

ENVIRONMENTAL IMPACT ASSESSMENT REPORT
SUBTHERAPEUTIC USE OF ANTIBIOTICS FOR ANIMAL FEEDS

Sponsor: A. L. Laboratories, Inc.
452 Hudson Terrace
Englewood Cliffs, New Jersey 07632

Sponsor No.: 46573

Drug: Bacitracin Methylene Disalicylate

NADA: Bacitracin Methylene Disalicylate Feed Grade, 46-592

I. Introduction into the Environment

- a) Total quantity of the drug produced for all uses, portion used subtherapeutically in animal feeds, relative magnitude of other uses, uses in humans.

Total quantity of bacitracin methylene disalicylate produced annually for all uses is about 135,000 kg. Of this amount, 125,000 kg are used subtherapeutically in animal feeds and 10,000 kg are used therapeutically in animal drinking water.

None is used in humans.

- b) Pollutants generated and resources consumed by the manufacture of the drug, premix, including energy uses.

Any pollutants generated are negligible and controlled. In the manufacture of the product for subtherapeutic purposes in feed, the total fermenter contents goes by closed system into a spray drier. The water vapors, odors and gases are retained in a closed system and passed through an incinerator at 1500°F with only carbon dioxide and water vapor returned to the atmosphere. The manufacture of Bacitracin-MD involves a fermentation using harmless nutrients and a non-pathogenic organism. Airborne products involve only carbon dioxide enriched air. (See attachment 1)

In the manufacture of the soluble bacitracin methylene disalicylate, the air-borne products involve only carbon dioxide enriched air having a slight, non-persistent odor from the fermentation step and moisture laden air from the spray drier, with negligible amounts of product dust.

Solid products involve essentially only the water-wet materials resulting from the filtration of the fermented broth. Each batch will contain a total of about 21,000 lbs of the filter aids, mycelium and insolubles from the broth nutrients. This solid material is essentially biodegradable or harmless inert material and is disposed of via sanitary land fill.

The liquid waste product is generated at one point only - that is where the active completed component is filtered off in insoluble form, and the aqueous liquor discarded to municipal sewage system for handling in the treatment facility. About 20,000 gallons are discharged per batch containing minor (1-2%) amounts of non-toxic salts and biodegradable organics with no basic problems created that can have a measureable lasting or cumulative effect on the environment. (See attachment 2)

No objections have been raised by any agencies, organizations or individuals to the current operations. (See attachments 3, 4 and 5)

Resources consumed in the manufacture of feed grade bacitracin methylene disalicylate (Fortracin Concentrate TSD):

<u>Resource</u>	<u>Per standard kg.</u>
City Water	20.67 gal.
Steam condensate	8.33 "
Soya flour	21.67 pounds
Magnesium sulfate	4.33 "
Degerminated cornmeal	3.33 "
Calcium carbonate	0.33 "
Hodag M-8	0.94 "
Methylene disalicylic acid	1.33 "
Sulfuric acid (50%)	4.84 "
Sequesterene NA2	.03 "
Sodium hydroxide (50%)	.42 "
Cabosil	.03 "

Resources consumed in the manufacture of the bacitracin methylene disalicylate soluble (Fortracin Soluble Concentrate):

<u>Resource</u>	<u>Per standard kg.</u>
City water	31.00 gal.
Steam condensate	12.50 "
Soya flour	32.50 pounds
Magnesium sulfate	6.50 "
Degerminated corn meal	5.00 "
Calcium carbonate	0.50 "
Hodag M-8	1.41 "
Hydrochloric acid 20° Baume	9.00 "
Methylene disalicylic acid	2.50 "
Sequesterene NA2	0.05 "
Sodium hydroxide (50%)	4.50 "
Sodium hydrosulfite	0.05 "
Perlite filter aid	4.00 "
Hyflo Super Cel	10.00 "
Solka-floc	1.00 "
Sodium bicarbonate	0.31 "
Sodium hydroxide USP pellets	0.25 "
De-ionized water	1.25 "

In the manufacture of bacitracin methylene disalicylate soluble concentrate, 1,783,430 BTU are used for each standard kg. For the feed grade bacitracin methylene disalicylate TSD 3,690,000 BTU are used in production of each standard kg.

A representative formula for a 1200 pound batch of soluble premix is:

249 lbs. Soluble Fortracin Concentrate - 241 grams* of Bacitracin (Master Standard) per pound
120 lbs. Bicarbonate of Soda USP
300 lbs. Fruit Granulated Sugar (X fine granulated sugar)
300 lbs. Cerelose Anhydrous Dextrose 2421
230-1/2 lbs. Cerelose Anhydrous Dextrose 2401
1/2 lb. Petro Ag. Special Ultra Fines Anti-caking Agent

*The Soluble Fortracin Concentrate received is un-standardized and, therefore, is not in every case 241 grams bacitracin per pound. To the extent that it varies from this figure, minor adjustments are made with the ingredient weights shown on the representative batch formula to obtain a standardized product of 50 grams bacitracin per pound.

- 3
- c) Routes through which the drug may pass into the environment, amounts passing through various routes, during manufactures, preparation of premixes, excretion by target animals.

Any dust generated in blending of the premix is subject to pickup by a dust collector and is considered only a minor source going into the environment.

The antibiotic passes through the animal in the excreta. Its disappearance from the faeces is surprisingly rapid.

The following example shows this with broiler chickens fed continuously a mash feed containing 500 g bacitracin MD per ton of feed:

<u>Sample</u>	<u>Bacitracin found* (ppm)</u>
Fresh faeces	6.17
Same held 24 hours RT	5.00
Same held 72 hours RT	4.89
Same held 7 days	1.30
Same held 14 days	0.14
Same held 21 days	0.14

*All values are on a dry matter basis. The experiment was done by Dr. T. Chang, Michigan State University, E. Lansing.

3

Inactivation of zinc bacitracin in faeces from laying hens was studied by S. Thomassen and K. Vaaji, A/S Apothekernes Laboratorium, Oslo, Norway (1976). In their first experiment, zinc bacitracin was mixed with faeces from laying hens to a final concentration of 10 and 100 ppm. The faeces was stored in plastic bags at 15°C for 15 days and assayed at regular intervals. A rapid inactivation of the antibiotic was observed. The half-life of the antibiotic was estimated to 6 days.

In a second experiment, the hens were fed feeds with 100 ppm zinc bacitracin. The faeces were stored for 11 days in open glass jars. The half-life was estimated at 4 days.

3

The objective of a third experiment was to study the inactivation of zinc bacitracin in faeces from laying hens after storage under natural conditions in the dung in the hen house. This experiment was in a commercial layer flock of 15,000 birds, half was fed 100 ppm zinc bacitracin in their diet, the other half was fed the same diet without antibiotic. The birds were caged on a mesh floor and the faeces was deposited in a pit under the floor. Sampling was carried out in May and August, 1975. The half-life estimates were 7 and 2 days for the May and August samplings.

From the cited examples, it appears that Bacitracin MD and zinc bacitracin are biologically inactivated rapidly in faeces with rate of disappearance being affected by temperature, moisture and pH.

II. Fate in the environment

- a) Mobility of the antibiotic in the environment measured by leaching potentials, vaporization, absorption in soils.

This has not been done, but the physical conditions of the media would cause rapid destruction.

- b) Stability and persistence of the antibiotic in those environments where it is determined that it will be introduced or those environments to which it is subsequently transported.

The available data indicates that the antibiotic is not stable in the faeces of animals, and consequently, would not reach or persist in the environment. (See I.c.)

- c) Potential for the antibiotic to be accumulated or bioconcentrated by plants, animals and micro-organisms measured by such factors as lipid/water partitioning or studies with animals.

This has not been investigated. The cited work shows that the half-life of the antibiotic is short and that it is not absorbed by target animals.

The antibiotic is not absorbed from the intestinal tract of the animal as shown by the fact that no detectable bacitracin has been found in the tissues or eggs when the feed of chickens, turkeys, and laying hens were consuming feeds containing as much as 1000 grams antibiotic per ton of feed on the day that they were sacrificed for tissue harvest. No detectable bacitracin residues have been found in tissues of cattle or swine when they had been consuming feeds containing 500 g antibiotic per ton. Reference is made to the bacitracin MD submission of January 15, 1971, pp 440-697 in NADA 46-592.

III. Environmental Effects

- a) Effects of antibiotic on organisms important to key ecological processes, such as fresh water algae, nitrogen-fixing bacteria, nitrifying bacteria, soil fungi, and bacteria responsible for nutrient mineralization.

This has not been investigated. The bacitracins are effective

against gram-positive organisms, not gram-negative organisms. Most nitrogen-fixing bacteria, nitrifying bacteria, etc., are gram-negative bacteria. For example: the Azotobacter is an aerobic, free-living nitrogen fixer; Rhizobium are Aerobic symbiotic nitrogen fixers; Nitrosomonas, nitrobacter, Thiobacillus, pseudomonas, and acetobacter are aerobic organisms that oxidize inorganic and/or organic compounds.

The following table was taken from Microbiology, 2nd ed., Davies, et al, Harper Row, Hagerstown, MD:

GRAM-NEGATIVE BACTERIA, EXCLUDING PHOTOSYNTHETIC FORMS

<u>Cell Shape</u>	<u>Motility</u>	<u>Other distinguishing characteristics</u>	<u>Genera</u>	<u>Families</u>			
Cocci	Permanently Immotile	Aerobic Anaerobic	Neisseria	Neisseriaceae			
			Veillonella				
			Brucella	Brucellaceae			
			Pasteurella Hemophilus Bordetella				
Straight rods	Motile with peritrichous flagella, and related immotile forms	Facultative anaerobic Mixed acid fermentation of sugars Butylene glycol fermentation of sugars	Escherichia	Enterobacteriaceae			
			Erwinia				
			Shigella				
			Salmonella Proteus Enterobacter Serratia				
		Aerobic	Free-living nitrogen fixers	Azotobacter	Azotobacteriaceae		
			Symbiotic nitrogen fixers	Rhizobium	Rhizobiaceae		
			Motile with polar flagella	Aerobic	Oxidize inorganic compounds	Nitrosomonas	Nitrobacteriaceae
					Oxidize organic compounds	Thiobacillus Pseudomonas Acetobacter	Thiobacteriaceae
Curved rods	Motile with polar flagella	Comma-shaped Spiral Aerobic Anaerobic	Photobacterium	Spirillaceae			
			Zymomonas				
			Aeromonas				
			Vibrio Desulfovibrio Spirillum				

- 3
- b) Effects on fish, mammals and other vertebrates that are important to man as food, or food for human-food producing animals or organisms that are of aesthetic interest to man, etc.

This has not been investigated. The bacitracins are non-toxic drugs that are used in animals consumed as food by humans, and the animal by-products are consumed by other animals. The antibiotic is not absorbed from the intestinal tract, thus it is concluded that there would be no effect.

- c) Indirect effects on populations or organisms and communities that might arise from the subtherapeutic use of the drug.

The requirements have been satisfied for 21 CFR 558.15. The accumulated data showed that the Animal-Human Health criteria have been met for safe use of low levels of bacitracin(s) in animal feeds. Dr. Gerald B. Guest's letter of September 27, 1976 concludes that "the review of required data for bacitracin is hereby concluded. Results indicated that the use of low levels of bacitracin in animal feeds satisfied the animal and human safety criteria for safety as specified by the Antibiotics in Animal Feeds Task Force."

In these investigations, it was shown that the low level feeding of bacitracin to swine and chickens did not affect the salmonella or E. coli populations or mediate a change in resistance or cross resistance to antibiotics used in human medicine. Reports are on record in Bureau of Veterinary Medicine.

1050 Wall Street West, Lyndhurst, New Jersey 07071 • Telephone: (201) 935-6600 • Telex: 133525

a Unit of CPC International Inc.

Address Reply To:
S.B. PENICK & COMPANY
640 New York Avenue
Lyndhurst, N.J. 07071
Phone: (201) 438-6000

July 12, 1977

ENVIRONMENTAL IMPACT ANALYSIS
FORTRACIN CONCENTRATE TSD 46-592

Introduction

This Environmental Impact Analysis is being submitted in response to a request published in the Federal Register of Friday, May 27, 1977 (pp. 27264-27266). The above product has been produced by S. B. Penick and Company for over 10 years and in its present spray-dried version for the last 4 to 5 years.

Name of Applicant

A. L. Laboratories, Inc.
452 Hudson Terrace
Englewood Cliffs, New Jersey 07632

Custom Manufacturer:

S. B. Penick & Company, a Unit of CPC International Inc.
158 Mt. Olivet Avenue
Newark, New Jersey 07114--Manufacturing Plant

1. Manufacturing Procedure

The manufacture of Fortracin Concentrate TSD 46-592 involves a fermentation using harmless nutrients and a non-pathogenic organism, followed by the addition of an organic complexing agent and subsequent spray drying; blending, and packaging to obtain the final bulk product.

All steps are carried out at the Newark, New Jersey Plant of S. B. Penick & Company.

Continued

2. Probable Impact on the Environment

No significant impact on the environment is believed created, for the following reasons:

- a) There are essentially no by-products. No filtration cakes, nor waste mother liquors are created for disposal.
- b) The exhaust air from the spray dryer is incinerated at approximately 1500°F, thereby eliminating all possible discharges of odors and dust from this process.
- c) No solvents are utilized in this process.

3. Probable Adverse Environmental Effects Which Cannot be Avoided

No adverse environmental effects are being created.

4. Alternatives to the Current Method of Operation

No practical alternatives to the current method of operation are known, which would offer less impact on the environment.

5. Relationship-Local Short-Term Uses of Environment; and the Maintenance and Enhancement of Long-Term Productivity

No measurable lasting or cumulative effect on the environment is foreseen, due to the current method of operation.

6. Irreversible or Irrecoverable Commitments of Resources Due to Current Operation

Current operations cause no irreversible or irretrievable commitment of resources.

7. Objections Raised by Other Agencies, Organizations or Individuals

No objections to current operations by any agencies, organizations or individuals are known to have been raised, or to be in existence.

8. Action Schedule

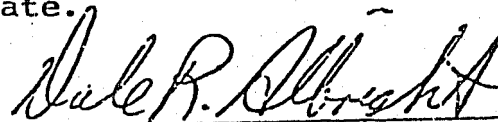
Since no change is contemplated over the current, long-standing method of operation, no schedule problems are involved.

Continued

July 12, 1977

9. Benefits vs Risk to the Environment

The negligible risks to the environment due to the operations involved are far overshadowed by the benefits to mankind created, by making a valuable food additive and growth stimulant available to the food producing industry, at a time when global food requirements are drastically inadequate.



D. Albright, Plant Manager
Newark Plant

DA:bg

Address Reply to:
158 Mt. Olivet Ave.
Newark, N. J. 07114
Phone: (201) 243-4662

January 12, 1976

ENVIRONMENTAL IMPACT ANALYSIS
SOLUBLE FORTRACIN CONC.65-280

Introduction

This Environmental Impact Analysis is being submitted as requested by Robert A. Baldwin, of the Department of Health, Education & Welfare, of FDA in a letter dated September 4, 1975, for record purposes for the above product, which has been produced by S.B. Penick & Company for over 10 years.

Name of Applicant

A.L. Laboratories, Inc.
452 Hudson Terrace
Englewood Cliffs, New Jersey 07632

Custom Manufacturer:

S.B. Penick & Company, a Unit of CPC International Inc.
158 Mt. Olivet Avenue
Newark, New Jersey 07114--Manufacturing Plant
and
540 New York Avenue
Lyndhurst, New Jersey 07071--Manufacturing Plant (Spray Drying Only)

1. Manufacturing Procedure

The manufacture of Soluble Fortracin Conc.65-280 involves a fermentation using harmless nutrients and a non-pathogenic organism, followed by isolation by filtration of a solid active component, with subsequent spray drying of the solubilized component; blending, and packaging to obtain the final bulk product.

All steps are carried out at the Newark, New Jersey Plant of S.B. Penick & Company, except for the spray drying, which is done at their Lyndhurst, New Jersey Plant.

Continued.....

WDA 65-280

Environmental Impact Analysis

Page 2

January 12, 19762. Probable Impact on the Environment

No significant impact on the environment is believed created, for the following reasons:

- a) The quantity being produced per year is small. Typical annual production might be a total of 25 batches, giving a total annual production of approximately 7,500 standard kilograms.
- b) Airborne by-products involve only (1) Carbon dioxide enriched air having only a slight, non-persistent odor from the fermentation step, and (2) Moisture laden air from the spray dryer, which might have also 10-12 Kg/batch of product dust (an animal feed enrichment component, and basically harmless).
- c) Solid by-products involve essentially only the water-wet filter cake resulting from the filtration of the fermented broth. Each batch will contain about 13,000 lbs. of filter aids; 4,000 to 6,000 lbs. of mycelium; and 4,000 to 6,000 lbs. of insolubles from the broth nutrients. This solid material, essentially biodegradable or harmless inert materials, is disposed of via sanitary landfill at the Kearny Municipal Facility.
- d) Liquid waste by-product is generated at essentially one point only--that where the active complexed component is filtered off in insoluble form, and the aqueous mother liquor discarded to the Newark Municipal Sewage System, for handling in the treatment facility of the Passaic Valley Sewerage Commissioners. About 20,000 gallons are discharged per batch. With minor (1%-2%) amounts of nontoxic salts, and also of biodegradable organics present, no basic problems with respect to the environment are created.
- e) No solvents are utilized in this process.

3. Probable Adverse Environmental Effects Which Cannot be Avoided

No adverse environmental effects are being created.

4. Alternatives to the Current Method of Operation

No practical alternatives to the current method of operation are known.

5. Relationship-Local Short-Term Uses of Environment; and the Maintenance and Enhancement of Long-Term Productivity

No measurable lasting or cumulative effect on the environment is foreseen, due to the current method of operation.

Continued.....

Environmental Impact AnalysisPage 3January 12, 19766. Irreversible or Irretrievable Commitments of Resources Due To Current Operation

Current operations cause no irreversible or irretrievable commitment of resources.

7. Objections Raised by Other Agencies, Organizations or Individuals

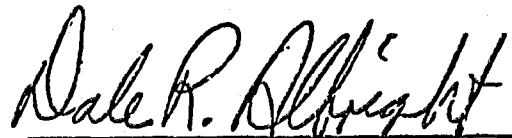
No objections to current operations by any agencies, organizations or individuals are known to have been raised, or to be in existence.

8. Action Schedule

Since no change is contemplated over the current, long-standing method of operation, no schedule problems are involved.

9. Benefits vs Risk to the Environment

The negligible risks to the environment due to the operations involved are far overshadowed by the benefits to mankind created, by making a valuable food additive and growth stimulant available to the food producing industry, at a time when global food requirements are drastically inadequate.



D. Albright, Plant Manager
Newark Plant

DA/rp

August 2, 1977

TO WHOM IT MAY CONCERN:

After July 31, 1977, Soluble Bacitracin Methylene Disalicylate Bulk Concentrate will no longer be manufactured in the United States by S. B. Penick & Company, Mt. Olivet Avenue, Newark, New Jersey.

Approval of MF 3683 will allow production at the Oslo, Norway facility. The procedure that is proposed for the A/S Apothekernes Laboratorium site will eliminate the aqueous liquid effluent release into the environment by evaporating the water from the effluent. Any remaining solids will be treated in a manner to satisfy the environmental standards of the Oslo and the Norwegian authorities.

A. L. LABORATORIES, INC.

Ralph F. Elliott

Ralph F. Elliott, Ph.D.
Director
Animal Technology Department

RFE:kec

NEW JERSEY STATE DEPARTMENT



OF ENVIRONMENTAL PROTECTION

APPLICATION FOR PERMIT TO CONSTRUCT, INSTALL OR ALTER CONTROL APPARATUS OR EQUIPME

TO: New Jersey State Department of Environmental Protection
Bureau of Air Pollution Control
P. O. Box 1390
Trenton, New Jersey 08625

Date April 10, 1972

Use instructions, Air-D13

Sec. A	1. Full Business Name <u>S.R. Penick, a Unit of CPC International</u>		
	2. Address of equipment and/or control apparatus:		
	<u>158</u> No.	<u>Mt. Olivet Ave.,</u> Street	
	<u>Newark</u> Municipality	<u>Essex</u> County	
	3. Location on premises (Bldg., Dept., area etc.) <u>Bldg. 27</u>		
	4. Nature of Business <u>Fine Chemicals Manufacturing</u> SIC No. <u>2833</u>		
Sec. B	1. <input checked="" type="checkbox"/> New process equipment and new air pollution control apparatus <input type="checkbox"/> New air pollution control apparatus on existing process equipment <input type="checkbox"/> New process equipment with no control apparatus <input type="checkbox"/> Other: _____		
	2. Prior permit numbers covering this installation. Specify. <u>None</u>		
	3. Estimated starting date <u>4-15-72</u> Estimated completion <u>12-15-72</u>		
Sec. C	1. Description of operation <u>Spray drying operation for the production of animal feed grade antibiotics.</u>		
	2. Identify process equipment <u>DeLaval Spray Dryer and Flex-Kleen bag product collector</u>		
	3. Raw materials (names) <u>Aqueous slurries/solutions of animal feed grade antibiotics</u>		
	Total pounds per hour <u>6,200 of sol'n.</u> Total pounds per batch _____		
	4. Operating procedure: <input checked="" type="checkbox"/> Continuous: <u>24</u> hrs. per day <u>20</u> days per <input type="checkbox"/> week <input checked="" type="checkbox"/> month <input type="checkbox"/> Batch: _____ hrs. per batch _____ Batches per <input type="checkbox"/> day <input type="checkbox"/> week		
Sec. D	Physical and chemical nature of air contaminants which must evolve from operation and be emitted into the open air:		
	AIR CONTAMINANTS	AMOUNTS OF CONTAMINANTS	
		With Control Apparatus	Without Control Apparatus
	Feed Grade Antibiotics	Less than 0.1 Lb/hr	16 lbs/Hr.
		of mineral ash,	Feed grade antibiotic
		chiefly Calcium	dust
		& Magnesium	
	Sulfates		
Operation will not add odors to the atmosphere detectable beyond property limits.			

1. Describe air pollution control apparatus The air from the Spray Dryer is first passed through a Flex-Kleen bag-type dust collector; then through a Cor-Pak fume incinerator for incineration at 1200°F for 0.5 seconds, followed by passage through heat exchangers to the stack, for discharge to the atmosphere.
2. Efficiency of control apparatus: 99.9 % min. for the dust collector
3. Height of discharge above ground 50 ft.
4. Distance from discharge to nearest property line 160 ft.
5. Volume of gas discharged into open air 11,000 cu. ft. per min. at stack conditions
6. Exit linear velocity at point of discharge 62 ft. per minute at stack conditions.
7. Temperature at point of discharge 360 °F
8. Will emissions comply with existing local requirements? Yes
9. Initial cost of control apparatus \$ 285,000
10. Estimated annual operating cost \$ 94,000

Sec. E

This application is submitted in accordance with the provisions of N.J.S.A. 26:2C-9.2, and to the best of my knowledge and belief is true and correct.

<u>S. B. Penick & Co.</u>	<u><i>M. Michiela</i></u> Signature - all copies
<u>540 New York Ave.</u>	<u>M. Michiela</u> Name (Print or type)
<u>Lyndhurst, N.J. 07071</u>	<u>Chief Engineer</u> Title
<u>Zip Code</u>	<u>201-438-6000</u> Telephone No.

DO NOT WRITE BELOW

PERMIT TO CONSTRUCT, INSTALL OR ALTER CONTROL APPARATUS OR EQUIPMENT

Application for permission to construct, install or alter the equipment and/or control apparatus as set forth above is APPROVED.

Date 4-28-72

Approved by: *[Signature]*

PERMIT NO. P-7469

Supervisor, Permits & Certificates

Submit original and three (3) copies

M5379



NEW JERSEY STATE DEPARTMENT OF ENVIRONMENTAL PROTECTION
APPLICATION FOR CERTIFICATE TO OPERATE CONTROL APPARATUS OR EQUIPMENT

TO: New Jersey State Department of Environmental Protection
Bureau of Air Pollution Control
P. O. Box 1390
Trenton, New Jersey 08625

Date November 8, 1972

Use Instructions, Air-D-14

Sec. A	1. Reference Permit No. <u>P-7669</u> SIC No. <u>2833</u>
	2. Full Business Name <u>S.B. Penick, a Unit of CPC International</u>
	3. Address of equipment and/or control apparatus: <u>158 Mt. Olivet Ave., Newark, Essex</u> No. Street Municipality County
	4. Location on premises (Bldg, Dept., area, etc.) <u>Bldg. 27</u>
Sec. B	1. Identify process equipment <u>Fume Incinerator & Spray Dryer for the production of animal feed grade antibiotics.</u>
	2. List air pollution control apparatus <u>Fume Incinerator</u>
	3. Date equipment to be put in use <u>November 28, 1972</u>
Sec. C	Plant Contact: <u>H. Daners</u> <u>201 243-4662</u> Name (Print or Type) Telephone No.
	<u>Plant Sup't.</u> Title Telephone Extension

This application is submitted in accordance with the provisions of N.J.S.A. 26:2C-9.2, and to the best of my knowledge and belief is true and correct.

M. Michiels
Signature - all copies

M. Michiels
Name (Print or Type)
Chief Engineer
Title

Mailing Address, Zip

DO NOT WRITE BELOW

CERTIFICATE TO OPERATE CONTROL APPARATUS OR EQUIPMENT	
TEMPORARY DURATION	5 YEAR DURATION
Certificate No. _____	Certificate No. <u>C-7365</u>
Date Approved _____	Date Approved <u>5-14-73</u>
Expiration date _____	Expiration date <u>5-14-78</u>
Approved by: _____ Supervisor, Permits & Certificates	Approved by: <i>[Signature]</i> Supervisor, Permits & Certificates

NEW JERSEY STATE DEPARTMENT OF HEALTH - Community Health Services
1911 PRINCETON AVENUE, TRENTON, NEW JERSEY 08648

№ 0165

1977

CERTIFICATE OF REGISTRATION

N.J.S.A. 24:6B-5 - "If any location of a registered business is to be changed, the registrant shall give the department written notice prior to the change of the address of such new location and the name and address of the individual to be in charge thereof. A fee of \$10.00 shall accompany such notification."

Registered as: manufacturer; wholesaler which conducts business at the following locations in this State:

- | | |
|--|---|
| 1. <u>540 New York Ave., Lyndhurst</u> | 4. <u>215-225 Watchung Ave., Orange</u> |
| 2. <u>158 Mt. Olivet Ave., Newark</u> | 5. <u>CPC International Warehouse</u> |
| 3. <u>Taylorstown Rd., Montville</u> | <u>Ridgefield</u> |

Reg. No.
#51

S. B. Penick & Company
A Unit of CPC International, Inc.
1050 Wall St., West
Lyndhurst, NJ 07071
Att: Harold Johnson

ISSUED PURSUANT TO
N.J.S.A. 24:6B

James E. Frey

State Commissioner of Health

EXPIRES
JAN. 31, 1978

DDC-9 Oct. 76

ESTABLISHMENT

ction

my

Institut für Bodenbiologie
Forschungsanstalt für Landwirtschaft
Braunschweig-Völkenrode
Direktor: Prof. Dr. K. H. Domsch

Braunschweig, D.O. 1977
Fernruf 59 63 41

Prof. Ja/Fe

ORIGINAL
Må ikke fjernes

Institut für Bodenbiologie, Bundesallee 50, 3300 Braunschweig

Herrn Dr. Küther
Lohmann Tierernährung
GmbH
Postfach 446
2190 Cuxhaven

Betr.: Ihr Schreiben vom 20.6.1977 - Dr.Kü/bö. -

Sehr geehrter Herr Dr. Küther!

Wir haben unsere Persistenzuntersuchungen im Hühnerkot und Hühnerkot-Bodenmischungen auf Tetracyclin, Flavomycin, Zink-Bacitracin und Spiramycin beschränkt. Virginiamycin werden wir vorerst nicht untersuchen, da jetzt uns erst noch mögliche Einflüsse der persistenteren Verbindungen (Flavomycin und Tetracyclin) auf die N-Umsetzungen im Boden interessieren.

Das von Ihnen vertriebene Zink-Bacitracin wird in Kot sowohl unter Luft als auch unter Stickstoff sowie im Boden innerhalb einer Woche völlig inaktiviert und kommt für weitere Untersuchungen von Nachwirkungen deshalb nicht in Frage.

Mit freundlichem Gruß


(Prof. Dr. G. Jagnow)

From: Ree

August 23, 1977.
HR/IH

To: ~~A.L. Laboratories~~
Dr. J.B. Careri
Dr. W. Fürst
I. Hasle
Dr. G.D. Rosen
Thomassen

cc: Dir. E.W. Sissener
K. Kristiansen
Larem

TECHNICAL REPORT NO. 175..

Re.: Inactivation of ZB in faeces and soil.

For your information please find enclosed a photocopy of a letter from Professor Dr. G. Jagnow to Dr. Küther of August 5, 1977, as well as a translation in English.

Kind regards,



Encl.

Helge Ree



DIVISION OF ENVIRONMENTAL QUALITY
BUREAU OF AIR POLLUTION CONTROL

CERTIFICATE TO OPERATE CONTROL APPARATUS OR EQUIPMENT (90 DAY EXTENSION)

Permit and Certificate Number 0 4 1 4 4 2

DEP Plant ID 0 0 3 9

(Mailing Address)

(Plant Location)

Mr. Nathan H. Cohen, President
Products Blending Corporation
185 LeGrand Avenue
Northvale, New Jersey 07657

(same)
Bergen County

Applicant's Designation of Equipment Torit Model 124 Collector and duct system

N.J. Stack No. 0 0 1

No. of Stacks 0 1

No. of Sources 0 0 4

Approval 12 06 78
Mo. Day Year

Start Up 11 07 78
Mo. Day Year

Expiration 06 05 79
Mo. Day Year

THIS TEMPORARY CERTIFICATE IS BEING EXTENDED TO ALLOW FOR:

1. SUBMITTAL OF REQUIRED STACK TESTS. (SEE OTHER SIDE)
2. COMPLETION OF THE INSTALLATION OF THE EQUIPMENT COVERED.
3. FURTHER FIELD/OFFICE EVALUATION.
4. EQUIPMENT ADJUSTMENTS.
5. AMENDMENT OF THE EXISTING PERMIT (S) OR SUBMITTAL OF NEW PERMIT APPLICATION (S) BECAUSE OF MODIFICATIONS OR ALTERNATIONS TO THE EQUIPMENT COVERED.

THIS EXTENSION SHALL NOT BE CONSTRUED TO EXTEND THE COMPLIANCE DATE (S) OF ANY ORDER ISSUED BY OR ENTERED INTO WITH THE DEPARTMENT AS THE RESULT OF AN ADMINISTRATIVE OR JUDICIAL ACTION.

IF WE DO NOT INSPECT THIS EQUIPMENT DURING THIS 90 DAY PERIOD, THIS TEMPORARY CERTIFICATE WILL BE EXTENDED. YOU NEED NOT APPLY FOR SUCH AN EXTENSION.

QUESTIONS ABOUT THIS DOCUMENT SHOULD BE DIRECTED TO THE PERMITS AND CERTIFICATES SECTION AT 609-292-6716 OR THE ADDRESS BELOW.

NOTE: This document must be readily available for inspection at the source location.

Approved by: Allan T. Edwards
Supervisor
Permits & Certificates Section

N.J. Department of Environmental Protection
Bureau of Air Pollution Control
CN-027
Trenton, New Jersey 08625

NEW JERSEY STATE DEPARTMENT OF HEALTH -- Community Health Services
1911 PRINCETON AVENUE, TRENTON, NEW JERSEY 08648

No 0500

1979

CERTIFICATE OF REGISTRATION

N.J.S.A. 24:66-5 -- "If any location of a registered business is to be changed, the registrant shall give the department written notice prior to the change of the address of such new location and the name and address of the individual to be in charge thereof. A fee of \$10.00 shall accompany such notification."

Registered as: manufacturer; wholesaler which conducts business at the following locations in this State:

1. Same
2. -----
3. -----

Reg. No. 1088 Products Blending Corporation
185 LeGrand Ave.
Northvale, NJ 07647

ISSUED PURSUANT TO
N.J.S.A. 24:6B

EXPIRES
JAN 31, 1980

State Commissioner of Health

DDC-9 Nov. 78

ESTABLISHMENT

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ANNUAL REGISTRATION OF DRUG ESTABLISHMENT

Instructions are on the last page. Read carefully before completing this form.
Furnish all attachments in TRIPLICATE.
IF YOU HANDLE DEPRESSANT, STIMULANT, OR HALLUCINOGENIC
SUBSTANCES, SEE ITEM SO TITLED IN THE INSTRUCTIONS.

FDA VALIDATION
REGISTERED FDA
JUN - 4 1979

FOR THE YEAR (380)	FOR FDA USE ONLY	CONTROL (1-5)	ID (20)
79		049874	2242563

FDA ONLY	REPORT DATE			TYPE OF OWNERSHIP	CODES FOR REASONS FOR SUBMISSION	A C H N R S T	ANNUAL REGISTRATION OF DRUG ESTABLISHMENT ANNUAL REGISTRATION OF BLOOD BANK OUT OF BUSINESS OWNER OR OPERATOR CHANGE (PARENT CO.) RE-ENTRY INTO BUSINESS WITH SAME NAME CHANGE IN NAME OF OWNER, PARTNER, DIRECTOR ADDITIONAL NDC REQUESTED	BIOLOGIC L.I.C. NO.	U. S. POSTAL SERV. CODE FOR STATE OF INC.	NATIONAL DRUG CODE LABELER CODE (NDC)
	MO.	DAY	YR.					34	58	20
13	14		27							049874
	5	24	79	CORPORATION						

PARENT COMPANY IDENTIFIERS				REPORTING FIRM DRUG ESTABLISHMENT REGISTRATION NO.		FOR FDA USE ONLY
NDC LABELER CODE	ESTAB. REGISTRATION NO.	ID (FDA USE ONLY)				
281	312	385	373	320		2242963

ITEM NO.	NAME OF REPORTING FIRM, PARENT CO., AND MAILING ADDRESS	ITEM NO.	SITE ADDRESS
61	PRODUCTS BLENDING CORPORATION		
272		101	185 LEGRAND AVENUE
176	185 LEGRAND AVENUE	159	ROCKSVILLE, NJ
214	ROCKSVILLE, NJ	161	07647
236	07647		

To delete an item printed, dash a line through it. To delete one of the unprinted items which follow, enter the item no. and date under the heading CHANGES and dash out. To make a correction in either printed or unprinted items enter under the heading CHANGES the item no., which alphanumeric characters below the title of the or at its left, and the correct data. Unprinted items are:	6	ID	NDC LABELER CODE	OTHER FIRM NAMES
	13	T6	T40	T61
ITEM NO.	DATA ITEM			
46	REPORTING FIRM SHORT NAME			
257	PARENT CO. SHORT NAME			
B27	NAME OF OWNER OR NAME AND TITLE OF OFFICER, DIRECTOR OR BOARD MEMBER.			
T46	SHORT NAME OF OTHER FIRM NAME.			

CHANGES (NOTE: REGISTRATION CHANGES NEED NOT BE REPORTED SEPARATELY FOR THE DRUG LISTING ACT OF 1972.)	LAST NAME AND INITIALS OF PERSON SUBMITTING DATA
ITEM NO. NEW DATA OR CHANGED DATA. ATTACH ADDITIONAL CHANGES ON PLAIN PAPER WITH NAME	FDA USE ONLY 328
	AREA CODE AND TELEPHONE NO.
	333
	SIGNATURE AND TITLE OF AUTHORIZING OFFICIAL
	<i>William Klee</i> President

NOTE: VALIDATION OF THIS FORM IS NOT TO BE CONSTRUED AS FEDERAL GOVERNMENT ENDORSEMENT OR APPROVAL OF THE ESTABLISHMENT OR ITS PRODUCTS.
FORM FD 2456E (7/73)

Translation

ORIGINAL
Må ikke fjernes

INSTITUT für BODENBIOLOGIE
Forschungsanstalt für Landwirtschaft
Braunschweig-Völkenrode
Direktor: Prof. Dr. K.H.Domsch

Braunschweig, 5.8.1977
Fernruf 59 63 41
Prof. Ja/Fe

Institut für Bodenbiologie
Bundesallee 50
3300 Braunschweig

Dr. Küther
Lohmann Tierernährung GmbH
Postfach 446
2190 Cuxhaven

Dear Dr. Küther,

Our investigations have been limited to the study of the inactivation of Tetracyclin, Flavomycin, Zinc Bacitracin and Spiramycin in poultry manure and in a mixture of poultry manure with soil.

As we are being primarily interested in the more stable compounds' (Flavomycin, Tetracyclin) influence on the nitrogen-cycle in the soil, we are for the time being not going to test Virginiamycin.

The sample of Zinc Bacitracin obtained from you was completely inactivated within one week when the samples of faeces or faeces/soil mixture were kept in a normal atmosphere or in a nitrogen atmosphere. Further experiments on secondary effects of Zinc Bacitracin in faeces or soil are therefore not necessary.

With kind regards,

Yours sincerely,

signed
(Prof. Dr. G. Jagnow)

NADA# 46-592, 65-280,
and 98-452

Ralph F. Elliott, Ph.D.
A. L. Labs, Inc.
452 Hudson Terrace
Englewood Cliffs, NJ 07632

RE: FEDERAL REGISTER
May 27, 1977
Docket No. 77N-0152

Dear Dr. Elliott:

We acknowledge receipt of your submissions dated August 3, 1977, in response to the FEDERAL REGISTER announcement of May 27, 1977, entitled "Restriction on Subtherapeutic Use of Antibacterials in Animal Feeds Intent to Propose Rules and Call for Environmental Impact Data." All information received in response to the aforementioned announcement as well as other data pertinent to environmental impact will be utilized for the specific assessment stated in the announcement.

However, the consideration of the environmental impact for a drug subject to this specific announcement, i.e., its subtherapeutic use, does not alter the Agency's consideration of the need for an environmental impact statement in accordance with Part 25 (21 CFR Part 25). That is, environmental impact for an approved new animal drug application would be considered when necessitated by an appropriate supplemental application or on the basis of new information before the Agency. Insofar as there would be an overlap in the request for environmental information, previously submitted information need only be referenced.

This acknowledgment of receipt is not a determination on or evaluation of your submissions, nor does it alter the proposed action as stated by the Commissioner in the subject FEDERAL REGISTER announcement.

Sincerely yours,

Donald A. Cable, D.V.M.
Special Assistant to the
Associate Director for
Scientific Evaluation
Bureau of Veterinary Medicine

cc: Orig; Dugg Trip
HPV-5 (Feinman)
HPV-100DAGABLE/slc/11/23/77

DRAFT ENVIRONMENTAL IMPACT STATEMENT

SUBTHERAPEUTIC ANTIBACTERIAL AGENTS IN ANIMAL FEEDS

Prepared in Accordance with Section 102(2)(C) of P.L. 91-190

Prepared by:

Susan E. Feinman, Ph.D.

and

John C. Matheson III, M.S.P.H.

Bureau of Veterinary Medicine
Food and Drug Administration

Single copies may be obtained from the Hearing Clerk, Food and Drug
Administration, Room 4-65, 5600 Fishers Lane, Rockville, Maryland 20857

A.2. Substitute Drugs

A.2.1. Bacitracin

The bacitracins are a group of polypeptide antibiotics produced by Bacillus subtilis. The methylene disalicylate and zinc salts of bacitracin are used as feed additives to promote growth and for disease control in poultry, swine and cattle. These salts disassociate upon ingestion, releasing the active bacitracin base. Bacitracin is used topically in human medicine to treat skin infections and infected superficial wounds.

A.2.1.1. Physical and Chemical Properties

The structure of bacitracin is shown below. It is composed of amino acids joined in a cyclic polypeptide. The antibiotic is a hygroscopic powder, stable at room temperature. Bacitracin is water soluble and quickly deteriorates in aqueous solution unless refrigerated. It is practically insoluble in ether, chloroform and acetone. No lipid-water partition coefficients are available; however, the coefficient should be low, based upon the high water solubility of the drug. Bacitracin is stable in acid solution. In alkaline medium, bacitracin changes to a less active molecular form (Merck Index, 9th Ed.).

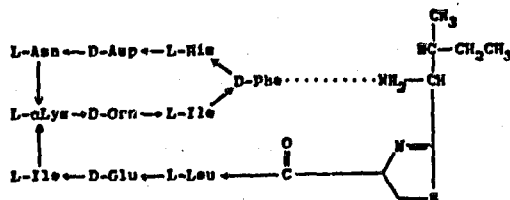


Figure A-8. Structure of Bacitracin (Merck Index, 9th Ed.)

A.2.1.2. Antimicrobial Spectrum and Mechanism of Action

Bacitracin is highly active against many species of Gram-positive bacteria and pathogenic Neisseriae. The pathogenic hemolytic streptococci (Lancefield's Group A) are especially sensitive. Minimum Inhibitory Concentrations (MICs) against Streptococcus and Staphylococcus range from 0.21 to 130 ug/ml (ppm). Some other MICs in ug/ml are: Staphylococcus 0.5-5.0, E. coli 250-500, Aerobacter 250-500, Bacillus 500, Klebsiella 31-100, Vibrio 0.07-5.0, Bacteroides 7.8, Pasteurella 0.003-10 (NADA 46-592, Vol. 12, p.13). Bacitracin methylene disalicylate has the ability to inhibit Streptococcus bovis, an organism causing severe acidosis in cattle. However, bacitracin inhibits other rumen bacteria at the same time (Klatte and Thomas, 1967). Feeding diets containing 10 or 100 ppm bacitracin to chickens did not influence significantly the amount of Salmonella excreted, when compared with non-medicated birds (Smith and Tucker, 1975). Similar results were obtained in studies submitted to FDA by the Animal Health Institute (MF 3596, MF 3577, Dec. 17, 1974).

Bacitracin inhibits biosynthesis of peptidoglycan, a macromolecular polymer in the bacterial cell wall, acting at a different reaction site from that of penicillin (Anderson et al., 1972; Stone and Strominger, 1971). Resistance to bacitracin has not been observed on bacterial plasmids. A chromosomal mutation may occur in vitro but is rarely found in vivo (Szybalski and Bryson, 1952; Stone, 1949).

A.2.1.3. Introduction into the Environment

A.2.1.3.1. Manufacturing Wastes

One of four firms manufacturing bacitracin has submitted a statement that it produces about 125,000 kg bacitracin methylene disalicylate annually, its manufacture involving a fermentation using nutrients and non-pathogenic organisms (Bacillus subtilis). Airborne products involve only CO₂-enriched air. Solid materials containing filter aids, mycelia and insoluble biodegradable and inert materials are disposed of via sanitary landfill. Liquid wastes are disposed of in the municipal sewage system. These contain only non-toxic salts and biodegradable organisms. The firm stated that this process is in accordance with local and state environmental and health regulations. Another firm indicated only that production is in accordance with environmental standards. No data are available for other manufacturers.

A.2.1.3.2. Occupational Exposure

Hypersensitivity reactions to bacitracin occur but are uncommon (Weinstein, 1975; Pirilia and Rantanen, 1960; Huber, 1977). No data are available which deal with occupational contact allergy reactions or other effects on workers.

A.2.1.3.3. Introduction into Environment through Excretion by Target Animals

Chickens fed 11 ppm zinc bacitracin contained 31 to 54 ppm (wet weight) in their intestines, according to Bare et al. (1965), while litter from facilities where chickens were fed bacitracin continuously contained from 0.05 to 8.5 ppm (Webb and Fontenot, 1975).

In swine, bacitracin administered by oral gavage was poorly absorbed from the gastrointestinal tract and excreted primarily in feces and, to a lesser extent, in urine. The small amounts absorbed across the gut wall did not accumulate in any organs

except kidney (Grezin et al, 1974). Plasma of pigs fed 252 ppm zinc ¹⁴C bacitracin for 3 days contained 1.5 to 2.1% of the radioactivity, none was found in liver, kidney, muscle, brain mesentery or skin tissues; about 1.7% was excreted in urine and about 92% in feces. It is uncertain whether bacitracin or a metabolite was excreted (Donoso et al, 1970).

No data on bacitracin metabolism and excretion in cattle were submitted in response to the Agency's May 1977 Call for Environmental Information (42FR27264) or were located in a literature search.

Absorption of bacitracin from the gastrointestinal tract in other mammals is limited (Huber, 1977). Bacitracin administered orally to dogs in doses of 26 mg/kg body weight (1000 units) per day afforded plasma concentrations of 0.002 mg/ml (2 ppm) and urinary concentration of 0.006 mg/ml (5.7 ppm) (Bond et al, 1948).

A.2.1.3.4. Residues in Human Foods

Bacitracin, even at high levels, does not produce detectable residues in animal tissues due to its poor absorption (Scudi et al, 1947). Data have not been published by USDA on bacitracin residues, however. (See also A.2.1.4.3. Bioaccumulation).

A.2.1.4. Fate in the Environment

A.2.1.4.1. Persistence and Degradation

The types, quantities, and bioactivity of bacitracin metabolites present in the excreta of target animals are not determined in any studies reviewed by the Agency for the preparation of this EIS. We believe that the polypeptide chemical structure, absence of hard-to-degrade chemical substituents (such as halogens) and high water solubility suggest that bacitracin is biodegradable, probably by successive deamination and dealkylation reactions catalyzed by enzymes present in most soil bacteria and fungi.

Bacitracin excreted in feces has been found to be unstable when incorporated into soil. An environmental half-life of about 10 days was observed for bacitracin when exposed to normal environmental soil conditions of moisture, temperature, and pH (Bacitracin EIAR, IMC Chemical Group, 11-25-77).

Bacitracin inactivation has been examined in excreta from broiler chickens continuously fed mash containing 500 g bacitracin MD per ton of feed (Bacitracin EIAR, AL Laboratories, 8-3-77). Results were as follows:

Table A-XII
Bacitracin Inactivation in Chicken Excreta

<u>Sample</u>	<u>Bacitracin found (ppm) dry weight basis</u>
Fresh feces	6.17
Same held 24 hrs. rm. T	5.00
Same held 72 hrs. rm. T.	4.89
Same held 7 days	1.30
Same held 14 days	0.40
Same held 21 days	0.40

Half-life was estimated to be 4 to 7 days.

A.2.1.4.2. Mobility in the Environment

Pinck, Soulides, and Allison (1961) demonstrated bacitracin to be one of a group of amphoteric antibiotics, including chlortetracycline and oxytetracycline, which are weakly adsorbed and easily released in active form from clay-antibiotic complexes in soils. These antibiotics were released from all soil types and clays tested. Based on these data and the high water solubility of bacitracin, we conclude that this antibiotic is mobile in soils, with temporary or partial retention occurring depending on soil pH and clay composition and content.

A.2.1.4.3. Bioaccumulation in Target Anima

No tissue residues of bacitracin have been found in chickens, turkeys, or laying hens consuming feed containing bacitracin at as much as 1000 g/ton (1100 ppm) until the day of sacrifice. No detectable residues have been found in tissues of cattle or swine consuming bacitracin MD at 500 g/ton (550 ppm) (Bacitracin EIAR, AL Laboratories, 8-3-77).

Since bacitracin has high solubility in water and low solubility in organic compounds (properties favoring efficient excretion A.2.1.1.), has poor absorption in target animals (A.2.1.3.3.), and is inactivated in animal wastes and soils (A.2.1.4.1.) we concluded that it is unlikely that long term bio accumulation would occur with environmental residues of bacitracin.

A.2.1.5. Environmental Effects

A.2.1.5.1. Toxicity to Non-pathogens

Bacitracins, like other polypeptide antibiotics, have produced hypersensitivity reactions in man. Surveys of human patients yielded a range of prevalence of dermal hypersensitivity to bacitracin from 0.3% of 380 patients (Schwank, 1965) to 7.8% of 17,500 patients by patch testing (Pirilia and Rantanen, 1967). Bacitracin is not used systemically in man since it is extremely nephrotoxic (toxic to kidney tissue).

Quantities of bacitracin required for induction of oral acute toxicity among rabbits were found to be more than 5200 mg/kg body weight (Payne et al, 1951). In acute toxicity studies with mice, the oral LD₅₀ was found to be 3375 mg/kg body weight (Bacharach et al, 1959).

Bacitracin at 25 mg/kg body weight had no effect upon the reproductive function of swine/(Shikhova et al 1974). Fed to chickens at 300 mg/kg of feed for 90 days, there were no toxic effects; however, bacitracin at 1000 mg/kg of feed led to slight effects on the kidney tubules (Simeonov et al, 1975). Bacitracin is not used parenterally in animals because of potential nephrotoxicity. Lethal doses produce renal tubular damage.

Bacitracin-related phytotoxicity was not observed in the limited data available. Bacitracin at 50-200 ppm prevented microbial contamination of the periwinkle, Vinca rosea, in tissue cultures, without exhibiting any toxic effects upon callus tissue-growth (Carew and Patterson, 1970). Data from one greenhouse study indicate that bacitracin stimulates production of clover nodules and numbers of fungi in cropped soil (Hervey, 1955). Bacitracin from the excreta of medicated target animals did not affect yield in potted oats (Tietjen, 1975).

In insects, the data available indicate that bacitracin is of low toxicity. Bacitracin was toxic to rice-weevil larvae (Sitophilus oryza) fed at 20,000 ppm (Baker and Lum, 1973). The toxic level for larvae of Agria affinis (flesh-eating flies) was greater than 50,000 ppm in feed (Singh and House, 1970).

Bacitracin inhibits growth of Halobacterium, a genus of bacteria found in salt water, which lacks the peptidoglycan layer characteristic of the cell wall of most prokaryotes (Mescher and Strominger, 1975). We believe that bacitracin probably has no effect upon the Gram-negative free-living nitrogen

fixers (Azotobacter) or symbiotic nitrogen fixers (Rhizobium) or upon the nitrate and sulfate oxidizing organisms (Nitrosomonas, Nitrobacter, Thiobacillus) since it acts mainly upon Gram-positive organisms and Gram-negative cocci. However, there are no specific data to confirm this speculation.

The short environmental persistence of bacitracin bioactivity precludes long-term toxic effects from environmental residues, in any event.

A.2.1.5.2. Drug Resistance

Resistance to bacitracin has not been observed on bacterial plasmids. A chromosomal mutation may occur in vitro but is rarely found in vivo (Szybalski and Bryson, 1952; Stone, 1949). In studies carried out for FDA by industry, as well as in scientific literature, the use of bacitracin in feeds given to swine or chickens did not mediate a change in the resistance patterns of E. coli or Salmonella populations to Gram-negative antibiotics used in human medicine (Animal Health Institute, MF 3596, letter to FDA 9-27-76).

A.2.2. Tylosin

In veterinary medicine, tylosin has been used for growth promotion at subtherapeutic levels and (at therapeutic levels) to control chronic respiratory disease of chickens due to Mycoplasma gallisepticum and experimental coccidial infections. It is also used, at subtherapeutic levels, to prevent vibriotic dysentery of swine and for production efficiency. It is not used in human medicine.

A.2.2.1. Chemical and Physical Properties

Tylosin (M.W.=16.14) is a macrolide antibiotic produced by the fungus, Streptomyces fradiae. Its structure is similar to that of other macrolides, e.g., erythromycin and oleandomycin. Macrolides consist of a large lactone ring, a ketone group and a glycosidically linked amino sugar. They are basic with pKa values between 6.0 and 9.0.

Tylosin is soluble in common organic solvents and moderately soluble in water (at 25°C, 5000 ppm), varying inversely with temperature. Lipid/water partition coefficients could not be found. With mild acid hydrolysis, desmycosin and a sugar, mycarose, are produced. Desmycosin is also microbiologically active (NADA 12-491, Summary Nov. 9, 1960; Merck Index, 9th Ed., 1976).