The Use of Melengestrol Acetate (MGA) in Cattle Feed and the Impacts on Food Safety in Canada
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Introduction to the Use of Anabolic Hormones in Food Animals

The use of steroid hormone analogues in animals used for human consumption has been a source of international debate for many years. In the European Union, a total ban of anabolic agents for growth promotion in food animals has been in place since 1988 on the bases of unknown or poorly demonstrated food safety (Stephany 2001). After a review of 17 scientific studies by the Scientific Committee on Veterinary Measures Relating to Public Health, the European Commission concluded that hormonally-treated meat poses a risk to consumers (SCVPH 2002). Conversely, in Canada and the USA, certain synthetic and natural anabolic steroid hormones are approved for use under controlled regulations (Stephany 2001). Interestingly, after a review of the same 17 studies, Health Canada concluded that residues in beef pose no undue risk to human health, provided the drugs are used and administered appropriately (Health Canada 2012).

Melengestrol acetate (MGA) is one of six steroidal hormone growth promoters approved for use in Canada (Health Canada 2012). These products are used to improve growth rate and feed efficiency, as well as to suppress estrus in beef heifers (CFIA 2008). They are not approved for use in any species other than beef cattle meant for slaughter (Health Canada 2012). MGA is the only drug of its kind that is administered in animal feed, and its labelled dose in Canada is 0.4mg per heifer per day (CFIA 2008). A mandatory withdrawal of 2 days before slaughter is applied to any animal that is administered MGA (CFIA 2008).

In order to construct an informed opinion about the safety of meat from beef cattle that have been fed MGA, a number of questions must be answered. The purpose of this paper is to review the following general concerns regarding hormonally-treated cattle as they relate to food safety and public health:
1. the effects of MGA on laboratory animals and humans;
2. the level of MGA that is safe for human consumption, if any; and
3. the amount of MGA residue present in edible tissues at slaughter.

Effects of MGA on Laboratory Animals and Humans

In 2000, the World Health Organization released a toxicological evaluation of MGA based on reviews of multiple clinical trials and decades of research (WHO 2000). Although it is beyond the scope of this paper to review each one, certain studies that comply with Good Laboratory Practices are presented.

Reproductive Toxicity
Paterson and Hall (1983) found mammary and endometrial hyperplasia in rats fed MGA at doses of 0.15mg/kg/day or higher for 90 days. Studies in rats have found dose-dependent decreases in ovarian, testicular, and/or uterine weights attributed to the progestational activity of MGA, but no change in gonadal function (Paterson and Hall 1983; Wood et al., 1983). The no observable effect limit (NOEL) for these studies varied from 15 to 55µg/kg/day.

Chenault et al. (1993) found that adult female cynomolgus monkeys given MGA over the course of three consecutive menstrual cycles exhibited altered menstrual cycles, ovulations, and/or sex hormone profiles at doses over the NOEL of 5µg/kg/day. Similarly, MGA delayed the onset of menses in women at single doses higher than 80µg/kg or five daily doses of 42µg/kg (Duncan et al., 1964). It is worth noting that MGA is widely used in oral and injectable forms for the purposes of contraception,
prevention of endometrial hyperplasia and endometrial carcinoma, and the treatment of endometriosis
in women (WHO 2000). The safety of the drug has been tested in several multicentre epidemiological
studies, which found that its long-term use:

a. Does not increase the risk of breast, cervical, ovarian, or liver cancer;
b. Protects against endometrial hyperplasia and endometrial carcinoma in estrogen-treated
post-menopausal women;
c. Does not increase the risk of circulatory disease;
d. Does not impair adrenal function;
e. Has no immunological effects;
f. Causes no important change in liver function;
g. Does not harm fertility, pregnancy, or lactation in treated women; and
h. Does not harm child development in treated lactating women

Carcinogenic Effects

Multiple studies have found an increase in the incidence of mammary tumours - particularly
mammary adenocarcinomas - in mice and rats fed high doses of MGA (WHO 2000). The incidence of
mammary tumours in mice increased in a dose-related manner from the NOEL of 500µg/kg/day, with
the greatest incidence in younger animals (WHO 2000). The WHO Committee concluded that MGA
indirectly modulates mammary tumorigenesis in mice and rats, possibly as a result of stimulating
endogenous prolactin secretion.

At very high doses of at least 5000µg/kg/day, MGA decreased the incidence of ovarian tubular
adenomas, but increased the incidence of hepatocellular adenomas in mice (WHO 2000).

Other Effects

Multiple studies on laboratory animals have found no evidence for MGA-induced hepatotoxicity or
genotoxicity (WHO 2000). Similarly, no evidence of MGA-related hepatocellular proliferation or
tumorigenesis has been found in short- and long-term studies on laboratory animals fed MGA at doses
below 5000µg/kg/day (WHO 2000).

Several studies have found a dose-dependent decrease in adrenal gland weight from animals fed
MGA (WHO 2000). These effects have been attributed to the glucocorticoid activity of the drug, which is
approximately 1/40th as efficacious as dexamethasone in suppressing serum cortisol concentrations in
humans (Nugent et al. 1975). Despite the corticosteroid effects of MGA, long-term clinical trials in
humans have found no adverse effects on immune function at doses below the NOEL of 166µg/kg (WHO
2000). Similarly, MGA did not suppress serum cortisol concentrations in cynomolgus monkeys at doses
below 25µg/kg/day (Chenault et al. 1993). A study on developmental toxicity in rabbits found that MGA
was embryotoxic and teratogenic at doses above the NOEL of 400µg/kg/day, which was attributed to its
corticosteroid activity (Goyings et al. 1975).

Level of MGA that is Safe for Human Consumption

The NOEL for MGA varies by species, study length, and effects measured. Since no clear NOEL is
present, the WHO chose 5µg/kg/day to be the most relevant from the studies reviewed. This level is the
NOEL for altering the menstrual cycle of cynomolgus monkeys, and is one of the lowest NOELs from all
of the studies reviewed (WHO 2000). In order to establish an acceptable daily intake of MGA for human
consumption, the WHO applied a safety factor of 200 times to this level. As a result, the WHO
concluded that a maximum acceptable daily intake of MGA in people is 0.03µg/kg/day (WHO 2000).
Health Canada has established an acceptable daily intake of 1.8µg/day/person, which is in accordance with the level calculated by the WHO, assuming an average adult body weight of 60kg (Health Canada Veterinary Drugs Directorate 2005).

**Amount of MGA Residue Present in Edible Tissues at Slaughter**

MGA accumulates in different tissues at different rates as a result of its lipophilic nature (Daxenberger et al. 1999). The highest residues are found in liver and fat tissues (Daxenberger et al. 1999). Regardless of the dose administered to the cattle, the estimated concentration of MGA residues will be 4-8 times higher in liver, and 40 times higher in fat, than in muscle or kidney (Daxenberger et al. 1999). In Canada, the maximum residue limits in liver and fat are 6µg/kg and 14µg/kg, respectively (Health Canada Veterinary Drugs Directorate 2005).

Daxenberger et al. (1999) fed varying doses of MGA every day to heifers for 56 days and measured the residues in fat, liver, kidney, and muscle tissues at slaughter. No heifers were fed the current labelled dose in Canada of 0.4mg/animal/day. However, two experimental groups were fed 0.5mg/animal/day, one with and one without a 48 hour withdrawal period (Daxenberger et al. 1999). Of these groups, the highest residues were found in the fat of the no withdrawal group and averaged 7.5µg/kg; the lowest levels were found in the muscle of the 48 hour withdrawal group and averaged 0.2µg/kg (Daxenberger et al. 1999). None of the tissues of animals fed 0.5mg/day exceeded the current Canadian maximum residue limits, regardless of whether they were from animals given a 48 hour withdrawal (Daxenberger et al. 1999).

**Conclusions**

Despite a wealth of research examining the safety of MGA and other steroidal growth promoters use in food animals, the subject is still up for debate. Unfortunately, this contentious issue is further clouded by a lack of understanding from the general public, whose beliefs are often based on anecdotes or the opinions of interest groups, rather than solid clinical research. It is also important to remember that the research presented in this paper is valid only for labelled MGA dosages and does not address the issues of MGA metabolite residues or the interactions between multiple hormonal growth promoters administered to the same animal. Regardless, veterinarians have an obligation to inform clients, to the best of their ability, about food safety issues from a scientific and unbiased standpoint. To this end, a summary of the research presented in this paper is as follows:

1. The World Health Organization has identified the reproductive effects of MGA as the most relevant to human health and food safety. As a result, the WHO acceptable daily intake for human consumption is 0.03µg/kg/day. This was calculated by dividing the no observable effect limit on reproductive effects in monkeys by a factor of 200. Canada's acceptable daily intake of 1.8µg/person/day is in accordance with the WHO’s, assuming an average body weight of 60kg.
2. The maximum residue limits for MGA in Canada are 6µg/kg in liver and 14µg/kg in fat. Although no limit is given for muscle, any animal that meets these requirements would have muscle residues of approximately 1.5µg/kg or lower due to the differential accumulations of MGA in the various tissues. In other words, a person would need to eat 1.2 kilograms of meat or 128 grams of pure fat to reach the acceptable daily intake in Canada, assuming the tissues contained the maximum allowable residues.
3. Canadian beef cattle may be fed MGA at the labelled dose of 0.4mg/animal/day, provided a 2 day withdrawal is given before slaughter. Studies on heifers fed a similar dose of 0.5mg/animal/day found that the residue levels were well below the maximum allowable limits in Canada, even in animals sent to slaughter without a withdrawal period.
References


Health Canada Veterinary Drugs Directorate. 2005. Food and drug regulations, division 15, part B. Ottawa, ON, Canada.


