ENVIRONMENTAL ASSESSMENT FOR THE USE OF MICOTIL 300 INJECTION IN EARLY TREATMENT OF BOVINE RESPIRATORY DISEASE

1. **DATE** October 1996

2. **APPLICANT** Elanco Animal Health
A Division of Eli Lilly and Company

3. **ADDRESS** Lilly Corporate Center
Indianapolis, Indiana 46285

4. DESCRIPTION OF THE PROPOSED ACTION

Micotil 300 injection is already registered for treatment of bovine respiratory disease. A supplement to NADA 140-929 was submitted to allow use of Micotil 300 injection in the early treatment of bovine respiratory disease. This amendment provides environmental information for this supplemental use of Micotil 300 injection. A dose of up to 10 mg/kg will be injected into each treated animal. Approval of this supplement would authorize manufacture, formulation, packaging, and sale of tilmicosin for this use by the same production facilities of Eli Lilly and Company (Lilly Road, Shadeland, IN; Lilly Technology Center, 1200-1555 Kentucky Ave., Indianapolis, IN) that currently make the product.

Based on the proposed action, tilmicosin could potentially be introduced into the following environments:

a. The environment adjacent to the manufacturing plant and the formulating and packaging plant.

b. Cattle feedlots where tilmicosin may be found in animal waste.

c. Agricultural lands where waste products from cattle are used as fertilizer.

d. Aquatic systems where runoff may collect from sites receiving waste products from cattle.

5. IDENTIFICATION OF THE CHEMICAL SUBSTANCE

Micotil 300 injection and the active ingredient, tilmicosin, have been fully described in the environmental assessment provided for NADA 140-929, the original new animal drug approval for use of Micotil 300 injection in the treatment of bovine respiratory disease. The description is the same for Micotil 300 injection that is used for early treatment of bovine respiratory disease.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

A. Introduction of Substances from the Manufacturing Sites

Tilmicosin and Micotil 300 injection will still be made at the same facilities identified in the environmental assessement provided for NADA 140-929, the original new animal drug approval for use of Micotil 300 injection in the treatment of bovine respiratory disease. The permits allowing discharge from these facilities have been applied for or renewed. The NPDES permit (No. IN 0002861) for the plant near Lafayette, IN has been extended by application pending issuance of a new permit by the Indiana Department of Environmental Management (IDEM). The Office of Air Management of the IDEM issued permit number 79-04-09-0383 for the building where the synthesis of tilmicosin occurs. This permit will be superseded by a Title V permit when the application that has been submitted is processed by IDEM. Discharge of wastewater from the formulation facility is still governed by permit number 283002 issued by the Indianapolis Department of Public Works, which will expire December 31, 2000. Emissions to the atmosphere from the formulation facility would be too low to require a permit; such permits are not issued for emissions of particulate matter less than de minimus rates of 5 lbs/hour or 25 lbs/day. All production, formulation, and packaging facilities will continue to comply with applicable regulations concerning emission control and waste treatment.

B. Introduction of substance from the use site

Information from the United States Department of Agriculture (1988) show that there were about 26 million beef cattle fed for slaughter in the United States in 1987. Most of this production was centered in the states of Arizona, California, Colorado, Idaho, Iowa, Illinois, Kansas, Minnesota, Nebraska, Oklahoma, South Dakota, Texas, and Washington. As noted in the original environmental assessment for use of Micotil 300 injection in the treatment of bovine respiratory disease (NADA 140-929), an average of 5.8 percent of cattle exhibited respiratory symptoms. Micotil 300 injection will normally be used to treat pneumonia in calves. With a maximum dose rate of 10 mg/kg, a 275-kg calf could be injected with as much as 2.75 g of tilmicosin. The original environmental assessment indicated that about 9 percent of cattle raised on feedlots needed treatment, and 70 percent of those were treated for respiratory symptoms, resulting in an upper use of Micotil 300 injection in about 6 percent of the feedlot cattle. Extension of the use of Micotil 300 injection to early treatment would allow use of the product in up to 30 percent of the cattle entering a feedlot, which are characterized as high-risk cattle for respiratory diseases. The remaining low to medium-risk cattle entering the feedlot would still have about a 6 percent chance of treatment. Up to 15 percent of the high-risk cattle initially treated, may have to be treated a second time. This is equivalent to a possibility of up to 38.7 percent of the cattle entering a feedlot being treated once (ie. 30 percent + (70 percent X 6 percent) + (30 percent X 15 percent)). If all the calves in the United States were treated with Micotil 300, up to 27,670 kg of tilmicosin (26,000,000 animals X 0.00275 kg/animal X 38.7 percent) and 92,235 L of Micotil 300 could be used annually. A more realistic estimate is that Micotil 300 would be used for about 60 percent of the treatments in calves. This would result in use of about 16,600 kg of tilmicosin and 55,340 L of Micotil 300 in the United States in one year.

As noted in the original environmental assessment, tilmicosin may be introduced into the environment via waste products from treated cattle. Assuming all the tilmicosin is excreted in its active form in about 2 days, the calculated concentration in the treated calf manure would be about 85 ppm (2,750 mg tilmicosin/32.5 kg manure). The concentration in mixed manure from a feedlot would be significantly lower. Assuming that the residence time of cattle in a feedlot is 180 days and that up to 1000 cattle could be held on a 6 acre lot, up to the equivalent of 387 cattle could be treated every 6 months under the new early treatment process for bovine respiratory disease. This is equivalent to 774 doses (total of 2129 gm) of tilmicosin being excreted into the manure produced in the feedlot in one year, 8200 tons (45 lbs of manure per animal per day). The calculated concentration of tilmicosin in the manure in this situation would be up to about 0.29 ppm ppb (2.129 kg tilmicosin/7,400,000 kg manure).

7. FATE OF EMITTED SUBSTANCE IN THE ENVIRONMENT

The environmental fate characteristics of tilmicosin and reports supporting this information have been provided in the original environmental assessment for NADA 140-929. This information has been supplemented by environmental assessment data submitted for Pulmotil Type A Medicated Article under NADA 141-064. Tilmicosin hydrolyzes slowly at pH 9, undergoes rapid photolysis in water, strongly adsorbs to soil, and only degrades very slowly. Tilmicosin is a non-volatile solid and it is possible to introduce it into feedlots and cropland via manure from cattle. It is also possible for tilmicosin to move into aquatic systems adjacent to land treated with manure.

A. Potential Concentrations in Soil

The highest concentration of tilmicosin would probably be found in a feedlot. This concentration would depend on how deeply manure was mixed into the soil. The highest concentration would be no higher than the highest concentration found in manure from treated calves and probably around the levels found in mixed piles of manure, 0.29 ppm.

The highest concentration of tilmicosin expected in cropland soil in one year can be estimated using calculations similar to those provided in the original environmental assessment for NADA 140-929. Using a concentration of 0.29 ppm in manure, a manure application rate of 20 tons per acre, and an incorporation depth of six inches, the highest initial concentration of tilmicosin in cropland soil can be calculated to be up to 0.006 ppm ((0.29 mg tilmicosin/kg manure X 44,800 kg manure/ha)/(2,250,000 kg soil/ha)).

Based on measured sorption coefficients, tilmicosin would be strongly adsorbed to soil. It is unlikely that tilmicosin would leach through soil. Tilmicosin mixed with soil may biodegrade very slowly. Even if no degradation of tilmicosin occurred in soil, the concentration after 10 years would be no higher than 0.06 ppm.

B. Potential Concentrations in Aquatic Systems

Movement of tilmicosin through runoff into aquatic systems could occur from cropland soils or from feedlots. The highest possible aquatic concentrations of tilmicosin would be found in runoff water before it is diluted by streams and ponds where aquatic organisms dwell. Although the solubility of tilmicosin varies with the pH of water, the solubility levels at different pH values are high enough to have little impact on the concentration of the compound in runoff water. Tilmicosin degrades quickly in water, with a half-life from aqueous photolysis of about 0.8 hours. Based on episodic

introduction of tilmicosin to surface water from runoff and the short half-life in water due to photolysis, any exposure of nontarget aquatic organisms to tilmicosin would be of short duration.

Concentrations of tilmicosin in runoff water from a feedlot or cropland can be calculated. The highest theoretical concentration of tilmicosin in two inches of runoff from a six-acre, 1000-animal feedlot would result from extraction of all 2129 gms of tilmicosin used in a total of 774 treatments. This highest theoretical concentration would be 1.7 mg/L (2,129,000 mg tilmicosin/(6 acres X 2 in. of runoff X 102794 L/acre-in)). If all the tilmicosin was extracted from fertilized cropland, the highest theoretical concentration of tilmicosin in a 2-inch runoff event would be 0.25 mg/L ((0.29 mg tilmicosin/kg manure X 20 tons manure/acre/yr X 907 kg/ton X 10 yrs) ÷ (2 in. x 102,794 L/acre-in)).

More realistic concentrations of tilmicosin in runoff water can be estimated by accounting for the potential of tilmicosin to desorb from soil. If desorption of tilmicosin from manure and cropland soil was as high as its desorption from sandy loam soil, the highest expected concentrations of tilmicosin in runoff water would be about 3% of the highest theoretical concentrations. The highest expected concentrations of tilmicosin in runoff water from a feedlot and cropland would then be 0.051 and 0.0075 mg/L, respectively.

Any tilmicosin delivered to surface water would photodegrade rapidly and would have little propensity to bioconcentrate in aquatic organisms. The highest n-octanol/water partition coefficient for tilmicosin is 376 at pH 9. A regression equation for projected steady-state residue concentrations in trout muscle versus measured n-octanol/water partition coefficients for a variety of synthetic compounds is as follows:

$$\text{Log BCF (bioconcentration factor)} = 0.542\ (\log K_{OW}) + 0.124.$$

Using this equation and the log K_{OW} (2.575) for tilmicosin, the predicted BCF for tilmicosin is about 33. Since tilmicosin would be photodegraded and continuously diluted in surface water, only transient exposure of aquatic organisms to tilmicosin would occur. Given the episodic nature of exposure, low exposure concentrations, and a low propensity to bioconcentrate, it is very unlikely that tilmicosin would accumulate in the tissues of aquatic organisms.

8. EFFECTS ON THE ENVIRONMENT OF RELEASED SUBSTANCES

A. Mammalian Toxicity Studies

A testing program has been completed with various laboratory animal species and tilmicosin. Complete reports of all of these studies have been submitted and were summarized in the original environmental assessment for NADA 140-929.

B. Potential Adverse Effects of the Proposed Action on Human Health

Information associated with the production and use of Micotil 300 injection was provided in the original environmental assessment for NADA 140-929. Since methods of production and use of Micotil 300 injection will not change, workers or people applying Micotil 300 injection for early treatment of bovine respiratory disease are not expected to be adversely affected. Use of Micotil 300 injection for early treatment of

bovine respiratory disease is not expected to adversely affect human health through the food supply.

C. Potential Adverse Effects of the Proposed Action on Nontarget Organisms

Additional use of Micotil 300 injection for early treatment of bovine respiratory disease should result in very little exposure of nontarget organisms. Since tilmicosin is injected into cattle, avian species and nontarget mammals should have no opportunity to be exposed to tilmicosin. Low concentrations (0.051 or 0.0075 mg/L) of tilmicosin are expected in runoff water from feedlots and cropland, and rapid photodegradation of tilmicosin (half-life about 0.8 hr) would result in even lower exposure levels for aquatic organisms in surface waters. Organisms associated with soil may be exposed to tilmicosin for a longer period of time. Concentrations in feedlot soil should be no higher than 0.29 ppm, and cropland soil should not have concentrations higher than 0.06 ppm. Studies have been conducted to determine the effects of tilmicosin on nontarget organisms and results of these studies have been summarized in the original environmental assessments for NADA 140-929 and NADA 141-064. Reports supporting the summaries of these studies have also been submitted and reviewed.

The concentration of tilmicosin expected in runoff water from cropland (0.0075 ppm) is about 347 times lower than the concentration (2.6 ppm) which resulted in no effects on any of the aquatic animal species tested. The highest expected concentration of tilmicosin in runoff from a feedlot (0.051 ppm) is about 51 times lower than this no-acute-effect concentration for aquatic animals. Actual exposure of aquatic organisms to tilmicosin in surface waters would be episodic, depending on runoff from rainfall. Concentrations of tilmicosin in surface water would rapidly decline due to photolysis. Any exposure to tilmicosin delivered by runoff from cropland into surface waters is not expected to have adverse effects on populations of aquatic organisms.

Tilmicosin has some potential to inhibit microorganism activity in cattle manure and in feedlot soil. The highest concentration of tilmicosin in mixed manure and feedlot soil would probably be about 0.29 ppm. This level was lower than the MIC values for a mold, fungus, soil bacteria, nitrogen fixing bacteria, and a blue-green alga. While a few groups of microbes have been shown to be sensitive to tilmicosin at this or lower levels, tilmicosin does adsorb strongly to soil which may make it unavailable to soil microbes. Certainly any significant inhibition of microbial activity in cropland soil at tilmicosin concentrations up to 0.060 ppm is not likely.

Other terrestrial organisms should not be affected by exposure to levels of tilmicosin that may be found in cropland soil. Worms were not adversely affected at tilmicosin concentrations in soil up to 918 ppm, a level that is about 15,300 times higher than the highest possible tilmicosin concentration in cropland soil. Terrestrial plants grown in sandy loam soil were not adversely affected by exposure to a tilmicosin concentration of 100 ppm, a level about 1667 times higher than the possible level in cropland soil. Even plants grown in sand were not adversely affected at a tilmicosin concentration of 3 ppm, a level that is 50 times higher than the level of tilmicosin that could possibly accumulate in soil after 10 years.

The proposed action would not be likely to result in any sustained adverse effects on terrestrial or aquatic nontarget organisms associated with cropland.

9. UTILIZATION OF NATURAL RESOURCES AND ENERGY

As noted in the original environmental assessment for the use of Micotil 300 injection in the treatment of bovine respiratory disease (NADA 140-929), production and formulation of tilmicosin will occur at facilities designed for the production and formulation of other animal drugs and pharamaceuticals. These facilities are operated according to Good Manufacturing Practices. These operations and disposal of waste from the manufacturing processes do not require use of unusual amounts of energy or natural resources. Production, formulation, and use of Micotil 300 for early treatment of bovine respiratory disease will not affect endangered or threatened species, nor will it affect properties listed in or eligible for listing in the National Register of Historic Places.

10. MITIGATION MEASURES

The proposed action would not be expected to have any substantial adverse effect on human health or the environment. As noted in the original environmental assessment for use of Micotil 300 injection in the treatment of bovine respiratory disease, precautions are effective in minimizing exposure to tilmicosin in production and formulation facilities. The label for Micotil 300 injection provides users with appropriate caution information. A material safety data sheet is available for this product and was included in the original environmental assessment.

11. ALTERNATIVES TO THE PROPOSED ACTION

The proposed action would not be expected to have substantial adverse effects on human health or the environment. Therefore, alternatives to the proposed action do not need to be considered.

12. LIST OF PREPARERS

The following personnel of Eli Lilly and Company are responsible for the preparation of the Environmental Assessment:

Roger D. Meyerhoff, Ph.D.
Head, Environmental Science and
Hazard Communications

15-Oct-1996
Date

Neil J. Parke, M.A.
Senior Environmental Affairs Representative
Environmental Affairs

10/15/96
Date

Melton N. Novilla, D.V.M., Ph.D.
Project Leader
Pathology, Toxicology Division

October 15, 1996
Date

13. CERTIFICATION

The undersigned official certifies that the information presented in this Environmental Assessment is true, accurate, and complete to the best of his knowledge.

Gregory S. Probst, Ph.D.
Executive Director
Toxicology and Drug Disposition

October 15, 1996
Date

10-16-96P02:20 RCVD

14. REFERENCES

Provided in original environmental assessment for the use of Micotil 300 injection in the treatment of bovine respiratory disease (NADA 140-929).

15. APPENDICES

Provided in original environmental assessment for the use of Micotil 300 injection in the treatment of bovine respiratory disease (NADA 140-929).