*, eds. Meissonnier & Mitchell-Vigneron, Office International des Epizooties (OIE), Paris, France, 15-17 February 1983 OIE Symposium (ISBN 92-9044-118-6).

J. W. Lauderdale
lauderents@aol.com