MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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November 10, 2015

To: File for Melengesterol Acetate (CAS # 2919-66-6)

From: Mike Depa, Toxics Unit, Air Quality Division

Subject: Initial Threshold Screening Level

Previously, the averaging time (AT) assigned to melengesterol acetate was 24 hours, as per the default methodology (Rule 232(2)(b))(see attached memo from Robert Sills dated September 10, 1993). The current file review concludes that the AT may appropriately be set at annual, based on the nature and duration of the key study and the ITSL value derivation, as allowed under Rule 229(2)(b). Therefore, the AT is set to annual.

MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

September 10, 1993

To: File for Melengesterol Acetate (CAS # 2919-66-6)

From: Robert Sills, Surface Water Quality Division

Subject: Screening Level Derivation

A review of the available literature (via CAS-online, NTIS, and NLM Toxiine, July 1993) and standard references revealed a modest number of publications describing the toxicity of melengesterol acetate (MGA). Occupational exposure guidelines and an EPA RfD/RfC are unavailable. Sud and Meites (1971) administered MGA at 5 µg/g feed (or control, untreated diet) to groups of adult female rats, with or without castration. The experimental period was 30 days, followed by sacrifice of all animals. Organs were weighed and examined histologically. MGA treatment significantly reduced the weight of the anterior pituitary, ovaries, uterus and adrenals in intact animals. Histologically, the adrenal tissue did not differ between treated and control groups, but MGA treatment did result in changes in mammary tissue. Assuming that female Sprague-Dawley rats consume food at approximately 0.080 kg/kg b.w./d (EPA, 1988), the LOAEL of 5 µg/g feed is approximately 0.4 g/kg/d or 400 mg/kg/d.

Lauderdale et al. (1977) reported on a variety of experiments in several animal species which investigated the dose—response of the progestogenic effects of MGA, including harmful effects. They report that MGA is a steroid with both progestational and glucocorticoid activity. They estimated a human minimum effective dose (MED) for contraceptive effects of MGA was 0.7 mg/d, and a no-effect dose was 0.4 mg/d, based on a comparison to the effective doses of other progestational drugs. Animal model studies determined the oral potency of MGA as measured by estrous cycle inhibition. Listed in order from the most to the least sensitive, in terms of the daily oral dose of MGA to inhibit the estrous cycle, were the cow (0.00055 mg/kg), dog (0.0088 mg/kg), man (0.1376 mg/kg), rat (0.22 mg/kg), and mouse (0.758 mg/kg). Studies in cattle, dogs, rabbits, monkeys and mice were then conducted to investigate if MGA might exert subtle effects on other aspects of normal physiological functions or on the ability to conceive while ovulating. Cows and bulls received 1.0 mg (estimated to be 0.0022 mg/kg) MGA daily for 2 years, except treatment was periodically stopped in cows to allow estrous cycling. Calf birth weight was reduced significantly, and adrenal weight was reduced in bulls. Also, it was noted that 1.6 mg/day was reported elsewhere to reduce testicular weight in the bull.

Lauderdale et al. (1977) also investigated the effects of MGA in dogs. A dose of 0.008 mg/kg for one year blocked estrus, and the treatment was stopped to allow mating. Dosing was reinstated at 0.004 mg/kg, which interfered with parturition. Pup losses were elevated, but there were no abnormalities. No effects were seen at the lower doses of 0.001 or 0.002 mg/kg for 2 years, including reproduction endpoints, body weight, pup birth or weaning weight, histopathology, hematology, urinalysis, etc.

The rabbit was selected by Lauderdale et al. (1977) for a teratology study. Rabbits were given MGA on gd 6-18 via the diet. Levels of 6,250 ppb or less had no effect, while 12,500 ppb or higher concentrations resulted in teratogenic effects and fetotoxicity. The authors reported that the NOAEL of 6,250 ppb was approximately 0.4 mg/kg-day.

Female rhesus monkeys received MGA orally at 0, 0.01, 0.1, 0.5 or 1.0 mg per monkey during days 2-36 after menses, to evaluate effects on the menstrual cycle (Lauderdale et al. 1977). Effects seen at doses of 0.1 mg and higher included blockage of ovulation and delay of menses.

In a mouse study, Lauderdale et al. (1977) investigated the biological activity of 14GA associated with the incidence of tumors, and C3H strain mice of both sexes were given 0, 110, or 110,666 ppb in the diet during the entire lifespan. The high-dose female C3H mice had a statistically significant increase in the incidence of mammary tumors. The authors concluded that MGA was not demonstrated to be carcinogenic, and that the observed increase in mammary tumors was apparently caused by the promotional effect of elevated serum prolactin levels induced by the MCA. Under this assumption, a viral agent could transform the prolactin stimulated lobuloalveolar development to tumors. The authors concluded that neither MGA or progesterone is carcinogenic or cocarcinogenic, but that they can produce a hormonal state (possibly increased prolactin levels) or an alteration of immunocompetent mechanisms which, in interaction with a virus or certain genetic constitution, can produce elevated mammary tumors in certain instances. These apparent mechanisms, the authors state, would be characterized by a threshold. A subsequent bioassay in C3H mice involving life-span exposure via feed at up to 125,000 ppb resulted in no pattern of elevated mammary tumors. However, there was a significant increase in uterine effects (cystic endometrial hyperplasia, a progestational effect) in mice receiving 25,000 ppb or greater. This dose was reported as 100 µg/d. Assuming that female mice weigh approximately 250 g (EPA, 1988) this dose is 0.4 mg/kg/d.

Duncan et al. (1964) reported clinical studies with MGA. Oral treatment of women for 20 days resulted in delay of menses at 7.5 and 10 mg. No delay was encountered at the 5 mg dose. Withdrawal bleeding occurred in estrogen-primed amenorrheic women treated with 2.5 mg daily for 5 days or with single doses of 5-10 mg. In subchronic animal studies, rats given 1, 3 and 10 mg/kg/d for 28 days showed corticosteroid and progestational effects. Dogs receiving 1, 3 and 10 mg/kg for 28 days had reduced adrenal, spleen, uterus and cervix weights, reportedly due to expected hormonal effects.

The most appropriate basis for ITSL derivation is the reported no-effect dose in women at 0.4 mg/d (0.0057 mg/kg/d, assuming 70 kg female weight) (Lauderdale et al., 1977). Other species (e.g., cows, dogs) have been shown to be more sensitive to the progestational effects of MGA, but the human data are preferable. Animal studies have not shown that MGA can cause any other, more subtle effects than menses blockage in animal species (Lauderdale et al., 1977). Also, the limited and inconsistent finding of elevated mammary tumors in mice and the postulated mechanisms for this observation (Lauderdale et al., 1977) do not indicate the need to regulate MGA as a carcinogen.

The ITSL is derived from the human (female) no-effect dose for the most sensitive endpoint of menses blockage. This NOAEL dose refers to a sensitive subpopulation (menstruating females) and is inferred to be applicable to long—term exposures. It is also noted by Lauderdale et al. (1977) that the half-life in women has been estimated to be 3.5 days for doses of 3-5 mg, with excretion via the urine and feces. However, these researchers also found that residues of MGA and its metabolites do occur in liver and fat of cattle. A single 10-fold UF is used in ITSL derivation, to ensure the protection of sensitive subpopulations (e.g., children). This appears prudent given the steroidal nature of the compound, the tendency to result in residues in fatty tissues, and the very narrow difference between the no-effect level (0.4 mg/d) and the minimally effective dose for menses delay/blockage (0.7 mg/d). Data are not available to indicate that oral route to inhalation route extrapolation is inappropriate.

RfD = (0.4 mg/d)/(70 kg x 10) = 0.00057 mg/kg/d

ITSL = 0.00057 mg/kg/d x 70kg/20m^3 = 0.002 mg/m^3

= 2 µg/m^3, averaging time is 24 hours.

REFERENCES

Duncan, G.W. et al. 1964. Biologic effects of melengestrol acetate.Fertility and Sterility 15:419-432.

Lauderdale, J.W. et al. 1977. Studies of a progestogen (MGA) as related to residues and human consumption. J. Tox. Env. Health 3:5-33.

Sud, S.C. and J. Meites, 1971. Effect of melengestrol acetate on the organ weight and the mammary lobulo-alveolar development in rats. Indian J. Exp. Biol. 9:138-141.

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RS:ma