Intravaginal Progesterone Inserts

ENVIRONMENTAL ASSESSMENT

Expert Report

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1. APPLICANT

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Date: 16 November 2001

2. PROPOSED ACTION

The Applicant seeks approval of a New Animal Drug Application (NADA) providing for the marketing of an intravaginal progesterone insert to be used for the purpose of synchronizing estrus in beef cows and in beef and dairy heifers. Estrus synchrony facilitates the use of artificial insemination, which allows the application of superior genetics essential to breed improvement. Synchrony also provides other benefits including having a calf crop of a uniform age and size.

The product has been used widely internationally for approximately 10 years and is approved and is now marketed in at least 24 countries including Canada, England, New Zealand, Australia and Japan. The applicant is aware of no adverse environmental consequences as a result of its use or disposal.

Used containers and used inserts will be disposed of in compliance with Federal, state and local regulations, usually by incineration or by discarding into approved landfills. To this end, the product label will read as follows: "Removed inserts should be stored in a plastic bag or other sealable container until they can be properly disposed in accordance with local, state and Federal regulations."

3. IDENTIFICATION OF SUBSTANCES THAT ARE SUBJECT OF THE ACTION

The intravaginal progesterone inserts consist of a "T" shaped nylon spine, the body of which is approximately 13.5 cm long and the "wings" are each approximately 7.5 cm in length. The device is coated by injection molding with a 1 mm thick coating of silicone rubber containing progesterone (10 % w/w). The wings are closed during insertion by utilization of an insertion applicator. The insert is equipped with a polyester "tail" to facilitate removal from the vagina. Each insert contains 1.38 g progesterone[1]. In the animal, as progesterone is

absorbed by the vaginal mucosa from the surface of the insert, progesterone deeper in the silicone rubber continuously diffuses toward the reduced concentrations nearer the surface of the insert.

Progesterone is a naturally occurring compound that is ubiquitous in nature because it is the predominant ovarian hormone during the menstrual/estrous cycle and during pregnancy in mammals including mankind. It is also predominant in birds and reptiles, and it is commonly found in other classes of animals as well as in some plants. The progesterone used in insert manufacture is produced (Pharmacia) by bioconversion and chemical synthesis from soy sterol precursors. It is chemically and physically identical to progesterone produced in nature and its fate is identical to that of natural progesterone (described in detail in section 5.1.1.1).

The silicone rubber matrix which serves as the releasing mechanism for the active ingredient, progesterone, is a polydimethylsiloxane which is used as a vehicle for other approved new animal drugs as well as in many biomedical applications including breast implants. It is identified as Silastic® Q7-4840 A/B Medical Grade Liquid Silicone Rubber and is supplied by Dow Corning. Each insert contains approximately 12 g silicone. The elastomer, in general, is chemically inert to environmental decomposition and will not disperse into the environment. This material is subject to complete decomposition when incinerated. The type of combustion and heat generated will determine the extent of decomposition and quantity and distribution of decomposition products. Typically, silica, silicic acid, carbon monoxide, carbon dioxide and some hydrocarbons are produced. Under intense heat, the elastomer will oxidize to particulate and gaseous byproducts.

Nylon 6/6 (Ultramid® A3K) of which the insert spine is composed, is a well known and widely used polymer and is supplied by BASF. BASF certifies that the material complies with the provisions of 21 CFR 127.1500 "Nylon resins" allowing for contact with food. Each insert spine weighs approximately 12 g. Nylon resins are a common component of clothing and are widely used as a major component of carpeting. The material resists biodegradation, but it is combustible and burns at 280° C.

The polyester insert "tail" (Hytrel® 5526) complies with the provisions of 21 CFR 177.1590 and 21 CFR 177.2600 and is supplied by DuPont. Each tail weighs approximately 1.55 g. It resists degradation, but it is combustible and burns at 200° C.

4. DESCRIPTION OF THE ECOSYSTEM AT THE SITE(S) OF INTRODUCTION

The primary sites of introduction of the insert progesterone into the environment will be at rural farms and ranches where beef cattle and dairy heifer breeding and raising are practiced. In general, the beef cow-calf operations utilize grazing lands which are unsuited for crop raising due to low soil fertility, low rainfall or rolling topography. While beef cattle raising

occurs in every state, the primary cow-calf populations occur in the central states of Texas, Oklahoma, Missouri, South Dakota, Nebraska, Kansas and Montana[2]. The raising of dairy cattle, on the other hand, occurs primarily in the eastern or western states, e.g., California, Wisconsin, New York, Pennsylvania, Minnesota, Idaho and Michigan.

The number of inserts used at any one herd will vary; however, at those farms that use the intravaginal progesterone insert it is assumed that all cows/heifers of breeding age will be administered one insert per year. The primary users are thought to be commercial beef cattle breeders who use artificial insemination as a means of improving the genetics of their herds. According to a USDA National Agricultural Statistics Service report[2], there were approximately 33.9 million beef cows in the USA in July 2001. Of these, approximately 5% (1.7 million) are involved in estrus synchrony programs. If successful in obtaining product registration, DEC International would hope to achieve an early market penetration of 10% or approximately 170,000 inserts annually. The same report identifies 3.6 million dairy heifers in the USA. It is estimated that 10% of these animals are in estrus control programs and DEC international would hope to achieve an early market penetration of 20% of these, or 72,000 inserts. These sales would be expected to increase over time.

In 2000, there were 830,880 beef cow operations in the US[3]. Therefore, the average beef cow herd size in the US is 33,900,000/830,880 = 41 cows. Approximately 50% of the beef cows in the US are found in the seven states shown above[2]. The average herd size for these states = 16,900,000 cows/287,000 operations = 59 cows/operation. However, an average of 59% of the total numbers of beef cows in these states are found on operations with $\geq$ 100 cows[4]. For the purposes of this assessment, an estimate of the number of intravaginal progesterone inserts used per year per farm site will be made. The following are conservative assumptions:

- herd size at a given beef operation is 100 cows
- 12 month breeding cycle is typical
- 100% of the cows/heifers with in the herd will be treated
- only one insert will be used per cow per year

Therefore, 100 inserts would be used per year. The 100 inserts would, upon removal from the animal, typically be placed into a waste container lined with a standard plastic trash bag. This bag would be closed and would become a component of solid waste that would be delivered to an approved incinerator or sanitary landfill for burial in accordance with local, state and Federal regulations. Each used insert weighs approximately 27 g and 100 inserts would weigh 2700 g or approximately 5.9 lb. Thus, the weight of relatively inert materials going to solid waste disposal for the average 100 cow herd would average less than 6 lb. per operational site yearly.

Given the mass and dimensions of the insert, the numbers likely to be used at each site, the geographical distribution of the use sites, and the instructions for disposal of the inserts, excessive litter from use of the inserts is extremely unlikely.

5. ANALYSIS OF DATA ON THE SUBSTANCES

5.1 ANALYSIS OF SUBSTANCE FATE

5.1.1 Progesterone

5.1.1.1 Progesterone in the Insert: The progesterone in the intravaginal insert is synthesized (Pharmacia) from soy sterol precursors. Insert progesterone is identical to progesterone produced by mammals[5], and the fate of progesterone absorbed from the insert is identical to that of progesterone made endogenously by cows. The Material Safety Data Sheet[6] for progesterone and a Pharmacia progesterone batch Quality Control report[7] show the safety of progesterone and the physico-chemical identity of the manufactured progesterone by comparison with pregn-4-ene-3,20-dione, the natural hormone secreted by the corpus luteum in mammals. The intravaginal progesterone insert contains 1.38 g of progesterone[1]. About 0.63 g [(0.702 g + 0.564 g + 0.597 g + 0.659 g)/4] progesterone is absorbed by the cow during a 7-day treatment period[1]. Therefore, 1.38 g - 0.63 g = 0.75 g remains in each spent insert after the 7-day insertion period.

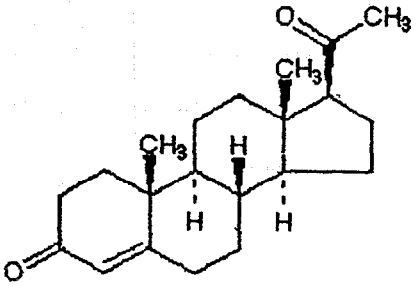
Progesterone (progesterone and estradiol benzoate, 21 CFR, 522.1940--Synovex®) is approved for use as a subcutaneous ear implant "for increased rate of weight gain" in beef steers and calves[8, 9]. It is also approved for use in humans (Prometrium®)[10]. In all of these cases, the FDA has issued FONSIs (NDA 19-781, NADA 009-576, NADA 110-315), thus concluding that progesterone should not have adverse environmental effects when it is released into the environment due to use of these types of veterinary and human products.

5.1.1.2 Progesterone in Nature: Progesterone is ubiquitous in the environment because it is the predominant ovarian hormone produced during the estrous cycle and during pregnancy in mammals. It is also a predominant hormone in birds and reptiles, and it is commonly found in other classes of animals as well as in some plants. Thus, while we know of no estimate of the total natural production of progesterone, the amount that will be added by the proposed product could be no more than a tiny fraction of the total produced naturally.

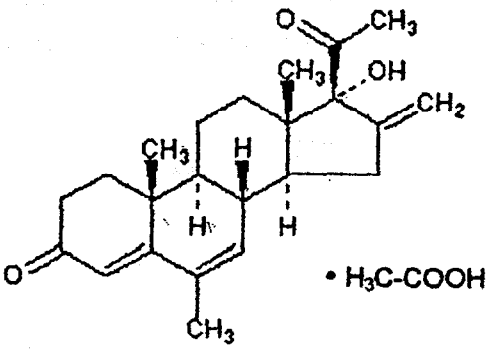
Ubiquitous environmental microbes, especially *Norcardia* spp., "*Proactinomyces*" spp. and various gram-negative bacteria degrade naturally occuring sterols or steroids[11, 12, 13, 14, 15]. Progesterone was utilized as the sole carbon source by "*Proactinomyces*" spp. and gram-negative rods[16]. Progesterone was mineralized by "*Norcardia restrictus*"[17]. Because it is considered insoluble in water[18], progesterone from excreta on land or from inserts in a landfill would be absorbed onto adjacent particulate matter. It would be subjected to

microbial degradation when it could be attracted from the soil particles by microbes with affinities for progesterone greater than those of the soil particles. Data on the behavior of progesterone in soil are lacking. However, data are available for melengestrol acetate (MGA)[19]. MGA is a progesterone agonist and is chemically similar to progesterone. The molecular structures for MGA and progesterone are shown below.

progesterone



MGA



MGA was designed to resist metabolism. Therefore, these data represent a worst case for progesterone because:

- MGA is more biologically active than progesterone
- MGA is metabolized slowly by comparison with progesterone
- progesterone is less polar than MGA, so progesterone should bind more tightly to soil and therefore become less available in solution for potential ecotoxicological effects.

MGA is tightly bound to soil particles; the soil partition coefficient ranged from 549 to 1009 for adsorption and from 201 to 400 for desorption[19]. Desorption $\log_{10} K_{oc}$ estimates for three different soil types were 4.3, 4.4 and 4.5. Of the MGA binding to soils, less than 5% would be desorbed and transported to aquatic systems following rainfall events. Any MGA which found its way into terrestrial animals would be rapidly cleared by conversion to compounds with reduced lipophilicity. The half-life of MGA in soils ranged from 4.3 to 27.8 days, depending upon the soil type. The data supported the conclusion that MGA biodegradation in soil occurs through conversion to multiple metabolites, none of which appear to accumulate and that ultimately, slower conversion of these metabolites to carbon dioxide occurs. Progesterone should bind to soils at least as tightly and it should degrade at least as rapidly as MGA.

In overview, whether progesterone from the insert leaves the cow in excreta or as residual material in the used insert, it is degraded completely by several environmental microbes. This is the normal fate of naturally occurring progesterone in the environment.

5.1.1.3 Fate of Insert Progesterone in Cows: Because the progesterone from the insert is identical to that produced by the cow, it is metabolized and excreted exactly as the progesterone which is normally produced by the cow. Progesterone is readily metabolized in the bovine liver and adipose tissues to form glucuronide conjugates[20]. The metabolites are excreted mainly by the hepato-enteric pathway into the feces[21, 22, 23]. Little to no progesterone is detectable in feces of domestic animals including cattle[23, 24, 25, 26]. Six immunoactive metabolites were detected in feces eluting (HPLC) as 5α- and 5β-reduced pregnanes containing a 20-oxo group[25]. All showed polarities similar to but not identical to progesterone. Such metabolites would be expected to have significantly reduced biological activity in target species relative to the activity of progesterone.

In a study by Bunt et al.[27], blood levels of progesterone in treated cows returned to pretreatment levels within about 8 hours after the insert was removed. Therefore, the progesterone absorbed from the insert by the cow is either metabolized to inactive forms or excreted in the feces or the urine within about 8 hours. All 0.63 g finds its way into the feces or urine, either in the form of conjugated progesterone or as inactive metabolites of progesterone. For nearly all beef cattle and dairy heifers, the excreta are deposited on the farmland where the animal resides or is spread on the land near the same farm.

5.1.1.4 Progesterone Added to the Terrestrial Environment from the Insert:
In excreta from a cow or if some small, unabsorbed amount was released into the environment from solid waste disposal, ultimately the progesterone is degraded by various environmental microorganisms as documented above.

The duration of the estrous cycle in cattle averages 21 days and gestation averages 282 days. During the estrous cycle, blood progesterone increases to above 5 ng/ml on about day 8, and is about 10 ng/ml on days 10 to 18 declining thereafter during regression of the corpus luteum[28, 29]. Blood progesterone concentrations remain at about 10 ng/ml throughout gestation[30, 31, 32]. Blood concentrations of progesterone in lactating dairy cows may be somewhat lower than that observed in beef cattle[29], at least in part due to increased rate of progesterone metabolism. The high feed intake to maintain high milk production in modern dairy cattle results in increased hepatic blood flow with attendant increased progesterone metabolism[33].

A direct estimate of progesterone production by the corpus luteum of cattle could not be found in the scientific literature, however, it can be calculated from existing data utilizing a pharmacological approach based on progesterone metabolic clearance rate. At steady state, the input of a given substance will equal the output or in this case metabolism of the substance. This is one definition of steady state. Progesterone is at or very nearly at steady state during the mid-luteal phase of the estrous cycle of cattle. Progesterone metabolic clearance rate has been determined to be 3734 L/h in lactating Holstein dairy cows and 2700 L/h for dry, non-lactating Holsteins[34]. Data from non-lactating Holsteins can be extrapolated

to beef cows, beef heifers and dairy heifers. Using blood progesterone concentration during the mid-luteal phase of the estrous cycle and during pregnancy of 5 ng/mL in beef cattle and dairy heifers, the total clearance rate of progesterone is 5 ng/ml X 2700 L/h = 13.5 mg/h or 324 mg/day. Therefore, the steady state production of progesterone is 324 mg/day for beef cows, beef heifers and dairy heifers. These are conservative estimates because the blood concentrations of progesterone during both the luteal phase of the estrous cycle and during gestation are higher than 5 ng/ml for dairy heifers and beef cattle.

During an annual production cycle, heifers and beef cows would be expected to be in anestrum for about 20 days, cycle three times before becoming pregnant and then are pregnant for 282 days. Assuming no progesterone production during anestrum, 12 days of high progesterone concentration during the estrous cycle (days 6 through 17), three estrous cycles before becoming pregnant, 282 days of high progesterone during gestation, and a daily production of 324 mg progesterone during the luteal phase of the estrous cycle and during pregnancy, the annual production of progesterone is estimated to be 103 g (318 days X 324 mg/day) per animal.

Intravaginal progesterone inserts are administered for 7 days, an interval shorter than the normal luteal phase of the estrous cycle when blood concentrations of progesterone are high, naturally. In cattle administered an insert in the absence of a corpus luteum, the concentration of progesterone detected in blood[27, 35] does not exceed that observed during the luteal phase of the estrous cycle or during pregnancy. Therefore, the amount of progesterone absorbed from the insert and potentially excreted into the environment is less than that normally excreted by cattle on a daily basis. A total of 0.63 g of progesterone is absorbed from the intravaginal insert during a 7-day insertion period[1]. This equates to 90 mg/day, considerably lower than the estimated 324 mg/day produced by heifers and beef cows with a functional corpus luteum. Moreover, this 0.63 g of progesterone represents 0.6% [(0.63 g ÷ 103 g) x 100%] of the annual progesterone produced by beef cows and beef and dairy heifers. However, progesterone from the insert is metabolized by the animal using the same metabolic pathways as progesterone from endogenous sources prior to excretion into the environment. Therefore, parent progesterone absorbed from the insert is excreted by the animal into the environment as metabolites that have considerably lower biological activity than that of progesterone. In summary, the average amount of progesterone absorbed by cows given one intravaginal progesterone insert a year will represent 0.6% of that produced endogenously by untreated cows annually.

5.1.2 Structural constituents

The structural parts of the used intravaginal progesterone inserts, i.e., silicon rubber, nylon spine and polyester tail, will be disposed in accordance with local, state and Federal regulations.

5.2. PREDICTED ENVIRONMENTAL CONCENTRATION (PEC) OF PROGESTERONE FROM THE INSERT IN SOIL AND WATER

The scenario in which insert progesterone will enter the environment is by excretion from animals on pasture. The PEC of residues in fresh dung from cows on pasture is estimated. In addition to the assumptions in the cited references, there are several other key assumptions pertinent to the PEC calculations:

- *Animal cycles/year*

  A goal of beef producers is to have a 12-month calving interval. In this EA, it will be assumed conservatively that the calving interval is 12 months. Therefore, on an annual basis, one animal cycle will be used in the estimation of PEC_{soil}.

- *Percentage of herd treated with intravaginal progesterone inserts and number of treatments*

  It will be assumed conservatively that 100% of the beef cows and breeding age heifers are treated and that there will be one intravaginal progesterone insert treatment per animal per year.

- *Excretion of progesterone*

  It will be assumed that the insert progesterone will be excreted from the animal at 100% of the absorbed dose. This assumption is especially conservative, because progesterone is extensively metabolized by the cow prior to excretion[20, 21, 22, 23].

- *Production of excreta*

  The total amount of excreta (feces plus urine) produced by beef cows and beef and dairy heifers will be assumed to be 29 kg/day based on a typical animal mass of 500 kg[36]. Yearly manure production, therefore, is equal to 10585 kg per animal.

- *Stocking density*

  The stocking density of insert-treated cattle will be assumed to be 4 animals/acre. This value is conservative relative to beef cattle husbandry practices [e.g., see the CVMP Note for Guidance (EMEA/CVMP/055/96-FINAL, p. 16)].

- *Biodegradation*

  Data are not available for the half-life of progesterone (DT_{50}) due to biodegradation in soil or manures. In the calculations that follow, a value of 28 days for the DT_{50} in soil will be used. The 28-day value is a conservative one because it is the DT_{50} for melengestrol acetate (MGA), a synthetic progesterone analog designed to resist metabolism[19]. First-order decay kinetics are assumed for biodegradation.

- *Infiltration depth of progesterone residues*

  It is assumed that insert progesterone residues entering the environment are distributed homogeneously to a depth of 5 cm of pasture soil.

Other assumptions not discussed previously are given in Table 1.

Table 1. PEC_{soil} Estimates of Progesterone From Administration of Intravaginal Progesterone Inserts to Beef Cows and Beef and Dairy Heifers on Pasture.

Amount of insert progesterone absorbed/day (A) =	90 mg/day
Number of days insert is in animal (D) =	7 days
Fraction of insert progesterone excreted (F_E) =	100%
Total amount of insert progesterone absorbed, then excreted (T) =	90 mg/(cow•day) x 7 days = 630 mg/cow
Fraction of cows treated (F) =	100%
Stocking density (SD) =	4 cows/acre
Total amount of progesterone/(acre•year) T_P =	4 x 630 = 2520 mg/acre
Bodyweight of cow (BW) =	500 kg
Yearly manure production (M) =	29 kg/(day•cow) x 365 days/year x 4 cows/acre = 42,340 kg (acre•year)
Soil bulk density (BD) =	1500 kg/m^3
Number of days between inserts (Ip)=	365 days
Depth of mixing of insert progesterone with soil (Depth) =	0.05 m

Mass of soil in top 0.05 m (5 cm) = (S):

Area of acre = 4047 m^2

Volume = Depth x area of acre = = 0.05 m x 4047 m^2 = 202.35 m^3

Mass = Volume x BD = 202.35 m^3 x 1500 kg/m^3 = 303,525 kg

Concentration in soil (C_s) = $T_P/(M + S)$ = 2520/(42,340 + 303,525) = 7.29E-03 mg/kg

Half-life of progesterone in soil (DT_{50}) = 28 days

Residence time of insert progesterone in soil (T_s) = 365 - 7 = 358 days

Progesterone in manure/soil following biodegradation = $C_s \times e^{[-(\ln 2/DT50) \times Ts]}$

= 7.29E-03 x $e^{[-(.6931/28) \times 358]}$ = 1.04E-06 mg/kg = 1.04E-03 µg/kg = 1.04 ppt

Table 2. PEC_{water} Estimates of Progesterone From Administration of Intravaginal Progesterone Inserts to Beef Cows and Beef and Dairy Heifers on Pasture.

The PEC_{soil} is used for calculation of PEC_{water}. The base level calculation assumes that 5% of the total drug per acre applied to 10 hectares of soil moves into a one-hectare pond, which is 2 m deep[37]. This also assumes incorporation of the excreta into soil. The calculations below use area in acres instead of hectares.

MA (the amount of progesterone) entering a pond = PEC_{soil} x weight of soil per acre x 0.05 x 10 acres. Wet weight of soil plus manure in the top 5 cm = (303,525 kg + 42340 kg)

MA = 1.04E-06 mg/kg x (303,525 + 42,340) x 0.05 x 10 = 0.1798 mg.

A one acre pond with a depth of 2 m has a volume of 4047 m^2/acre x 2 m x 1000 L /m^3 = 8,094,000 L.

PEC_{water} (max) = MA/Mass of water in pond = 0.1798 mg/8,094,000 L = 2.22E-08 mg/L water = 2.22E-05 µg/L = 2.22E-02 ng/L = 0.0222 ppt

These estimates, 1.04 ppt for soils and 0.0222 ppt for a surface water run-off scenario, are extremely low and well below existing regulatory trigger limits for approval of veterinary products in the US (FDA CVM Guidance for Industry # 89, 7 March 2001) and EU (VICH guideline CVMP/VICH GL6 June 2000). These estimates are expected to be even lower because of the following conservative assumptions that were included in calculation of the PEC:

- No consideration was given for the degradation of progesterone by the cow. Little intact progesterone is found in excreta of domestic animals. Parent progesterone excreted would be considerably less than the 90 mg per day absorbed from the insert and the metabolites excreted would have reduced biological activity relative to that of progesterone.

- The rate of application of manure to land usually will be less than that used in the calculation, based on crop type, nutrient utilization and soil type. Lower application rates would result in a lower PEC_{soil}.

- No consideration is given for potential photolysis of progesterone. MGA, an analog of progesterone designed to resist degradation is photolytically degraded with a half-life for loss estimated to be less than 1 hour[19].

- The highest stocking density for the calculation was used. Lower stocking densities would yield lower PEC_{soil}.

- The highest DT_{50} for MGA loss from three soil types was used[19].

Given that the active ingredient in the intravaginal progesterone insert (progesterone) is a naturally occurring substance and that there is less than a 1% increase in progesterone excretion relative to the amount produced by a cow over a period of a year, it should be classified as among those substances addressed by question two of the VICH guideline (CVMP/VICH/592/98)- Phase I. Specifically, "*Is the VMP a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment? Yes, then STOP*", then the assessment for this product may stop at question two. Additionally, because progesterone is extensively metabolized by the bovine, the assessment may stop at question six of the Phase I Decision Tree "*Is the VMP extensively metabolized in the treated animal? Yes, then STOP*". In addition to the VICH Phase I guideline, 21 CFR Part 25.33(c) normally exempts from environmental assessment concerns, "...substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment." Progesterone released into the environment from use of the insert qualifies for exemption under the aforementioned regulations, given the minor contribution (< 1%) to the amount produced endogenously and the extremely low concentrations (≤ 1 ppt) predicted to be present in soils and water arising from use of the insert.

5.3 POTENTIAL FOR ENDOCRINE DISRUPTION

Extensive literature searches including the National Center for Biotechnology Information's PubMed and the Institute for Scientific Information's Current Contents® revealed no data documenting that progesterone at ≤ 1 ppt has acute or chronic endocrine-disrupting effects.

Progesterone released into the environment by use of the intravaginal insert in beef cattle and dairy heifers likely will not negatively impact non-target environmental species given the following: 1) the PECs are extremely low (1 ppt in soil and 0.022 ppt in water), 2) progesterone would bind tightly to soil and sediment matrices, 3) progesterone is expected to be readily biodegraded, 4) the amount of insert progesterone contributed to the environment relative to that from normal physiological state of cattle and relative to all natural sources entering the environment is expected to be negligible. It is concluded that exogenously supplied progesterone from the inserts would pose no endocrine disruptive effects.

Progesterone is a naturally occurring substance and products containing this substance have been reviewed by both CDER and CVM in the past. As examples, CDER concluded that a progesterone-containing product intended for humans (Prometrium®) can be "manufactured, used and disposed of without any expected adverse environmental effects." (FONSI, NDA 19-781). Additionally, four animal drug products, Component® E-C with Tylan, Component® E-S with Tylan (NADA 10-315), Synovex®-C and Synovex®-S (NADA 009-576) were granted FONSIs. Thus, the FDA has concluded in the past that progesterone should not negatively impact the environment.

5.4 ANALYSIS OF EFFECTS

Extensive literature searches failed to identify published data on effects of progesterone on non-target environmental species. However, there are data for the progesterone analog MGA[19]. The earthworm, *Lumbricus terrestris*, was exposed to 2 ppm MGA with no adverse effects noted. Seed germination and root elongation for corn, perennial ryegrass, wheat, radish, soybean and tomato were exposed to 2 ppm MGA. No significant negative effects were noted. Additionally, no negative effects of MGA at 1 ppm on *Daphnia magna* and at 2 ppm on goldfish were observed. The concentrations of MGA used in these effects tests were at least 1000-fold higher than the PECs for exogenously released progesterone released from the insert. Therefore, it is reasonable to assume that there will be negligible, if any, negative effects of the use of the intravaginal progesterone insert on non-target environmental species. Based upon the above analysis of substance fate (i.e., minimal environmental release of a readily biodegradable, naturally occurring active substance, a small volume of waste disposal of the insert, and commonly used polymers), there should be no adverse environmental effects associated with the proposed action.

6. A RISK CHARACTERIZATION BASED UPON THE EXPOSURES AND THE HAZARDS

Use of intravaginal progesterone inserts to synchronize estrus in beef cows, and in beef and dairy heifers is not expected to negatively impact the environment. Extensive literature searches including the National Center for Biotechnology Information's PubMed and the Institute for Scientific Information's Current Contents® revealed no useable information on effects of progesterone on non-target environmental species. While data are not available on the risks of exogenously applied progesterone in the environment, melengestrol acetate (MGA), an analog of progesterone designed to resist metabolism, can be used as a "worst case" comparator. This is based on the following findings and expectations:

- Progesterone is a naturally occurring substance. The amount of progesterone excreted into the environment from cows treated with the insert is less than 1% of that excreted by non-treated cows on an annual basis. The amount of insert progesterone excreted by the target species is negligible compared to all natural sources of progesterone that enter the environment.

- Progestrone is metabolized to more polar compounds in beef cows and heifers. Therefore, excretion of progesterone into the environment will be less than 100% of the 90 mg absorbed/(cow•day) during the 7-day treatment period.

- Concentrations of progesterone occurring in the environment from use of the intravaginal progesterone insert are predicted to be extremely low (≤ 1 ppt). Furthermore, the assumptions used in the calculation of the PEC of insert progesterone are highly conservative. More realistic PEC estimates would be expected to pose even less of a risk to non-target species in the environment.

- Based on conclusions reached for MGA, progesterone is at least as likely to be biodegraded in soils to more polar metabolites and carbon dioxide. Several microbial species in the environment can use progesterone as a source of carbon and energy. It is likely to be biodegraded in excreta as well.

- Progesterone is not expected to be mobile in soils, based on the physico-chemical characteristics of MGA, a closely related structural analog. Any parent progesterone and/or progesterone-like residues should bind extensively to soil matrices and, therefore, become less bio-available to non-target environmental species.

In conclusion, there are no identifiable adverse exposures or hazards associated with the action. In particular, it is not expected that the ultra-low concentrations (≤ 1 ppt) of progesterone predicted to arise from use of the insert should exert endocrine disrupting effects on non-target species in the environment.

7. DESCRIPTION OF ANY ALTERNATIVES TO THE PROPOSED ACTION

The only known alternative would be to deny the proposed action. Based upon the above analyses, this would be totally unjustified and would deny the availability of a substantial technological development and its potential to allow enhanced use of genetic improvements and other advantages associated with the use of artificial insemination. This would put American beef producers and dairymen at a competitive disadvantage compared to producers in scores of countries in which the product is approved and used, including Australia, Canada, Japan, Mexico and United Kingdom.

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9. SIGNATURES

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10. REFERENCES

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