RATIONALE FOR THE SAFETY OF IMPLANTS

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INTRODUCTION

Hormonal stimulants have been used to improve growth and efficiency of beef cattle since 1954 (Preston, 1975 and 1987; Hancock et al. 1991). After feeding a nutritionally adequate diet, hormone implants are "the best technology that the cattle industry has for improved efficiency and decreased carcass fat" (Preston, 1993), or, more correctly, increased lean. Safety of implants, both for cattle and for people consuming beef, is assured by U. S. Food and Drug administration (FDA) approval prior to implant use in commercial practice. The compounds used in implants are classified as natural or synthetic, even though all are synthesized chemically. "Natural" compounds are those found in normal body metabolism; "synthetic" compounds have actions similar to the natural compounds but are not found in normal body metabolism. Freedom of Information Summaries, prepared by the manufacturer and available from the FDA, provide information on efficacy, dosage, investigators, animal safety, pharmacology, residue, human safety, and indications for use of all approved implant products. Estrogens and androgens are the primary compounds used in implants, although progestins also are found in some products.

Estrogens

Diethylstilbestrol (DES) was the first hormonal growth stimulant used for cattle. It is a synthetic estrogen. Because it has activity when fed orally, it was either fed or implanted. Approval of DES was based on a residue bioassay sensitive to 3 ppb (Preston et al, 1956) that utilized its hormonal activity to increase the uterine weight of immature female mice. Potential intake from beef containing residues less than this amount were considered infinitesimal compared to human doses of DES used at that time for the prevention of miscarriage (later shown to be ineffective) and as a contraceptive (Marcus, 1994). Thus, in a sense, a "no hormonal effect level" (3 ppb) was used as the basis for the approval of DES for cattle production. Use of DES in cattle production was discontinued in 1979, after 25 years of use, not because of any safety problems associated with its use in cattle.

Estradiol (17-beta, E2) is a natural estrogen found in many implant products. The rationale for its safety was similar to that used for DES. This can be illustrated by comparing potential estrogen intake from various foods (Table 1); hormonal activity is present "naturally" in many human foods. Table 2 shows relative estrogen levels secreted by humans in various physiological stages and the daily payout of estrogen from an estrogen implant in a steer averaged over 120d, and the potential estrogen intake in beef from implanted cattle. Considering that the oral effectiveness of natural estrogens is low (approximately 10%), it is readily apparent that estradiol implants pose no human safety risk.

Zeranol also is used as an estrogenic implant compound. Classified as a synthetic estrogen, it was discovered as a fungally produced contaminant in moldy corn. Like estradiol, the potential intake of zeranol in beef from cattle implanted with this product is infinitesimally small (Stob et al, 1954).

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Table 1. Estrogenic activity of several common foods.

Food	Estrogenic activity[1]
Soybean oil	1,000,000
Cabbage	12,000
Wheat germ	2,000
Peas	2,000
Eggs	17,500
Ice cream	3,000
Milk	65
Beef from pregnant female	700
Beef from implanted cattle	11
Beef from non-implanted cattle	8

[1]ng/500 g of food.

Table 2. Estrogen production in humans, estrogen payout from a typical estrogen implant, and potential estrogen intake in beef from implanted cattle.

Item	Estrogen amount
Estrogen production in humans:	
Pregnant woman	90,000,000 ng/d
Non-pregnant woman	5,000,000 ng/d
Adult man	100,000 ng/d
Pre-puberal children	40,000 ng/d
Synovex-S implant (120 d)	120,000 ng/d
500 g beef from implanted cattle	11 ng

Androgens

The primary androgen used in implant products is trenbolone acetate (TBA). Testosterone propionate is used in some implant products based on a no "hormonal effect level" for testosterone of .64 ppb; observed residue levels in beef from heifers 30 days after implantation were .101, .339, .034 and .450 ppb, respectively, for muscle, fat, liver and kidney, indicating a wide margin of safety for implant products containing testosterone propionate.

Activity of androgens can be partitioned into androgenic (male characteristics) and anabolic (muscle stimulation) effects. Compared to testosterone, the anabolic activity of TBA is much greater (8 to 10 fold) whereas its androgenic activity is relatively less (3 to 5 fold; Neuman, 1975). This is a major reason for TBA use in the newer implant products. During metabolism, the acetate group is hydrolyzed leaving the active compound, 17-beta trenbolone (17-beta TBOH), the primary form found in muscle. Via epimerization, 17-beta TBOH is converted to a less active metabolite, 17-alpha trenbolone (17-alpha TBOH), the primary form found in the liver, bile and feces (Heitzman and Harwood, 1977).

Based on radioimmunoassay procedures, residues of trenbolone 63 days after implantation are shown in Table 3 (Heitzman and Harwood, 1977); the difference in residue level between these two treatments probably is due to the difference in TBA dosage between the two implants rather than an effect of estradiol. Table 4 shows residues of 17-beta TBOH and 17-alpha TBOH 60 days after implantation with TBA (Dixon and Heitzman, 1983). The residue from 17-beta TBOH was much higher than from 17-alpha TBOH in muscle and fat, whereas the opposite was true for liver and kidney.

Table 3. Trenbolone residues (ppb) in steers implanted[1] with TBA[2] or TBA+E2[3].

Tissue	Control	TBA	TBA+E2
Muscle	0.05	0.30	0.25
Fat	0	0.24	0.18
Liver	0.02	0.39	0.21
Kidney	0	0.11	0.06

[1]63 d prior to slaughter
[2]300 mg TBA
[3]140 mg TBA + 20 mg estradiol

Table 4. TBA residue forms and concentrations (ppb) from a cow implanted[1] with TBA[2].

Tissue	17B-TBOH[3]	17A-TBOH[4]
Muscle	0.27	0.04
Fat	0.25	0.15
Liver	0.28	1.42
Kidney	0.16	0.41

[1]60 d prior to slaughter
[2]300 mg TBA
[3]17beta-trenbolone
[4]17alpha-trenbolone

Do these residue levels of TBA pose a human safety problem? Part of any approval requirement is the determination of a "no hormonal effect level" (NHEL) in several animal species (Table 5). For the more active metabolite (17-beta TBOH), the pig is the most sensitive animal because it gives the lowest NHEL. Using the NHEL for both metabolites in the pig and a safety factor of 100, an acceptable daily intake (ADI) for a 60 kg human is calculated to be 6 and 216 ug/day (Table 6). Using an assumed consumption value for beef muscle, fat, liver and kidney (Table 7), consumption of both metabolites can be calculated as a maximum of .129 and .181 mg/day. These potential consumption amounts are then compared to ADI amounts for both metabolites (Table 8). As can be seen, both metabolites have very large safety factors. These results gave rise to a joint FAO/WHO conclusion that "the low residue levels of TBA and its metabolites in meat products would result in exposures far below levels at which hormonal activity was observed in animal models" (FAO/WHO, 1983).

Table 5. No hormonal effect level (NHEL) in several animals.

Animal	Sex	Compound	NEHL[1]
Rat	Male/Female	TBA	25
Mouse	Male/Female	TBA	50
Pig	Barrow	17B-TBOH	10
	Barrow	17A-TBOH	>360
Monkey	Castrate male	17B-TBOH	>40
	Female	TBA	>240

[1]No hormonal effect level; ug/kg body weight.

Table 6. Acceptable daily intake (ADI)[1] for humans[2].

Metabolite	NHEL[3](pig)	ADI
17B-TBOH	10	6 ug/d
17A-TBOH	360	216 ug/d

[1][(NHEL)(BW)] / (safety factor = 100).
[2]60 kg body weight (BW).
[3]No hormonal effect level.

Table 7. Potential human consumption of TBA metabolites.

Tissue	Consumption[1]	17B-TBOH[2]	17A-TBOH[2]
Muscle	300	.081	.012
Fat	50	.012	.007
Liver	100	.028	.142
Kidney	50	.008	.020
Totals	500	.129	.181

[1]Assumed consumption, g/d
[2]ug/d.

Table 8. Potential human consumption of TBA metabolites relative to ADI.

Item	17B-TBOH	17A-TBOH
PDI[1]	.129	.181
ADI[2]	6	216
Safety factor[3]	4,650x	119,300x

[1]Potential daily intake, ug/d.
[2]Acceptable daily intake, ug/d.
[3]Including the 100x safety factor used in calculating ADI.

Implications

The safety of properly administered hormonal implants in beef production is assured when FDA approves their use; such approval is highly important in national and international deliberations. Implant safety also is implied by the fact that historical (over 40 years) usage in cattle production has resulted in no observed safety problem. Furthermore, the following agencies and committees have concluded that the use of hormonal implant technology in cattle production poses no safety risk to humans consuming beef:

- U. S. Food and Drug Administration
- World Health Organization (WHO)
- Food and Agriculture Organization (FAO)
- Codex Alimentarius
- European Economic Community (EEC) Scientific Working Group on Anabolic Agents (1981)
- European Community (EC) Scientific Conference on Growth Promotion in Meat Production (1995)

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QUESTIONS & ANSWERS

Question: It is common knowledge that athletes and sports enthusiasts use various steroids. Are implants being used by humans and what side effects are apparent?

A: I'm not aware of any abuse, but abuse may occur. Health defects may not show up for many years as was the case for DES used for pregnant women and effects on uterine cancer in their daughters. So effects of estrogen or steroid abuse may be very delayed.