Part 10. Environmental Assessment Report (EA)

This Environmental Assessment Report is submitted in accordance with 21 CFR § 25.31

1. Date

23 May 1991

2. Name of applicant/petitioner

The Upjohn Company

3. Address

The mailing address of The Upjohn Company is 7171 Portage Road, Kalamazoo, Michigan 49001. The telephone number for Upjohn's Headquarters in Kalamazoo is (616 323-4000).

4. Description of the proposed action

Approves the use of neomycin sulfate for the oral treatment of cattle (excluding veal calves), swine, sheep and goats for bacterial gastroenteritis caused by susceptible organisms and other diseases caused by organisms susceptible to neomycin. Maximum dosage is 7 mg neomycin base (10 mg neomycin sulfate) per pound of body weight per day for 14 days.

Neomycin sulfate has been used by veterinarians and farmers throughout the United States for over 30 years to treat livestock suffering from bacterial infections susceptible to its antibacterial action. Neomycin enters the environment primarily in animal feces and primarily in the rural areas of the United States.

4.1. Request approval - Need for the action

This environmental assessment is necessary for the approval of the new animal drug application (NADA) for NEOMIX® 325 Soluble Powder, NEOMIX® AG 325 Soluble Powder .

4.2. Location where the product will be produced

The finished product manufacturing site for NEOMIX 325 Soluble Powder, and NEOMIX AG 325 Soluble Powder is located at The Upjohn Manufacturing Company site located east of Portage Road between Centre Street and Bishop Road in the City of Portage, Michigan. This is the present site of the Company's headquarters and main pharmaceutical manufacturing complex.

4.3. Location where the product will be used

Finished products will be stored in distribution centers prior to transportation for sale to veterinary clinics and animal health outlets. The ultimate use of the finished product will be on the livestock producer's farm or feedlots.

4.4. Locations where product will be disposed

Disposal of product may result during manufacturing activities in the form of discarded off-specification lots, from the discarding of return goods; or from end-user disposal of individual units of empty or partly empty finished product vials. Bulk quantities of material for disposal will be generated only at the manufacturing site and will be handled with other compatible waste materials resulting from current operations. The present infrastructure at the proposed manufacturing sites provide for recovery and/or ultimate disposal mechanism.

Individual empty or partly empty end products disposed by consumers will be handled along with household garbage by the community's solid waste management system. Only minute traces of product would be expected to remain with empty product containers.

4.5. Type of environment present at and adjacent to manufacturing locations.

The Portage site complex consists of approximately 80 buildings including chemical/pharmaceutical manufacturing operations, offices, laboratories, utility operations, and various other support building (see Figure 14-1). 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 Portage, Michigan. AGA Gas, Inc. is located south of the plant with the remainder of the plant surrounded by farm land and open spaces. The area is relatively flat and rural with the nearest school located approximately three kilometers to the southwest. The area is dominated largely by agriculture, forest land, and undeveloped open spaces. The plant is located, in terms of the Universal Transverse Mercator Coordinate System (UTM), 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.

5. Identification of chemical substances that are the subject of the proposed action

The following summary describes the main properties of the ingredients used in the formulation of the drug products:

A. Neomycin Sulfate

$C_{23}H_{46}N_6O_{13}SO_4$
M.W. = Variable
CAS # 1405-10-3

Non-flammable amorphous powder soluble in water.

B. Sucrose

$C_{12}H_{22}O_{11}$
M.W. = 342.30
CAS # 57-50-1

Non-flammable white crystals soluble in water.

For additional information for Section 5, please refer to the Animal Health Institute Master File for the EA dated 13 October 1987, which was revised in June 1988 and submitted to the Agency 1 July 1988. The EA was found adequate in a letter from the Agency to AHI dated 3 March 1989.

6. Introduction of substances into the environmental - Control Systems

For additional information for Section 6, please refer to the Animal Health Institute Master File for the EA dated 13 October 1987, which was revised in June 1988 and submitted to the Agency 1 July 1988. The EA was found adequate in a letter from the Agency to AHI dated 3 March 1989.

Portions of the materials listed in Section 5 will be released to the environment from the bulk manufacturing site in the form of air emissions, liquid waste streams and solid wastes.

6.1. Chemical processing

Most of the emissions generated from the chemical process consist of volatile organic compounds that result from bulk material transfer, heating, filtration, distillation and drying operations. However, the use of condensers and closed systems minimize the resulting emissions to appropriate control levels in accordance to local and federal standards as outlined in the EPA's "OAQPS Guideline Series Publication No. 1.2-105, Control of Volatile Organic Emissions from Manufacture of Synthesized Pharmaceutical Products," December 1978. The finished bulk drug intermediate is transferred into fiber drums for transportation to pharmaceutical formulation area.

Adequate protection is provided to employees by preventing unnecessary exposure to emissions from the manufacturing process. All solvent tanks and reactors are equipped with approved safety vent systems.

Aqueous waste streams resulting from the chemical process consist of residual wastewater from sanitary use, process wastewater

streams containing trace amounts of various solvents and impurities, and liquid waste streams containing waste solvents.

At the Portage Road plant, the sanitary wastewater is currently discharged to the Kalamazoo Water Reclamation Plant presently performing tertiary treatment. The process wastewater is discharged to the Kalamazoo Water Reclamation Plant and/or on-site deepwell injection facility. The discarded solids are rinsed prior to removal for disposal at a local landfill along with the other solid wastes generated at the plant site. Waste solvents are either sent to an existing solvent recovery area where they are reprocessed for reuse or sent to an off-site approved facility for ultimate disposal. The waste solvent storage area has received interim authorization from the EPA as a hazardous waste facility.

6.2. Pharmaceutical formulation

Air emissions in the form of particulate matter and volatile organic compounds will result from product formulation operations. However, these will be minimal since appropriate controls are provided to reduce emissions to acceptable levels according to local and federal standards. Adequate protection will be provided to employees by preventing unnecessary exposure to resulting uncontrolled emissions.

Liquid waste streams resulting from the pharmaceutical facility consist of residual wastewater from sanitary use and washing operations which will be discarded to the sanitary sewer system for treatment at the local wastewater treatment plant. Adequate capacity for wastewater treatment is available at the proposed location. Current limitations on the pharmaceutical categorical pretreatment standards do not apply to the expected waste stream. Nonetheless, the general pretreatment standards will be met as per contractual agreement with the owners of the treatment facility presently in effect.

Solid wastes consists mainly of cardboard, paper and plastics which will be temporarily stored in containers presently located at the proposed facilities and disposed along with other current solid wastes generated at the site. Ultimate disposal of currently generated solid wastes is disposed in a sanitary landfill.

6.3. Effect of the Approval of the Proposed Action - Statement of Compliance

Approval of the proposed action will not result in any modifications since the NEOMIX 325 Soluble Powder, NOEMIX AG 325 Soluble Powder are presently being produced at The Upjohn Company where the following regulations or standards are cited as applicable to the proposed action:

1. Clean Air Act PL 91-604, as amended.

2. Clean Water Act PL 95-217, as amended.

3. Resources Conservation and Recovery Act of 1976 PL 94-580, as amended.
4. Occupational Safety and Health Act of 1970, as amended.
5. American National Standards Institute Standards.
6. National Fire Protection Agency Standards.
   a. National Electrical Code Standards.
   b. Life Safety Requirements.
7. Act #348 of 1965, Michigan Air Pollution Act.
8. Act #245 of 1929, Michigan Water Resource Commission Act.
9. Act #399 of 1976, Michigan Safe Drinking Water Act.
10. Act #136 of 1969, Michigan Liquid Industrial Waste Disposal Act.
11. Act #315 of 1969, Michigan Mineral Well Act.
12. Act #641 of 1978, Michigan Solid Waste Management Act.
13. Act #64 of 1979, Michigan Hazardous Waste Management Act.
14. Act #368 of 1978, Public Health Code.
15. Chapter 28 of the Kalamazoo City Code (Services and Wastewater) as amended by ordinance No. 1190.
16. Michigan Occupational Safety and Health Act of 1970, as amended.

(Local regulation applicable to the State of Michigan.)

6.4. Use and Disposal of products

It is estimated that the maximum yearly market volume of the drug product will be approximately 43,081.5 kilograms of the bulk drug and 553,792 packets and drums of the finished product by the end of the first year of production. The disposal of packaging material and empty containers by users will represent a small increment on consumer's refuse.

7. Fate of emitted substances in the environment

For additional information for Section 7, please refer to the Animal Health Institute Master File for the EA dated 13 October 1987, which was revised in June 1988 and submitted to the Agency 1 July 1988. The EA was found adequate in a letter from the Agency to AHI dated 3 March 1989.

8. Environmental effects of released substances

For additional information for Section 8, please refer to the Animal Health Institute Master File for the EA dated 13 October 1987, which was revised in June 1988 and submitted to the Agency 1 July 1988. The EA was found adequate in a letter from the Agency to AHI dated 3 March 1989.

9. Use of resources and energy

The use of natural resources and energy for this product is a very small increment of present total plant usage and can be handled by the existing infrastructure. The resources committed will be the materials listed in Section 5, the utilities used in manufacturing and minor miscellaneous support materials.

10. Mitigation measures

To avoid potential adverse impact associated with proposed action, adherence to all applicable state and federal regulations shall be followed as outlined in Section 6.3.

11. Alternatives to the proposed action

Resources and facilities are being used effectively to produce a quality product with minimal environmental impact. No other alternatives are contemplated.

12. List of preparers

Enclosed is a list of those persons, and corresponding qualifications, that participated in the preparation of this assessment. No government agency was consulted for this specific evaluation other than for routine implementation of ongoing environmental programs conducted at existing facilities.

J. P. Mabin	Environmental Affairs Technician Technical Experience - 12 years
J. S. Mehring	Health and Safety Regulatory Affairs Manager PhD-Agriculture Professional Experience - 21 years
M. W. Gauthier	BS - Biology Pharmaceutical Formulation Experience - 16 years
T. J. Gilbertson	Director, Biochemistry & Residue Analysis PhD - Organic Chemistry Certified Clinical Chemist Professional Experience - 16 years

13. Certification

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

Randal S. Senger (Date) 5/30/91
(Signature of responsible official)
(Title) Corporate Environmental Affairs Manager

J.S. Mehring (Date) 6 JUNE 91
(Signature of responsible official)
(Title) Health and Safety Regulatory Affairs Manager

14. References

The following figures are included in this section as referenced in 21 CFR 25.31:

Figure	
14-1	Upjohn's Portage Site Complex

15. Appendices

Material Safety Data Sheets

Environmental Assessment

Neomycin EA

OCTOBER, 1987

Revised June, 1988

Neomycin Environmental Assessment

1. Date

   October 13, 1987

2. Name of Applicant

   Animal Health Institute

3. Address of Applicant

   119 Oronoco St.
   Box 1417 - D50
   Alexandria, VA 22314

4. Description of the Proposed Action

   Approves the use of neomycin sulfate for the oral treatment of cattle, calves, swine, dogs, cats, turkeys, chickens, ducks, and mink for bacterial gastroenteritis caused by susceptible organisms and other diseases caused by organisms susceptible to neomycin. Maximum dosage is 7 mg neomycin base per pound of body weight per day for 14 days.

   Neomycin sulfate has been used by veterinarians and farmers through the United States for over 30 years to treat livestock suffering from bacterial infections susceptible to its antibacterial action. Neomycin enters the environment primarily in animal feces and primarily in the rural areas of the United States.

5. Identification of Chemical Substances that are the Subject of the Proposed Action.

   Neomycin is a complex organic molecule containing only carbon, oxygen, nitrogen, and hydrogen.

   Neomycin sulfate is a mixture of the antibiotics, neomycin B and neomycin C as their sulfate salts. The proportion of neomycin B ranges from 70-99%. The empirical formula for both salts is $C_{23}H_{46}N_6O_{13} \cdot 3H_2SO_4$. The CAS registry number for the mixture of sulfate salts is 1405-10-3. The chemical name for neomycin B is 0-2, 6-diamino-2,6-dideoxy-α-D-glucopyranosyl-(1→4)-0-2, 6-diamino-2,6-dideoxy-β-L-idopyranosyl-(1→3)-β-D-ribofuranosyl-(1→5)-2 deoxy-D-streptamine. The chemical name for neomycin C is 0-2,6-diamino-2,6-dideoxy-α-D-glucopyranosyl-(1→4)-0-(0-2,6-diamino-2,6-dideoxy-α-glucopyranosyl-(1→3)-β-D-ribofuranosyl-(1→5)-2 deoxy-D-streptamine. The structure of neomycin B is found in Figure 1.

Neomycin sulfate is a white to slightly yellow amorphous powder or cryo-desiccated solid. It is odorless or nearly so and is hydroscopic (1). It has no definite melting point or boiling point. The optical rotation for neomycin B sulfate is $[\alpha]^{25}_{D} = +83°$ and for neomycin C sulfate, it is +121° (2). Neomycin sulfate is very soluble in water, 6300 mg/L and less soluble in other solvents, methanol, 225 mg/L; isoamyl alcohol, 247 mg/L; ethanol, 95 mg/L, and cyclohexane, 80 mg/L (3).

Neomycin B and neomycin C can be determined at µg levels or greater by GLC (4) and HPLC (5). They are most commonly assayed for by microbiological methods (6).

Neomycin sulfate is stable in water, pH 6 buffer and pH 8 buffer at 23° for 24 months. In pH 4 buffer at 23° for 24 months, 12% of the activity was lost. In water, pH 4 buffer,, pH 6 buffer and pH 8 buffer at 45° for 24 months, its activity declined 27%, 94%, 50%, and 80%, respectively (7).

6. Introduction of Substances into the Environment

Orally administered neomycin is very poorly absorbed from the gastrointestinal tract. It is difficult to determine the amount of neomycin in feces. Therefore, alimentary absorption is based on the difference between the amount given and the amount excreted in the urine. The amount excreted in urine from oral administration has been studied in the dog (8), pig (9) and in man (10-11). The results are shown in Table 1. Therefore the worse case would be about 7% of the dose excreted in the urine as microbiologically active material.

Table 1
Amount of Neomycin Dose Excreted in the Urine

Species	Dose	% Excreted in Urine	Time of Urine Collection	Reference
dog	120 mg/kg	2.6-6.6%	24 hours	8
pig	11 mg/kg	1.1%	3 hours	9
man	33 mg/kg	<1.0%	48 hours	10
man	66 mg/kg	<1.0%	24 hours	11

Table 2
Amount of Neomycin Dose
Inactivated in Feces

Species	Dose	Dilution of Feces	% Inactivated	Reference
mouse	204 mg/kg	none	99%	13
rat	200 mg/kg	1/4	75%	13
man	200 mg/kg	1/4	90%	14
man	2500 mg/kg	1/4	90%	12

Most of the neomycin (93-99%) will enter the environment in animal feces. However, most of the neomycin in feces appears to be bound to solids and hence cannot exert its microbiological activity (12-14). This is summarized in Table 2. In one report (14), it was concluded that the mechanism was binding to the solids rather than destruction of the neomycin because the supernate activity did not decrease with time. It should be noted that all except one study was done in vitro with diluted feces. The single mouse in vivo study gave the highest removal of microbiological activity. Note also that the inactivation is dose related. The lower the dose, the more complete the removal of the microbiological activity. Therefore, the feces from animals treated at 7 mg/lb would be expected to have the potential to inactivate most of the neomycin in the feces and most of the activity from the urine which gets mixed with feces. In most cases, 90-99% of the dose will be inactivated.

A worst case estimate of the amount of neomycin to be introduced into the environment can be made as follows. At the present time, the biggest use of neomycin appears to be the treatment of colibacillosis in veal calves. In 1986, 3,478,034 veal calves were slaughtered in the United States (33). If we assume a body weight of 150 pounds per calf, each calf would receive 7 mg/lb X 150 pounds or 1.05 g of neomycin free base per calf. If every calf was treated, the amount used would be 1.05 g/calf/d x 3.5×10^6 calves or 3.67×10^6 g /d. If each calf was treated for the maximum time period, the amount used would be 3.67×10^6 g/d x 14 d or 51.4×10^6 g. This can be converted into a concentration by dividing by the amount of wet feces produced by the total number of veal calves over a 14 day period. The calves would be expected to produce 15 lb/calf/day of wet feces. The total excreta produced would be 15 lb/calf/day x 3.5×10^6 calves x 14 days or 735×10^6 lb or 334×10^6 kg of feces. The concentration of neomycin in the feces would be 51.4×10^6 g of neomycin divided by 334×10^6 kg of feces or 0.153 g/kg or 153 mg/kg or 0.153 mg/g of feces. The data shown in Table 2 suggest that at least 90% of this material will be bound to feces solids.

7. Fate of Emitted Substances in the Environment

   a. Neomycin sulfate is not volatile at 50°C (15) and therefore is not expected to enter the air.

   b. Neomycin and the salts of neomycin are very soluble in water (3). While the biological degradation products have not been identified, it is logical to expect that they will be amino sugars that will also be water soluble. Neomycin B does degrade slowly in aqueous mild acid conditions to neamine and neobiosamine B(3). This results in a large drop in microbiological activity as only neamine is active and it is 5 to 25 times less active than neomycin (22). Under more virgorous conditions, it is hydrolyzed to neamine, D-ribose and 2,6-diamino-2,6-dideoxy-L-idose(2). It is highly probable that neamine can be hydrolyzed further to 2-deoxystreptamine and 2,6-diamino-2,6-dideoxy-D-glucose. The three sugars should be readily degraded by microorganisms. Streptamine should be degraded only slightly slower. Neomycin will be mainly bound to the solids of feces (12-14) or soils (19-20). Therefore, little will reach the aqueous environment. The small amount that does will be destroyed by hydrolysis and degradation by microorganisms.

   c. Neomycin is a strongly basic compound. It is bound to the soil components: montmarillonite, vermiculite, illite, and kaolinite (19). Its binding ranges from 10 mg/g of soil to 160 mg/g. See Table 3. It is not readily released from the above materials by aqueous buffers (20). The microbiological activity is poorly recovered as shown in Table 4. It can be released from attapulgite, bentonite, and magnesium aluminum silicate by magnesium ions (21). However, this only occurs under conditions in which the number of clay binding sites remains constant and the number of cations can increase as needed. In most places in the environment, the amount of free cations and soil components will be in a relatively steady state and the number of binding sites for neomycin should remain constant.

      A worst case estimate of the concentration of neomycin that would result from the use of neomycin in veal calf production can be made. Four states produce 45% of the veal calves, New York, Wisconsin, Pennsylvania and California. These states have 66,000,000 acres of farm land. Probably no more than 0.1% of this land or 66000 acres will be exposed to veal calf feces. The concentration in the first 6 inches of this soil can be estimated. One hundred fifty three (153) mg/kg neomycin concentration in feces x $9x10^3$ kg/acre application rate of wet feces divided by $909x10^3$ kg of soil/acre for a concentration of 1.5 mg neomycin/kg of soil = 1.5 ppm. It can be seen from Tables 3 and 4, that this amount of material should be totally bound by the clay in soils. Therefore, little neomycin would be expected to enter the aqueous environment. It should remain bound to feces and soil until it is destroyed by hydrolysis or microbiological activity.

Table 3
Amount of Neomycin
Bound to Soil

Type of Soil or Clay	Amount of Neomycin Bound (mg neomycin/g soil)	Reference
H-montmarillonite	161 mg/g	19
Ca-montmarillonite	160 mg/g	19
Vermiculite	69 mg/g	19
illite	42 mg/g	19
kaolinite	10 mg/g	19

Table 4
Microbiological Activity
of Neomycin in the
Presence of Soil

Type of Soil of Clay	Amount of Neomycin Added/g of soil	% Antibiotic Activity	Reference
Buffer Control	0.8 mg/g	100%	20
Kaolinite	0.8 mg/g	87.5%	20
Montmarillonite	0.8 mg/g	0	20
Illite	0.8 mg/g	0	20

8. Environmental Effects of Released Substances

The mammalian toxicity of oral neomycin is moderate. The major manifestations of toxicity at high doses are nephrotoxicity and ototoxicity (23). The acute toxicity of oral neomycin is low. The summary of this by Umberger (23) shows the following LD_{50}'s at high doses.

Animal Species	Route of Administration	Mean LD_{50} mg/kg
Mouse	Oral	14250
Mouse	Oral	>2850
Rat	Oral	>2850

A lifetime feeding study was done in rats (24). The doses were 0, 6.25, 12.5, and 25 mg/kg/day. Survival rates, growth curves, and body weights of the treated groups did not differ significantly from the controls. There were no significant clinical laboratory or histological parameter differences between the treated and the controls. No significant oncogenic effects were observed. No auditory function differences were observed.

A three-generation reproduction teratology study was run in rats (25). The reproduction portion used doses of 6.25, 12.5, and 25 mg/kg/day.The teratology portion used doses of 62.5, 125, and 250 mg/kg/day. No reproduction or teratology effects were observed.

A one-year tolerance study was run in the adult cat at doses of 0, 6.25, 12.5, and 25 mg/kg/day (26). Most clinical laboratory and histological parameters showed no difference between the treated and controls. The high-dose male cats showed slightly elevated BUN levels but no histological evidence of nephrotoxicity. Qualitative auditory acuity testing during the study showed no changes. Histological examination of the ear showed changes. However, the changes were not dose-related, so no conclusion on ototoxicity could be drawn.

A 30-day study at 400 mg/kg/day orally in adult cats found nephrotoxicity but no ototoxicity (27). This is consistent with the first study results.

A 90-day oral ototoxicity study was run in the guinea pig (28). The doses were 0, 1.0, 5.0, and 10 mg/kg/day. No treatment-related changes in the Preyer pinna reflex threshold or cochlear hair cell counts were observed for any dose. Positive controls receiving 100 mg/kg/day subcutaneously did show the expected changes.

Neomycin has been observed to be toxic to starved daphnia at 25 µg/ml. It also shortened the life span of the daphnia at 12 µg/ml (29). This test was preliminary and demonstrates the range of toxicity for daphnia. Neomycin has been shown to be toxic to the fly, Agria affinis, above 500 µg/ml (30). It has been administered to fish with no toxic effects noted (31). Because of its binding to soil and feces, concentrations in water are expected to be very low.

Neomycin is biologically active against a broad range of bacteria, but it is inactive against fungi and viruses (22). Some of the sensitivities are shown in Table 5. The lowest sensitivity shown is 0.16 µg/ml. As previously shown, the soil concentration might reach 1.5 µg/g. It is expected that all of this will be bound.

Table 5
MIC's of Some Microorganism Sensitive to Neomycin
(Reference 22)

Organism	Sensitivity Range µg/ml
B. Subtilis	0.16-0.3
B. Cereus	1-3.33
E. coli	0.3->200
Br. bronchiseptica	3
Pr. vulgaris	1.9-31.2
A. aerogenes	0.4>26
M. flavus	<3
A. cloacae	>30
A. fecalis	0.6-50
Sal. schottmulleri	0.6-16.5

The greatest environmental effect of neomycin would be expected to be against bacteria. However, this antibacterial effect should be destroyed by several mechanisms: destruction in feces, binding to soil, hydrolysis to less active compounds, and degradation by microorganisms. Destruction in feces and binding to soils occurs rapidly and renders neomycin inactive until it can be completely destroyed by the other two mechanisms. There is evidence that this is correct for the related antibiotic, streptomycin (32). Therefore, no environmental effect is expected from released substances from the use of neomycin.

9. Use of Resources and Energy

10. Mitigation Measures

No mitigation measures are required.

11. Alternatives to the Proposed Action

No alternatives have been identified.

12. Preparer

Terry J. Gilbertson	Director, Biochemistry & Residue Analysis Ph.D. Organic Chemistry Certified Clinical Chemist 16 years experience with pharmaceutical industry

13. Certification

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

T. J. Gilbertson (Date) 6/27/88

T. J. Gilbertson, Ph.D.
Director, Biochemistry & Residue Analysis
The Upjohn Company

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