Veterinary Medicine Research & Development
Kalamazoo, Michigan 49007
United States

Environmental Assessment for the Use of SYNOVEX® ONE Grower Implants in Growing Beef Steers and Heifers in a Dry Lot

Active Ingredients: Trenbolone Acetate, Estradiol Benzoate

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ABBREVIATIONS

CAS	Registry numbers assigned by the Chemical Abstracts Service
EA	Environmental assessment
EB	Estradiol benzoate
EDC	Endocrine disrupting compound(s)
IUPAC	International Union for Pure and Applied Chemistry
LDPE	Low-density polyethylene
MW	Molecular weight
NADA	New animal drug application
NOEC	No observed effect concentration
PEC or PEC_{water}	Predicted environmental concentration (in water). PEC and PEC_{water} are used interchangeably in this EA.
PNEC	Predicted no effect concentration
RQ	Risk quotient
TBA	Trenbolone acetate

EXPLANATION OF TERMS

Aggregate exposure	Exposure to a single chemical by multiple pathways and routes of exposure (e.g., runoff from feedlots, pastures, and cropland).
Cumulative exposure	Concurrent exposure by all relevant pathways and routes with a similar mechanism of action (e.g., EDCs).
Endocrine disrupting compound (EDC)	A compound that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones responsible for homeostasis, reproduction, development, or behavior.
Mixed-use watershed	A watershed receiving drug residues from multiple exposure pathways. These include runoff from manured croplands, manure from pasture cattle, manure from animal feeding operations with <1000 beef cattle, and application of runoff water collected from a lagoon to cropped fields from concentrated animal feeding operations with ≥1000 beef cattle.
NOEC	The highest concentration of a toxicant producing no significant observable effect on the organism(s) exposed to it
PNEC	A NOEC value divided by an assessment factor (safety factor) based on the quantity and reliability of data for the compound.
RQ	The predicted environmental concentration (PEC) for a substance divided by its predicted no effect concentration (PNEC)
Surrogate estradiol compound	A single estradiol-like compound with the physical-chemical and environmental fate properties that are a conservative composite of the properties of the primary metabolites of estradiol benzoate (17β-estradiol, 17α-estradiol, and estrone).
Surrogate trenbolone compound	A single trenbolone-like compound with the physical-chemical and environmental fate properties that are a conservative composite of the properties of the primary metabolites of trenbolone acetate (17β-trenbolone, 17α-trenbolone, and trendione).

SUMMARY

SYNOVEX® ONE Grower (ONE Grower) is an extended-release ear implant approved for use in growing beef steers and heifers fed in confinement for slaughter (feedlot cattle) and for growing beef steers and heifers on pasture (slaughter, stocker, and feeder). The active ingredients are trenbolone acetate (TBA) and estradiol benzoate (EB). The proposed action evaluated in this environmental assessment (EA) is for the use of ONE Grower for increased rate of weight gain in growing beef steers and heifers in a dry lot.

The potential risk of adverse effects on the environment from this new use was evaluated using information from the 2024 EA for SYNOVEX® PRIMER™ and SYNOVEX Choice® in beef steers and heifers on pasture [1]. Although ONE Grower was not evaluated in that EA, predicted environmental concentrations of estradiol-related and trenbolone-related metabolites were determined for feedlot cattle administered a higher-dose implant (SYNOVEX® ONE Feedlot). Because all feedlot and dry lot cattle in an intensive-use, mixed-use watershed were combined into the 'feedlot' category for risk assessment purposes, environmental inputs of drug metabolites from dry lot cattle were therefore included in the previous risk assessment.

Based on all available information and the RQ values determined for ONE Feedlot (an implant containing 33% higher dosages of TBA and EB than ONE Grower) in feedlot/dry lot cattle in the 2024 EA, use of ONE Grower in dry lot cattle is not expected to pose a significant risk to terrestrial or aquatic environments on an individual farm or in a watershed.

1. PURPOSE AND NEED

SYNOVEX® ONE Grower (ONE Grower) is an extended-release ear implant approved for use in growing beef steers and heifers fed in confinement for slaughter (feedlot cattle) and for growing beef steers and heifers on pasture (slaughter, stocker, and feeder). The active ingredients are trenbolone acetate (TBA) and estradiol benzoate (EB).

In accordance with the Code of Federal Regulations 21 CFR 25.15(a), all applications or petitions requesting agency action require an EA or a claim of categorical exclusion to determine whether approval of the product will significantly impact the environment. Although ONE Grower is approved for use in feedlot and pasture cattle, increased use of a drug may occur if the drug will be administered at a higher dosage level, for a longer duration, and/or for a different indication than previously in effect (21 CFR 25.5(b)(4)). Because ONE Grower is not approved for use in dry lot cattle, the United States Food and Drug Administration's Center for Veterinary Medicine has determined that an EA is required to support this new use.

2. DESCRIPTION OF PROPOSED ACTION

The proposed action is a supplemental approval to NADA 141-348 for the use of ONE Grower in growing beef steers and heifers in a dry lot.

3. ACTIVE INGREDIENTS

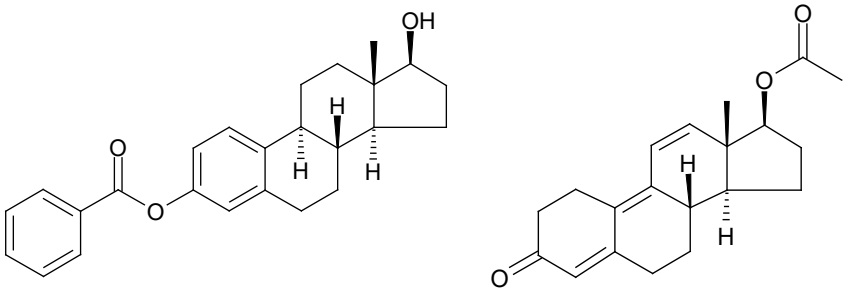
SYNOVEX ONE Grower contains two active ingredients: trenbolone acetate (TBA) and estradiol benzoate (EB).

Estradiol benzoate – The IUPAC (International Union for Pure and Applied Chemistry) name for estradiol benzoate (CAS 50-50-0) is: [(8R,9S,13S,14S,17S)-17-hydroxy-13-methyl-6,7,8,9,11,12,14,15,16, 17-decahydrocyclo-penta[a]-phenanthren3-yl] benzoate. Molecular weight = 376.5 g/mol.

Trenbolone acetate – The IUPAC name for trenbolone acetate (CAS 10161-34-9) is: [(8S,13S,14S,17S)-13-methyl-3-oxo-2,6,7,8,14,15,16, 17-octahydro-1H-cyclopenta[a]-phenanthren-17-yl] acetate. Molecular weight = 312.4 g/mol.

The chemical structures of estradiol benzoate and trenbolone acetate are shown below.

Estradiol Benzoate (EB) Trenbolone Acetate (TBA)



4. PRODUCT CHARACTERISTICS

4.1. Product Description

SYNOVEX® ONE Grower (ONE Grower) and SYNOVEX® ONE Feedlot (ONE Feedlot) extended-release ear implants are manufactured according to procedures approved under NADA 141-348. Both implant products contain individual coated pellets containing 3.5 mg EB and 25 mg TBA per pellet. ONE Grower contains 6 pellets, and ONE Feedlot contains 8 pellets. Pellet ingredients are described in Table 1. Ingredients in the polymeric film coating are described in Table 2.

Table 1. SYNOVEX Pellet Ingredients

Ingredient	Function
Trenbolone acetate	Active ingredient
Estradiol benzoate	Active ingredient
Povidone (K-90), USP	Binder
Polyethylene glycol 8000, NF	Binder
Magnesium stearate, NF	Lubricant
Purified water, USP	---

Table 2. SYNOVEX ONE Pellet Coating Ingredients

Ingredient	Function
Ethylcellulose aqueous dispersion, NF	Film coating
Dibutyl sebacate, NF	Plasticizer
Polyethylene glycol 8000, NF	Pore former
Purified water, USP	---

Coated pellets are placed in molded low-density polyethylene (LDPE) cartridges intended for use with an implant applicator. The 10 channels in a cartridge are filled with either 6 or 8 film-coated pellets, depending on the product. Ten cartridges of the same product are placed on a plastic tray, and the tray is sealed in a laminated foil pouch.

4.2. Administration and Dosage

SYNOVEX implants are administered by subcutaneous injection in the middle third of the caudal aspect of the ear of cattle using an implant applicator. A cartridge is loaded into the implant applicator and all of the pellets in the channel are implanted in the ear as a series of individual pellets.

ONE Grower contains 21 mg EB and 150 mg TBA per implant. The related higher-dose product, SYNOVEX ONE Feedlot, contains 28 mg EB and 200 mg TBA per implant. Dosages of EB and TBA in these products are shown in Table 3.

Table 3. Amounts of TBA and EB Per Implant Dose

Product	Number of Coated Pellets	EB (mg)	TBA (mg)
SYNOVEX® ONE Grower	6	21	150
SYNOVEX® ONE Feedlot	8	28	200

Both EB and TBA are extensively metabolized by cattle. See Sections 9 and 10 of the 2024 EA for SYNOVEX® PRIMER™ and SYNOVEX Choice® in beef steers and heifers on pasture [1]. Upon absorption from the ear, the ester groups of EB and TBA are rapidly cleaved to form 17β-estradiol and 17β-trenbolone, respectively.

The relative activities of estradiol and trenbolone in an implant are determined by multiplying the total dosages of EB and TBA by their respective molecular weight (MW) conversion factors. The relative activities of estradiol and trenbolone in SYNOVEX ONE implants are shown in Table 4.

Conversion Factor for EB = MW of estradiol ÷ MW of EB = 272.38 ÷ 376.49 = 0.7235
Conversion Factor for TBA = MW of trenbolone ÷ MW of TBA = 270.37 ÷ 312.40 = 0.8655

Table 4. Relative Activities of Estradiol and Trenbolone in SYNOVEX ONE Products

Product	Trenbolone Acetate (TBA)		Estradiol Benzoate (EB)	
	Total Dosage of TBA (mg)	Trenbolone-Equivalent Dosage (mg)	Total Dosage of EB (mg)	Estradiol-Equivalent Dosage (mg)
ONE Grower	150	129.8	21	15.19
ONE Feedlot	200	173.1	28	20.26

4.3. Drug Release Characteristics

Both EB and TBA are released from ONE Grower and ONE Feedlot implants for more than 200 days in cattle. The average daily release of TBA is 0.9466 mg/day for ONE Feedlot and 0.7100 mg/day for ONE Grower. The average daily release of EB is 0.1049 mg/day for ONE Feedlot and 0.0787 mg/day for ONE Grower. Due to the different dosages of TBA and EB in these products, higher daily amounts of TBA and EB are released from ONE Feedlot than ONE Grower. However, the average duration of release of TBA (211 days) and average duration of release EB (267 days) are similar for the two products. These data are summarized in Table 1 of Appendix 1 of the 2024 EA.

4.4. Label Indications for Use

This EA addresses the following label claim for SYNOVEX ONE Grower: for increased rate of weight gain in growing beef steers and heifers in a dry lot.

4.5. Frequency of Use

Dry lot cattle may be implanted once with one SYNOVEX ONE Grower implant.

4.6. Disposal of Implants

MSDS: "Avoid release to the environment. Do not discharge into drains, water courses or onto the ground. Considering the relevant known environmental and human health hazards of the material, review and implement appropriate technical and procedural wastewater and waste disposal measures to prevent occupational exposure and environmental release. It is recommended that waste minimization be practiced. The best available technology should be utilized to prevent environmental releases. This may include destructive techniques for waste and wastewater. Dispose of contents/container in accordance with local/regional/ national/international regulations."

Label: "SYNOVEX® ONE Grower waste materials should be disposed of according to prescribed Federal, State, and Local guidelines."

5. RISK CHARACTERIZATION

5.1. Approach

The potential risk of adverse effects on the environment from the use of ONE Grower in dry lot cattle was evaluated using information from the 2024 EA for SYNOVEX PRIMER and SYNOVEX Choice in beef steers and heifers on pasture [1]. A brief description of the approach is provided below. The reader is referred to that EA for additional information.

Because EB and TBA are extensively metabolized by cattle, physical-chemical and environmental fate properties were determined for their metabolites. Parameters for EB were established for a "surrogate estradiol compound" which is an estradiol-like compound with properties that are a composite of the properties for 17β-estradiol, 17α-estradiol, and estrone. Parameters for TBA were established for a "surrogate trenbolone compound" which is a trenbolone-like compound with properties that are a composite of the properties of 17β-trenbolone, 17α-trenbolone, and trendione. See Table 4 of Appendix 1 in the 2024 EA.

For each implant use or reimplant regimen, predicted environmental concentrations (PECs) for the surrogate estradiol and surrogate trenbolone compounds were determined for a 30-year simulation period using a mixed-use watershed model. PECs for the surrogate estradiol and surrogate trenbolone compounds were determined for the Sioux/Lyon watershed in Iowa which is a representative intensive-use watershed in the United States. Each PEC included the aggregate (additive) inputs from three sources of runoff or erosion: manure from 'feedlot' operations (cattle in feedlots and dry lots combined), manured cropland, and manure deposited by pasture cattle. The maximum 21-day moving average concentrations for the surrogate estradiol and surrogate trenbolone compounds were determined for each year of the simulation, and the 90th percentile values were used for risk assessment. See Section 12 of the 2024 EA for additional information.

Data for the effects of 17α-estradiol, 17β-estradiol, 17α-trenbolone, and 17β-trenbolone on fish reproduction were used to establish a predicted no effect concentration (PNEC) for each compound. PNEC values are summarized in Table 8 of Section 11 of the 2024 EA.

Lastly, the potential risk associated with an implant use was determined using the risk quotient (RQ) method in which RQ equals the ratio of PEC to PNEC. Two types of RQ values for estradiol and trenbolone were evaluated for each implant use: (1) RQ values based upon the 90th percentile PECs, and (2) daily RQ values to identify times of higher short-term drug exposure during the 30-year simulation period. RQ values in the range of 1 or less indicate that significant environmental effects are highly unlikely. See Section 13 of the 2024 EA for additional information.

5.2. Risk Assessment for the Use of ONE Grower in Dry Lot Cattle

ONE Feedlot was evaluated in the 2024 EA for use in feedlot cattle. Because ONE Feedlot contains 33% higher dosages of EB and TBA than ONE Grower, environmental exposure from ONE Feedlot will be greater than ONE Grower in the same population of cattle. Further, because all feedlot and dry lot cattle in the watershed were combined into the 'feedlot' category for risk assessment purposes, the previous risk assessment for ONE Feedlot in feedlot cattle in the 2024 EA is appropriate to conservatively evaluate the use of ONE Grower in dry lot cattle.

RQ values for ONE Feedlot in feedlot cattle (feedlot and dry lot cattle combined) based on 90th percentile PECs were 0.04 for the surrogate estradiol compound (Table 11 of Section 13.1 of the 2024 EA) and 0.32 for the surrogate trenbolone compound (Table 12 of Section 13.2 of the 2024 EA). As shown in Figures 5 and 9 in Appendix 1 of the 2024 EA, there were no occasions when a daily RQ for the surrogate estradiol or surrogate trenbolone compound exceeded 1. RQ values less than 1 indicate that significant environmental effects are highly unlikely from the use of ONE Feedlot – and thus ONE Grower – in feedlot and dry lot cattle.

A comprehensive literature search was conducted to determine if environmental fate properties, environmental effects data, or any other information should be updated for this EA. No new information was found that alters the results or conclusions of the 2024 EA regarding the use of ONE Feedlot in feedlot/dry lot cattle and thus the use of ONE Grower in feedlot/dry lot cattle.

6. CUMULATIVE EXPOSURE ASSESSMENT

Endocrine disrupting compounds (EDCs) are natural or synthetic compounds that interfere with the synthesis, secretion, transport, binding, action, or elimination of natural hormones responsible for homeostasis, reproduction, development and/or behavior. Major sources of EDCs in the environment include steroid hormones and their metabolites that are naturally produced and excreted by humans, wildlife, and livestock; natural or synthetic hormones used in humans and livestock; and biocides, plasticizers, pharmaceuticals, and other non-steroidal EDCs used in humans and livestock.

EDCs entering terrestrial and aquatic environments may affect the endocrine function of wildlife. For example, endocrine disrupting effects potentially could occur in fish and amphibians in water bodies located near animal feeding operations if drug residues in manure enter the aquatic environment at high enough concentrations, persist for a sufficient duration, or add significant mass to EDCs already present in that environment.

The potential for cumulative impact from the use of ONE Grower in dry lot cattle was evaluated for three scenarios: (1) use for multiple indications on the same farm, (2) use for different species on the same farm, and (3) use for the same species (and/or different species) on different farms in the same watershed. Scenario 2 and the multi-species aspect of scenario 3 do not apply because SYNOVEX implants are approved for use only in cattle.

To address the use of SYNOVEX implants in cattle for the first and third scenarios, it was assumed in all exposure modeling conducted for ONE Feedlot in the 2024 EA that *all* beef cattle in *all* feedlots and *all* dry lots in the watershed are implanted with ONE Feedlot and that *all* facilities are stocked at full capacity. Second, it was assumed that manure remains in an animal facility for the entire time animals are present so that drug residues are *always* available for runoff or erosion. Third, it was assumed that *all* pasture cattle on *all* farms in the watershed are implanted with a SYNOVEX implant approved for use in pasture cattle (SYNOVEX PRIMER, SYNOVEX Choice, or ONE Grower). Lastly, it was assumed that the *maximum* amount of manure from implanted cattle is always applied to cropland.

The exposure assessment conducted for the 2024 EA therefore included the combined inputs from all significant environmental sources of TBA and EB metabolites. Further, due to the finite cattle holding capacity of a watershed and the assumption that all cattle in the watershed are implanted with a SYNOVEX implant, *any* use of ONE Grower in dry lot cattle will supplant the use of other approved SYNOVEX implants approved for use in dry lot cattle such as SYNOVEX PRIMER and SYNOVEX Choice. Therefore, no increase in cumulative exposure is expected from dry lot cattle implanted with ONE Grower.

7. CONCLUSIONS

This environmental assessment was prepared to support the use of ONE Grower in dry lot cattle. The potential risk of adverse effects on the environment from this new use was evaluated using information from the 2024 EA for SYNOVEX PRIMER and SYNOVEX Choice in beef steers and heifers on pasture [1]. Although ONE Grower was not evaluated in the 2024 EA, PECs for estradiol-related and trenbolone-related metabolites were determined for feedlot cattle administered a higher-dose implant (ONE Feedlot) assuming that all feedlot and dry lot cattle in an intensive-use watershed were implanted.

Based on all available information and the RQ values determined for ONE Feedlot (an implant containing 33% higher dosages of TBA and EB than ONE Grower) in feedlot/dry lot cattle in the 2024 EA, use of ONE Grower in dry lot cattle is not expected to pose a significant risk to terrestrial or aquatic environments on an individual farm or in a watershed.

8. ALTERNATIVES TO PROPOSED ACTIONS

The only alternative to the proposed action is the “no action” alternative, which is failure to approve the new supplemental claim to NADA 141-348 for the use of ONE Grower in growing beef steers and heifers in a dry lot. Because significant environmental impacts are not expected to occur from this new use, the “no action” alternative was not considered.

9. PERSONS AND AGENCIES CONSULTED

This EA was prepared with input and assistance from members of the United States Food and Drug Administration’s Center for Veterinary Medicine.

10. REFERENCES

1. Environmental Assessment for Use of SYNOVEX® PRIMER™ and SYNOVEX Choice® Implants in Beef Steers and Heifers on Pasture (Stocker, Feed, and Slaughter). https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadEA/4842