ENVIRONMENTAL ASSESSMENT

NADA 34-254, MGA® 100/200 Premixes
NADA 39-402, MGA® 500 Liquid Premix
(Type A Medicated Articles)

Melengestrol Acetate (MGA) for Suppression of Estrus for Heifers Intended for Breeding

THE UPJOHN COMPANY

June 1996

In 1995, The Upjohn Company became a wholly owned subsidiary of Pharmacia & Upjohn, Inc. The Upjohn Company continued to conduct its business under the same legal entity name until June 11, 1996, at which time the change of the name to Pharmacia & Upjohn Company became effective. All references to The Upjohn Company in this Environmental Assessment for melengestrol acetate refer to the company now named Pharmacia & Upjohn Company.

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ENVIRONMENTAL ASSESSMENT REPORT (EA)

1. DATE

June 12, 1996

2. NAME OF APPLICANT

The Upjohn Company

3. ADDRESS

The mailing address and telephone number of The Upjohn Company's headquarters are:

7000 Portage Road
Kalamazoo, Michigan 49001
Corporate telephone number: (616) 833-4000

4. DESCRIPTION OF THE PROPOSED ACTION

4.1. Requested Approval/Need for Action

This EA for melengestrol acetate (MGA®) is being submitted as part of a supplemental New Animal Drug Application (NADA) to NADA Nos. 34-254 (MGA 100/MGA 200 Premix) and NADA 39-402 (MGA 500 Liquid Premix). The labelled indications of MGA will be expanded to include suppression of estrus (heat) in all heifers intended for breeding. Currently, MGA is approved for increased rate of weight gain, improved feed conversion efficiency and suppression of estrus in heifers intended for slaughter. The expansion of the label for MGA, to include all heifers intended for breeding, will provide a new reproduction management tool for dairy and beef producers.

4.2. Production Locations

The drug substance and formulated drug product for MGA 200 Premix and MGA 500 Liquid Premix will be manufactured at The Upjohn Company in Kalamazoo, Michigan. MGA 100 is no longer manufactured or sold in the U.S., although it is

currently manufactured at The Upjohn Company's Canadian subsidiary for sale outside the U.S.

4.3. Locations of Product Use

MGA 200 and MGA 500 premixes (Type A Medicated Articles) are stored in distribution centers prior to transportation to feed mixing facilities. At feed mixing facilities, the Type A articles are diluted to make Type B and/or Type C Medicated Feeds (supplements) which may be used either on the premises (cattle feedlot) or sold as a commercial feed to cattle producers. The latter process will be the dominant situation for the expanded use of MGA described in this EA.

Type C Medicated Feeds (supplements) containing MGA are administered according to label at a rate of 0.5 to 2.0 pounds/animal/day, in order to deliver 0.50 mg MGA/animal/day for this indication. Supplements containing MGA may be top dressed or mixed in with complete feed. For the purposes of this EA, the highest approved daily dose of 0.5 mg MGA/animal/day will be used to predict concentrations of MGA in the environment (see Section 8).

MGA will be used on farms, dairies and ranches by cattle producers who grow heifers (beef or dairy) to be used as herd replacements. For producers of dairy heifers, use of MGA will be centered in the states of CA, TX, WI, NY, MN, PA, OH, IA and MI. For beef heifers, use of MGA will be centered in the states of TX, OK, KS, NE, IA, MT and SD. Regardless of heifer type, MGA will be fed to animals in confinement (pens) most often. This will be done to ensure that each individual heifer consumes an efficacious dose of MGA. Heifers may be turned out to pasture following consumption of the daily drug dose.

4.4. Disposal Sites

4.4.1. Bulk Drug

Disposal of bulk drug does not occur normally as it is reprocessed until it meets specifications. Disposal of drug product may result from processing or distribution activities in the form of off-specification lots, returned goods, or from end-user disposal of individual units of empty or partially empty product containers. Off-specification lots and any returned goods shipped to The Upjohn Company will be incinerated in the incinerator described below. (Interim Status Treatment Storage and Disposal Facility).

4.4.2. Formulated Drug Product

Under normal conditions, no disposal of the product is expected at feed mixing facilities due to the high cost of the finished product. Similarly, no disposal of product is expected at the user level, whether it be farm, ranch or dairy. The Type C Medicated Feed (supplement) has costs associated with it that include the drug product and the other components of the supplement: grain, minerals and protein. Producers will buy only enough drug-containing supplement to meet their needs. Therefore, wastage and hence disposal of drug product by the end-user should be negligible.

4.4.3. Returned Finished Goods

4.4.3.1. *On-Site Incinerator.* An on-site approved incinerator is being operated as a Resource Conservation and Recovery Act (RCRA) interim status treatment storage and disposal facility under #MID000820381 in compliance with 40 CFR 264, Subpart O requirements. Additionally, 40 CFR 265.1(b) and Section 3005(e) of RCRA provide for the continued operation of an existing facility that meets certain conditions, until final administrative disposition of the owner's and operator's permit application is made.

A hazardous waste RCRA Part B/Act 451, Part 111 permit application has been submitted to the Waste Management Division of the Michigan Department of Natural Resources (now the Michigan Department of Environmental Quality , MDEQ) in Lansing, Michigan. The Upjohn facility is operating under interim status provisions until action is taken on the permit application. MDEQ action on the permit application is expected in 1996.

The MDEQ Air Quality Division air permit issued on July 15, 1980 (#242-80), revised to incorporate the Act 451, Part 111 requirements, was approved on May 26, 1993.

The incinerator is a two-stage system: the primary chamber rotary kiln operates at a minimum of 700°F; the secondary chamber, where final destruction of the product and off-gasses occurs, operates at a minimum of 1,904°F. The incinerator is equipped with a pollution control equipment train designed to remove gaseous and particulate pollutants. The pollution control equipment consists of: a quench section, an acid-gas pre-scrubber, a Venturi scrubber, an entrainment separator, an induced draft fan, and an exhaust stack.

All necessary permits are in place for the manufacture of this product to begin, as an existing interim status facility in accordance with Section 3005(e) of RCRA and Michigan Act 451, Part 111 licensing requirements.

4.4.3.2. *Hazardous Waste Landfills.* Ash generated as a result of the incineration process will be sent to a permitted hazardous waste landfill. At the present time, Upjohn uses the following facilities:

- Chemical Waste Management of Indiana, Inc., 4636 Adams Center Road, Fort Wayne, IN, operating license listed under Indiana Dept. of Environmental Management (IDEM) Permit No. IND 078911146;

- Environmental Quality Co., 1349 South Huron Street, Ypsilanti, MI: Michigan Disposal, Inc., 49350 North I-94 Service Drive, Belleville, MI (treatment) operating license listed under EPA ID No. MID 000 724 831; Wayne Disposal, Inc., 49350 North I-94 Service Drive, Belleville, MI (disposal) operating license listed under EPA ID No. MID 048 090 633; or

- Upjohn may use other facilities for such disposal which are suitable for that purpose and are properly permitted.

Upjohn has contracts with each of these facilities that require the facility to be in compliance with all applicable laws and regulations. The waste stream profile support documentation established with the hazardous waste landfill sites affirm compliance status. All facilities are audited and approved for use by an Upjohn environmental auditor prior to the first shipment of waste from Upjohn to the site. In addition, Upjohn personnel conduct periodic environmental audits of off-site disposal facilities during use of the facilities.

4.5 Type of Environment Present at and Adjacent to Manufacturing Locations

Production of the drug substance and formulated drug product will be done at The Upjohn Company, 7171 Portage Road, Kalamazoo, Michigan 49001, located in the northern portion of the City of Portage in Kalamazoo County, Michigan. Kalamazoo County is in the southwest corner of the State approximately 140 miles equidistant from Chicago and Detroit. The facility is 1.7 miles northeast of the center of the City of Portage, 5.4 miles south of the center of the City of Kalamazoo, and south of the Kalamazoo/Battle Creek International Airport.

The area in the immediate vicinity of the Upjohn production complex is a mix of zoning including heavy and light industry, general business, and single- and multiple-family residences. The Upjohn complex is on land zoned for heavy industry. The site is directly bordered by airport property, residences, and undeveloped land. In terms of the Universal Transverse Mercator Coordinate System (UTM), the plant is

located in Zone 16 at 619.1 km east and 4674.1 km north, which corresponds to latitude 42°12′42″ north and longitude 85°33′25″ west.

The Upjohn production complex consists of approximately 80 buildings including chemical and pharmaceutical manufacturing operations, offices, laboratories, utility operations, and various other support buildings (see Appendix 1). The plant site occupies a portion of approximately 810 hectares lying south of Bishop Road, east of Portage Road, north of Centre Street, and west of Sprinkle Road in the City of Portage.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

Melengestrol acetate (MGA) is a progestogen that is in the class of compounds known as steroids. It is closely related to two other progestogens that are commercially available, medroxyprogesterone acetate (PROVERA®) and megestrol. Melengestrol acetate is formed from progesterone by modifying positions 6 (methyl group and C-C double bond added), 16 (methylene group added), and 17 (acetoxy group added).

The material safety data sheet (MSDS) for MGA is provided in Appendix 2. The chemical structure and materials used in manufacturing MGA are provided in Appendix 3. Ingredients used in formulating MGA 100/MGA 200 Premix and MGA 500 Liquid Premix are identified in Appendix 4.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

The drug substance and formulated product are not expected to be introduced into the environment through transportation and storage. MGA is not regulated as a hazardous material under current DOT regulations. Product ready for shipment will be stored in either the manufacturing facility or distribution centers. Both types of facilities maintain security by limiting access.

Portions of the materials cited in Section 5 (Appendices 3 and 4) may be released into the environment as a result of the proposed action. These will be generated from the manufacturing site in the form of air emissions, liquid waste streams and solid wastes.

Applicable permits, actions and environmental regulations in force at Upjohn's production complex, with permit numbers and expiration dates where applicable, are summarized in the Permits Chart (Appendix 5).

6.1. Chemical Processing--Emissions

Most of the emissions generated from the chemical process consist of volatile organic compounds due to bulk drug material transfer, heating, filtration, distillation and drying operations. The use of condensers and vacuum distillation systems will minimize the resulting emissions to appropriate control levels in accordance with local, State and Federal standards.

6.1.1 Air/Solvent Emissions

The Upjohn Company is operating under a consent judgement with the MDEQ dated March 15, 1991, which required that an inventory be taken by December 1991 of all equipment with either the potential to emit a contaminant or used as a control device. This consent judgement further stipulated that approved permits be in place for the equipment included in the inventory. The inventory was submitted to MDEQ July 1, 1991. Where applicable, Lowest Achievable Emission Rate (LAER) controls were installed on the volatile organic compound portion of the process by December 31, 1995. The MGA production facility is part of Regions II and III in Chemical Operations. All subject equipment in Regions I and II are covered under Air Permit numbers 108-92 and 424-92, respectively.

Solvent emissions from the equipment used in the production of MGA will be controlled through the use of process condensers. These condensers operate with an efficiency rating of up to 90%, depending on the vapor pressure of the solvent. Any solvent emissions not trapped by the condensers will go into regional control (cryogenic condenser) systems that operate with a 95% efficiency rating.

6.1.2 Aqueous Waste Streams

6.1.2.1 *Chemical Process Water Management (CPWM).* Aqueous waste streams resulting from chemical processes will be disposed of on-site by a chemical process water management (CPWM) injection system in accordance with this facility's Underground Injection Control permits granted pursuant to the Safe Drinking Water Act. Only those aqueous streams not allowed to be discharged to the sanitary sewer are sent to the CPWM. Upjohn's CPWM injection operations are conducted in accordance with this facility's Underground Injection Control permit Nos. MI-077-1W-0001 and MI-077-1W-0002 granted by Region 5 of the U.S. Environmental Protection Agency (USEPA) pursuant to the Safe Drinking Water Act.

With respect to Upjohn's permits to dispose of liquid waste by the CPWM system, the Federal Underground Injection Control Permits restrict the types and concentrations of contaminants in the injected fluid. The contaminants are the same contaminants which Upjohn is allowed to handle under our hazardous waste permit application. These permits require that the concentration and type of contaminants listed in the permits are to be monitored on a monthly basis and reported to the USEPA, Region 5. In addition, groundwater is protected through the construction and design of the CPWM injection system, the operating procedures employed and the continuous monitoring program, all of which are described in the permit. A steam stripper was recently added to the CPWM to further reduce contaminants in the injected fluid. Volatile contaminants are now removed from this waste stream by steam stripping and recovered by our solvent recovery and distribution process.

All chemicals listed in Section 5 may be expected to be included in the injected wastes either through direct discharge of spent materials or as trace contaminants in equipment washing.

With respect to the permit application terminology, The Upjohn Company wells are identified as "class 1" by USEPA. Class 1 wells are used to inject hazardous wastes below the deepest underground source of drinking water. A confining formation consisting of an impermeable geologic stratum prevents any upward migration of injected fluids into underground sources of drinking water. A containment system (pressurized annulus) prevents leakage of injected fluids from the injection wells into any aquifer outside the injection zone.

A further description of EPA's requirements for the issuance of UIC permits is contained in 40 CFR Part 144.

6.1.3 Liquid Process Waste Streams

Aqueous waste streams resulting from chemical processing will consist of residue wastewaters from sanitary use and washing operations which will be discharged into the municipal sewer system for biological treatment at the City of Kalamazoo Water Reclamation Plant or through Upjohn's Chemical Process Water Management (CPWM) system.

6.1.3.1 *Industrial Pretreatment Program (IPP).* In response to Federal and State requirements governing the City of Kalamazoo's Industrial Pretreatment Program (IPP), The Upjohn Company has been issued a discharge permit in the form of an Industrial Control Document (ICD) dated March 25, 1994 through March 31, 1999. In addition, The City of Kalamazoo Sewer Use Ordinance and Sewer Use Regulations Nos. are incorporated by reference below:

- 1-89 (dated December 5, 1989), providing details on violations and penalties for noncompliance;
- 91-1 (dated April 29, 1991), detailing pollutant discharge limits for metals; and
- 94-1 (dated February 9, 1994) detailing pollutant discharge limits for petroleum hydrocarbons.

These documents detail additional specific discharge requirements and regulations. All discharges from the production of ceftiofur sodium are permitted and, through the fifth year of production, will not impact the limits imposed under the ICD and accompanying Sewer Use Regulations.

6.1.3.2. Spent Solvents. Used solvent mixtures are either directed to the Solvent Recycling and Distribution (SRD) unit for recycle and reuse within the Portage manufacturing facility, used as a fuel in an on-site approved incinerator at the Portage manufacturing site, or are sent to an approved off-site facility as part of a waste-derived fuels program at permitted facilities where the waste is either blended with other solvents for incineration or directly injected for incineration.

6.1.3.3. Solvent Recycling & Distribution (SRD). Used solvents at The Upjohn Company are collected at the production areas and conveyed via pipeline to a solvent recycling and distribution (SRD) facility within the plant site.

The SRD system receives the various solvents into dirty tanks and then feeds them into one of five distillation/reclamation columns that fractionate the constituents through the application of heat. At the different temperatures, various solvent species are recovered and sent to a clean tank where they are then distributed to the various production operations located throughout the plant site.

Those portions of the fractionation process that do not result in a product that is usable in Upjohn production operations are sent off-site for disposal. The vast majority of this material is used as a waste-derived fuel that replaces or enhances other fossil fuels burned for energy. Other disposal options are the local waste water treatment plant and high temperature incineration, dependent upon the chlorine and water content of an individual stream.

A chart highlighting the Exit Streams resulting from the MGA chemical process is included as Appendix 6.

6.1.4 Solid Wastes

6.1.4.1. *Nonhazardous Waste Landfills.* Any bags, boxes, and filter cartridges used during manufacturing of MGA are disposed of at an approved sanitary landfill, along with the other solid wastes generated at the plant site. Landfills used include the following:

- Westside Landfill in Three Rivers, MI (Waste Management of Michigan, Inc.), operating under State of Michigan Solid Waste Disposal License No. 8147 for bulk, uncrushed material;
- Orchard Hills Landfill in Watervliet, MI, operating under State of Michigan Solid Waste Disposal License No. 8113 for any finished drug product; or
- a comparable facility.

Upjohn has contracts with the aforementioned facilities requiring that the facility be in compliance with all applicable laws and regulations. The underlying agreements with the sanitary landfills affirm compliance status. All facilities must be audited and approved for use by Upjohn environmental auditors, prior to the first shipment of waste from Upjohn to the site. In addition, Upjohn personnel conduct periodic environmental audits of off-site disposal facilities during use of the facilities.

6.1.4.2. Recycling. The Upjohn Company operates extensive solid waste recycling programs. All production and distribution locations have solid waste recycling programs in place. Solid wastes that are recycled include paper from product inserts, corrugated board from secondary containers, and in some cases excess plastic. Disposal of solid waste in a landfill or incinerator is done only after exhausting other options. The primary container, which may be contaminated with product, must be rinsed prior to recycling or disposed of in a landfill or incinerator.

6.2 Micronizing

6.2.1. Air Emissions

Air emissions in the Micronizing unit have been included in the Michigan Department of Environmental Quality (MDEQ, formerly MDNR) Permit to Install No. 207-93. This application was approved by the MDEQ on October 10, 1994.

Particulate emissions from the production of this product in the Micronizing unit are controlled by a Roto-clone wet scrubber with a control efficiency of 75% for

this material. A 0.064% loss of all melengestrol acetate processed in this area is directed to enter the Roto-clone wet scrubber.

Melengestrol acetate may also be micronized in the Potent Drug facility as production schedule and room availability dictate. The Potent Drug area has been permitted under Permit to Install No. 105-93 which was approved by the MDNR as part of the consent decree on September 27, 1993. An application for a Permit to Operate was submitted to the MDNR on November 1, 1993. Particulate losses from this area are directed to HEPA filters with a 99.97% removal efficiency.

6.2.2 Solvent Emissions

There are no volatile organic compound (VOC) emissions resulting from this production process. Emission of VOCs to the general in-plant environment occurs during the periodic cleaning of the micronizing equipment using an SD alcohol CD19 solution. Approximately 2,100 lbs of SD alcohol is lost to the in-plant environment on an annual basis. This loss represents 4% of the alcohol used annually for cleaning in this area. Remaining spent alcohol is drummed, labeled as hazardous waste, and sent to the Waste Control Unit for disposal at an approved off-site hazardous waste facility.

In the Potent Drug facility, VOC emissions would occur in the same manner as is in the Micronizing unit from the cleaning with SD alcohol.

6.2.3. Aqueous Waste Streams

Aqueous waste streams are generated from two different locations in the Micronizing process. The first is the water used for scrubbing particulate in the Roto-clone exhaust systems. This stream is discarded to the municipal sewer system for treatment at the City of Kalamazoo Water Reclamation Plant. The second stream is water used for cleaning the equipment, and this stream is also discarded to the municipal sewer system for treatment at the City of Kalamazoo Water Reclamation Plant.

6.2.4. Solid Wastes

Solid waste from the Micronizing Unit is disposed as follows:

- soiled plastic bags - sent to Upjohn's approved on-site incinerator.
- soiled Tyvek® protective garments - sent to Upjohn's on-site incinerator.

- used filter media from exhaust systems - sent to Upjohn's on-site incinerator or sent off-site to an approved non-hazardous landfill for special burial.

6.3. Pharmaceutical Formulation--Emissions

6.3.1. Air Emissions

Because of the nature and minute quantities of air emissions resulting from the Agricultural Premix Facility, the only air pollution equipment are a bag-type dust collectors and/or wet Roto-clones. These devices will remove particulates from the exhausted air prior to dispersion into the atmosphere. The Air Use Permit Application (#854-92) was approved by the MDNR (now MDEQ) September 28, 1993.

6.3.2. Liquid Waste Streams

Liquid waste streams resulting from formulation of MGA consist of residual wastewater from sanitary use and washing operations. These streams are discharged to the sanitary sewer system (see Section 6.1.3.1.).

6.3.3. Solid Wastes

Solid wastes generated during formulation of MGA consist mainly of cardboard, paper and plastics and are disposed as follows:

- MGA-containing fiberboard drums: recycled;
- Dry flow starch fiber drums: nonhazardous landfill;
- Off-specification 50# size bags for packaging: recycled;
- Plastic fiberboard drum liners: nonhazardous landfill.

6.4. Citation of and Statement of Compliance with Applicable Emission Requirements

The following regulations or standards are cited as applicable to the proposed action:

United States

1. Federal Food, Drug and Cosmetic Act, PL 75-717, as amended, including subsections 306(a) and (b) [debarment].

2. Clean Air Act PL 91-604, as amended.
3. Clean Water Act PL 95-217, as amended.
4. Safe Drinking Water Act PL 93-523.
5. Resources Conservation and Recovery Act of 1976 PL 94-580, as amended.
6. Occupational Safety and Health Act of 1970, as amended.
7. Hazardous Materials Transportation Act of 1975, as amended.
8. Standards from the American National Standards Institute.
9. National Fire Protection Agency Standards.
   a. National Electrical Code Standards
   b. Life Safety Requirements
10. Act # 451 of 1994, Michigan Natural Resources and Environmental Protection Act, as amended including:
    - Part 31, Water Resources Protection
    - Part 55, Air Pollution Control
    - Part 111, Hazardous Waste Management
    - Part 115, Solid Waste Management
    - Part 121, Liquid Industrial Waste
    - Part 625, Mineral Wells
11. Act #399 of 1976, Michigan Safe Drinking Water Act, as amended.
12. Act #368 of 1978, Public Health Code.
13. Chapter 28 of the Kalamazoo City Code (Services and Wastewater) as amended by ordinance No. 1190.
14. Michigan Occupational Safety and Health Act of 1970, as amended. (Local regulation applicable to the State of Michigan.)

Canada

15. Canadian Environmental Protection Act.
16. Ontario Environmental Protection Act.
17. Reg. 308 of the EPA (Ontario) (Air).
18. Reg. 309 of the EPA, Waste Classification and Registration.
19. Bill 143, Management of Waste in the Greater Toronto Area.

6.4.1. Emission Requirements

Upjohn states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees or administrative orders applicable to the manufacture of MGA at its facilities in Kalamazoo, Michigan, as well as emission requirements set forth in applicable Federal, State, and local statutes and regulations applicable to the manufacture of MGA at its facilities in Kalamazoo, Michigan.

6.4.2. OSHA Requirements

Upjohn certifies that it has comprehensive programs and practices in place addressing OSHA requirements.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

7.1. Target Animal Metabolism

Metabolism studies were conducted in heifers using ^{14}C- or ^{3}H-labeled MGA fed daily at doses of 0.5 to 4 mg of MGA for intervals up to 23 days. Residues in edible tissues at six hours following the last dosing (28,29,30,31), and residues in feces and urine excreted during the dosing interval (12,13) were measured following dosing with either ^{14}C-MGA (0.5 mg) for seven days (13,29,31) or ^{3}H-MGA (0.5 mg) for 23 days (12,28,30). In liver, kidney and muscle 20% to 40% of the radioactivity detected was intact MGA. The balance of the radioactivity detected consisted of metabolites more polar than MGA (28,29). Thin-layer chromatographic analysis of liver extracts (^{14}C study) revealed, in addition to MGA, five other radiolabeled bands (metabolites) more polar than MGA (31). Incubation of MGA with bovine liver homogenates corroborated the results found *in vivo* (23). In fat, 80% of the radioactivity was identified as intact MGA (28,29). Approximately 60% and 10% of the total administered dose was detected in feces and urine, respectively (12,13). The exact nature of the metabolites excreted is unknown, however, they are presumed to be steroidal in nature.

Daily dosing for eight or 15 days with 4 mg ^{3}H-MGA (8X overdose) showed that MGA does not bioaccumulate in heifers (20,21). Radioactivity recovered in excreta increased during the first four to six days of MGA dosing. At this point, the radioactivity detected in the excreta was approximately equal to the amount of radioactivity being administered. Following cessation of dosing with ^{3}H-MGA, radioactivity began to decline within two days. The interpretation that MGA is rapidly cleared from the heifer, and does not bioaccumulate, is further supported by extensive studies done using non-labeled MGA (22,26,27). The latter studies showed that MGA in fat is positively correlated with the administered dose and that MGA in fat rapidly declines following cessation of MGA administration. The half-life for MGA loss from the heifer and from human females has been reported to be approximately three days (33). Collectively, these data support the interpretation that MGA will not accumulate in the tissues of heifers.

In summary, MGA is metabolized to multiple intermediates in the heifer. The identities of the metabolites excreted in urine and feces are unknown, however they are more polar than MGA and presumably steroidal in nature. For the purposes of

this EA, it will be assumed conservatively that the excreted metabolites have equivalent bioactivity compared with MGA. Furthermore, it will be assumed conservatively that all of the MGA fed is excreted. Given that the highest approved dose for MGA is 0.5 mg/heifer/day, this quantity is the maximum amount of MGA that will enter the environment from a heifer fed MGA.

7.2. Physical/Chemical Properties and Partitioning

Estimates of the water solubility, octanol/water partition coefficient (K_{ow}), vapor pressure and the soil sorption/desorption coefficient (K_{oc}) were measured in accordance with FDA TAD (Technical Assistance Document) 3.01, 3.02, 3.03 and 3.08 guidelines, respectively. The water solubility of MGA was determined to be 1.06 µg/mL (ppm) at pH 7.1 and 25 °C (10). An average $\log_{10} K_{ow}$ for MGA of 3.98 was obtained, based on triplicate determinations at each of two MGA concentrations (37). At 25 °C, the vapor pressure for MGA was estimated to be less than 10^{-7} torr (8). K_{oc} estimates for soil adsorption and desorption were estimated for MGA using sandy loam, loam and silty loam soils (38). MGA was tightly bound to the soils tested. The bound fraction ranged from 96 to 97% of total MGA incorporated into the soils, with only 3 to 5% of the bound MGA being readily desorbed. The soil K_d (soil partition coefficient) values ranged from 549 to 1009 for adsorption and from 201 to 400 for desorption. For adsorption of MGA, estimates of $\log_{10} K_{oc}$ (organic matter partition coefficient) were 4.6, 4.8 and 4.9 for the sandy loam, loam and silty loam soils, respectively. For these same soils, desorption $\log_{10} K_{oc}$ estimates were 4.3, 4.4 and 4.5 (38).

The water solubility, octanol-water partitioning, and binding of MGA to soil are generally consistent with empirical relationships developed for other uncharged organics. The average $\log_{10} K_{oc}$ estimate for MGA can be predicted to within a factor of 10 from the average $\log_{10}$ of the MGA water solubility limit (Figure 1). Furthermore, the average $\log_{10} K_{oc}$ for MGA can also be predicted to within a factor of 10 from the average $\log_{10} K_{ow}$ for MGA. That MGA behaves similar to other organics suggests that general empirical relationships developed by the USEPA's Office of Toxic Substances for other classes of uncharged organics (51) may be useful in predicting ecotoxicological endpoints (eg, LC_{50} values) for MGA (see Section 8.2).

The measured water solubility, K_{ow} and K_{oc} estimates for MGA predict that MGA will be relatively immobile in soils, and therefore, MGA is expected to partition largely into the terrestrial compartment of the environment. Of the MGA that binds to soil, little (less than 5%) is expected to be desorbed following rainfall events and be transported to groundwater or carried to aquatic systems with runoff. Partitioning of MGA into the atmosphere is not expected based on the low vapor pressure for MGA.

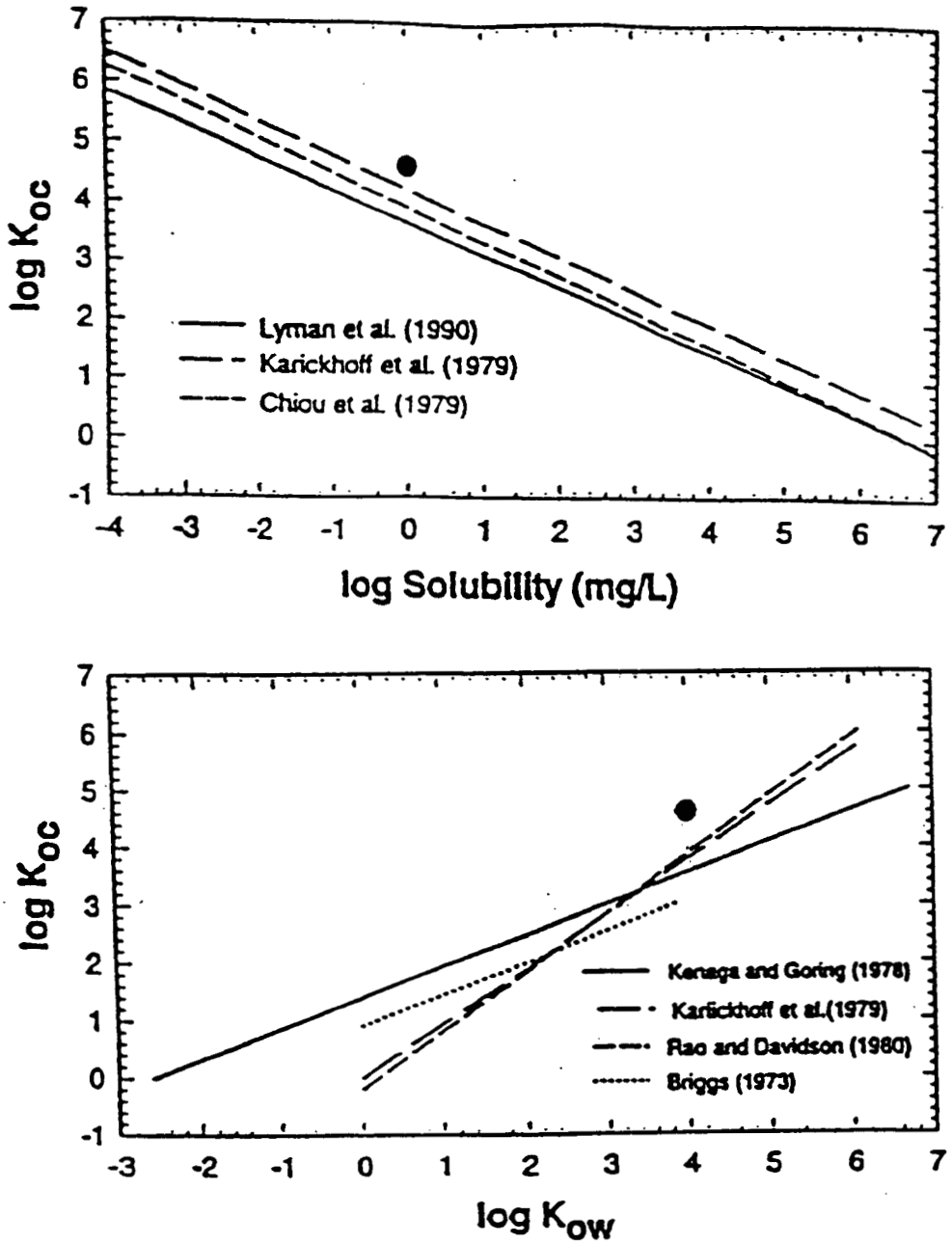

Figure 1. Comparisons of MGA against empirical relationships (1,4,24,25,34,42) developed for other compounds to predict the $\log_{10} K_{oc}$ from $\log_{10}$ water solubility and the $\log_{10} K_{oc}$ from the $\log_{10} K_{ow}$. Filled circle in both panels is defined by the mean values of the indicated physicohemical properties obtained for MGA (10,37,38).

The potential for MGA to partition into biomass (bioaccumulate) can be estimated by using the following empirical relationship cited by Mill (36):

BCF (bioconcentration factor) = $[0.893 \times \log_{10}(K_{ow})] + 0.607$

The average $\log_{10} K_{ow}$ determined for MGA was 3.98 (see Section 7.2). Using this value in the above equation, the predicted BCF value is 4.2. Compounds which may bioaccumulate have $\log_{10} K_{ow}$ values in the range from two to six (5). Thus the BCF estimate for MGA predicts that it has the potential to bioaccumulate in animals such as fish. The relatively high K_{oc} estimates for MGA (38) support the prediction that the partitioning of MGA into aquatic environments will be limited and therefore, bioaccumulation in fish or other aquatic species is not expected. Furthermore, MGA is metabolized in animal tissues to a number of more polar intermediates. Clearance from the bovine, which is considered to be the most sensitive animal species, occurs with a half-life of three days (see Section 7.1). Thus notwithstanding a predicted BCF value for MGA of 4.2, this compound is predicted to be cleared rapidly from terrestrial animals by way of conversion to compounds with reduced lipophilicity.

7.3. Hydrolytic and Photolytic Degradation

The potential for MGA to be hydrolyzed was assessed according to FDA TAD 3.09 guidelines (11). Hydrolysis was assessed first at 50 °C using a test duration of five days. MGA was not hydrolyzed at pH values of 5 and 7 at 50 °C and thus was not tested at pH values of 5 and 7 at 25 °C. At pH 9 at 50 °C, MGA was completely hydrolyzed. The hydrolysis of MGA was subsequently measured at pH 9 at 25 °C using a test duration of 35 days. Under the latter experimental conditions, approximately 70% of the initial MGA concentration (0.4 µg/mL) was hydrolyzed by the end of the 35-day test period (11). The data obtained at pH 9 at 25 °C were fitted to a first-order decay equation by using linear regression. The estimated half-life for hydrolysis of MGA at pH 9 at 25 °C was 468 hours or approximately 20 days. Findings of the hydrolysis study suggest MGA will be hydrolytically stable in environments with pH values close to neutrality.

The potential for MGA to be photolytically degraded was examined according to FDA TAD 3.08 guidelines (47,48). The half-life for loss of ^{14}C-MGA in pH 7 buffer at 25 °C was estimated to be 0.922 hours. MGA was stable in the quartz tubes not exposed to the xenon arc lamp. Total recovery (^{14}C-mass balance) ranged from 98.1 to 108% for the exposed tubes (mean = 102%) containing ^{14}C-MGA and ranged from 91.0 to 105% for the nonexposed tubes (mean = 101%). The reaction quantum yield for MGA was estimated to be 4.26×10^{-3} and 3.41×10^{-3}, based on mean solar data for light intensity at equinox 40° N latitude and direct measurements of the intensity of light from the xenon arc lamp, respectively (48). Using the quantum yield data, estimated

half-lives for MGA at pH 7 in flat bodies of water ranged from a low of 3.84 hours (summer, 30° N) to a high of 25.3 hours (winter, 50° N). Photolysis may not be a major degradative mechanism in soil, however, the short half-life for MGA in water (approximately one hour) suggests that photolysis will contribute to the breakdown of MGA in aquatic ecosystems exposed to sunlight.

7.4. Biodegradation

The biodegradability of MGA in soils under aerobic conditions was assessed in two different studies (9,50). The FDA TAD 3.12 guidelines served as the basis for the design of both experiments. In the first study (9), 13.2 mg (10 mg carbon) of non-labeled MGA/50 g dry weight of soil were added to three different soil types. This amount of MGA equates to 264 µg/g (ppm) of soil, on a dry weight basis. Aerobic mineralization was assessed by measuring production of CO_2 over the 77-day test period. The production of CO_2 ranged from 11 to 15% of theoretically expected CO_2 for two of the three soils tested. Mineralization of MGA in the third soil appeared to be inhibited. Degradates from MGA metabolism, other than CO_2, were not identified or quantitated. In summary, MGA was not extensively mineralized in soils under the conditions used in the first biodegradation study.

There are several reasons why MGA may not have been mineralized in the soil biodegradation study of Davis et al (9). First, MGA cannot be mineralized by soil microflora, ie, MGA is recalcitrant to microbial metabolism. Second, the organic matter contents of the soils tested (9) were too low. Biodegradation potential is positively correlated with the organic matter content of soils and the soils used in the first biodegradation study were at the lower limit of the organic matter content range specified in the TAD 3.12 guidelines. Third, the bioavailability of the 264 ppm initial MGA soil concentration was presumably limited by the water solubility of MGA, which is 1.06 ppm. The fourth reason why mineralization of MGA may have been limited in the first biodegradation study is that the initial concentration of MGA, 264 ppm, may have been inhibitory to the soil microflora. It is probable that more than one of these four reasons contributed to the limited biodegradation observed in the Davis et al. (9) study.

The second biodegradation study (50) was designed with several modifications to the experimental approach to reduce or eliminate the effects of factors that may have limited biodegradation of MGA in the first study (9). First, two of three soils used had higher organic matter contents compared to soils used previously. Second, MGA was added to the test soils in a soluble form to increase its bioavailability. The initial soil concentration (dry weight basis) was approximately 130 ppb, which is more consistent with predicted environmental concentrations of MGA (see Section 8.3). The third modification of the approach was that ^{14}C-MGA (radiolabeled in the 6-methyl and

16-methylene positions; Figure 2) was used, rather than non-labeled MGA. The use of ^{14}C-MGA was a necessity for monitoring mineralization, given the low initial concentrations of MGA (approximately 130 ppb) tested. Furthermore, use of ^{14}C-MGA allowed quantitation of transformation products of MGA. Artificial root exudate (ARE), a mixture of sugars, organic acids and amino acids representative of those excreted by plants into the rhizosphere, was used as the cometabolic substrate (50). Use of ARE (or an alternative) is consistent with TAD 3.12 recommendations that a cometabolic substrate should be used when the test substrate is added to soils at less than 10 mg carbon.

As in the Davis et al (9) study, the objective of the second biodegradation study (50) was to determine the aerobic mineralization potential of MGA using three different soil types (Michigan, Texas, Washington). In addition to mineralization, the potential for MGA to be transformed to degradates other than CO_2 was also examined. The potential for mineralization and transformation were assessed in the absence or presence of the cometabolic substrate, ARE. Mineralization of MGA was assessed by monitoring $^{14}CO_2$ production. Loss of ^{14}C-MGA and transformation to ^{14}C-intermediates was monitored by analyzing soil extracts by using an HPLC equipped with a radiometric detector (HPLC-RAM). Radiolabel mass balances were calculated by summing $^{14}CO_2$, ^{14}C-labeled intermediates (extractable), and soil-bound ^{14}C radioactivity (non-extractable) determined by soil combustion. Metabolic activity of the microflora in each soil was verified by monitoring CO_2 production from non-labeled glucose.

Overall results for the second soil biodegradation study are summarized in Table 1. The Michigan loam soil (minus ARE and plus ARE) mineralized 40.1% and 44.7% of the MGA to $^{14}CO_2$ after 98 days of incubation. The Texas clay loam soil mineralized 28.6% and 29.7% of the MGA to $^{14}CO_2$ after 98 days of incubation. The Washington silt loam soil mineralized 7.9% and 8.9% of the MGA to $^{14}CO_2$ after 98 days of incubation (Table 1). The half-life for MGA loss in the Michigan, Texas and Washington soils without ARE was 5.3, 4.3 and 27.8 days, respectively. With ARE, the half-life for MGA loss was 4.9, 4.3 and 27.8 days for the respective soils (Table 1).

Table 1. Potential for ^{14}C-MGA to be transformed and mineralized in three soils incubated under aerobic conditions

	Michigan		Texas		Washington	
ARE present	No	Yes	No	Yes	No	Yes
Mean total % of radiolabel recovered (mean of days 0, 14, 28, 56 and 98)	104.2%	101.0%	98.4%	97.2%	99.7%	101.3%
% ^{14}Carbon Extracted at 98 days	12.3%	10.9%	21.4%	20.0%	69.9%	70.0%
% $^{14}CO_2$ Recovery at 98 days	40.1%	44.7%	28.6%	29.7%	7.9%	8.9%
% ^{14}Carbon bound to soil at 98 days	49.0%	43.5%	43.2%	37.1%	20.7%	19.6%
Half-life of MGA (days)	5.3	4.9	4.3	4.3	27.8	27.8
Half-life of the summed potentially bioactive compounds (PBC) (days)	12.5	9.4	28.6	24.5	153	140

Radiochromatography of soil extracts indicated similar extractable intermediates within each of the three soils; nine transient, non-MGA intermediates were detected. Rates of production and disappearance of intermediates depended on soil type. The dominant early intermediate was Δ^1-melengestrol acetate (dMGA). Radioactivity recovered in the two peaks less polar than MGA, dMGA, plus a peak that co-chromatographed with melengestrol (MG) were summed with MGA to determine a half-life for potentially bioactive compounds (PBC). The half-life of PBC in the Michigan, Texas and Washington soils without ARE was 12.5, 28.6 and 153 days respectively. With ARE, the half-life of PBC was 9.4, 24.5 and 140 days for the respective soils (Table 1).

A major sink for the radioactivity added to the soil was non-extractable (soil-bound) radioactivity. At day 98, the Michigan, Texas and Washington soils without ARE had 49.0%, 43.2% and 20.7%, respectively, of the radioactivity bound to soil. With ARE, 43.5%, 37.1% and 19.6% of the radioactivity was bound to the respective soils (Table 1). The mass balance for the sum of $^{14}CO_2$, extractable and soil-bound (non-extractable) radioactivity was 100.3% (mean across all times for all soil/treatment combinations). The mass balance for the Texas soil prior to day 56 was 100.7%. After 56 days, both treatments of the Texas soil (minus ARE and plus ARE) indicated a trend for reduced total radiolabel recovery, with 7.8% and 13.8% unrecovered at 98 days (Table 1). The unrecovered radioactivity may be associated with production of volatile intermediates such as $^{14}CH_4$. Taking this into account, mineralization of MGA in the Texas soil may have been as high as 35.7% and 43.3% in the absence and presence of ARE, respectively.

Based on criteria identified in the protocol, (50), this study demonstrated positive test results for transformation of MGA. Half-lives for loss of MGA from soil ranged from 4.3 to 27.8 days. Half-lives for PBC ranged from 9.4 to 153 days. Major sinks for MGA (in order of magnitude) were the soil-bound fraction and mineralization, with CO_2 being the major product of the latter process. Transient intermediates from the metabolism of ^{14}C-MGA were produced during the 98 days of incubation. At 98 days, dMGA was the only intermediate present at greater than 5% of the radioactivity initially added to the Texas and Washington soils. Addition of a cometabolic substrate (ARE) was generally stimulatory to transformation of intermediates and production of $^{14}CO_2$, but not to MGA transformation. Therefore, in contrast to the soil biodegradation study run using non-labeled MGA, the soil biodegradation study conducted using ^{14}C-MGA demonstrated extensive loss of MGA from soils. The low, more environmentally relevant concentrations of MGA used in this second study, presumably contributed to the differences observed between the two experiments.

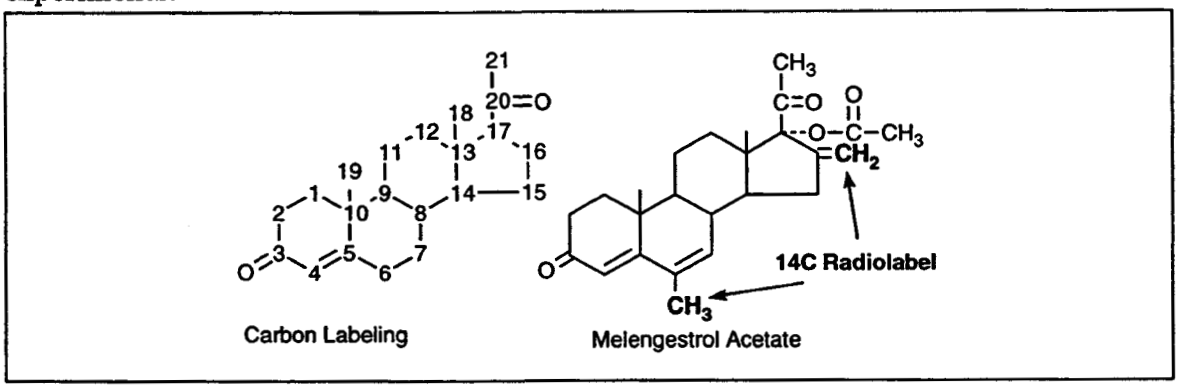

Figure 2. Carbon numbering scheme and positions of radiolabel in the ^{14}C-MGA used for the soil biodegradation study of Smolenski et al (50)

With respect to the ^{14}C-MGA used in the second soil biodegradation study, ^{14}C was not incorporated into any of the carbons comprising the cyclopentanoperhydrophenanthrene skeleton (rings A, B, C and the five-membered ring, D) of MGA (Figure 2). The ^{14}C MGA used was labeled in the 6-methyl and 16-methylene carbon positions (Figure 2). Reactions where one or both of these carbons could be removed and leave the steroid ring intact are theoretically possible. Based on known chemical reactions, removal of the 16-methylene carbon as CO_2 should be the easiest, however, a literature search failed to locate any reference describing chemical or biochemical removal of 16-methylene groups from steroids.

A search of the scientific literature also failed to identify references to the chemical or biochemical removal of the 6-methyl group of steroids. References were located, however, describing oxidation of 6-methyl steroids (6,7,19). In the first and second reports, 6-hydroxymethyl MGA and 6-hydroxymethyl megestrol acetate were reported to be metabolites of MGA and megestrol acetate in rabbits, respectively (6,7). In the other report, *Rhizopus arrhizus* was shown to hydroxylate androstenedione at carbon position 6 (19).

Studies on microbiological transformations of steroids have shown that the A and B rings of steroids can be metabolized to CO_2 (49,54). Studies of progesterone and sitosterol have revealed that these compounds are metabolized by introduction of a Δ-1 double bond followed by hydroxylation at position nine, and a Δ-1 double bond intermediate was observed in the ^{14}C-MGA soil biodegradation study (50). This is followed by cleavage of the B-ring (Figure 2) with subsequent conversion to CO_2. It is probable that a similar series of reactions would be needed to have released the ^{14}C-methyl carbon at position six as $^{14}CO_2$ from the ^{14}C-MGA used in the soil biodegradation study.

The primary evidence supporting that release of the 6-methyl and 16-methylene ^{14}C groups as $^{14}CO_2$, without cleavage of the steroidal ring structure, did not occur in the radiolabeled MGA soil biodegradation study (50) is the difference in rates of ^{14}C-MGA and ^{14}C-PBC loss versus $^{14}CO_2$ production. The time for 50% disappearance of PBC was approximately 10, 26 and 150 days for the Michigan, Texas and Washington soils, respectively. The time for 50% recovery of $^{14}CO_2$ was approximately 140, 205 and 550 days for these soils, respectively. If the 6-methyl or 16-methylene group was cleaved off of these PBC steroidal compounds without opening the ring structure, then a one-carbon compound would be produced that would in turn be rapidly converted to CO_2. Therefore the time for 50% production of CO_2 should have been closer to the rate of 50% loss of radiolabeled steroid compounds. These data are more consistent with a mineralization process in which MGA is rapidly transformed to a variety of transient intermediates that do not accumulate, and after a period of time these compounds are ultimately mineralized to CO_2. This hypothesis is further supported by the detection of nine radiolabeled non-MGA intermediates, indicating that the mineralization to CO_2 was a cascade of transformations and not simply the removal of the radiolabel from the steroid. In summary, the appearance and subsequent disappearance of metabolites support the interpretation 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 CO_2 is possible.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

8.1. Effects on Terrestrial Species

The potential for MGA to have negative impacts on earthworms and terrestrial plants has been assessed (44,46). A 28-day test (FDA TAD protocol 4.12) was conducted using *Lumbricus terrestris* exposed to the following conditions: untreated control, vehicle blank (acetone control), and 0.002, 0.02, 0.2 and 2 ppm (µg/g) of MGA in artificial soil (44). Acetone was used as the solubilizing agent in order to increase solubility of MGA above the water solubility limit of 1.06 ppm (µg/mL). A single worm mortality was observed at the highest concentration of MGA tested, 2 ppm. This result was concluded to be aberrant and not compound related because there were no other mortalities or adverse effects noted (44). Based on the data obtained, the LC_{50} for MGA against *L. terrestris* was estimated to exceed 2 ppm. Furthermore, the NOEC (mortality and mean worm weight) was greater than or equal to 2 ppm in the artificial soil employed (44).

A seed germination and root elongation study (FDA TAD 4.06) was performed in two phases (preliminary and definitive) with seeds of monocots and dicots to assess the potential for MGA to negatively impact terrestrial plants (46). In the preliminary phase, seeds of corn, perennial ryegrass, wheat, radish, soybean and tomato were exposed to the following six treatments: water blank (water control), vehicle blank (acetone control), and MGA concentrations of 0.002, 0.020, 0.2 and 2-3 ppm (µg/mL). In the definitive phase, seeds of corn and soybean only were exposed to the following six treatments: water blank (water control), vehicle blank (acetone control), and nominal MGA concentrations of 0.1, 0.3, 0.5, 1 and 3 ppm of MGA (46). Acetone was used as the solubilizing agent to increase solubility of MGA above the water solubility limit of 1.06 ppm. Percent germination was unaffected in all six plant species up to the maximum MGA concentration used. Therefore, the NOEC for % germination was estimated as being greater than or equal to an MGA concentration of 2 ppm (46).

In the preliminary phase of the plant study (46) radicle length was unaffected in all species except for corn and soybean, therefore, only these two plant species were tested in the definitive phase. For the other four species, the NOEC for radicle length was estimated as being greater than or equal to 2 ppm of MGA. No significant negative effects on radicle length were detected in corn and soybean during definitive testing. Therefore, the NOEC for radicle length in corn and soybean was estimated as being greater than or equal to the highest MGA concentration tested, 3 ppm (46).

Based on the above findings for earthworms and plants, the worst-case PEC_{soil} (see Section 8.3) of approximately 2 ppb (µg/kg) is not expected to negatively impact the terrestrial environment. Support for this assertion stems from the 1000-fold or

(greater) difference between the NOEC estimates obtained for the terrestrial species tested (44,46).

Of all terrestrial species tested, the bovine is considered to be the most sensitive mammal to MGA based on inhibition of estrus and ovulation, and definable uterine changes (Table 2).

Table 2. Minimal effective doses (MEDs) for MGA in different mammals

Species	MED (μg)	Animal weight (kg)	MED (mg/kg/day)
Mouse	100	0.03	3.33
Rat	50	0.23	0.22
Man	7500	60	0.125
Dog	80	10	0.008
Heifer	250	500	0.0005

The minimal effective dose (MED) for this species can be used along with a worst-case predicted aquatic exposure scenario to calculate how much water a heifer would have to drink to reach the MED. An estimate of the worst-case concentration for MGA in water exposed to MGA-containing soils (see Section 8.3) is 9.0 ppt. A heifer would have to drink approximately 25,000 L [(0.227 mg MGA/heifer/day) ÷ (9.0×10^{-6} mg MGA/L)] of water at an MGA concentration of 9.0 ppt to reach the daily MED (Table 2). Clearly, this margin of safety is adequate for a species as sensitive to MGA as the bovine.

An extensive toxicology package has been generated for MGA (Appendix 7). This compound is relatively nontoxic following acute exposure (Table 3). MGA has been shown not to be a carcinogen. The results of multiple genotox studies (16,35,39,40,52,55) and three mouse lifespan studies (15,32,41) support this claim.

Table 3. Acute toxicity of MGA in the mouse and rat

Species/Route of administration	$LD_{50\ (mg/kg)}$	Reference
Mouse/Intraperitoneal	>2500	3,53
Rat/Intraperitoneal	>2000	3
Rat/By mouth	>8000	2
Rat/Subcutaneous	>5000	43

8.2. Effects on Aquatic Species

The effects of MGA on aquatic species have been tested (14,45). In an FDA-TAD 4.08 study (45), *Daphnia magna* was exposed to MGA concentrations up to 2 ppm (µg/mL). The upper concentration tested is approximately twice the water solubility of MGA (1.06 ppm), which was achieved by using ethanol as a solubilizing agent. At 24 hours, there was 0% daphnid immobility in the control and vehicle blanks (0.10 µL/mL ethanol) and in the test chambers containing MGA concentrations of 0.13, 0.25, 0.50, 1.0 and 2.0 ppm MGA (45). At 48 hours, 0% immobility was observed for the daphnids in all test chambers, except for the MGA test concentration of 2.0 mg MGA/L, for which 5% immobility was observed (one daphnid). Other than this single daphnid, no other immobilities or abnormalities were observed during the study. Given that 10% immobility is accepted as normal for untreated daphnids, the immobility of the single daphnid was considered to be aberrant and unrelated to MGA exposure (45). Based on these findings, the 24- and 48-hour EC_{50} values for MGA were greater than 2.0 ppm. The 48-hour NOEC was greater than or equal to 2.0 ppm (45).

A non-FDA TAD study was conducted to test the toxic effects of MGA on fish (14). Goldfish were exposed to MGA at a concentration of approximately 1 ppm (µg/mL) for 21 days. No toxicity to the fish was noted during the 21-day observation period. Lack of toxic effects on the goldfish used in this study is consistent with expectations, based on the predicted LC_{50} for freshwater fish cited above (Table 4). Therefore, at the worst-case PEC_{water} for MGA of 9.0 ppt (pg/mL), impact of MGA on aquatic species is not anticipated.

The above experimental results are consistent with predictions based on empirical relationships used by the USEPA's Office of Toxic Substances [Table 4; equations are cited in Table 7.2 of Suter (51)] to predict the toxicological effects of other uncharged organics. These relationships predict that the LC_{50} values for the indicated tests would be above the water solubility limit (1.06 ppm) of MGA (Table 4). Furthermore, the lowest predicted LC_{50} value (daphnid, chronic exposure) is 200,000-fold higher than the predicted water PEC for MGA of 9.0 ppt (see Section 8.3).

Table 4. Predicted fish and daphnid LC_{50} values from empirical relationships used by the USEPA's Office of Toxic Substances for uncharged organics (51).

Organism/Parameter	Equation[1]	Concentration (µg/mL or ppm)
Fish/96-hr LC_{50} acute test	$\log_{10}(LC_{50})=$ $-0.94x\log_{10}(P)+0.94x[\log_{10}(0.000068xP)+1]-1.25$	24
Fish/14-d LC_{50} chronic test	$\log_{10}(1/LC_{50})=0.871x\log_{10}(P)-4.87$	10
Daphnid/48-h LC_{50} acute test	$\log_{10}(1/LC_{50})=0.91x\log_{10}(P)-4.72$	5.0
Daphnid/16-d LC_{50} chronic test	$\log_{10}(1/LC_{50})=0.64x\log_{10}(P)-3.27$	2.1

1 P=antilog of $\log_{10}K_{ow}$ of 3.98, ie, $10^{3.98}$.

8.3. Predicted Environmental Concentrations for Soil (PEC_{soil}) and Water (PEC_{water})

This EA is being submitted specifically for the additional indication of feeding MGA to heifers intended for breeding. In the following calculation of PEC values, both feedyard and pasture-fed scenarios are considered because they represent two possible extremes. Considering actual field-use practices and regulations governing use of MGA (21 CFR 558.3.2), the PEC_{soil} value will lie closer to the feedyard scenario PEC_{soil} than a pasture-fed scenario PEC_{soil} because few heifers are expected to be fed MGA outside of a confinement facility (feedyard; see Section 4.3). This is because MGA must be top dressed onto or mixed into a complete diet and hence, MGA will not be fed typically in situations where heifers will defecate MGA-containing urine and feces in pastures. Rather, the manner in which MGA must be fed dictates that exposure scenarios in which MGA-containing manure will be collected, dried, spread and plowed into agricultural soils are more realistic. This fact notwithstanding, feedyard and pasture-exposure scenarios are developed first and then conditions under which MGA is actually used and environmental fate factors are considered that will reduce the PEC_{soil} values for MGA.

At the highest approved daily dose for MGA of 0.5 mg of MGA/heifer/day, the total amount of MGA fed for a 120-day stay in a feedyard would be 0.5 x 120=60 mg. Assume conservatively that all MGA fed is excreted (urine plus feces), all cattle in the feedyard are heifers, and that all heifers are on MGA. A 1000 lb (454 kg) animal in a feedlot excretes approximately 6% of its body weight in wet manure daily, or 27.2 kg wet weight. Manure (feces plus urine) is 70-80% water (17). Using an average value

of 25% for solids, 27.2 kg wet weight of feces converts to 6.80 kg dry weight. For a 120-day stay and assuming that manure production is as high for smaller cattle as it is for a 454 kg animal, total manure production would be 6.81 kg/day x 120 days = 817 kg dry matter. The estimated concentration of MGA in the manure produced over this time interval would be 60 mg/817 kg = 0.0734 ppm or 73.4 ppb MGA on a dry matter basis. A typical application rate of manure to soils is 15 tons/acre (17), but conservatively assume 20 tons/acre is applied. Given a bulk density for soil of 1.2 g/cm^3 (18), one acre of soil to a depth of 0.5 ft (6 in) weighs $7.41x10^5$ kg [(0.405 Ha/acre) x 1 acre x (10^4 m^2/Ha) x (10^4 cm^2/m^2) x (30.5 cm/ft) x 0.5 ft x (1.2 g soil/cm^3 soil)]. Again the concentration of MGA in the 20 tons of applied manure is 0.073 ppm. Thus, total MGA applied to the soil would be 20 tons x (2000 lb/ton) x (0.454 kg/lb) x 0.0734 ppm MGA = 1330 mg MGA. If all of this MGA were uniformly incorporated into an acre of soil to a depth of six inches, the MGA concentration would be 1330 mg MGA/$7.41x10^5$ kg soil = $1.80x10^{-3}$ mg MGA/kg soil or 1.80 ppb MGA.

Using the above exposure scenario, terrestrial organisms would be exposed to somewhere between 1.80 ppb (PEC_{soil}) and 73.4 ppb (manure PEC) of MGA, at the most. Exposure to 73.4 ppb would be expected only in situations where heifers are fed MGA in a pasture situation, ie, direct exposure of soil fauna to MGA in excreta defecated onto the surface of pastures. As noted above, MGA must be top dressed onto or mixed into a complete diet and for this reason heifers intended for reproduction (or for slaughter) will be fed MGA in confinement. Thus exposure of earthworms or other soil fauna directly to MGA-containing manure (73.4 ppb) is expected to be minimal or nonexistent. Thus the conservative exposure scenario, yielding a PEC_{soil} of 1.80 ppb, is more realistic given the way in which MGA must be fed to heifers.

The PEC_{soil} value of 1.80 ppb is overly conservative given a number of assumptions associated with this calculation:

- First, MGA is metabolized to more polar compounds in heifers and hence, excretion of MGA into the environment will not be 100% of the 0.5 mg of MGA allowed/heifer/day.

- Second, the biodegradability of MGA is ignored in calculation of the 1.80 ppb figure, and data from the second biodegradation study support that MGA bioavailability in soils will be reduced due to degradation and binding to soils.

- Third, the new indication proposed in this EA for MGA is for the feeding of MGA to heifers intended for reproduction. As such, the product label will stipulate that MGA is to be fed for no more than 24 days. Taking this label restriction into account, MGA-containing manure to be spread

onto soils for fertilizer will be reduced by the fraction, 24/120, ie, the fraction of time MGA will be fed to heifers intended for reproduction over the time MGA might be otherwise fed to heifers intended for slaughter (see the 120-day scenario above). This reduction would reduce the PEC_{soil} from 1.80 ppb to 1.80 ppb x (24/120)=0.36 ppb.

- Fourth, calculation of the 1.80 ppb assumes all manure applied to soil is derived from heifers fed MGA. In practice, manure from cattle confinement facilities will be derived primarily from steers. Assuming that at most 1/3 of the manure applied to soil is derived from heifers, reduces the 1.80 ppb figure to 0.60 ppb.

All of the above four conservatisms support that the PEC_{soil} of 1.80 ppb should be an upper limit on the possible exposure of MGA in manure to soil fauna.

MGA is not expected to partition into aquatic systems, based on the extent to which it binds to soil (see Section 7.2). Notwithstanding this prediction, the concentration of MGA in water can be predicted from data obtained from the soil sorption/desorption study. The concentration of MGA in the soil water phase can be calculated from the K_d according to the following equation:

$K_d = K_{oc}$ x fractional soil organic matter content

Using the lowest K_d measured in the soil/sorption desorption study, the predicted MGA concentration (PEC_{water}) in the interstitial water of soil would be 1.80 ppb/201=0.00896 ppb (ng/mL) or approximately 9.0 ppt (pg/mL). This calculation assumes 100% water saturation and reversible soil binding kinetics. The 9.0 ppt value is thus consistent with a worst-case scenario because the condition of 100% water saturation in soil does not exist 100% of the time, and binding of MGA to soil is not readily reversible (38).

In all of the above calculations, the positive contribution of degradation (biological and photolytic) processes to reducing MGA PEC estimates is ignored. The following calculations illustrate the potential positive impact of MGA biodegradation occurring in soils following localized introduction of MGA into soils following 30 years of continuous MGA use, which is the approximate length of time that MGA has been on the market.

The calculation of the PEC_{soil} for MGA in an acre of soil to six inches assumes MGA is homogeneously distributed when it is incorporated into the soil (i.e., plowed under). If all MGA applied did not degrade in soil and accumulated over 30 years, then the expected concentration in the soil using the above assumptions would be 1.80

ppb MGA x 30 years = 54.0 ppb. It is more conservative to assume that the MGA in manure that is incorporated into soil will be localized within individual "hot spots" containing 73.4 ppb (manure PEC). Of course, repeated plowing over 30 years would produce a more homogeneous distribution of MGA in soil. But if it is assumed conservatively, that the MGA incorporated in subsequent yearly manure applications enriches these MGA "hot spots" from previous years (beginning with year one), then the following table provides data on the expected accumulation of MGA in these sites given different half-life values for biodegradation of MGA following 30 years of annual incorporations.

Table 5. Impact of various biodegradation half-lives on the predicted concentration of MGA soil following 30 years of continuous (once annual), localized or homogeneous incorporations of MGA-containing manure into soil[1]

Half-life (Days)	Soil PEC (ppb MGA after 30 years of 73.4 ppb annual localized incorporations)	Soil PEC (ppb MGA after 30 years of 1.80 ppb annual homogenous incorporations)
30	73.4	1.80
56	74.2	1.82
60	74.5	1.83
90	78.1	1.92
120	83.5	2.05
240	113	2.76
360	145	3.57
365	147	3.60

[1] First-order decay kinetics is assumed with each annual application beginning with what was present at the end of the previous year plus the next annual localized (73.4 ppb) or homogenous (1.80 ppb) incorporation of MGA-containing manure into soil.

Thus if the biodegradation half-life for MGA was 365 days, then MGA would accumulate in these "hot spots" up to a level equal to twice that added at each annual application of MGA-containing manure (73.4 ppb) in soil at the end of 30 years (Table 5).

Assuming MGA incorporation into soils is localized, occurring only in "hot spots", is unrealistic. Table 5 also summarizes calculations done assuming that MGA is incorporated homogeneously into soil with 1.80 ppb contributions being added at the start of each year of the 30-year span of product use. Here too the calculations

performed assume different biodegradation half-lives with first-order decay kinetics governing the process. In this situation, MGA would accumulate to no more than approximately 4 ppb if the degradation half-life was 365 days. The information presented in Table 5 reinforces the limited potential for accumulation of MGA, even after 30 years of continuous use, where half-lives significantly longer than those determined experimentally in the Smolenski et al (50) study are assumed.

8.4. Risk Assessment

Use of MGA to control estrus (heat) in heifers intended for breeding is not expected to negatively impact the environment. This is based on the following reported findings and expectations:

- MGA is not expected to bioaccumulate in terrestrial or aquatic organisms.
- MGA is relatively nontoxic to non-target organisms, especially at the low ppb to ppt concentrations expected to be released into the environment. A wide margin of safety exists between the upper limit PEC value (approximately 2 ppb in soil and 9 ppt in water) compared to predicted or known levels at which MGA would potentially exert negative ecotoxicological effects. Degradation processes (biological and photolytic) would be expected to widen the margins of safety even further.
- MGA is not expected to be mobile in soils and any parent MGA and/or MGA-like residues should bind extensively to soils.
- MGA will biodegrade in soils to more polar metabolites and other products, including CO_2.
- MGA is not expected to accumulate in soils to ecotoxic levels even after 30 years of continuous use.

9. USE OF RESOURCES AND ENERGY

The use of natural resources and energy for the manufacture of this product will be less than 2% (at the fifth year) of present total plant usage and can be handled by the existing infrastructure. The resources committed will be the materials referred to in Section 5, the utilities used in manufacturing, and minor miscellaneous support materials.

Under the authority of the National Historic Preservation Act of 1966, as amended, The Upjohn Company has received an opinion letter from the State Historic Preservation Officer that, since this activity does not involve the alteration, demolition or construction of building or any earth-disturbing projects, historic property determination is not required (Appendix 8).

No effects on endangered or threatened species are anticipated as a result of drug approval. Results of a preliminary ecological assessment for The Upjohn Company manufacturing headquarters did not reveal the presence of endangered or threatened species, and did not demonstrate adverse impacts of manufacturing operations on aquatic or terrestrial biota including plants and waterfowl (Appendix 9).

10. MITIGATION MEASURES

Adherence to all applicable Federal, State and local regulations as outlined in Section 6.3 above shall be followed to avoid potential adverse impact associated with the proposed action.

Measures taken at the manufacturing site to avoid potential adverse environmental impacts associated with the proposed action include:

- Use of equipment systems to prevent emission levels from exceeding limits established by Federal, State and local regulations;
- Disposal of aqueous waste streams into the municipal sewer system for biological treatment at the City of Kalamazoo Water Reclamation Plant or through an on-site waste management system used in accordance with this facility's permit granted by the U.S. EPA pursuant to the Safe Drinking Water Act;
- All outside facilities are audited by The Upjohn Company's Environmental Auditing unit as a condition of doing business with Upjohn to verify compliance with all Federal and State hazardous waste regulations; and
- An extensive spill control plan to protect employees and environmental compartments is in place at The Upjohn Company Portage Road facility to mitigate any adverse effects of inadvertent releases to the environment.

Material Safety Data Sheets (MSDSs) are available on site. Employees associated with the manufacture of MGA have appropriate training. Employee protective clothing (e.g., gloves, uniforms, and safety shoes) and protective equipment (e.g., safety glasses and approved respirators) are used during manufacture of MGA to assure compliance with applicable occupational safety requirements.

The Upjohn Company has a comprehensive occupational health and safety program. This includes conduct of preplacement physical examinations of employees and periodic health surveillance examinations of all employees in manufacturing areas. Additionally, the company operates a health clinic to address any employee illness and/or injury occurring during the course of employment. The above procedures will serve to monitor employees for the development of conditions attributable to exposure.

11. ALTERNATIVES TO THE PROPOSED ACTION

Resources and facilities are being used effectively to produce a quality product with minimal environmental impact. The alternative of no action, depriving beef and dairy producers of a reproduction management tool for heifers, is not anticipated.

12. LIST OF PREPARERS

Following is a listing of those persons, and corresponding qualifications, who participated in the preparation of this EA. No government agency was consulted for this evaluation other than for routine implementation of ongoing environmental programs conducted at existing facilities.

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13. CERTIFICATION

The undersigned officials certify that the information presented is true, accurate, and complete to the best of their knowledge.

The undersigned officials certify that the EA summary document and Appendices contain non-confidential information and acknowledge that this information will be made available to the public in accordance with 40 CFR §1506.6.

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