

ENVIRONMENTAL ASSESSMENT

NADA 140-897

**REVALOR[®]-G (TRENBOLONE ACETATE, 40 mg & ESTRADIOL 17 BETA, 8 mg)
FOR PASTURE HEIFERS (SLAUGHTER, STOCKER & FEEDER HEIFERS)****1. DATE**

1 April, 1996

2. NAME OF APPLICANT / PETITIONERSponsor

Roussel Uclaf SA

US Agent

Hoechst-Roussel Agri-Vet Company

3. ADDRESS OF APPLICANT / PETITIONERSponsorAnimal Health Division
102 Route de Noisy
93235 Romainville Cedex
FranceUS AgentRoute 202 / 206
PO Box 2500
Somerville, New Jersey 08876-1258
USA**4. DESCRIPTION OF PROPOSED ACTION**

The subject of the proposed action is an ear implant, Revalor[®]-G (Trenbolone Acetate, 40 mg and Estradiol 17 Beta, 8 mg) for Pasture Heifers (Slaughter, Stocker & Feeder Heifers) for improved rate of weight gain. Hoechst-Roussel Agri-Vet Company is requesting approval for the use of this implant which will be manufactured by Roussel-Uclaf SA in France and shipped to the United States for distribution by Hoechst-Roussel Agri-Vet Company of Somerville, New Jersey.

Revalor-G will be administered by subcutaneous implantation on the posterior aspect of the ear by means of an implant gun. An individual animal will receive a single implant consisting of two pellets, each of which contains 20 mg trenbolone acetate (TBA) and 4 mg estradiol 17 beta. This product is intended for use in growing heifers which are being grown for slaughter for human consumption.

The population treated will be weaned pasture heifers. The total number of animals in this population is 6 to 7 million in a given year. It is estimated that 10% of the population (approximately 700,000 animals) will be implanted with this product on an annual basis. Because it is industry practice to implant cattle when they arrive at the pasture site, the overall

compete with other anabolic products already in the marketplace and its use will be in place of another product.

The active ingredients of Revalor[®]-G, TBA and estradiol 17 beta, are manufactured at the Roussel Uclaf facility in 63480 Vertolaye, France. They are then formulated into implants each consisting of two pellets at Usiphar, a subsidiary of Roussel Uclaf SA, Route de Choisy-au-Bac, 60205 Compiègne, France. Ten such implants are pre-packaged into a cartridge. The packaged dosage form will be imported from France, and then distributed and sold "over the counter" throughout the United States by Hoechst-Roussel Agri-Vet Company. The packages are prepared in France and are not intended to be opened until immediately prior to use on the farm or ranch. Each implant for use in an individual animal contains a pre-measured quantity of the active ingredients which do not require any direct handling by the end user as a result of packaging the pellets into a cartridge. Such packaging also avoids spillage of the drugs into the environment. Unused implants are retained in the cartridge until used.

The following environments may be affected by the proposed action:

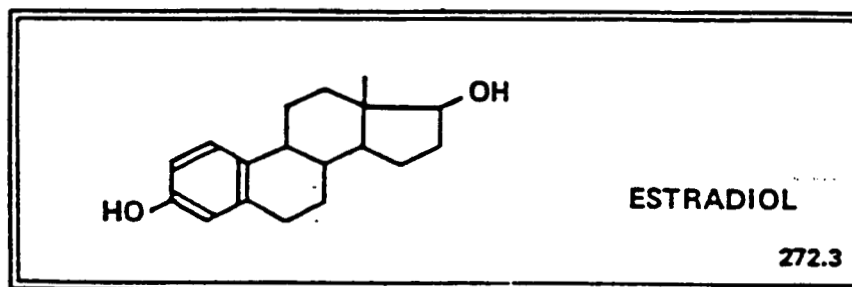
- The environments adjacent to the production facilities located in France.
- Farms and ranches in the United States where the implanted cattle are grazed on pasture.

5. IDENTIFICATION OF THE CHEMICAL SUBSTANCE(S) WHICH ARE THE SUBJECT OF THE PROPOSED ACTION

The chemical substances which are the subject of the proposed action are Trenbolone Acetate (TBA) and Estradiol 17 Beta. Both are well known substances used to enhance the rate of growth of beef cattle and are approved for use in other approved products being sold currently in the United States. This includes Revalor[®]-S for feedlot Heifers (21 CFR 522.2477) where six pellets are used per steer to provide 120 mg trenbolone acetate and 24 mg estradiol 17 beta. In the proposed action, two pellets will be used to provide 40 mg TBA and 8 mg estradiol 17 beta.

5.1 Estradiol 17 Beta

Structural formula

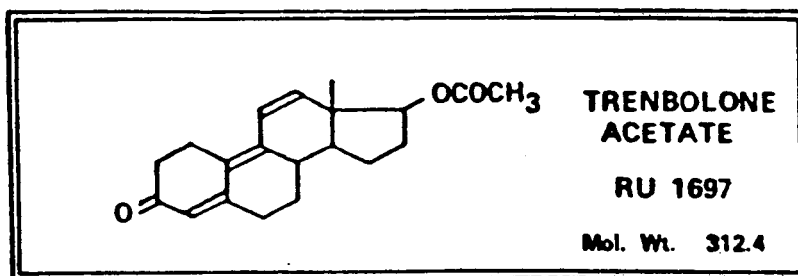


Estradiol 17 beta

Chemical name	Estra-1,3,5(10)triene-3,17b-diol
CAS Registry No.	50-28-2
Molecular formula	C ₁₈ H ₂₄ O ₂
Molecular weight	272.37

5.2 Trenbolone Acetate (TBA)

Structural formula



Trenbolone acetate (TBA)

Chemical name	17b-(acetyloxy)estra-4,9,11-triene-3-one
CAS Registry No	10161-34-9
Molecular formula	C ₂₀ H ₂₈ O ₃
Molecular weight	312.39
Company code	RU 1697
WHO number	2916

Physicochemical properties:

- Appearance Pale yellow, crystalline powder
- Melting point 95 to 97°C
- α_D +39 to +43°C (C = 0.5% methanol)
- Desiccation loss 1g/100g
- E 1%/1 cm 920 to 980 (at 337 nm in ethanol)
- Sulfuric ash 0.2g/100g
- Vapor pressure (25°C):
 - ps (TBA) 10⁻⁹ Torr
 - ps (TBOH-17-alpha) 7 x 10⁻¹⁰ Torr
 - ps (TBOH-17-beta) 8 x 10⁻¹¹ Torr
- Water solubility:
 - TBA 17 to 21 mg/L (practically insoluble)
 - Trenbolone 17-alpha 40 to 42 mg/L
 - Trenbolone 17-beta 340 to 380 mg/L
- HCl (0.1N) solubility Practically insoluble
- NaOH (0.1N) solubility Approx 0.5% w/v
- Ethyl acetate solubility 1 g in 2 mL

- Acetone solubility 1 g in 2 mL
- Benzene solubility 1 g in 1 mL
- Chloroform solubility 1 g in 1 mL
- Dimethylformamide solubility 1 g in 2 mL
- Dioxane solubility 1 g in 2 mL
- Ethanol solubility 1 g in 5 mL
- Ethyl ether solubility 1 g in 9 mL
- Methanol solubility 1 g in 3 mL
- Pyridine solubility 1 g in 1 mL
- Hexane solubility Approx 0.4% w/v

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

The active ingredients of Revalor[®]-G, trenbolone acetate (TBA) and estradiol 17 beta are manufactured at the Roussel Uclaf facility in 63480 Vertolaye, France. They are then formulated into implants each consisting of two pellets at Usiphar, a subsidiary of Roussel Uclaf SA, Route de Choisy-au-Bac, 60205 Compiègne, France. Ten such implants are pre-packaged into a cartridge. The packaged dosage form will be imported from France, and then distributed and sold "over the counter" throughout the United States by Hoechst-Roussel Agri-Vet Company. The packages are prepared in France and are not intended to be opened until immediately prior to use on the farm or ranch. Each implant for use in an individual animal contains a pre-measured quantity of the active ingredients which do not require any direct handling by the end user as a result of packaging the pellets into a cartridge. Such packaging also avoids spillage of the drugs into the environment. Unused implants are retained in the cartridge until used.

6.1 For The Sites Of Production

Care is taken to minimize the waste of intermediates and final product in the manufacture of trenbolone acetate (TBA). All wastes generated in the manufacture of TBA are handled in compliance with local and central government regulations in France. See the Finaplix[®] (trenbolone acetate) Environmental Assessment in NADA 138-612 in which statements of compliance were provided as Attachment 7 on page 83 of the April 1987 submission. Liquid wastes are transferred to a biological treatment station with recovery and/or incineration. The solid waste is removed by a specialized firm for further treatment or disposal at an authorized site. In the manufacture of the formulated product, there is essentially no product waste and no impact on the environment. The French plants manufacturing the active ingredient operate under the surveillance of a French government agency which is charged with enforcing the environmental protection regulations.

The Environmental Assessment for the manufacturing site is referenced in NADA 140-992 (60 FR 4375, January 23, 1995).

6.2 Through Treated Pasture Animals - Site Of Use

Estradiol has been approved previously for use separately in pasture heifers (21 CFR 522.840) and its introduction into the environment not changed by this approval because the overall use of anabolic implants will not change.

The use of this product will introduce no heavy metals, pesticides, radiation or other persistent or toxic materials into the environment. The toxicity of trenbolone acetate (TBA) has been assessed in lifetime feeding studies, reproduction studies and a teratogenicity study. There has been no indication of insidious toxicity of this compound.

The metabolism, distribution and excretion patterns of trenbolone acetate can be found in the environmental assessments from NADAs 138-612 (52 FR 24994 - July 2, 1987) and a supplemental submission to 140-897 (Revalor[®]-G for pasture steers).

7. CHEMISTRY & FATE OF SUBSTANCES EMITTED INTO THE ENVIRONMENT

The fate of trenbolone acetate (TBA) in the environment has been summarized in the Environmental Assessment for Finaplix[®] (NADA 138-612; 52 FR 24994 - July 2, 1987) and in the Revalor[®]-G for pasture steers supplemental NADA 140-897.

Since the amount of estradiol released from the implant daily to treated heifers is much lower than that produced by heifers during estrus, studies to determine the fate of excreted compounds are unwarranted. Also, the amount of estrogens excreted by heifers is small compared to the amount excreted by pregnant cows. The relatively large amounts produced by the human body and other mammals also argue against the need for evaluations of the fate of excreted estrogenic substances in the environment.

Currently implanted animals receive estradiol benzoate implants (21 CFR 522.840), zeronal implants (21 CFR 522.2680) and estradiol implants (21 CFR 522.840). Revalor[®]-G implants will compete with such products in the marketplace and its use generally would be substituted for their use. The overall use of anabolic implants as a result of this proposed action is not expected to increase.

Since all anabolic estrogens exert a similar physiological effect, it is reasonable to assume that the substitution of the estradiol in Revalor[®]-G implants for other estradiol benzoate, estradiol or zeronal containing implants should not appreciably alter the concentration and distribution of such products into the environment.

8. EFFECTS OF SUBSTANCES EMITTED INTO THE ENVIRONMENT

The environmental effects of trenbolone acetate (TBA) are fully documented in the Environmental Assessment for NADA 138-612 - Finaplix[®]; 52 FR 24994 - July 2, 1987 and in the Revalor[®]-G for pasture steers supplemental NADA 140-897.

Estradiol and its metabolites are found in the normal physiological environment of both males and females as well as in the human food supply. The physiology, pharmacology, and toxicology of estradiol are well established. Estradiol is synthesized by the gonads and/or adrenals of all mammalian species including the human. There is accumulated evidence that supports a role for estradiol in the development of certain types of cancer, including human cancer. When estradiol is administered to animals in very large doses, estradiol has the potential to cause toxic, including carcinogenic, effects in the exposed animals. The evidence however, also indicates that estradiol is not a direct acting carcinogen but is a permissive carcinogen requiring administration of physiological dose levels over long periods of time in the presence of a true carcinogen before it "permits" tumors. For more additional background information see 46 FR 24694 - May 1, 1981 and 44 FR 1463 - Jan. 5, 1979.

Of critical importance in the determination of the safety of estradiol is the fact that estradiol is a naturally occurring and essential hormonal substance. Also, most of this estrogen is cleared from the body and excreted in the urine. Little is known about the effects of excreted estradiol and its metabolites. Since it is endogenous to all mammals there appears to be little reason for concern or to conduct studies to evaluate such effects. The amount of these compounds expected to be excreted as a result of the proposed action is very small compared to the amount of estradiol normally produced in the human body, excreted by normal cattle and compared to the amounts of estradiol present in food.

9. USE OF RESOURCES AND ENERGY

It is expected that there will be no significant depletion of natural resources associated with the approval of this NADA. There is expected to be no effect on the depletion of natural resources due to the manufacture of the drug substance or the final dosage form. There will be negligible demand for the use of energy or petrochemicals.

The indirect effect of approval of this NADA will be a saving of natural resources and energy due to the beneficial effect of the use of the product on the performance of pasture cattle treated with trenbolone acetate. The result will be the more efficient use of feed resources.

10. MITIGATION MEASURES

In light of the data presented in this environmental assessment, there is no need to take measures to avoid or mitigate potential environmental effects of the use of trenbolone acetate (TBA) in pasture cattle. No significant adverse environmental effects following the use of TBA in pasture cattle have been identified.

A copy of the MSDS for Revalor[®]-G (trenbolone acetate and estradiol 17 beta) is attached.

11. ALTERNATIVES TO THE PROPOSED ACTION

Alternatives to the proposed action are not provided because no potential significant adverse environmental impacts have been identified.

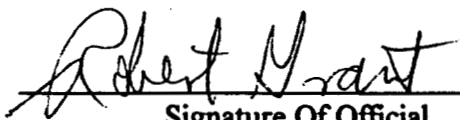
12. LIST OF PREPARERS

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Somerville, NJ 08876-1258

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13. CERTIFICATION

The undersigned official certifies that the information presented is true, accurate and complete to the best knowledge of the firm or agency responsible for the preparation of the environmental assessment.



Signature Of Official

3/14/95
Date

Robert J. Grant, Ph.D.
Group Manager, Nutritional Research
Hoechst-Roussel Agri-Vet Company.

Product Name: REVALOR®G
Product Code: 20102225
MSDS Number : 01139
Version Date: 03/06/1995

Page 1 of 4

Material Safety Data Sheet

Print date - March 10th, 1995 1:41 p.m. PS PSA PSFHV - 2.1 (2/5)

1. CHEMICAL PRODUCT and COMPANY IDENTIFICATION

Product Name: REVALOR®G
Product Code: 20102225
MSDS Number : 01139

HOECHST-ROUSSEL AGRI-VET COMPANY
ROUTE 202-206
P.O. BOX 2500
SOMERVILLE, NJ 08876-1258
USA

PRODUCT USE:

This product contains trenbolone acetate and estradiol, which increases rate of weight gain in a slow release delivery system. This product is for use in pasture steers and heifers.

2. COMPOSITION / INFORMATION on INGREDIENTS

COMPONENT	CAS NUMBER
TRENBOLONE ACETATE	10161-34-9
ESTRADIOL	50-28-2

3. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW:

This product is packaged within small plastic cartridges and poses no exposure risk unless cartridges are damaged.

POTENTIAL HEALTH EFFECTS

DELAYED/LONG TERM EFFECTS

CARCINOGENIC:

This product contains Trenbolone Acetate, an anabolic steroid, which is listed as a possible carcinogen based on animal tests (IARC 2A). When handled according to directions, there is no exposure to the active agent.

EMERGENCY: HUMAN, FIRE, SPILL OR ENVIRONMENTAL: 1-800-228-5635 EXT 132 24 HRS
ANIMAL: 1-800-345-4735 EXT 104 24 HRS
PRODUCT INFORMATION: 1-800-247-4838 9:00 A.M. - 5:00 P.M. EST

Hoechst-Roussel Agri-Vet Company

Hoechst 
Roussel 

Product Name: REVALOR®G
 Product Code: 20102225
 MSDS Number : 01139
 Version Date: 03/06/1995

Page 2 of 4

Print date - March 10th, 1995 1:41 p.m. PS PSA PSFHV - 2.2 (3/5)

4. FIRST AID MEASURES

SKIN:

Wash thoroughly with soap and water.

EYES:

Immediately flush eyes with water for 15 minutes. If irritation develops, get medical attention.

INGESTION:

If swallowed, do not induce vomiting. Give activated charcoal. Seek immediate medical attention. Take this sheet and the original container with you.

5. FIRE FIGHTING MEASURES

EXTINGUISHING MEDIA:

Water, water mist, foam, CO2 or dry chemical.

FIRE FIGHTING INSTRUCTIONS:

Wear full bunker gear, including SCBA, for fighting fires involving this material. Keep upwind.

6. ACCIDENTAL RELEASE MEASURES

PROCEDURES IN CASE OF SPILL OR LEAK:

Collect thoroughly and place in a plastic bag for disposal. Rinse area with water.

7. HANDLING and STORAGE

HANDLING:

Follow directions on package insert. Keep away from food, drink, and animal feeding stuffs. Keep out of reach of children.

STORAGE:

Store in refrigerator (36-47°F) and protect from sunlight.

EMERGENCY: HUMAN, FIRE, SPILL OR ENVIRONMENTAL: 1-800-228-5635 EXT 132 24 HRS
ANIMAL: 1-800-345-4735 EXT 104 24 HRS
PRODUCT INFORMATION: 1-800-247-4838 9:00 A.M. - 5:00 P.M. EST

Hoechst-Roussel Agri-Vet Company

Hoechst 
Roussel 

Product Name: REVALOR®G
Product Code: 20102225
MSDS Number : 01139
Version Date: 03/06/1995

Page 3 of 4

Print date - March 10th, 1995 1:41 p.m. PS PSA PSFHV - 23 (4/5)

8. EXPOSURE CONTROLS / PERSONAL PROTECTION

PROTECTIVE EQUIPMENT

None Required

9. PHYSICAL and CHEMICAL PROPERTIES

APPEARANCE : Yellow Pellets
MELTING POINT : 94.0°C (201.2°F) TO 97.0°C (206.6°F)

10. STABILITY and REACTIVITY

CHEMICAL STABILITY:

Stable

HAZARDOUS POLYMERIZATION:

Will not occur.

11. TOXICOLOGICAL INFORMATION

Oral LD50 (rat) : >5000 mg/kg (Trenbolone Acetate)
Oral LD50 (mouse) : 2700 mg/kg (Trenbolone Acetate)

Trenbolone Acetate is a physiologically active compound.
This product is not to be used in humans.

12. ECOLOGICAL INFORMATION

Biodegradable

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Hoechst-Roussel Agri-Vet Company

Hoechst 
Roussel 

Product Name: REVALOR®G
 Product Code: 20102225
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 Version Date: 03/06/1995

Page 4 of 4

Print date - March 10th, 1995 1:41 p.m. PS PSA PSFHV - 24 (5/5)

13. DISPOSAL CONSIDERATIONS

To avoid disposal, all attempts should be made to utilize the product completely, in accordance with its intended use. If this is not possible, follow applicable Federal, State, Provincial and Local regulations regarding waste management.

14. TRANSPORT INFORMATION

Not Regulated by DOT

15. REGULATORY INFORMATION

U.S. FEDERAL REGULATIONS

SARA 313 : No components listed

16. OTHER INFORMATION

DISCLAIMER:

The information contained herein is offered only as a guide to the handling of this specific material. Since such information does not relate to use of the material with any other material or in any process, any person using this information must determine for themselves its suitability for any particular application. The buyer and user assumes all risk and liability of use, storage and/or handling of this product not in accordance with the terms of the product label.

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