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ABBREVIATIONS

AAAP	American Association of Avian Pathologists
Amp	ampicillin
Cm	chloramphenicol
CFR	Code of Federal Regulations
DNA	deoxyribonucleic acid
EA	environmental assessment
EIS	environmental impact statement
Em	erythromycin
FR	Federal Register
g/ton	grams per ton, a measurement often used to describe the concentration of a drug in animal feed
Km	kanamycin
LC_{50}	lethal concentration in the environment which kills 50% of the test organisms, e.g. the concentration in water kills 50% of the test fish in a fish toxicity test
LD_{50}	lethal dose for 50% of the test organisms
MIC	minimum inhibitory concentration
motile	term applied to bacteria with flagella, whip-like structures used to propel the cells
NADA's	new animal drug applications
NAS-NRC	National Academy of Sciences/National Research Council
NF-180	furazolidone
NF-260	furaltadone
NF-7	nitrofurazone
NF-64	nihydrazone

Nm	neomycin
pH	an indication of hydrogen ion concentration or acidity, pH = -log [H+]
ppm	parts per million
Sm	streptomycin
Su	sulfonamides
Tc	tetracyclines
TL_{50}	median tolerance limit, the concentration at which 50% of the test organisms survive
ug/ml	micrograms per milliliter (parts per million)

Environmental Assessment for the Prohibition of Use of Three Nitrofuran Compounds in Food-Producing Animals.

SECTION 1. STATEMENT OF THE PROBLEM

1.1. The Problem

Four nitrofuran drugs, furazolidone (NF-180), furaltadone (NF-260), nitrofurazone (NF-7), and nihydrazone (NF-64) were approved by the Food and Drug Administration (FDA) in 1953, 1962, 1948, and 1963, respectively, for a broad spectrum of uses in food-producing and nonfood-producing animals. In the late 1960's and 70's, new evidence became available to the Bureau of Veterinary Medicine of the Food and Drug Administration (Bureau*) which, taken together with the data available at the time of the original approval of these drugs, showed that residues in food derived from animals receiving these drugs are not safe for human consumption. The new evidence showed that furazolidone is a carcinogen and called into question the safety of the total drug tissue residues present in meat from treated animals. The other three drugs are both tumorigens and suspect carcinogens.

1.2. Proposed Actions

On May 13, 1976 (41 FR 19797) the Bureau issued a notice of opportunity for hearing on a proposal to withdraw approval of new animal drug applications (NADA's) for the use of furazolidone in food-producing animals in accordance with section 512(e)(1)(B) of the

* On March 19, 1984, the Bureau of Veterinary Medicine was redesignated as the Center for Veterinary Medicine.

Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b(e)(1)(B)) (the Act) on the grounds that furazolidone is carcinogenic and adequate, reliable, and practicable methods of analysis are not available for monitoring food nor can conditions of use be specified in the labeling to assure that no residue of the drug will be found in any edible portion of such animals, as required by section 512(d)(1)(H) of the Act (21 U.S.C. 360b(1)(H)), the so-called Delaney Clause. On August 17, 1976, (41 FR 34891, 34899, 34908) the Bureau issued notices of opportunity for hearing on proposals to withdraw approval of NADA's for the use of furaltadone, nitrofurazone, and nihydrazone in food- producing animals in accordance with section 512(e)(1)(B) on the grounds that those drugs are not shown to be safe under either the approved or currently labeled conditions of use (the Safety Clause).

Firms holding NADA's for furazolidone (NF-180), nitrofurazone (NF-7), and furaltadone (NF-260) filed written appearances requesting hearings on the Bureau's proposals,* and by Advance Notice of Hearing published in the FEDERAL REGISTER of April 8, 1977 (42 FR 18660), the Acting Commissioner of Food and Drugs announced that a formal evidentiary public hearing would be held on the continued approvability of these NADA's. This Environmental Assessment accompanies Notices of Hearing on the Bureau's proposals issued by the Commissioner of Food and Drugs. The Notice of Hearing for furazolidone announces that the Bureau is proposing to withdraw approval of the furazolidone NADA's

*Neither the holders of the NADA's nor any other person requested a hearing on nihydrazone, and the NADA's for that drug were withdrawn April 8, 1977 (42 FR 18660). Therefore, nihydrazone will not be considered further in this environmental assessment.

under the Safety Clause of section 512(e)(1)(B) of the Act on the grounds that new evidence shows that the drug is not shown to be safe under either the approved or currently labeled conditions of use, as well as under the Delaney Clause.

1.3. Regulatory Alternatives to the Proposed Actions

1.3.1. Limits on types of action that can be taken under the Food, Drug and Cosmetic Act.

The Delaney Clause, section 512(d)(1)(H) of the Act (21 U.S.C. 360b(1)(H)), flatly prohibits the use of a carcinogenic animal drug in food-producing animals unless FDA finds that the drug will not harm the animal for which the drug is intended and that no residue of the drug will be found, by an analytical method approved by FDA by regulation, in food derived from the treated animal. Thus, if furazolidone is a carcinogenic animal drug whose continued use in food-producing animals violates the Delaney Clause, then withdrawal of the NADA's for the drug is required by statute. The Safety Clause, section 512(e)(1)(B) of the Act (21 U.S.C. 360b(e)(1)(B)), requires withdrawal of a new animal drug approved for use in food-producing animals if new evidence shows that residues of the drug in food derived from such animals are not shown to be safe for human consumption.

Economic effects, environmental impacts, and other possible consequences may be considered in such decisionmaking only insofar as such factors do not conflict with the basic statutory requirements.

1.3.2. Regulatory Alternative 1--No action.

In accordance with the Council on Environmental Quality regulations (40 CFR 1508.9) and the FDA's proposed NEPA-implementing regulations (proposed 21 CFR 25.31(b), 44 FR 71747, December 11, 1979) the environmental impacts of the "no action" regulatory alternative will be considered.

It should be noted that "no action" in this case is not without possible environmental effects. Although not possible to quantify, there is some degree of risk involved in the manufacture, distribution, preparation and use of animal feeds containing carcinogenic and tumorigenic nitrofuran drugs.

"No action" becomes a serious consideration if it is found that the proposed action and other regulatory alternatives would result in significant adverse impacts on the environment. This alternative is, in any event, useful as a reference point from which to compare the proposed action and other regulatory alternatives.

1.3.3. Regulatory Alternative 2--Controlled use of furazolidone for uses not completely covered by alternate drugs.

If the present uses of nitrofuran drugs in food-producing animals

violate either the Delaney Clause, the Safety Clause, or both, then is it possible to determine procedures for use of the drugs which would not result in unsafe residues of the drugs in the human food supply? One approach might be to permit use of nitrofuran drugs for those indications not completely covered by alternate drugs but only under closely monitored controls. Withdrawal of the drug from treated animals for a period long enough to assure the absence of nitrofuran residues and a mechanism to assure that the withdrawal period was scrupulously enforced would be necessary. The feasibility of such an approach will be explored.

1.3.4. Regulatory Alternative 3--Proposed actions plus mitigation.

Under 40 CFR 1508.25 of the CEQ regulations, regulatory alternatives may include the proposed action plus mitigation measures not in the proposed action. Aside from the proposed actions only, this alternative is probably the easiest to implement within the confines of the Delaney and Safety Clauses of the Act. Mitigation measures that may minimize adverse environmental effects of the proposed actions will be explored.

1.4. History of Environmental Analysis of the Proposed Actions and Purpose of This Reassessment

The Bureau filed its Environmental Impact Analysis Report and Assessment of Four Nitrofuran (5-Nitro) Compounds (hereinafter, "Environmental Assessment") on May 4, 1976, in conjunction with the series of Notices of Opportunity for Hearing on the proposed actions prohibiting the use of furazolidone, nihydrazone, nitrofurazone, and furaltadone in food-producing animals. The Environmental Assessment concluded that the impacts associated with the proposed actions would not significantly affect the quality of the human environment and that, consequently, an Environmental Impact Statement (EIS) would not be required. Also, the Environmental Assessment noted that a reassessment would be performed should new information become available that might alter the conclusions of the Environmental Assessment.

Subsequent to the Federal Register publication of the Notice of Opportunity for Hearing on Furazolidone (NF-180) (41 FR 19907, 5/13/76), the Agency received a request for hearing from a manufacturer of the drug declaring, among other things, that ". . . there would indeed be a significant impact on the environment if furazolidone were to be made unavailable to the poultry and swine industries." The drug manufacturer submitted a point-by-point review of the environmental assessment accompanied by references for the purpose of demonstrating the environmental assessment to be "seriously inadequate" and to show the need to prepare an EIS. A second furazolidone manufacturer submitted a request for hearing including as a hearing issue the lack of an EIS for the proposed action. The second request,

however, did not include any data to support the need for an EIS. Similar requests for an EIS for the proposed NF-7 and NF-260 actions were filed without supporting evidence for the request. No other comments regarding the environmental impact of the proposed actions were received in response to the Notices of Opportunity for Hearing for the nitrofuran drugs.

Since the submission of these requests for hearing by the nitrofuran manufacturers, the Bureau has obtained additional information which could assist in the environmental review of the nitrofuran proposals. The following reports, in particular, contain data relevant to the nitrofuran environmental analysis.

1. Office of Technology Assessment. 1979. Drugs in Livestock Feed, Vol. 1. Congress of the United States, Washington, D.C. 20510.

2. Economics, Statistics, and Cooperatives Service. 1978. Economic Effects of Prohibition on the Use of Selected Animal Drugs. Agricultural Economic Report No. 414, U.S. Dept. of Agriculture, Washington, D.C. 20250.

3. Feinman, S.E. and J.C. Matheson, III. 1978. Draft Environmental Impact Statement: Subtherapeutic Antibacterial Agents in Animal Feeds. Bureau of Veterinary Medicine, U.S. Food and Drug Administration, Rockville, Md. 20857.

The purpose of this reassessment is to examine the comments and requests from the firms affected by the proposed nitrofuran actions and the additional information available since the 1976 Environmental Assessment was completed and to determine whether this information alters the Bureau's decision not to prepare an Environmental Impact

Statement on the subject. (Appendix A contains a review of the scientific literature submitted by a drug manufacturer in support of its claim that an EIS is required for the proposed withdrawal of furazolidone.) This reassessment assumes for the purpose of predicting environmental impacts, that the Bureau's findings as they relate to human health safety will be proven correct. Otherwise, there would be no basis for a Federal action requiring environmental analysis.

SECTION 2. ENVIRONMENTAL ASSESSMENT

2.1. Findings of the Bureau's Original (1976) Nitrofuran Environmental Assessment

Although the then available data were insufficient to predict the magnitude of the effects, the 1976 Environmental Assessment identified a number of potential environmental impacts which were the consequences of events that might follow the implementation of the proposed actions. Briefly summarized these events were:

1. Reductions in the manufacture and use of nitrofuran drugs. Nitrofuran production would be limited to that required for non-food animals.

2. Increased manufacture and use of alternate drug products and use of management practices instead of or to compensate for prohibited nitrofuran uses in food-producing animals.

3. Decreased productivity in food-producing animals, increased food-producing animal morbidity and mortality, and increased condemnation of food-producing animals at slaughter, only in those cases where alternate drugs and/or management practices do not adequately compensate for the absence of nitrofuran drugs.

The potential environmental impacts associated with each event include:

For event 1, reduced manufacture and use of nitrofurans --

1. Reduced environmental introduction of nitrofuran compounds, with consequent decreased environmental exposure of humans and other organisms to agents with carcinogenic, tumorigenic, and other possible consequences;

2. Reduced energy and natural resources utilized to manufacture nitrofuran drugs.

For event 2, increased manufacture and use of alternative drugs and use of management practices to compensate for prohibited nitrofuran uses --

1. Increased environmental introduction of alternate drugs, with consequent potential of increased exposure of humans and other organisms to alternate drug residues in the environment;

2. Increased use and environmental introduction of disinfectants, insecticides and other chemicals used in animal management to control disease spread;

3. Increased labor, energy, and natural resources associated with alternate animal management practices;

4. Increased drug-resistant microbial populations associated with increased use of alternate drugs and consequent increase in human diseases not amenable to drug treatment.

For event 3, decreased swine and poultry productivity, increased morbidity, mortality and condemnation at slaughter in those cases where alternate drugs and/or management practices did not adequately compensate for the absence of nitrofuran drugs--

1. Increased use of animal feed and feed supplements and increased waste generated per amount

of marketed meat/product (due to decreased growth rate, mortalities, and condemnations) with secondary impacts on land, fertilizer, energy, and labor used to produce food-producing animals and animal feed;

2. Disposal of animal carcasses due to increased mortality on the farm and increased condemnations at the processing plant;

3. Decreased availability of meat products for humans.

The 1976 Environmental Assessment concluded that the magnitude of the above potential impacts would not be significant, largely because adequate alternate drugs and management practices existed for the restricted nitrofuran claims and because the low level of sales of the nitrofuran drugs compared to existing alternate drugs did not indicate that nitrofurans are essential for the vast majority of the uses that would be prohibited.

2.2. Comments Submitted by Furazolidone Manufacturers in Response to the Bureau's 1976 Nitrofuran Environmental Assessment

A number of comments supported by references were submitted by one firm (now Norwich-Eaton Pharmaceuticals) which were intended to show the essential nature of nitrofuran products for controlling animal diseases, particularly those arising from infections

with Salmonella spp. (See Appendix A for a review of these references.) We summarize the scenario of events postulated by the firm as follows:

1. Food and Drug Administration withdraws nitrofuran NADA's (the proposed actions).

2. Alternate drugs are used in greater quantities to replace nitrofurans, particularly in controlling Salmonella spp.-related diseases in poultry and swine.

3. Salmonella spp. become resistant to the alternate drugs more quickly without recourse to nitrofurans.

4. FDA limits animal uses of alternate drugs to preserve their effectiveness in humans.

5. Diseases associated with Salmonella spp. infections dramatically increase in swine and poultry populations, resulting in increased mortality and decreased productivity in these populations. Drug-resistant microbial genetic material proliferates.

6. Swine and poultry products for human consumption are increasingly contaminated with drug-resistant Salmonella organisms.

7. Human salmonelloses increase; antibiotics are ineffective.

In other words, the furazolidone marketing firm believes that the potential environmental impacts identified in the Bureau's Environmental Assessment and summarized above (2.1) will be severe because furazolidone is currently essential to the prevention and treatment of certain, specific diseases in food-producing animals, that there are no adequate alternate drugs or management practices for controlling these diseases, and that the proposed withdrawal of nitrofuran approvals would precipitate uncontrolled problems with these diseases. A second firm (Hess and Clark) contended that an environmental impact statement is needed for the nitrofuran proposals, but did not submit evidence to support this contention.

2.3. Approach for Examining the Magnitude of Potential Environmental Impacts of the Proposed Actions

One major disagreement between the Bureau and the firms marketing furazolidone is over the magnitude of potential environmental impacts associated with the proposed actions. This report will examine the magnitude of these potential impacts by focusing on the following areas:

1. Essentiality of nitrofuran drugs in the control of disease and maintenance of animal productivity. Are these drugs essential for the control of any animal diseases and for increasing productivity of food-producing animals? Which diseases and classes of food-producing animals are affected? How frequently do these diseases occur? Are effective alternate drugs and management practices available?

2. Essentiality of nitrofuran drugs in controlling the selection and spread of drug-resistant bacteria. Are nitrofuran drugs an important means to control or reduce the reservoir of drug-resistant bacteria in food-producing animals and, consequently, in the exposure of humans to these bacteria?

3. Environmental impacts due to use of alternate drugs. Does the additional increment of use of alternate drugs due to a nitrofuran prohibition in food-producing animals create significant environmental impacts?

Objective analysis of these questions should provide a basis for determining whether the potential environmental impacts associated

with the proposed actions are significant enough to warrant preparation of an Environmental Impact Statement.

2.4. Essentiality of Nitrofuran Drugs in the Control of Disease and Maintenance of Animal Productivity

2.4.1. Current Approved Conditions of Use for Nitrofurans in Food-Producing Animals and Approved Alternate Drugs

The three nitrofuran drugs affected by the proposed actions were approved for use between 1948 and 1962. During this period, effectiveness data were not required to be submitted and broad, all-encompassing conditions for use appeared on the drugs' labels. When the Food, Drug, and Cosmetic Act was amended in 1962 (Public Law 87-781; 76 Stat. 780-1196), new animal drugs were required to be shown to be effective for particular conditions of use with adequate and well-controlled studies. In 1966, the FDA contracted with the National Academy of Sciences' National Research Council (NAS/NRC) to review the effectiveness data available for animal drugs approved prior to 1962 to determine whether there was appropriate scientific data to support the claims being made. The nitrofuran drugs were reviewed by NAS/NRC; however, the results of that review have not been generally disclosed because, shortly afterwards, human safety questions arose and FDA began proceedings to withdraw its approval of the drugs for use in food-producing animals. Since the recommendations of the NAS/NRC review have not been incorporated into the labels of nitrofuran drugs, the current conditions of use for the drugs may be in some instances somewhat broader and more general

than for those alternate drug claims revised pursuant to the NAS/NRC review or approved after 1962.

Tables 1, 2, and 3 list the current conditions of feed additive use for furaltadone, nitrofurazone, and furazolidone in food-producing animals, examples of available alternate drugs, and the methods of administration for the drugs. (Note that uses of these drugs in pets and in other nonfood-producing animals are unaffected by the Bureau's proposals and are, therefore, not considered.)

From the tables, it can be seen that there are plentiful alternate drugs for all approved furaltadone (Table 1) and nitrofurazone (Table 2) uses in food-producing animals. Furazolidone appears to be potentially important in the treatment and control of some economically important diseases or is the only drug available as a feed additive* for the following uses:

1. Prevention and treatment of paracolon infections (avian arizonosis) in chickens and turkeys;

2. Prevention and treatment of pullorum disease in chickens and turkeys;

*Alternate drugs which are used as feed additives are completely interchangeable with nitrofuran-medicated feeds. Other dosage forms of alternate drugs, e.g. drinking water solutions, may require some changes in management practices or facilities.

3. Prevention and treatment of fowl typhoid in chickens and turkeys;

4. Prevention and treatment of paratyphoid infections in chickens and turkeys;

5. Prevention and treatment of air sac infection (associated with E. coli) in chickens and turkeys (i.e., complicated chronic respiratory disease);

6. Control of ulcerative enteritis (quail disease) in poultry;

7. Prevention of infectious hepatitis in chickens; and

8. Treatment of blackhead (histomoniasis) in chickens.

There are numerous, effective drugs available which increase rate of weight gain and feed efficiency, as supported by data included in the Office of Technology Assessment Report ("OTA Report," U.S. Congress, 1979) on growth promotion effects of the various antibacterials in swine and poultry (Tables 4, 5, and 6). Note, however, that the author of the tables pooled the results of many effectiveness trials

to obtain the composite data presented. No measure of the variability of the results of the individual trials is given. For example, for any one drug, some trials could have resulted in small or negligible benefits and large benefits in others.

Both the USDA Economics, Statistics, and Cooperatives Service (1978) and the OTA Report identify chickens and turkeys as the major species affected by the Bureau of Veterinary Medicine's nitrofuran proposals. Turkeys, in particular, appear to frequently receive nitrofurans, usually early in life (Table 7). Tables 1-3 show adequate alternate drugs available for swine and cattle for the nitrofuran claims affected by the proposed actions. Neither the USDA nor the OTA study identifies adverse effects on swine or cattle to result from nitrofuran restrictions.

The Bureau's proposals would also prohibit the use of NF-7, NF-180, and NF-260 in topical and ophthalmic applications in food-producing animals. Assessing the availability of alternate drugs for these uses is difficult because many of the nitrofuran drug products, the alternate drug products, and their conditions of use are not listed in the Code of Federal Regulations (21 CFR) due to their approval prior to the 1962 FD&C Act amendments. Based on a survey of new animal drug applications in FDA's files, furazolidone (NF-180) and nitrofurazone (NF-7) are used in a number of preparations for wound and eye and ear treatment. Some examples and alternate drug products are shown in Table 8. Although a complete product by product comparison is not

Table 1. Furaltadone (NF-260) claims affected by the proposed actions and available alternate drugs.

NF-260 Claim	Dosage	Alternate Drugs	Claim	Dosage
§526.1014 treatment of bovine mastitis in lactating cows (no disease organisms specified)	intramammary infusion - 500 mg per infected quarter repeated 3 times	Erythromycin	§526.820 treatment of bovine mastitis in lactating cows	intramammary infusion - 300 mg per infected quarter repeated 3 times
"	"	Cloxacillin	§540.815 treatment of mastitis in lactating cows due to Streptococcus agalactiae and Staphlyococcus aureus, nonpenicillinase producing strains	intramammary infusion - 200 mg per infected quarter
"	"	Hetacillin	§540.829 treatment of acute, chronic or subclinical bovine mastitis in lactating cows caused by susceptible strains of Strep. agalactiae, Strep. disgalactiae, Staph. aureus, and Escherichia coli	intramammary infusion - 62.5 mg per infected quarter repeated 3 times
"	"	Procaine penicillin G	§540.874 treatment of bovine mastitis caused by Strep. agalactiae, Strep. disgalactiae, and Strep. uberus in lactating cows	intramammary infusion - 100,000 units per infected quarter repeated a maximum of 3 times

Table 1 continued.

NF-260 Claim	Dosage	Alternate Drugs	Claim	Dosage
"	"	Cephapirin	§529.365 treatment of lactating cows having bovine mastitis caused by susceptible strains of Strep. agalactiae and Staph. aureus	intramammary infusion - 200 mg per infected quarter repeated once
"	"	Novobiocin	§526.1590 use in lactating cows for treatment of mastitis caused by susceptible strains of Staph. aureus	intramammary infusion - 150 mg per infected quarter repeated once
"	"	Cephapirin benzathine	§526.363 treatment of mastitis in dry cows caused by susceptible strains of Strep. agalactiae and Staph. aureus	intramammary infusion - 300 mg per infected quarter after last milking
"	"	Benzathine cloxacillin	§540.814, 540.814a treatment and prophylaxis of bovine mastitis in nonlactating (dry) cows due to Strep. agalactiae and Staph. aureus	500 mg per quarter at the time of drying off

Table 2. Nitrofurazone (NF-7) claims affected by the proposed actions and available alternate drugs.

NF-7 Claim	Dosage	Alternate Drug*	Claim	Dosage
§558.15(g)(1) Use in chickens as an aid in prevention of coccidiosis when fed continuously	50 grams drug per ton of feed	Aklomide	§558.35 Aid in the prevention of coccidiosis caused by E. tenella and E. necatrix, in chickens except laying hens	227 grams drug per ton of feed, fed continuously
"	"	Aklomide plus sulfanitran	§558.35 same as aklomide plus E. acervulina	227 grams aklomide plus 181.6 grams sulfanitran per ton of feed, fed continuously
"	"	Amprolium plus ethopabate	§558.58 In broiler chickens as an aid in the prevention of coccidiosis	113.5 grams amprolium plus 3.6 grams ethopabate per ton of feed
"	"	Buquinolate+	§558.105 In broiler chickens similar to §558.175	75 grams drug per ton of feed, fed continuously
"	"	Clopidol	§558.175 In chickens as an aid in the prevention of coccidiosis caused by E. tenella, E. necatrix. E. acervulina, E. maxima, E. brunetti and E. mivati	113.5 or 227 grams drug per ton of feed, fed continuously up to age 16 weeks

Table 2 continued.

NF-7 Claim	Dosage	Alternate Drug*	Claim	Dosage
"	"	Decoquinate	§558.195 same as §558.175, but not for laying hens	27.2 grams drug per ton of feed, fed continuously
"	"	Lasalocid	§558.311 Similar claim to §558.175	68-113 grams drug per ton of feed, fed continuously
"	"	Monensin	§558.355 Similar claim to §558.175	90-110 grams drug per ton of feed, fed continuously
"	"	Nitromide plus sulfanitran	§558.376 same as §558.35 aklomide plus sulfanitran	227 grams nitromide plus 272 grams sulfanitran per ton of feed, fed continuously
"	"	Robenidine	§558.515 same as §558.175, not for laying hens	30 grams drug per ton of feed, fed continuously
"	"	Sulfaquinoxaline	§558.15(g)(1) In chickens as in §558.175	0.0125 to 0.025 percent in feed, fed continuously
"	"	Zoalene	§538.680 In replacement chickens, development of active immunity to coccidiosis	36.3 to 113.5 grams drug per ton of feed up to 14 weeks
			In broilers, prevention and control of coccidiosis	113.5 grams drug per ton

Table 2 continued.

NF-7 Claim	Dosage	Alternate Drug*	Claim	Dosage
§558.15(g)(1) In turkeys as an aid in controlling losses due to secondary bacterial invasions concurrent with coccidiosis outbreaks when fed continuously throughout the danger period.	50 grams drug per ton of feed, fed continuously	Amprolium (in combinations with various antibiotics)	§558.55 Prevention of coccidiosis	113.5 to 227 grams per ton of feed, fed continuously
"	"	Sulfadimethoxine plus ormetoprim	§558.575 Aid in the prevention of coccidiosis caused by all Eimeria species known to be pathogenic in turkeys	56.75 grams sulfadimethoxine plus 34.05 grams ormetoprim per ton of feed, fed continuously to turkeys not producing eggs for food
"	"	Sulfaquinoxaline	§558.15(g)(1) Aid in the prevention of coccidiosis due to E. meleagrides, E. meleagrimites, and E. adenocides	0.0175 percent in the feed, fed continuously
"	"	Zoalene	§558.680 Prevention and control of coccidiosis in turkeys grown for meat purposes	113.5 to 170.3 grams drug per ton of feed, fed continuously

Table 2 continued.

NF-7 Claim	Dosage	Alternate Drug*	Claim	Dosage
§558.15(g)(1) In swine, treatment of necrotic enteritis caused by Salmonella choleraesuis	500 grams drug per ton of feed, fed 5-7 days and repeated, if necessary	Carbadox	§558.115 Control of bacterial swine enteritis (salmonellosis or necrotic enteritis caused by Salmonella choleraesuis)	50 grams of drug per ton of feed, fed to swine up to 75 pounds body weight
"	"	Chlortetra-** cycline bisulfate-sulfamethazine bisulfate soluble powder	§546.113b Prevention and treatment of bacterial enteritis	250 mg chlortetracycline plus 250 mg sulfamethazine per gallon of drinking water
"	"	Chlortetra-** cycline powder	§546.110c Treatment of bacterial enteritis	200-400 mg drug per gallon of drinking water
"	"	Tetracycline** soluble powder	§546.180d Treatment of bacterial enteritis	200-400 mg drug per gallon of drinking water

* Listings of alternate drugs are not necessarily complete.

** This claim is not affected by the Bureau of Veterinary Medicine's proposal to restrict tetracyclines in animal feed (42 FR 56255, 10/21/77).

+ Buquinolate is approved for this use but not presently marketed.

Table 3. Furazolidone (NF-180) claims affected by the proposed actions and available alternate drugs.

NF-180 Claim	Dosage	Alternate Drugs*	Claim	Dosage
§558.15(g)(1) In chickens and turkeys, to stimulate growth and improve feed efficiency.	7 1/2 to 10 grams of drug per ton feed, fed continuously.	Arsanilate Sodium	§558.60 In chickens and turkeys for growth promotion and feed efficiency.	90 grams drug per ton of feed, fed continuously.
"	"	Arsanilic Acid	§558.62 Same as 558.60	90 grams per ton of feed, fed continuously.
"	"	Bacitracin, M.D.	§558.76 In chickens and turkeys for growth promotion and feed efficiency.	4 to 50 grams drug per ton of feed, fed continuously.
"	"	Bacitracin, zinc	§558.78 Same as §558.76	4-50 grams drug per ton of feed, fed continuously.
"	"	Bambermycins	§558.95 In broiler chickens for increased rate of weight gain and improved feed efficiency.	1-2 grams drug per ton of feed, fed continuously.
"	"	Erythromycin	§558.248 In chickens and turkeys for growth promotion and feed efficiency.	Chickens: 4.6-18.5 grams of drug per ton of feed, fed continuously. Turkeys: 9.25-18.5 grams per ton of feed, fed continuously.

Table 3 continued.

NF-180 Claim	Dosage	Alternate Drugs*	Claim	Dosage
"	"	Lincomycin	§558.325 In broiler chickens for increase in rate of weight gain and improved feed efficiency.	2 to 4 grams drug per ton of feed, fed continuously.
"	"	Oleandomycin	§558.435 In broiler chickens and growing turkeys for increased rate of weight gain and improved feed efficiency.	1-2 grams per ton of feed, fed continuously.
"	"	Roxarsone	§558.530 Same as §558.60	22.7 to 45.4 grams per ton of feed, fed continuously.
"	"	Tylosin	§558.625 In chickens for increased rate of weight gain and improved feed efficiency.	4-50 grams of drug per ton of feed, fed continuously.
§558.15(g)(1) In chickens and turkeys for prevention and treatment of fowl typhoid (Salmonella gallinarum), paratyphoid (S. typhimurium), and pullorum (S. pullorum).	Prevention: 100g/ton for first 2 weeks, then 50 g/ton continuously. Treatment: 100g/ton fed for at least 2 weeks.	Chlortetracycline**	§558.128 In turkey poults not over 4 weeks old, aid in reducing mortality due to paratyphoid caused by Salmonella typhimurium.	400 grams drug per ton of feed

Table 3 continued.

NF-180 Claim	Dosage	Alternate Drugs*	Claim	Dosage
"	"	Gentamicin	§522.1044 In day-old chicks for prevention of early mortality caused by E. coli, S. typhimurium, and P. aeruginosa.	0.2 mg subcutaneous injection
"	"	Spectinomycin	§522.2120 In 1-3 day-old chicks as an aid in control of mortality and to lessen severity of infections caused by M. synoviae, S. typhimurium, S. infantis, and E. coli.	2.5-5 mg subcutaneous injection
In chickens, for aid in prevention of coccidiosis caused by E. tenella, E. necatrix, or E. acervulina when fed continuously.	50 grams of drug per ton of feed	Refer to anticoccidials listed under NF-7 (Table 2):		
		Aklomide	§558.35	
		Aklomide plus sulfanitran	§558.35	
		Amprolium plus ethopabate	§558.58	
		Buquinolate+	§558.105	
		Clopidol	§558.175	
		Decoquinate	§558.195	

Table 3 continued.

NF-180 Claim	Dosage	Alternate Drugs*	Claim	Dosage
"	"	Lasalocid	§558.311	
"	"	Monensin	§558.355	
"	"	Nitromide plus sulfanitran	§558.376	
"	"	Oxytetracycline**	§558.450	
"	"	Robenidine	§558.515	
"	"	Sulfaquinoxaline	§558.15(g)(1)	
§558.15(g)(1) Use in chickens and turkeys for control of chronic respiratory disease (CRD, air sac infection).	100-200 grams drug per ton of feed	Chlortetra-** cycline	§558.128 In chickens as an aid in control of CRD caused by M. gallisepticum and E. coli.	200-400 grams drug per ton of feed
			§546.110c In chickens prevention and treatment of CRD.	200 mg per gallon drinking water
"	"	Erythromycin	§558.248 In chickens and turkeys as an aid in the prevention of CRD and reduction of lesions and in lowering the severity of CRD.	92.5-185 grams drug per ton of feed

Table 3 continued.

NF-180 Claim	Dosage	Alternate Drugs*	Claim	Dosage
"	"	Gentamicin	§522.1044 In day-old chickens, for prevention of early mortality due to E. coli, S. typhimurium, and Pseudomonas aeruginosa susceptible to gentamicin.	Subcutaneous injection, 0.2 mg per chick
"	"	Lincomycin plus spectinomycin	§520.1236b In chickens up to 7 days old as an aid in control of CRD caused by M. synoviae, M. gallisepticum and E. coli susceptible to lincomycin-spectinomycin.	2 grams antibiotic activity per gallon of drinking water, continuous for up to 7 days of age.
"	"	Oxytetra-** cycline	§558.450 In chickens for prevention and control of complicated CRD.	200-500 grams drug per ton of feed
"	"		§522.1662a In chickens and turkeys for treatment of CRD caused by M. gallisepticum and E. coli.	Subcutaneous injection at all life stages.

Table 3 continued.

NF-180 Claim	Dosage	Alternate Drugs*	Claim	Dosage
"	"	Spectinomycin	§522.2120 In turkey poults as an aid in control of CRD associated with E. coli. In baby chicks, to control mortality and lessen severity of infections caused by M. synoviae, S. typhimurium, S. infantis, and E. coli.	Subcutaneous injection, 5 mg per poult, 2.5-5 mg per chick.
"	"	Sulfadimethoxine plus ormetoprim	§558.575 In chickens as an aid in prevention of bacterial infections due to E. coli.	113.5 grams sulfadimethoxine plus 68.1 grams ormetoprim per ton of feed, continuously.
"	"	Tylosin	§558.625 In broiler and replacement chickens to aid in the control of CRD caused by Mycoplasma gallisepticum.	800-1000 grams drug per ton of feed, periodic administration
In chickens and turkeys, for control of infectious sinusitis, synovitis, non-specific	100 to 200 grams per ton of feed	Bacitracin,# M.D.	§558.76 In chickens and turkeys, prevention and treatment of infectious	50-200 grams of drug per ton of feed

Table 3 continued.

NF-180 Claim	Dosage	Alternate Drugs*	Claim	Dosage
enteritis (blue-comb, mud fever) and quail disease (ulcerative enteritis).			sinusitis, non-specific enteritis.	
"	"	Bacitracin# zinc	§558.78 In chickens and turkeys, same as §558.76.	50-500 grams drug per ton of feed
"	"	Chlortetra-** cycline	§558.128 In chickens and turkeys as an aid in the control of synovitis In turkeys, control of blue-comb.	100-200 grams per ton of feed 500 grams drug per ton of feed
"	"	Oxytetra-** cycline	§558.450 In chickens and turkeys as an aid in the control of synovitis. In turkeys. control of blue-comb.	100-200 grams of drug per ton of feed 500 grams per ton of feed
§558.15(g)(1) In chickens for prevention of infectious hepatitis.	100 grams drug per ton of feed	In chickens: Oxytetracy-cline.**#	§558.450 In chickens, except layers, for prevention of infectious hepatitis.	200 grams drug per ton of low calcium feed.

Table 3 continued.

NF-180 Claim	Dosage	Alternate Drugs*	Claim	Dosage
§558.15(g)(1) In chickens and turkeys for prevention and treatment of blackhead (histomoniasis).	100-200 grams drug per ton of feed	In chickens and turkeys: Nitarsone In turkeys only:	"not new" drug. Prevention of blackhead.	0.01875% in feed
		Carbarsone	§558.115 as an aid in the prevention of blackhead.	227-340.5 grams drug per ton of feed, fed continuously.
"	"	Dimetridazole	§558.240 for prevention and control of blackhead.	Prevention: 136-182 grams drug per ton of feed. Control: 544 to 725 grams drug per ton of feed for 7 days.
"	"	Ipronidazole	§558.305 for prevention and treatment of blackhead.	Prevention: 56.75 grams drug per ton of feed. Treatment: 227 grams drug per ton of feed.
"	"	Chlortetracycline	§558.128, prevention of hexamitiasis.	50-100 grams per ton of feed
"	"	Oxytetracycline	§558.450, prevention and/or control of hexamitiasis.	50-200 grams per ton of feed

Table 3 continued.

NF-180 Claim	Dosage	Alternate Drug*	Claim	Dosage
		Butynorate	"not new" drug. In turkeys, as an aid in the prevention of hexamitiasis	0.0375% in feed
§550.15(g)(1) In chickens and turkeys, treatment of paracolon (Arizona serotypes).	200 grams drug per ton of feed	Gentamicin	§522.1044 In turkeys as an aid in prevention of early mortality due to Arizona paracolon infections.	subcutaneous injection of 1 mg gentamicin per poult
"	"	Spectinomycin	§522.2120 In turkeys as an aid in the prevention of mortality associated with Arizona group infection.	subcutaneous injection of 1-2 mg per poult
§558.262 In sows, for prevention of bacterial scours in baby pigs; in swine, for prevention and treatment of bacterial enteritis.	150 grams drug per ton of feed	Bacitracin	§548.110 aid in prevention of bacterial swine enteritis (scours).	water soluble powder, 100-200 mg per gallon of drinking water.
"	"	Chlortetracycline**	§546.110c Control and treatment of bacterial enteritis caused by E. coli.	drinking water, 1 gram per gallon to provide 10 mg per pound body weight daily

Table 3 continued.

NF-180 Claim	Dosage	Alternate Drug*	Claim	Dosage
"	"	Chlortetracycline bisulfate/ sulfamethazine bisulfate**	§546.113b Prevention and treatment of bacterial enteritis.	drinking water, 250 mg of each drug per gallon
"	"	Spectinomycin	§520.2122 Treatment and control of infectious bacterial enteritis (white scours) associated with E. coli in pigs under 4 weeks old.	oral solution, 50 mg per 10 pounds body weight administered twice daily for 3-5 days
"	"	Sulfachlorpyridazine	§520.2200b Treatment of diarrhea caused or complicated by E. coli.	oral solution or drinking water, 20-35 mg per pound of body weight
"	"	Sulfaethoxypyridazine	§520.2240a Treatment of bacterial scours, pneumonia, enteritis, bronchitis, septicemia accompanying Salmonella infection choleraesuis.	drinking water, 1.9 to 3.8 grams per gallon for 3-9 days
"	"	Tetracycline**	§546.180d Prevention and treatment of bacterial enteritis.	drinking water, 100-200 mg per gallon for prevention; 200-400 mg per gallon for treatment.

Table 3 continued.

NF-180	Dosage	Alternate Drugs*	Claim	Dosage
§558.262 Prevention and treatment of vibrionic (bloody) dysentery in swine.	100-300 grams drug per ton of feed	Carbadox	§558.115 Control of swine dysentery (vibrionic dysentery, bloody scours, or hemorrhagic dysentery); control of bacterial swine enteritis (salmonellosis caused by S. choleraesuis).	50 grams drug per ton of feed to swine weighing less than 75 pounds
"	"	Lincomycin	§558.325 Control and treatment of swine dysentery.	40 and 100 grams per ton of feed respectively.
"	"	Tylosin	§558.625 Prevention, treatment, and control of swine dysentary (vibrionic).	40-100 grams per ton of feed following treatment with tylosin in drinking water 0.25 grams per gallon for 3-10 days.
"	"	Virginiamycin	§558.635 Prevention, treatment and control of swine dysentery in swine up to 120 pounds and in non-breeding swine over 120 pounds.	25-100 grams of drug per ton of feed
§558.262 Growth promotion in swine while on medication	100-300 grams per ton of feed	Bacitracin M.D.	§558.76 Growth promotion and efficiency.	10-50 grams per ton of feed

Table 3 continued.

NF-180 Claim	Dosage	Alternate Drugs*	Claim	Dosage
"	"	Bacitracin zinc	§558.78 Growth promotion and feed efficiency.	10-50 grams per ton of feed
"	"	Bambermycins	§558.95 Increased rate of weight gain and improved feed efficiency.	2 grams per ton of growing-finishing swine feed
"	"	Oleandomycin	§558.435 Increased rate of weight gain and improved feed efficacy for confined and pasture raised swine.	5-11.25 grams per ton of feed
"	"	Tylosin	§558.625 For increased rate of weight gain and improved feed efficiency.	10-100 grams per ton of feed
"	"	Virginiamycin	§558.635 For increased rate of weight gain and improved feed efficiency.	5-10 grams per ton of feed

* Listings of alternate drugs are not necessarily complete.

** This claim not affected by the Bureau of Veterinary Medicine's proposal to restrict tetracyclines (42 FR 56255, 10/21/77).

\+ Buquinolate is approved in animal feed for this use but not presently marketed.

\# This claim is subject to revision resulting from NAS/NRC efficacy review.

Table 4. Response of pigs to antibiotics.

Antibiotic	Average daily gain (% improvement)			Feed/Gain (% improvement)		
	Grower Starter	Growing-Developer	Finishing	Starter	Grower-Developer	Growing Finishing
Tetracycline	10.84	10.93	6.58	6.25	3.88	2.55
Penicillin	9.45	--	--	8.68	--	--
Penicillin-streptomycin	14.85	--	3.87	7.42	--	--
Tetracycline-penicillin-sulfamethazine	22.50	17.46	--	8.48	--	6.39
Bacitracin	9.72	5.10	2.50	3.26	2.50	2.67
Tylosin	14.81	10.94	4.64	6.03	4.20	1.47
Virginiamycin	11.00	10.69	5.73	5.02	6.60	3.25
Bambermycin	0.00	2.45	1.89	-0.99	1.17	1.17
Tylosin-sulfa	17.65	5.12	--	6.76	2.15	--
Mecadox (carbadox)	18.56	15.13	--	8.64	6.91	--
Lincomycin	11.11	--	--	7.57	--	--
Nitrofuran	8.00	--	1.42	2.33	--	0.58

Source: Office of Technology Assessment, 1979. Drugs in Livestock Feed, Vol. 1. Congress of the U.S., Washington, D.C. 20510.

Table 5. Response of chickens to antibiotics.

	Weight gain (% improvement)		Feed/Gain (% improvement)	
Antibiotic	4 weeks	8 weeks	4 weeks	8 weeks
Tetracycline	7.33	3.69	5.09	2.31
Penicillin	8.11	2.93	4.46	2.76
Bacitracin	6.30	0.95	3.24	2.20
Arsenicals	4.94	3.44	7.01	3.15
Bambermycin	3.77	2.35	1.80	1.94
Lincomycin	9.25	4.48	8.28	3.30
Nitrofuran	-3.28	1.98	-2.61	1.47
Oleandomycin	5.01	4.48	2.25	1.78
Streptomycin	7.26	—	1.89	—
Virginiamycin	15.98	--	9.06	--
Erythromycin	7.20	—	5.05	—
Tylosin	2.82	--	1.00	--

Source: Office of Technology Assessment, 1979. Drugs in Livestock Feed, Vol. 1. Congress of the U.S., Washington, D.C. 20510.

Table 6. Response of turkeys to antibiotics.

	Weight gain (% improvement)			Feed/Gain (% improvement)		
Antibiotic	4 weeks	8 weeks	To market weight	4 weeks	8 weeks	To market weight
Tetra-cycline	14.89	13.21	—	8.37	5.88	—
Penicillin	15.31	10.24	5.73	7.87	5.62	2.64
Bacitracin	9.82	4.97	7.23	4.71	2.73	1.59
Strepto-mycin	8.14	4.53	—	4.69	1.92	—

Source: Office of Technology Assessment, 1979. Drugs in Livestock Feed. Vol. 1. Congress of the U.S., Washington, D.C. 20510.

Table 7. Estimated percentage of various classes of poultry receiving drugs in feed at subtherapeutic levels.

Class of poultry and age	Penicillin	Tetracyclines	Nitrofurans
		Percent	
Breeder chickens, 5 months and older	10	40	20
Broiler chickens, 0-8 weeks	20	40	30
Egg-type replacement chickens, 0-5 months	20	30	20
Table egg laying hens, 5 months and older	10	20	1/
Turkey breeders, 24 weeks and older	15	15	15
Turkey poults, 0-8 weeks	30	30	90
Growing turkeys, 8 weeks to market	10	20	20

1/ Illegal to use nitrofurans in feed of table egg laying hens.

Source: USDA Economics, Statistics, and Cooperative Service. 1978. Economic Effects of a Prohibition on the Use of Selected Animal Drugs.

Table 8. Topical and ophthalmic uses of NF-180 and NF-7 in food-producing animals and examples of alternate drugs.

NADA#	Product Name	Drug	Conditions of Use
Nitrofurans			
6-475	Furacin dressing veterinary	NF-7	Treatment of surface bacterial infection, wounds, ulcers, cowpox, etc.
6-475	Furacin dressing veterinary with anesthetic	NF-7	Same
6-475	Furacin soluble powder veterinary/ Amifur soluble powder veterinary	NF-7	Prevention and treatment of surface bacterial infections of the eyes including pinkeye, and for wounds, burns, skin ulcers and abscesses
6-475	Furacin solution veterinary/Amifur solution	NF-7	Treatment of surface bacterial infections
	Furacin-penicillin gel	NF-7	Treatment and prevention of bacterial infections in wounds
	Furox aerosol powder	NF-180	Treatment of cattle for bacterial infections of the eye and pinkeye
Alternate Drugs			
	aerosol spray	oxytetracycline HCl and 524.1662a hydrocortisone	Prevention of bacterial infections in superficial wounds, cuts, abrasions, treatment of allergic dermatoses and infections associated with minor burns and wounds

Table 8 continued.

NADA#	Product Name	Drug	Conditions of Use
8-763	ophthalmic ointment	oxytetracycline HCl and polymyxin B sulfate 21 CFR 524.1662b	Prevention and treatment of ocular infections including pinkeye, keratitis, conjunctivitis, etc., and those due to bacterial inflammatory conditions secondary to other infectious diseases
8-763	Terramycin ophthalmic ointment	oxytetracycline	Treatment of eye conditions including conjunctivitis, corneal ulcer, and otitis
9-035	Ophthalmic solution	proparacaine HCl	Treatment of corneal ulcer and otitis
12-202	Decton (blue)	Dequalium chloride, methylene blue, and urea	Treatment of wounds and ophthalmically for keratoconjunctivitis
12-797	Pink Eye Powder	Neomycin sulfate, ambamide, benzocaine, and boric acid	Treatment of wounds and eye conditions, including keratitis
31-792	Tylan plus neomycin eye powder	Tylosin, neomycin and piperocaine HCl	Treatment of eye conditions including keratoconjunctivitis
34-872	Neo Predef Eye-Ear ointment	Neomycin sulfate and fluprednisolone	Treatment of wounds, ear and eye conditions

possible, the data available show that there are sufficient alternate antibacterial agents available for topical and ophthalmic uses of nitrofurans in food-producing animals.* Therefore, we conclude that these nitrofuran uses are not essential.

2.4.2. Sales of Nitrofuran Drugs

Do sales data for the nitrofuran drugs support the USDA estimated use data in Table 7? In order to address this question rigorously, one would need to know the quantities of nitrofuran drugs sold, the number of animals that could be medicated with those quantities, and the total number of animals that potentially could be medicated with either nitrofurans or alternate drugs. It would also be of interest to determine the numbers of animals not receiving any drug for conditions or indications covered by nitrofuran claims.

Unfortunately, sales figures for the various drugs are extremely limited particularly with respect to the species and indications for which the drug products are sold. Further, sales figures are in dollars rather than quantities of medication sold. Table 9 summarizes the data available from a 1977 survey of the feed additive and animal pharmaceutical market (IMS America, 1977, data were reviewed by IMS prior to their inclusion in this EA). Sales data for

*Norwich-Eaton Pharmaceuticals, one firm which markets nitrofurazone topical preparations, has voluntarily complied with a request by FDA that the labeling on these preparations be revised to limit claims to nonfood-producing animals.

Table . Summary of projected 1977 nitrofuran sales a[illegible]parison with total antibacterial and tetr. clines market for animals.

Sales category	Projected total sales, all drugs for this category (000 dollars)	Projected Nitrofuran sales (000 dollars) 1/	Nitrofuran % of total sales for all drugs for this category [(col. 3 col. 2) (100)]	Projected Tetracyclines sales (000 dollars)	Tetracyclines % of total sales for all drugs for this category [(col. 5 col. 2) (100)]
Column 1	2	3	4	5	6
Pharmaceutical (non-feed additive) antibacterials for animals 2/	119,679 3/	4,043	3.4	11,602	10.0
. . . mastitis preparations	10,469	191	1.8		
. . . topicals, ointments, nasal and ear solutions, aerosols		1668			
. . . liquids and soluble powders		1240			
. . . tablets, capsules, boluses		739			
Feed additive antibacterials 4/	189,260.8 5/	4932.8	2.6	133,084.2 6/	70.3
		NF-180 4884.5	2.6		
		NF-7 20.9	0.01		
		NF-64 27.3	0.01		

Extracted from: IMS America. 1977. U.S. Pharmaceutical Market, Animal and Poultry, Fourth Quarter and Feed Additive Market, Third Quarter. IMS America Ltd., Ambler, Pa. 19002.

1/ All nitrofuran drugs
2/ Includes food and non-food animal use as pharmaceuticals
3/ Antibiotics, sulfonamides, nitrofurans, and combinations
4/ Primarily food animals, data from Feed Additive Market, 3rd quarter, 1977 are projected to year basis from 3-quarter average
5/ Antibiotics, sulfonamides, nitrofurans, arsenicals, other antibacterials, and combinations
6/ Primarily chlortetracycline, oxytetracycline, and combinations with other antibacterials

tetracyclines (a major alternate drug) are included for comparison. Nitrofuran (all nitrofuran drugs) sales accounted for less than 4% of the animal pharmaceutical market projected sales and less than 3% of the animal feed additive market projected sales in 1977. Note that the proposed actions affect most of the feed additive sales but only part of the animal pharmaceutical sales, since nitrofuran use in pets and nonfood animals would continue.

It appears that nitrofuran use in food-producing animals is limited, although it is not possible to tell from sales data whether use is concentrated or distributed equally among turkeys, chickens and swine. Therefore, 1977 sales data suggest but do not prove definitively that the USDA estimated nitrofuran use in Table 7 is an overestimate.

2.4.3. Avian Diseases for which Furazolidone is Potentially Important and the Availability of Management Practices to Substitute for or Prevent and Control Those Diseases

The data in 2.4.1. establish that there are adequate alternate drugs for all the swine claims and most of the poultry claims for furazolidone feed medications. Adequate alternate drugs are available for all nitrofurazone and furaltadone feed and mastitis claims. While the data for nitrofuran topicals and ophthalmics and their alternatives are less detailed, it shows that there are adequate alternate drugs for these uses, as well.

Assuming that furazolidone is potentially important for the eight conditions in chickens and turkeys listed above in 2.4.1., the following sections will examine the etiology and incidence of each of the eight diseases or complexes of diseases, the effect of the disease or complex on animal productivity, available treatment and management practices which are being used or could be used in order to help control or prevent the condition. For each of the eight conditions, these factors will be considered to determine whether furazolidone is essential to the prevention or control of the condition.

2.4.3.1. Avian Arizonosis/Paracolon Infections in Poultry

Bacteria of the genus Arizona, previously called "paracolon" bacteria, are enterobacteria (gut bacteria) closely related to Salmonella and are similar in their lack of host specificity, modes of environmental transmission, and effects on poultry. Arizona bacteria have been isolated from birds, reptiles, man, dogs, cats, swine, sheep, rats, mice, a variety of other mammals and poultry feed. The majority of isolates have been from fowls and reptiles. In humans, Arizona infections cause gastroenteritis and may cause more serious enteric fever and focal infections. Arizona bacteria are worldwide in distribution and the many possible environmental reservoirs make its eradication difficult.

Among poultry, arizonosis is more frequently encountered among turkeys. Arizona hinshawii, the etiologic agent, may cause high mortality among young poults during the first few weeks of life

accompanied by diarrhea, leg paralysis, twisted necks, and blindness. Clinical symptoms or mortality from A. hinshawii are rarely seen in infected adult turkeys. Adult flocks may become infected by contact with environmental vectors and then serve as the source of infection to young poults. A. hinshawii infection in turkeys is systemic and transmitted to eggs (transovarian infection). Contamination of the shell surface with feces containing Arizona bacteria, coupled with the shell penetrating ability of the organisms, is accepted as resulting in the frequent presence of Arizona bacteria in eggs. (J. E. Williams (1978a) contains more detailed discussion.)

The American Association of Avian Pathologists (1979) reports diagnosed outbreaks of arizonosis in 115 turkey flocks and 2 chicken flocks in 1977. California had the largest number of turkey flock outbreaks, 32. Thus, while the disease may be serious when it occurs, it was probably not the cause of widespread problems and decreased productivity in 1977, especially with respect to chickens.

In turkey poults, subcutaneous injections of gentamicin or spectinomycin have been shown to be effective in reducing mortality and losses from arizonosis. These drugs, like furazolidone treatment, control losses due to arizona outbreaks in poultry flocks, but do not eliminate the disease.

Control and prevention management procedures for avian arizonosis are

similar to those used for paratyphoid (caused by the related Salmonella typhimurium, 2.4.3.2.3.). Obtaining arizona-free stock and maintaining arizona-free conditions through sanitation are the major preventative measures. Obtaining hatching eggs from arizona-free brood stock, minimization of fecal contamination of those eggs, egg-dipping (gentamicin is FDA-approved (21 CFR 529.1044b)) and fumigation immediately after collection, hatchery sanitation, isolation of poults and their facilities from other birds, frequent disinfection of water and feed containers all have been outlined as procedures useful in controlling and preventing arizona and salmonella infections. (See J. E. Williams (1978a) and AAAP (1971) for more details.)

In summary, furazolidone is the only agent available for use in poultry feed for the prevention and control of arizona infections; however, three factors would indicate that it is not essential to turkey and chicken rearing. First, arizonosis is a disease of young turkeys; adult turkeys may be carriers but usually show no signs of infection. Gentamicin and spectinomycin are injectable drugs which are shown effective and approved by FDA for reducing mortality losses in young poults due to the arizonosis. Second, sanitation and other management procedures are the only known measures for eliminating arizonosis. Such measures prevent other diseases, particularly those associated with salmonella. Third, the reported incidence of outbreaks of arizonosis is relatively low in turkeys and rare in chickens.

2.4.3.2. Avian Salmonelloses - Pullorum, Fowl Typhoid and Paratyphoid Diseases in Poultry

Enterobacteria of the genus Salmonella number over 1700 in known serological types. These bacteria are ubiquitous in the environment and the majority of Salmonella serotypes may infect and cause disease in a variety of animal hosts. Salmonella typhimurium and occasionally other motile serotypes cause paratyphoid disease in poultry and are examples of serotypes which may infect man and other animal hosts. Salmonella pullorum and S. gallinarum, the etiologic agents causing pullorum and fowl typhoid, respectively, are non-motile and host-specific to poultry. Domestic poultry constitute the largest single reservoir of salmonellae (J. E. Williams, 1978b).

Based on the statements of the furazolidone NADA holders and the advertised claims for the drug (Table 3), furazolidone would appear to be important in the prevention and treatment of Salmonella-related diseases. The following sections will examine these diseases of poultry and attempt to assess the importance of furazolidone in controlling and preventing the spread of these organisms.

2.4.3.2.1. Pullorum Disease

Pullorum disease is caused by infections of chickens and turkeys with Salmonella pullorum. This serotype is host specific, normally attacking chickens and, to a lesser extent, turkeys. It is rarely reported in other birds, mammals, or man. Pullorum is worldwide in distribution, but control efforts have eliminated nearly all cases in some areas.

In domestic poultry, pullorum is transmitted transovarially (through the eggs). Infections tend to be acute in young birds, with mortalities usually confined to the first 2-3 weeks of age. Survivors are retarded in growth, usually include a high percentage of carriers, and are, for that reason, usually destroyed. Mortality is variable, depending on the age and strain of the birds, management practices, and characteristics of exposure, ranging from no losses to 100%. Greatest losses occur the second week after hatching. In adult birds, pullorum causes few if any symptoms which allow infected birds to be identified by their appearance. Pullorum may result in reduced fertility and hatchability of eggs. (See Snoeyenbos (1978) for more detailed discussion of the disease.)

As the result of an intensive national control program aimed at pullorum and fowl typhoid, the National Poultry Improvement Plan (USDA, 1980), pullorum incidence has declined precipitously. The national program includes the annual testing of all flocks, establishes official pullorum/typhoid-free flocks and hatcheries, and prescribes farm and hatchery procedures designed to prevent the re-introduction of the diseases. The American Association of Avian Pathologists (1979) reported 50 pullorum outbreaks in chickens in the United States and no outbreaks in turkeys for 1977. Kansas and Alabama had the highest number of outbreaks in chickens, with 13 and 12, respectively.

Snoeyenbos (1978) summarizes the results of the U.S. pullorum testing program for chickens and turkeys in tables 10 and 11, respectively.

For the testing year, 1977-1978, the National Poultry Improvement Plan reported twenty-one states that qualified as "U.S. Pullorum-Typhoid Clean States" (USDA, 1979). Of the 1203 breeder flocks of egg-type chickens (4.6 million birds) tested by NPIP in 1977-78, only one flock was found to be positive for pullorum. For the second consecutive year, no meat-type chicken breeding flocks were found to be pullorum positive (25.5 million birds). 1977-78 was the eighth consecutive year where no pullorum-typhoid infected turkey breeding flocks were found (2.5 million birds tested) (USDA, 1979). These data indicate that pullorum is now a rare disease in chickens and in turkeys.

Table 10. Pullorum disease testing summary of U.S. chickens during 40-year period.

Item	1935-36	1949-50	1962-63	1974-75
Number of flocks	9,191	111,422	21,272	4,139
Number of birds	4,329,364	37,237,674	35,236,200	24,904,143
Percentage of positive tests	3.66	0.72	0.005	0.000006
Birds in pullorum-clean flocks	257,577	13,302,642	33,517,824	24,902,812

Source: Snoeyenbos (1978).

Table 11. Pullorum disease testing summary of U.S. turkeys during 32-year period.

Item	1943-44	1949-50	1962-63	1974-75
Number of flocks	2,489	4,717	2,297	817
Number of birds	982,904	2,340,574	3,879,861	2,882,958
Percentage of positive tests	2.00	0.39	0.003	0.0
Birds in pullorum-clean flocks	...	...	...	2,882,958

Source: Snoeyenbos (1978).

For treatment of pullorum, furazolidone is the only drug for use in feed approved by FDA. However, a water medication of sulfamethazine is presently approved for this use. Despite the fact that drugs are available for control of pullorum, the combination of blood testing and slaughter of positive reactors (infected birds) is the only solution for controlling this disease. If chicken or turkey commercial flocks are infected, eradication is indicated. No approved drug, including furazolidone, eliminates the carrier problems (recovered birds continue to carry and excrete the pathogen).

Since the disease manifests clinical signs in only young poultry, one has less investment to salvage if he elects to test and slaughter with no drug therapy. In short, measures which eliminate pullorum-infected flocks and prevent introduction of pullorum into healthy flocks are the only long-term effective measures presently available to the poultry industry.

Based on the present rare incidence of pullorum in U.S. poultry and the effectiveness of the national control program using preventative serologic, management and eradication measures in producing this decline in pullorum incidence, it is doubtful that a prohibition of furazolidone would have any effects on the control of this disease in poultry.

2.4.3.2.2. Fowl Typhoid Disease

Fowl typhoid disease is caused by infections of chickens and turkeys with Salmonella gallinarum. The bacterium is nonmotile, closely related to S. pullorum, and is relatively host specific, attacking chickens and turkeys and rarely, other domestic birds. Man and mammals are rarely found to be infected. S. gallinarum has worldwide distribution, but national eradication programs for fowl typhoid and pullorum are resulting in fowl typhoid-free areas.

In poultry, symptoms of fowl typhoid are similar to pullorum; however, acute infections and mortality occur more frequently in maturing birds. Like pullorum, fowl typhoid is transmitted transovarially. Chicks hatched from S. gallinarum-infected eggs experience high mortality. Carriers, birds that have recovered from the disease but still excrete S. gallinarum, are the main reservoir of the disease. (Refer to Pomeroy (1978) for a detailed discussion.)

Incidence of fowl typhoid in the U.S. has decreased dramatically, due largely to the National Poultry Improvement Plan which requires testing to identify and eliminate fowl typhoid and pullorum (USDA,

1980, 1979). (S. gallinarum and S. pullorum are so closely related that the antigen used in the serological testing for pullorum also agglutinates with S. gallinarum. Under the National Plan, all positive reactors, either fowl typhoid or pullorum, are slaughtered.) Table 12 contains representative, available data on past and current fowl typhoid incidence in the United States. In 1977-78, twenty-one states were classified as pullorum-typhoid clean (USDA, 1979).

Table 12. Fowl typhoid incidence in the United States.

Year	# Reports in chickens	# Reports in turkeys	Reference
1966-67	23	3	Pomeroy (1978)
1974	19	2	AAAP (1975)
1975	5	-	Pomeroy (1978)
1977	0	0	AAAP (1979)
1981	0	0	AAAP (1983)

Treatment of fowl typhoid is sometimes practiced when salvaging an infected flock. Sulfaquinoxaline for addition to feed or water is presently approved for this purpose. Treatment with either sulfaquinoxaline or furazolidone does not eliminate carriers; salvaged birds are slaughtered for food purposes.

As with pullorum, management procedures and eradication programs which identify, eliminate and prevent the spread of fowl typhoid are the most effective measures in controlling this disease. Pomeroy (1978) lists management and eradication program measures for fowl typhoid and other salmonella infections:

Management Procedures

1. Chicks and poults should be obtained from sources free of pullorum and typhoid.

2. Chicks and poults should be placed in an environment that can be cleaned and sanitized to eliminate any residual salmonella organisms from previous flocks.

3. Introduction of salmonellae from outside sources must be minimized.

   a. Although S. gallinarum does not commonly contaminate animal, poultry, and marine by-products, other salmonellae are commonly encountered. Poultry feeds free of salmonellae are highly desirable.

   b. Free-flying birds are commonly found carriers of salmonellae, but S. gallinarum is rarely encountered. Poultry houses should be bird proof.

   c. Rats, mice, rabbits, and other pests may be carriers of salmonellae but are rarely found infected with S. gallinarum. Nevertheless, poultry houses should be rodent proof.

d. Insect control is important, particularly against flies, poultry mites, and lesser mealworms. These pests may provide a means of survival of salmonellae and other avian pathogens in the environment.

e. Other animals such as dogs and cats may be carriers of salmonellae but rarely S. gallinarum. These animals should be kept from the poultry house.

f. Potable water must be used as a source of drinking water, or chlorinated water should be provided.

g. Man may be a mechanical carrier of the organism on his footwear and clothing as well as poultry equipment, processing trucks, and poultry crates. Every precaution should be made to prevent introduction of S. gallinarum by fomites.

h. Proper dead bird disposal is essential. S. gallinarum will survive in poultry carcasses for weeks, depending on the ambient temperatures.

Essentials of an Eradication Program for an Area

1. Pullorum disease and fowl typhoid must be mandatory reportable diseases.

2. Flocks where outbreaks occur are placed under quarantine and infected flocks are marketed under supervision.

3. All reports of pullorum disease and fowl typhoid are investigated by an authorized state or federal official.

4. Importation regulations shall require shipments of poultry and hatching eggs to be from sources considered free of pullorum disease and fowl typhoid.

5. Regulations shall require poultry going to public exhibition to be from flocks free from pullorum disease and fowl typhoid.

6. Total participation of poultry breeding flocks and hatcheries shall be required in a pullorum-typhoid control program such as National Plans programs or their equivalent.

Rare incidence of fowl typhoid, effective management and eradication programs that control the spread of the disease, and the availability of sulfaquinoxaline water and feed medications to salvage diseased adult birds lead to the conclusion that the prohibition of furazolidone for treatment and prevention of fowl typhoid would not have significant impact on the poultry industry.

2.4.3.2.3. Paratyphoid Disease

Paratyphoid disease in chickens and turkeys is caused by invasive Salmonella typhimurium and any of a number of other motile Salmonella serotypes. As opposed to S. gallinarum and S. pullorum, the nonmotile serotypes which cause fowl typhoid and pullorum, respectively, serotypes causing paratyphoid lack host specificity. For example, S. typhimurium can be isolated from birds, mammals, insects, and reptiles. In humans, S. typhimurium may cause gastroenteritis or, occasionally, invasive septicemic infections of a more serious nature. Serotypes which cause paratyphoid in poultry are worldwide in distribution, but certain serotypes may be more characteristic of one region than another. The large variety of environmental hosts for these bacteria makes it difficult to control paratyphoid in poultry flocks. Wild birds, insects, farm workers, reptiles, pets, and animal feed may all introduce paratyphoid bacteria into a disease-free flock.

Paratyphoid may cause high mortality among young chicks and poults, depending on the serotype responsible for the disease outbreak. Turkeys appear to be more susceptible to paratyphoid than chickens and other poultry. Older birds may be chronically infected, shedding salmonellae in excreta and laying Salmonella-contaminated eggs without showing clinical symptoms. Thus, the adult birds serve as the primary source of salmonellae for chicks and poults. Poultry meat and eggs are a source of salmonellae to humans and this transmission is a public health concern (Newell & Williams, 1971; Edel et al., 1973; Morehouse, 1972; Dougherty, 1974). (See J. E. Williams (1978b) for detailed discussion of paratyphoid in poultry.)

Incidence of paratyphoid in the U.S. is higher than pullorum and fowl typhoid. Table 13 contains representative, available data on paratyphoid incidence. Compare with tables 10, 11, and 12.

Table 13. Incidence of paratyphoid disease in U.S. chickens and turkeys.

Year	No. reported outbreaks in chickens (flocks)	No. reported outbreaks in turkeys (flocks)	reference
1974	422	534	AAAP(1975)
1977	512	611	AAAP(1979)
1981	576	541	AAAP(1983)

Drugs used for paratyphoid serve primarily to prevent or control mortality of chicks and poults early after hatching, when the disease is the most severe. As shown in table 3, subcutaneous injections of gentamicin and spectinomycin are approved for day-old chicks. (The same drugs are approved for turkey poults for the purpose of preventing closely-related arizonosis (2.4.3.1.).) Chlortetracycline at 400 grams per ton feed is approved for turkey poults not over 4 weeks old. A gentamicin egg dip is approved for turkey hatching eggs as effective against one paratyphoid serotype. None of these drugs, including furazolidone, eliminates paratyphoid carriers from poultry flocks. (Hess & Clark ARH 75:14, 1975; Norwich Interim Report 3, Proj. No. 475-24-36, 1975; Knivett & Tucker, 1972; Smith & Tucker, 1975).

Much has been written on management procedures to prevent the introduction of salmonellae into poultry flocks and control outbreaks. This literature has been reviewed in Williams (1978b) in detail. Paratyphoid preventative measures include egg sanitation and fumigation, hatchery sanitation, isolation of young birds from other flocks, breeding flock sanitation, prevention of salmonellae in animal feed, and controlling access to the flocks by feral birds, vermin, pets, insects, and farm workers (Williams, 1978b; Edel et al., 1973). In general, the measures required to prevent paratyphoid also prevent arizonosis, pullorum, and fowl typhoid. It should be noted that, although available, serologic testing for identifying paratyphoid carriers is more complicated due to the many Salmonella serotypes involved. Consequently, this procedure has not yet received the widespread acceptance observed for pullorum/fowl typhoid serologic testing programs.

From the standpoint of spread of salmonellae to humans, contamination of poultry and eggs with salmonellae during slaughter, packing, storage, and distribution is a concern additional to the measures above which protect poultry flocks. Dougherty (1974) found that, while the numbers of chickens harboring salmonellae are low when they enter a processing plant, a high percentage of carcasses become contaminated by the time defeathering has occurred, but prior to evisceration. Processing equipment spreads the bacteria to salmonella-free carcasses. Not surprisingly, it was found that the level of carcass contamination with salmonellae tends to remain high

through the remainder of processing. Such indications are in agreement with other studies on sources of contamination in poultry processing plants (Kauffman and Freely, 1968; Kumar et al., 1971; Morris and Wells, 1970; Surkiewicz et al., 1969; National Academy of Sciences, 1969; Wilder and MacCready, 1966). Therefore, the initial phase of processing is implicated in the spread of salmonellae in the poultry processing plant. It is possible that measures to reduce bacterial contamination of carcasses might be effective at this phase. Since the offal, feathers, blood and other by-products of poultry processing are frequently used as protein supplements in feed for poultry and other animals, salmonella contamination of animal feeds may occur.

Given that a certain level of salmonella contamination will occur in poultry and other meat products, additional attention to good hygiene would probably reduce the incidence of food-related human salmonelloses. Such hygiene measures include adequate refrigeration, eliminating contact between raw meat and other food products, thorough cooking, and disinfection of utensils such as chopping blocks used in preparing meat (Edel et al., 1973). Heat processing and pelleting have been examined as means of eliminating salmonellae from animal feeds (Edel et al., 1973).

From the above, we conclude: (1) that data show that the carrying, shedding, and spread of salmonellae are not eliminated in furazolidone-treated animals; (2) that it is doubtful that removal

of furazolidone from animal use will have a significant effect on the level of salmonella contamination of swine and poultry feeds or food for humans derived from these animals; (3) that the transport, storage and processing of poultry are significant factors in the spread of salmonellae to other animals and to uninfected carcasses; (4) that there are farm, hatchery and processing plant management procedures that are available that can have a significant effect on the incidence of salmonella infections in animals and the level of contamination of human foods; and (5) that there are drugs, besides furazolidone, available for preventing salmonella infections in young poultry, the critical life stage where most mortality and morbidity occurs. Note that for chickens these alternate drugs require a management shift to subcutaneous injections administered at day 1, before the chicks leave the hatchery. A drug administered in feed is available for young turkeys. Furazolidone is the only drug available for the treatment of outbreaks in older, more disease-resistant poultry but it does not eliminate carriers from flocks.

2.4.3.3. Chronic Respiratory Disease

Chronic respiratory disease in poultry (also called air sac disease, airsacculitis, C.R.D., complicated C.R.D., colibacillosis, and lower air sac form of infectious sinusitis) is caused by a complex of etiologic agents. Usually, there is a primary infection due to Mycoplasma gallisepticum and/or respiratory viruses such as infectious bronchitis virus and Newcastle disease virus. This primary infection

increases the susceptibility of poultry to secondary infection by pathogenic strains of Escherichia coli (E. coli). Healthy poultry are relatively resistant to inhaled E. coli. In chickens and turkeys, complicated C.R.D. causes reduced growth rates, poor utilization of feed, mortality, and condemnations of carcasses at the processing plant. It is a principal cause of condemnations in broiler chickens, causing fibrinous pericarditis, fibrinous hepatitis, and fibrinous peritonitis which result in an unacceptable product for human consumption (Table 14). (See Gross (1978) for more details.)

Despite the decreasing incidence of M. gallisepticum in broiler breeder chickens and turkeys due to U.S. eradication programs (USDA, 1979) and lowered incidence of respiratory virus infections due to judicious use of vaccines, air sac disease associated with E. coli remains a problem (Table 15). E. coli are ubiquitous in the environment and have many mammal, bird, reptile, and insect hosts.

Table 15. Incidence in the U.S. of chronic respiratory disease complicated with E. coli.

Year	# reported outbreaks in chickens (flocks)	# reported outbreaks in turkeys (flocks)
1974		
airsacculitis	1,060	540
colibacillosis	1,209	785
1977		
airsacculitis	4,390*	730
colibacillosis	2,050	1,766
1981		
airsacculitis	1,213	738
colibacillosis	3,229	1,889

Source: AAAP (1975, 1979, 1983)

*3000 reports in Hawaii

Table 14. Inspection and condemnation of U.S. poultry for airsacculitis in August 1979 and September 1983 (extracted from Crop Reporting Board, 1979 and 1983).

Poultry category	Year	Total inspected (no.)	Total condemned (no.)	Post-mortem condemnations for airsac-culitis (no.)	Total % of inspected condemned, all causes (cols. $\frac{2}{1}$ x 100)	Total % of inspected condemned for airsacculitis (cols. $\frac{3}{1}$ x 100)	% of condem-nations for air-sacculitis (cols. $\frac{3}{2}$ x 100)
		1	2	3	4	5	6
Young chickens	1979	366,235,000	4,297,654	994,864	1.17	0.27	23.15
	1983	341,877,000	2,282,685	494,760	0.67	0.14	21.67
Mature chickens	1979	17,973,000	533,888	2,448	2.97	0.01	0.46
	1983	13,817,000	398,109	1,468	2.88	0.01	0.37
Fryer-roaster turkeys	1979	1,053,000	15,611	1,312	1.48	0.12	8.40
	1983	483,000	2,921	136	0.60	0.03	4.66
Young (mature) turkeys	1979	17,085,000	231,070	38,197	1.35	0.22	16.53
	1983	16,606,000	200,075	47,997	1.20	0.29	23.99
Old turkeys	1979	114,000	4,110	513	3.61	0.45	12.48
	1983	76,000	1,059	218	1.39	0.29	20.58

Subcutaneous injectable antibiotics, drinking water solutions and feed additive antibiotics are available for the prevention, control and treatment of C.R.D. associated with E. coli infections in all chicken life-stages (table 3). Feed additive drugs for chickens that would serve as alternates to furazolidone-medicated feed include chlortetracycline, oxytetracycline, and sulfadimethoxine plus ormetoprim. For turkeys, antibiotics by subcutaneous injections appear to be the only alternates available for complicated C.R.D. Erythromycin in feed continues to be available for the prevention and treatment of C.R.D. (E. coli or other organisms not specified, Table 3).

In broiler chickens and turkeys, several factors suggest that prohibition of furazolidone for the treatment of C.R.D. complicated by E. coli will hamper the ability of poultry managers to control late outbreaks of the disease:

1. Complicated C.R.D. may occur at any period before marketing but several of the alternate drugs (the injectables) are most feasible for protecting poultry in the first few weeks of life.

2. Complicated C.R.D. presently accounts for a large percentage of condemnations of poultry at slaughter (Table 14), i.e., complicated C.R.D. is presently an economically important disease complex.

3. E. coli may develop resistance or tolerance to alternate drugs, which may make treatment of some cases of complicated C.R.D. more difficult (Craig, 1967; Hebert and Chang, 1969).

This suggests the need for more careful attention to C.R.D. prevention measures and judicious but sparing use of alternate drugs to prevent drug resistance or tolerance problems.

Management procedures cited by Gross (1978) for the prevention and control of C.R.D. include:

1. Obtaining and rearing birds free of Mycoplasma gallisepticum and reducing exposure to or vaccinating for virus respiratory diseases. [These diseases lower resistance to E. coli infection.]

2. Controlling fecal contamination of hatching eggs with E. coli by discarding cracked or contaminated eggs, and by prompt fumigation or disinfection of eggs, 1 1/2 to 2 hours after laying.

3. Assuring good hatchery sanitation, especially through reducing the number of eggs cracked during incubation, providing good ventilation to brooding chicks, having as few breeder flocks as possible represented in each incubator, and providing proper warmth and food for hatched chicks.

4. Reducing the level of E. coli-contaminated dust in air in poultry houses by increased ventilation. [It is recognized that ventilation control is best included in poultry houses in their original design and that it is frequently difficult to adjust ventilation in existing housing.]

5. Excluding vermin and wild birds from poultry houses; these carry E. coli and other pathogens. [It is recognized that total exclusion of vermin, particularly rodents and insects, is not readily achievable. However, one should attempt their control through careful housing design, farm rodent and insect population control, etc., to the extent possible.]

6. Using pelleted feeds, as these have lower levels of E. coli contamination.

7. Controlling flock-to-flock transmission by controlling access to flocks by farm workers, disinfecting and replacing litter in houses where disease occurs. [For broilers, where the life span is short, litter is commonly re-used for subsequent flocks as long as diseases do not cause excessive economic losses, due to the costs involved in replacing litter at frequent intervals. The practice of re-using litter is less attractive for egg-production flocks, where life span usually exceeds 18 months, and not

acceptable for raising breeding flocks which produce hatching eggs for new generations. See Zander (1978).]

8. Using other measures which isolate flocks from one another, particularly different age groups.

Given the above information one can conclude:

1. Complicated C.R.D. is presently a principal cause of broiler chicken and turkey condemnations at poultry processing plants.

2. There are at least three drug products for use in feed that are alternates for furazolidone available for chickens but none for turkeys. Subcutaneous injectables and drinking water solutions for complicated C.R.D. are approved for both chickens and turkeys. These latter modes of administration affect the cost of chicks and poults from the hatchery or may require adjustment of facilities to administer drugs in drinking water, with concurrent lowering of feed costs. Given even these alternate drugs, complicated C.R.D. outbreaks that occur late in the life cycle of broilers and turkeys may be difficult to treat in some cases.

3. Management measures which exclude pathogenic E. coli strains from poultry flocks are similar to those used for paratyphoid (Salmonella typhimurium and others.)

Therefore, we conclude that prohibiting furazolidone for prevention and treatment of complicated C.R.D. may decrease the ability of poultrymen to control late occurring outbreaks of complicated C.R.D. in chickens and turkeys. It is likely that stricter adherence to preventative management measures and increased use of alternate routes of administration for medications will be necessary.

2.4.3.4. Ulcerative Enteritis (Quail Disease)

Ulcerative enteritis or "quail disease" is caused by the anaerobic, spore-forming bacterium Clostridium colinum, usually following coccidiosis or stress conditions. Quail and grouse are particularly susceptible to the disease; chickens may occasionally become infected. Rapid onset of death is characteristic of this disease. In infected young quail, mortality may approach 100%. When outbreaks occur in chicken flocks, losses range from 2-10%. Apparently, Cl. colinum is worldwide in distribution; quail disease has been reported in England, Germany, India, and the United States (Peckham, 1978a). Incidence data in chickens and turkeys are not available.

Furazolidone is the only drug carrying a claim for control of ulcerative enteritis in poultry. This is probably not due to the inability of other drugs to work effectively, but probably because the disease is infrequent in domestic poultry of major economic importance. Peckham (1978a) describes effectiveness data for a number of drugs on experimental ulcerative enteritis in quail:

"Peckham and Reynolds (1962) reported on the efficacy of furazolidone, bacitracin, streptomycin, and chlortetracycline in the control of experimental ulcerative enteritis in quail. Their results confirmed those of Kirkpatrick et al. (1952b): prophylactic administration of streptomycin at a level of 2 g per gal of drinking water for 25 days gave complete protection against artificial exposure; 100 g of bacitracin per ton of feed also gave complete protection; however, 40% mortality was experienced in the groups receiving 200 g of furazolidone or chlortetracycline per ton of mash. In one drug trial, quail receiving streptomycin in the water or bacitracin in the feed were completely refractory to challenge after medication was discontinued. In another trial two groups receiving bacitracin were 100% susceptible to challenge after discontinuing medication."

Management procedures suggested by Peckham (1978a) for the prevention and control of ulcerative enteritis include:

1. Institution of management procedures to prevent coccidiosis, other diseases, and stress, since

ulcerative enteritis often appears secondary to these conditions;

2. Meticulous cleanup of facilities between succeeding flocks, because spores of the Cl. colinum may persist indefinitely in litter;

3. Isolation of infected groups from others;

4. Placement of birds (game birds) on 0.5 inch wire mesh on farms where the disease is a problem;

5. Isolation of survivors of an outbreak from unexposed birds, since survivors may be carriers.

Based on the above, a prohibition of the use of furazolidone for ulcerative enteritis probably would not have any significant effects on the poultry industry.

2.4.3.5. Avian Infectious Hepatitis

Avian infectious hepatitis, also called avian vibrionic hepatitis, is a chronic disease caused by infections with bacteria of the genus Vibrio. Chickens are the primary target for the disease (turkeys are not natural hosts) usually displaying symptoms when pullets are just beginning to lay eggs or in chickens in egg production for several months. The disease organism has been isolated from chickens of all ages, however.

The disease, spread by fecal contamination, is contagious in chickens. Signs of the disease are listlessness, loss of weight, and drop in egg production. Mortality rates of 2 to 15% have been reported (Peckham, 1978b). Often, the disease follows secondary to some other disease such as ascarids, capillaria, Marek's disease, pox, mycoplasma, coccidiosis, or E. coli infection (Peckham, 1978b).

Incidence data for vibrionic hepatitis were not found. This disease is not reported by the American Association of Avian Pathologists or identified individually by the Crop Reporting Board USDA Economics, Statistics and Cooperatives Service as a cause of condemnations (Poultry Slaughter, 1979). Broiler chickens reach market weight and are slaughtered prior to the age at which the disease is usually observed.

While Peckham (1978b) reviews a number of drugs observed to be effective in treating infectious hepatitis, there is no drug, including furazolidone, that is approved by FDA for use in the most affected groups, namely, older replacement chickens and laying hens. Management techniques that prevent the introduction and spread of diseases among chicken flocks apply to infectious hepatitis, since the disease often attacks chickens weakened by other diseases. (See previous sections 2.4.3.1. through 2.4.3.4.) In particular, infestations of internal parasites in flocks may favor establishment of infectious hepatitis (Peckham, 1978b).

Based on the above information, it appears that furazolidone is not essential to the prevention or control of avian infectious hepatitis.

2.4.3.6. Histomoniasis (Blackhead)

Histomoniasis is a protozoan disease of gallinaceous birds, particularly turkeys. The protozoan responsible for the disease is Histomonas meleagridis. Heterakis nematodes (cecal worms) serve as intermediate hosts for H. meleagridis and it is in the eggs of Heterakis that the histomonads are protected and gain entrance into the bird hosts. Earthworms may serve as mechanical vectors by swallowing, concentrating and transporting Heterakis eggs containing Histomonas. Turkey ranges and poultry yards may remain infected with Histomonas for years after birds are removed, due to the Histomonas present in long-lived Heterakis eggs present in the soil.

Turkey, chukar partridge, and ruffled grouse may be severely affected by histomoniasis. Chickens, peafowl, guinea fowl, bobwhite quail and pheasant may become infected but sometimes without apparent disease (Kemp and Springer, 1978). Turkeys and other susceptible species are not grown with chickens or in facilities or ranges where chickens were present, since the chickens may harbor both Histomonas and Heterakis. In infected flocks mortality in turkeys may exceed 70%, whereas, in chickens, mortality is generally low but has exceeded 30% (Kemp and Springer, 1978).

Incidence of histomoniasis is declining in the U.S. due to two management changes: (1) isolation of chickens from turkeys and (2) confinement rearing away from contaminated soil and also due to the availability of drugs for blackhead treatment and prevention in turkeys (Kemp and Springer, 1978). The American Association of Avian Pathologists (1975) reported histomoniasis in 101 and 97 chicken and turkey flocks in the U.S., respectively, for the year 1974. Thus, incidence is low, but proportionately higher in the smaller U.S. turkey population.

Drug prophylaxis for histomoniasis, when management measures fail to reduce histomoniasis to an acceptable level in turkey flocks, may include the organic arsenicals, carbarsone and nitarsone, or the nitroimidazole drugs, dimetridazole and ipronidazole, all FDA approved. Nitarsone is also approved for prevention of blackhead in chickens. Furazolidone is presently approved for both turkeys and chickens for prevention and treatment of histomoniasis (Table 3).

Prohibition of furazolidone for use in poultry to prevent blackhead would have no significant effect on the poultry industry. Several effective alternate drug products are available for turkeys, the most susceptible species. If drugs are needed for use in chickens, in addition to nitarsone, the medications used in turkeys would be a source of candidate drugs to be considered for FDA approval.

2.4.3.7. Summary and Conclusions

Examination (in sections 2.4.3.1.-6.) of the eight conditions in poultry for which furazolidone appears to be a probable choice indicates that furazolidone is not essential to maintaining poultry production. Alternate medications are available to support management procedures aimed at prevention and control of disease, although these medications sometimes must be administered by routes other than in feed, such as water and subcutaneous injection. Several of the conditions, e.g. pullorum and fowl typhoid, occur only rarely in the U.S. due to host resistance, national eradication programs, and/or careful preventative management procedures. Changes in management procedures that might result from a prohibition of use of furazolidone in food-producing animals appear to be minimal although more care in implementing and adhering to available prevention and control procedures is indicated.

Arizonosis and paratyphoid in young turkey poults and chicks would appear to be the diseases which presently result in frequent use of furazolidone. The mortality associated with these diseases, when they occur, is so high that producers probably choose to use the drug as a preventative measure to provide a buffer for other management procedures. Our review of possible alternate drugs, although probably not complete, found no single drug, other than furazolidone, that has claims for both arizonosis and paratyphoid in turkeys (table 3).

Spectinomycin and gentamicin subcutaneous injections, although approved for paratyphoid in chickens, are approved for arizonosis only in turkeys.

Chlortetracycline medicated feed is approved for use in reducing mortality due to paratyphoid (Salmonella typhimurium) in turkeys. Adult chickens and turkeys, while they may carry these organisms, seldom show clinical symptoms.

Chronic respiratory disease complicated by E. coli accounts for a large percentage of condemnations at slaughter for turkeys and chickens (Table 14). Those growers seeking to prevent or control outbreaks of this condition with drugs may be more inclined to include subcutaneous injections of antibiotics for chicks and turkey poults in the hatchery and water medications as well as using medicated feed in their prevention/treatment regimen, as a result of the Bureau's furazolidone proposal. Complicated C.R.D. in some instances may be more difficult to treat and thereby require these alternate medication routes or cause losses. The economic impact of such a shift depends on the comparative costs of the different routes of administration, the frequency at which the drugs are used for this purpose, the cost and effectiveness of other preventative and control measures. Data on these items for poultry are not available to the Agency.

Thus, the impact of the Bureau of Veterinary Medicine's nitrofuran proposals could be to reduce, but not eliminate, the ability of turkey

managers, and to a much lesser extent chicken managers, to back up good management practices with prophylactic drugs for these diseases; possibly resulting in increased management efforts to prevent and control disease. As pointed out for avian arizonosis and paratyphoid, drug products, including furazolidone, do not eliminate the presence of these disease organisms from flocks but, rather, reduce mortality in infected poults. Good management is the only way to eliminate or reduce the incidence of the disease organisms, as has been proven with the salmonella diseases, pullorum and fowl typhoid.

There should be no effect due to the Agency's nitrofuran proposals on egg production. Nitrofurans are not permitted in the feed of layers or for replacement birds over 14 weeks of age. The effects of the nitrofuran proposals on broiler chicken production should be minimal, if any. Alternate drugs are available; current use of nitrofurans in chickens is low. At least one large broiler producer has advised the Agency that nitrofurans are no longer used in their operations (May, personal communication, 1979). All nitrofuran claims for use in swine and cattle are duplicated by alternate drugs and current use is infrequent; therefore, no significant impact in production levels and practices for these species is anticipated.

2.5. Essentiality of Nitrofuran Drugs in Controlling the Selection and Spread of Drug-Resistant Bacteria

Microbial drug resistance and its transfer among different members of the microbial community is a potential hazard receiving increasing

attention. Transferable (also called "transmissible") resistance to antibacterial drugs may spread widely among bacteria. Furthermore, bacteria that inhabit the guts of animals may be transmitted to man through many different environmental routes (e.g. meat handling and ingestion, contamination of water-ways, contact with farm animals and their facilities, etc.).

Feeding of subtherapeutic antibacterials frequently results in animals excreting drug-resistant bacteria which may be transferred to man. Subtherapeutic administration of antibacterials for long periods provides an ideal environment in the gut for the selection and proliferation of both Gram-positive and Gram-negative drug-resistant bacteria. When exposed to an antibacterial, the organisms that are drug-resistant survive while the growth of other (drug-sensitive) bacteria is inhibited. Eventually, the drug-resistant organisms predominate.

Drug resistance is primarily determined by genetic elements on the bacterial chromosome or on "R-plasmids" (R-factors, R+). R-plasmids are small circles of DNA that occur separately from the bacterial chromosome. These R-plasmids carry genes which code for drug resistance and other characteristics such as the capacity to reproduce R-plasmids. Plasmids may determine resistance to more than one antibacterial agent. This multiple drug resistance may occur for as many as seven antibacterials. Plasmids can transfer from one bacterium to another and from non-pathogenic to pathogenic strains. Plasmid transfer occurs, although with varying frequency, among all members of the

enteric (gut) bacteria (e.g. Escherichia coli, salmonellae, shigellae, Klebsiella, and others) and also among members of other families of Gram-negative bacteria. The normal Gram-negative bacterial intestinal flora (largely E. coli) serve as a reservoir of R-plasmids; these R-plasmid-bearing bacteria interchange among animals, man, and the environment. Theoretically, the potential health hazard increases as the R-plasmid reservoir increases because the probability of R-plasmid transfer to pathogens increases.

Chromosomal drug resistance, on the other hand, is not usually transferable (non-transmissible) between bacteria. Some R-plasmid-mediated drug resistance is also non-transmissible. Non-transmissible drug resistance poses a hazard when, in the presence of continued selection pressure, a strain of drug-resistant pathogens develops and proliferates.

Drug-resistant pathogens of animal origin, either with transmissible or non-transmissible drug resistance, probably can cause disease in man that is refractory to treatment with antibacterials, as has been observed with penicillin-resistant gonorrhea of human origin. (See Feinman and Matheson (1978) for a more detailed discussion.)

Responding to the Bureau's original Environmental Assessment of the nitrofuran proposals, one furazolidone NADA holder stated that transferable resistance to nitrofurans has not been convincingly demonstrated, as opposed to evidence that this type of bacterial drug

resistance is common for many other antibacterials. The firm argued that nitrofuran drugs are essential in controlling drug-resistant E. coli and Salmonella that arise in animal populations. The firm stated that, furthermore, prohibition of nitrofurans results in increased use of alternate antibacterials which in turn exacerbates the drug resistance problem.

The Bureau identified this potential impact in the original Environmental Assessment of the nitrofuran proposals but could not quantify the magnitude of the impact. Since that time, the Bureau has prepared a draft environmental impact statement on subtherapeutic antibacterial agents in animal feeds, (Feinman and Matheson, 1978) which accompanied its tetracycline and penicillin restriction proposals.* The magnitude of impact that the nitrofuran proposals will have on the genetic makeup of the U.S. microbial population remains and probably will continue to remain unquantifiable. Evidence that may help to judge the approximate magnitude of the impact is examined in the following paragraphs.

*The Bureau of Veterinary Medicine has recognized the potential for animal use of antibacterials to contribute to an environmental pool of drug-resistant bacteria. Penicillin and the tetracyclines are very important to human medicine but also are used in large volumes in subtherapeutic concentrations in animal feeds. The Bureau proposed to restrict the use of these drugs in animals (42 FR 43772, 8/30/77 for penicillin; 42 FR 56254 and 43 FR 3032-3045, 10/21/77 and 1/20/78, respectively, for tetracyclines). These proposals have not been finalized, but instead have stimulated reviews of the data by the Office of Technology Assessment (June 1979) and the U.S. Department of Agriculture (1978) and have resulted in an intensified research program being directed by the Bureau with the assistance of the National Academy of Sciences which will attempt to quantify the hazard posed to human health by the subtherapeutic, long-term use of penicillin and tetracyclines in animal feeds. It will probably be some time before the studies are completed, the results interpreted, and a choice made among the Bureau's regulatory options.

2.5.1. Microbial Resistance to Nitrofurans

Watanabe et al. (1971) frequently isolated nitrofuran-resistant bacteria from ponds and fish in Japan where nitrofurans were used in fish culture. Although the nitrofuran resistance was non-transmissible, these organisms frequently carried R-plasmids for non-transmissible resistance to up to seven other antibacterials. Bacteria of the genera Aeromonas, Alcaligenes, Pseudomonas, Vibrio, Escherichia, Citrobacter, Achromobacter, Klebsiella, Enterobacter, and others were isolated with nitrofuran resistance.

Limited evidence indicates that nitrofuran resistance can be of the transferable type present on R plasmids. R-factor transferable nitrofuran resistance has been demonstrated by Aoki, Egusa, and Arai (1975) and Arai, Aoki, and Egusa (1976). Aoki, Egusa, and Arai (1975) isolated intermediately furazolidone-resistant (minimum inhibitory concentration to furazolidone: 0.2-1.0 ug/ml) strains of Escherichia coli, Aeromonas liquefaciens, Enterobacter spp., and Vibrio anguillarum. This furazolidone resistance was transferable to E. coli RC85 nal by bacterial conjugation and also by transduction using phage P1 (a bacterial virus). Resistance to streptomycin, aminobenzyl penicillin, sulfonamide, tetracycline, and chloramphenicol was transferred along with furazolidone resistance to E. coli RC 85 nal during this test, demonstrating that these resistance factors are located together in various combinations on R-plasmids. The level of furazolidone

resistance conferred to host bacteria with these R-plasmid resistance factors was less than that observed for bacteria with nontransferable (chromosomal) furazolidone-resistant mutations. Arai, Aoki, and Egusa (1976) observed that E. coli RC85 nal bearing these same plasmids containing furazolidone-resistant R-factors had an intermediate ability to inactivate nitrofurazone (NF-7) with nitrofuran reductase. The authors concluded:

"1. Some R factors decrease nitrofuran sensitivity of their host bacteria.

2. The appearance of these R factors are [sic] closely related to the low dose but continuous use of nitrofuran derivatives.

3. The mechanism of this reduced nitrofuran sensitivity is due to specific but indirect suppression of nitrofuran reducing activities of the host bacteria.

4. From the clinical point of view, the presence of these R factors pointed out that careless use of nitrofuran derivatives could select not only nitrofuran resistant bacteria, but also multiresistant bacteria, although they give a lower level of nitrofuran resistance to their

host bacteria [than nitrofuran-resistant chromosomal mutants.]"

This limited evidence suggests that transferable nitrofuran resistance occurs in enteric bacteria and that heavy use of the drugs might pose health hazards similar to that of other antibacterials where transferable drug resistance is observed. Thus, the present infrequent appearance of nitrofuran resistance in the environment may be due to the relatively infrequent use of the drugs in animal practice. (See Table 7 and 2.4.2. for nitrofuran use and sales data, respectively.)

2.5.2. Ability of Nitrofurans to Control Drug-Resistant Bacterial Disease Outbreaks in Animals

Is there any evidence to support the furazolidone NADA holder's suggestion that furazolidone is effective in controlling bacteria resistant to other antibacterials? Again evidence is limited. The effectiveness of nitrofurans to be used in such a manner would be dependent upon the rapidity at which nitrofuran resistance appeared in the population receiving treatment.

Anderson (1968) reports on the development of drug resistance patterns in Salmonella typhimurium phage type 29 in calves and other animals in England during the 1960's. The most common patterns of resistance were multiple: S Su T Fu, A S Su T Fu, and K N S Su T Fu (S=streptomycin, Su=sulphonamide, T=tetracycline, Fu=furazolidone, A=ampicillin,

K=kanamycin, N=neomycin). Although furazolidone resistance occurred in most cultures, it was apparently not transferable. Thus, although the genetic material conferring furazolidone resistance was not self-transmissible in this instance, it did become a common occurrence. In England, use of furazolidone did not prevent development and spread of multiply resistant S. typhimurium. Instead, the bacteria developed furazolidone resistance, too, although it was not shown to be self-transmissible.

The isolation of many genera of nitrofuran-resistant bacteria from water and fish in pond culturing units in Japan (Watanabe et al., 1971) further shows that intensive nitrofuran use selects for nitrofuran-resistant bacteria. Most of these isolations also contained R-plasmids and extensive multiple drug resistance patterns.

Thus, it would appear that furazolidone cannot be relied upon to control epidemic situations similar to those reported by Anderson (1968).* Careful attention to animal management and non-drug oriented disease control and prevention appears to be a more effective long-term approach to preventing the buildup of pathogens with

*It should be noted, however, that nitrofurans are not permitted for use in the feed of calves in the United States. The occurrences of the drug-resistant S. typhimurium in calves was probably not a function of any special characteristics of bovine strains but, rather, the selective pressure from drugs and the sanitation conditions. S. typhimurium attacks mammals, cold-blooded vertebrates, birds, and other organisms. It is not host specific. Therefore, we believe this example, although in calves, to be a valid demonstration of the inability of drugs, including furazolidone, to contain outbreaks of multiply-resistant salmonellae.

multiple drug resistance. Anderson (1968) discusses this latter factor in relation to the bovine S. typhimurium infections in England.

> "Most of the bovine cultures were isolated from calves. Investigations revealed that the infected calves were almost entirely from intensive farms; that the growth of intensive farming had been followed by a rise in incidence of S. typhimurium infection in calves, frequently accompanied by a high mortality; that infection was usually introduced into herds by newly bought calves, mostly supplied by dealers; and that certain dealers had spread infection in this way to many different parts of the country. The spread of disease was also aggravated by cross infection of calves in markets and during transport. Efforts to control infection were mainly by use of antibiotics and were ineffectual: but this treatment promoted the emergence of drug-resistant strains and provided a protective screen under which they could flourish."

[Note: Anderson connotes the term "antibiotics" to include synthetic antibacterial substances.]

2.5.3. Conclusions

Based on the preceding paragraphs, we conclude that the removal of furazolidone from animal use will probably have no significant net

long-term effect as far as the development of bacteria with drug resistance is concerned. Furazolidone could still be useful in the treatment of small scale disease outbreaks caused by bacteria with R-factor resistance patterns that include all alternate drugs but do not yet include furazolidone resistance. In these cases, increases in animal morbidity and mortality could be attributed in part to the proposed actions and in part to management practices which permitted the outbreak. However, based on the sales data and use data presented earlier (2.4.2. and Table 7) and the generally recognized widespread occurence of drug-resistant bacteria in farm animals, furazolidone does not appear to be used routinely for controlling drug-resistant bacteria.

2.6. Environmental Impacts Due to Increased Use of Alternate Drugs

When considering actions which would remove products from the market, it is important to examine the environmental effects of removing certain chemicals from the environment and replacing them with substitutes. Therefore, it is desirable to know about the environmental effects associated with the products to be removed and their substitutes.

Based on the limited marketing and use data available (2.4.1. and 2.4.2.), the Bureau's proposals to prohibit the use of three nitrofuran drugs in food-producing animals affects less than five percent

of the animal antibacterial market and, for most nitrofuran claims, there are numerous alternate products presently competing successfully with nitrofurans which would be expected to rapidly occupy the nitrofuran market. (See Tables 1-7, and 9.) Thus, small incremental increases in sales and use for already-approved alternate drugs are anticipated.

Significant impacts on the environment could be expected for the Bureau's nitrofuran proposals if: (1) one or more of the alternate drugs or bioactive metabolites are currently introduced into the environment at concentrations near or beyond some threshold level at which adverse effects on important organisms or communities of organisms occur, (2) the additional increment of environmental introduction of these alternate drugs resulting from a nitrofuran prohibition causes the threshold to be exceeded, and (3) the adverse impacts due to the additional increment of alternate drugs more than offset or cause effects different from the environmental impacts that result from using nitrofurans for those purposes. [Note: Based on 2.5, we believe there will be no significant impacts on the environmental pool of drug-resistant microorganisms as a result of the proposal.]

2.6.1. Environmental Data on Alternate Drugs

The Bureau assembled the available information on the environmental introduction of a number of alternate drugs in the Bureau's draft

environmental impact statement, Subtherapeutic Antibacterial Agents in Animal Feeds (Feinman and Matheson, 1978). Due largely to the drugs having received approval prior to the Agency's implementation of the National Environmental Policy Act of 1969, information is limited. Physical/chemical data, the results of laboratory toxicity testing with one species at a time, and tests for drug metabolism and degradation conducted in laboratory conditions were used to estimate the potential for adverse impacts to occur at the points where those drugs enter the environment, mostly as a result of their use. This approach is used by environmental scientists and regulatory agencies as an acceptable method for identifying potential environmental impacts when more definitive data are absent. (See 21 CFR 25.31(b), proposed December 11, 1979, 44 FR 71742-71752 for FDA's environmental assessment procedure; EPA's guidance for testing of chemicals for potential environmental impacts prior to their manufacture, under Sec. 5 of the Toxic Substances Control Act in 44 FR 16240-16292, March 16, 1979; EPA's guidance for testing pesticides for adverse environmental effects in 43 FR 29697-29741, July 10, 1978.) FDA permits petitioners to conduct environmental testing in laboratory systems rather than in field tests, unless the potential impacts are so serious or complex as to make field testing advisable.

Table 16, extracted from Feinman and Matheson (1978), presents a summary of available environmental information on alternate drugs. Synergistic environmental effects due to combinations of excreted drug residues are possible, but they have not been considered due to the total absence of toxicological or other environmental data

in this area, the many combinations of drug residues in the environment that are possible, and the lack of methodology to assess the potential for such effects.

The following paragraphs describe the codes used in Table 16.

Introduction into the Environment

The actual quantities and concentrations of drugs and drug-resistant bacteria excreted into the environment by target animals cannot be determined with any reliability for most drugs. The approximate percent of oral dose excreted in microbiologically active form by target animals and the occurrence of target animal excretion of bacteria with plasmid and chromosomal drug resistance are reported.

% Oral Dose Excreted - Microbiologically active forms plus metabolites easily converted back to the parent or other microbiologically active compounds are included.

"D" - Detectable in excreta but % excreted not known

"N/A" - There are no indicated uses for this drug for this particular target animal.

Resistant Bacteria Excreted - Transmissible, plasmid-mediated, drug resistance in Gram-positive (G+) and Gram-negative (G-) bacteria and

nontransmissible (usually chromosomal) drug resistance categories are included.

"-" - Reduces excretion of resistant bacteria

"0" - Bacteria resistant to this drug are not known to occur.

"+" - Bacteria resistant to this drug occur infrequently.

"++" - Bacteria resistant to this drug occur frequently.

Fate in the Environment

Environmental Half-Life -- Time required for half the material to be inactivated in excreta, soil, or water is given in days.

"?" - Indicates that this value has been based on indirect data rather than a specific test of stability in environmental conditions. Indirect data used to estimate environmental half-life include chemical structure, stability of aqueous preparations of the drug, stable pH range, whether the drug was produced

by fermentation or chemical synthesis, and the metabolism pattern in target animals.

Soil mobility is an indication of the potential for the drug to move through soils into ground water or surface run-off.

"0" - Not mobile

"+" - Adsorbed strongly to some soils but not others

"++" - Temporarily or partially adsorbed to and subsequently released in microbiologically active form from most soil types

"+++" - Not adsorbed, freely mobile

Bioaccumulation Potential -- If the drug is known to concentrate in specific tissues, these tissues are listed. Bioaccumulation potential was estimated, in those cases where no specific studies were performed, from indirect data which include metabolism and excretion data for target animals, water and organic solvent solubility, and environmental half-life.

"Low" - Short-term and long-term bioaccumulation judged to be highly unlikely

"Mod" - Short-term bioconcentration in individual organisms a possibility but long-term bioaccumulation including transfer through food webs unlikely.

"High" - Long-term bioaccumulation of compound with transfer through food webs likely.

Effects Upon Environment

This section of Table 16 attempts to identify potential environmental effects that are associated with the use in and subsequent introduction of drugs through target animals into the environment. When direct studies are not available, effects are determined from consideration of quantities of drug residues introduced into the environment, the fate of these residues in various environmental compartments, and physical, chemical, and toxicological data presented in Feinman and Matheson (1978, Appendix A).

Soil and Fecal Bacteria Growth Inhibition -- Conclusions are based on direct studies (where possible), excretion data, environmental half-life, spectrum of antimicrobial activity, and bioaccumulation potential. Can the drug be excreted in quantities sufficient to affect species composition and growth of bacteria in feedlot wastes in soils?

"?" - Not enough data available to make an estimate

"0" - Effects on bacteria in soil and feedlot wastes highly unlikely

"+" - Effects possible but not demonstrated

"++" - Effects demonstrated or highly likely but not irreversible or long-term (i.e. effects from one environmental introduction persist less than 1 year)

"+++" - Irreversible or long-term (greater than or equal to 1 year) effects highly likely

Algal and Phytotoxicity -- Can the drug be excreted and transferred to environmental compartments in quantities sufficient to be toxic to algae or higher plants?

"?" - Not enough data available to make an estimate

"0" - Effects highly unlikely

"+" - Effects possible but not demonstrated

"++" - Effects demonstrated or highly likely but not irreversible or long-term (i.e. effects from one introduction persist no longer than 1 year)

"+++" - Irreversible or long-term (greater than or equal to 1 year) effects highly likely

Fish Toxicity -- Based on drug toxicity studies, introduction and fate, what is the likelihood for the drug to adversely affect the survival of fish in streams and ponds receiving farm effluents?

Same code as for algal and phytotoxicity.

Mammalian Toxicity -- Based on drug toxicity data, introduction and fate, what is the likelihood for the drug to be present in sufficient concentrations to result in toxic effects in exposed mammals? Same code as for algal and phytotoxicity plus:

"C" - Carcinogen

"C?" - Suspect carcinogen

"T" - Tumorigen

Selection for Drug-Resistant Non-Enteric Bacteria -- Is the drug excreted in sufficient quantities and persistent enough to select for drug resistance in non-enteric bacteria present in the environment?

"?" - Not enough data to make an estimate

"0" - Effect highly unlikely

"+" - Effect possible but not demonstrated

"++" - Effect demonstrated

Examination of Table 16 shows many areas where there are not enough data to make a reasonable estimate, especially with regard to fate and effects of environmental drug residues. It can be seen, however, that tetracyclines, sulfonamides, neomycin, streptomycin, bacitracin, tylosin, lincomycin, bambermycins, monensin and the organic arsenicals are excreted as microbiologically active parent or metabolites in large quantities. Of those drugs which have high excretion rates, tetracyclines, sulfonamides, bacitracin, lincomycin and bambermycins are half-inactivated in less than a month. Monensin half-life varies up to 70 days. Arsanilic acid is half-degraded in about 4 months but the arsenic from both arsanilic acid and roxarsone continues to have bioactive potential indefinitely. Environmental half-life for the other drugs is not available.

Based on these introduction and persistence data and the spectrum of antimicrobial activity for the individual drugs, one can conclude that tetracyclines, sulfonamides, bacitracin, lincomycin, bambermycins, and monensin have either proven or have a strong potential for adversely affecting the growth of bacteria responsible for degrading and stabilizing fresh animal wastes. This has been demonstrated for chlortetracycline (Elmund et al., 1971). The other drugs are probably excreted

Table 16. Summary: Environmental Information on Veterinary Drugs

Drugs	Introduction into Environment: % Oral dose excreted as microbiologically active compound			Resistant Bacteria: Transmissible (Plasmid-mediated)		Resistant Bacteria: Non-transmissible (Chromosomal)	Fate in Environment: Envir. half-life (days)	Soil mobility	Bioaccumulation potential	Effects upon Environment: Inhib. soil and fecal bact.	Algal and phyto toxicity	Fish toxicity	Mammalian & avian toxicity	Drug resistant non-enteric bacteria
	chicken	cattle	swine	G+	G-									
Chlortetracycline	50?	75	40-50	+	++	+	> 20	++	High for bones, mod, for plants	++	0?	0	0	+
Oxytetracycline	50?	75?	40-50	+	++	+	> 20	++	High for bones, Mod. for plants	++	0?	0	0	+
Procaine Penicillin G	0	N/A	20	++	++	+	< 7?	+++	Low	0/+	0?	?	0	+
Sulfathiazole	N/A	50?	70	?	++	+	20?	++?	Mod	+	0	0	0	+
Sulfamethazine	N/A	50?	75	?	++	+	< 20	++?	Mod	+	0	0	0	+
Neomycin	?	95?	95?	+	++	+	?	+	Low	?	?	?	0	+
Streptomycin	100?	N/A	83?	+	++	+	7?	+	Mod	+	0/+	?	+	+

Table 16 continued. Summary: Environmental Information on Veterinary Drugs

Drugs	Introduction into Environment: % Oral dose excreted as microbiologically active compound			Resistant Bacteria: Transmissible (Plasmid-mediated)		Resistant Bacteria: Non-transmissible (Chromosomal)	Fate in Environment: Envir. half-life (days)	Soil mobility	Bioaccumulation potential	Effects upon Environment: Inhib. soil and fecal bact.	Algal and phyto toxicity	Fish toxicity	Mammalian & avian toxicity	Drug resistant non-enteric bacteria
	chicken	cattle	swine	G+	G-									
Bacitracin	95%	95	95	0	0	+	4-10	++	Low	+	0	0	0	0
Tylosin	28-76	32-40	29-67	+	0	+	?	+	?	+	0	?	0	+
Virginiamycin	N/A	N/A	0-31	+	0	?	7	?	Low	0/+	0	0	0	0/+
Carbadox	N/A	N/A	0?	0	0	?	?	?	?	?	0	0	c?	0
Lincomycin	100	N/A	100	+	0	+	20	+	Low?	+	?	?	0	+
Bambermycins	90	N/A	90	0	-	?	20	+?	Low	+	0?	?	0	0

Table 16 continued. Summary: Environmental Information on Veterinary Drugs

Drugs	Introduction into Environment: % Oral dose excreted as microbiologically active compound			Resistant Bacteria: Transmissible (Plasmid-mediated)		Resistant Bacteria: Non-transmissible (Chromosomal)	Fate in Environment: Envir. half-life (days)	Soil mobility	Bioaccumulation potential	Effects upon Environment: Inhib. soil and fecal bact.	Algal and phyto toxicity	Fish toxicity	Mammalian & avian toxicity	Drug resistant non-enteric bacteria
	chicken	cattle	swine	G+	G-									
Monensin	35	40-75*	N/A	0	0	+	10-70	+	Low-Mod	+/++	0	+	+	0/+
Oleandomycin	?		Little	+	?	+	?	+	?	+	?	?	?	?
Erythromycin	High	High	High	++	?	+	?	+	Mod?	+	0	0?	0	+
Arsanilic acid	99	N/A	5	+	+	+	116-129	+	Low-Mod	+	+	?	+/c?	+
(Arsenic, total)	100	N/A	100				Infin.							
Roxarsone	90	N/A	?	+	+	+	?	+?	Low-Mod	+	+	?	+/c?	+
(Arsenic, total)	100	N/A	100				Infin.							

*Data available since publication of the draft EIS from which this table is extracted show lower excretion (40-50%) of monensin than originally reported for steers. See A. Donoho, et al. 1978. Metabolism of monensin in the steer and rat. J. Agric. Food Chem. 26:1090-1095.

in concentrations above the minimal inhibitory level for many soil and fecal bacteria. In addition to affecting bacterial populations in fresh wastes, effects are possible where fresh waste containing drug residues are periodically added, as in compost piles and animal waste treatment lagoons. The bacterial spectrum of activity and/or excretion rate for tylosin, streptomycin, oleandomycin, erythromycin, and the organic arsenicals are less well known, but the potential for similar effects on bacteria present in wastes also exists.

While data are incomplete regarding the toxicity of the drugs to terrestrial plants and algae, the organic arsenicals appear to have the highest potential for adverse effects, due to the ability of pentavalent arsenate (a degradation product) to bioaccumulate in plants and interfere with phosphorus metabolism (Feinman and Matheson, 1978, Appendix A).

Of the drugs considered, acute fish toxicity data were available only for the tetracyclines, sulfamethazine, monensin and carbadox. These drugs are not acutely toxic to fish in concentrations around 10 ppm in water, except for monensin where the 6 day no effect level for bluegills was between 3 and 10 ppm (Eli Lilly Res. Labs., NADA 95-735/025, studies 1072-6, 1076-6 and 1079-6). Concentrations of these drugs in surface waters acutely toxic to fish are not likely to occur on a frequent basis as a result of runoff from feedlots and agricultural soils or effluent from animal waste treatment systems. Subacute effects on fish are possible but not clearly demonstrated.

Monensin, roxarsone, and arsanilic acid are the most acutely toxic to mammals and birds of the drugs considered, with oral LD_{50}'s ranging around 100 mg/kg body weight. These drugs are also largely excreted by target animals as bioactive residues. However, it is unlikely that mammals and birds could consume acutely toxic doses of these residues from excreta.

Chronic effects are also a possibility, since these typically occur at levels much below concentrations where acute toxicity is observed. However, data are insufficient to judge the probability or nature of these effects. Inorganic arsenic in high concentrations has been associated with cancer in occupationally and environmentally exposed humans (U.S. Occupational Safety and Health Administration, 1978). The arsenic degradation products from roxarsone and arsanilic acid would therefore, also be suspect carcinogens. Carbadox is a suspect carcinogen permitted in swine feed only with long withdrawal times. It poses unknown environmental risk since the compound is, for the most part, metabolized to other unidentified compounds which are excreted in very low quantities, according to the limited data available.

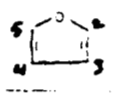
2.6.2. Environmental Data on Nitrofuran Drugs

The following paragraphs will summarize the environmental data available to the Bureau on the nitrofuran drugs affected by its proposed actions. Environmental assessments for these drugs were not submitted

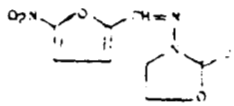
by the NADA holders because the approvals for the drugs preceded the Bureau's implementation of NEPA (1973) and no new approvals have been requested since that time that triggered retroactive environmental review procedures.

2.6.2.1. Chemical and Physical Properties

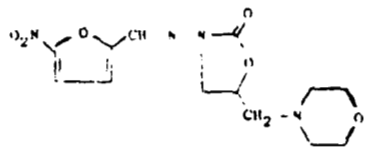
Furazolidone, nitrofurazone, and furaltadone are closely related chemical structures consisting of a furan ring substituted at the 2 position with an organic substituent, -C=N-N-R, and a nitro group at the 5 position (figure 1).



Furan



Furazolidone (NF-180)



Furaltadone (NF-260)

Nitrofurazone (NF-7)

Figure 1. Chemical structure of furan and nitrofuran drugs.

Table 17 presents basic chemical/physical data on NF-180, NF-7, and NF-260.

2.6.2.2. Mechanism of Antimicrobial Action and Spectrum of Activity

Dodd and Stillman (1944) concluded from their work with seventeen nitrofurans and their non-nitrated analogs that the nitro group in the 5-position conferred antibacterial action on derivatives of furan, 2-furaldehyde, 2-furfuryl alcohol, and 2-furoic acid.

The mechanism of antibacterial action of nitrofurans, however, is not well known. Paul and Paul (1964) reviewed the available data on the subject and concluded that nitrofuran drugs probably acted as antibacterial agents by inhibiting one or more bacterial enzyme systems involved in glucose metabolism. However, Lu and McCalla (1978) could find no correlation between inhibition of glucose metabolism or DNA synthesis and lethality in E. coli.

Additionally, numerous studies find nitrofurazone and furazolidone to cause bacterial cell mutations, single strand breaks in the DNA, and to inhibit DNA synthesis. Laboratory investigations with bacterial cultures found NF-7 and NF-180 to inhibit DNA synthesis in Escherichia coli and Vibrio cholerae (Nakamura and Shimizu, 1973; Chatterjee, et al., 1975). NF-180 and NF-7 have been found to be mutagenic for a Salmonella typhimurium strain used to detect mutagenesis by back-

Table 17. Chemical/Physical properties of nitrofuran drugs

	Furazolidone	Nitrofurazone	Furaltadone
Formula[1]	$C_8H_7N_3O_5$	$C_6H_6N_4O_4$	$C_{16}H_{16}N_4O_6$
Mol. wt.[1,2]	225.16	198.14	324.29
Common Synonyms	NF-180	NF-7	NF-260
Production	chemical synthesis	chemical synthesis	chemical synthesis
Physical Appearance[1]	yellow crystals	pale yellow needles	yellow crystals
Water Solubility[2] (mg/l = ppm)	40	210	750
Chloroform Solubility[2] (mg/l = ppm)	200	22	22,000
Stability[2]	photosensitive	photosensitive	photosensitive
Unstable pH Range[2]	> 10	> 10	> 10

[1]Merck Index, 9th edition (1976)

[2]H. E. Paul and M. F. Paul (1964)

mutations (Goodman, 1977; Yahagi et al., 1976; Green et al., 1977). NF-180, NF-7, and NF-260 were found to be mutagenic using a back-mutation assay with E. coli test strains (Green et al., 1977; McCalla and Voutsinos, 1974). These are but a few of the papers which indicate the mutagenicity of the various nitrofurans.

The nitrofuran drugs are used to treat infections due to a wide variety of Gram-positive and Gram-negative bacteria, as well as coccidia (protozoans). Table 18 shows the results of laboratory tests of furazolidone (NF-180) on cultures of pathogenic bacteria conducted by Yurchenco, Yurchenco, and Piepoli (1953).

2.6.2.3. Introduction into the Environment

2.6.2.3.1. Manufacturing and Processing

The manufacture and production of nitrofuran-medicated feed is accomplished in several stages with many sites of preparation, all of which could result in occupational exposure to nitrofurans. NF-180, NF-7, and NF-260 are synthetic antibacterial compounds. For example, nitrofurazone (NF-7) may be prepared by combining 2-formyl-5-nitrofuran and semicarbazide hydrochloride in the presence of sodium acetate (Merck Index, 1976). The synthesized pure compounds are then combined with inert ingredients into one or more "premixes" of specified drug concentration. The premixes are subsequently sold to feed mills approved to prepare medicated feeds, where nitrofuran-medicated feeds of specific concentrations for particular indications or claims are prepared.

Table 18. In Vitro Antibacterial Activity of Furazolidone.

Bacterial Species	Number of Strains	Minimum Inhibiting Concentrations (ug/ml=ppm) Mean 24 hrs.	Mean 96 hrs.	Range 24 hrs.	Range 96 hrs.
Salmonella typhimurium	4	1.2	3.7	0.8-1.9	2.0-4.7
Salmonella typhosa	6	1.2	3.0	0.6-2.0	1.0-3.8
Salmonella gallinarum	8	1.4	2.0	<0.2-4.4	0.4-5.5
Salmonella pullorum	4	0.3	0.7	<0.2-0.7	0.4-1.4
Shigella para-dysenteriae	11	0.8	1.3	0.4-1.8	0.5-10.0
Escherichia coli	3	0.7	1.4	0.5-0.8	0.7-2.5
Aerobacter aerogenes	5	5.0	10.2	0.5-17.4	1.0-34.8
Klebsiella pneumoniae	3	0.9	2.7	<0.6-1.1	2.3-2.9
Vibrio comma	1	0.3	0.3		
Proteus vulgaris	5	24.3	64.9	9.4-48.5	13.7-102.0
Pseudomonas aeruginosa	6	>99.0	>99.0	>97.0->102.0	>97.0->102.0
Pasteurella avicida	5	4.9	12.2	<0.4-6.1	12.1-12.4
Brucella abortus	3	5.9	11.8	5.5-6.7	11.0-13.4
Hemophilus pertussis	1	96.0	>96.0		
Micrococcus pyogenes var. aureus	7	3.5	6.1	2.1-5.0	3.3-17.5

Table 18 continued.

Bacterial Species	Number of Strains	Minimum Inhibiting Concentrations (ug/ml=ppm) Mean 24 hrs.	Mean 96 hrs.	Range 24 hrs.	Range 96 hrs.
Diplococcus pneumoniae	4	16.4	>100.0	3.7-30.0	39.0->100.0
Streptococcus pyogenes	4	13.1	20.0	7.5-20.0	15.0-25.0
Streptcoccus faecalis	2	12.1	60.6	12.1-12.1	24.2-97.0
Corynebacterium diphtheriae	5	21.2	50.8	10.9-45.5	23.8-91.0
Mycobacterium tuberculosis	1	19.5	>19.5		
Bacillus anthracis	4	0.9	1.7	<0.4-1.3	<0.4-5.0
Clostridium perfringens	1	0.2	2.0		
Clostridium tetani	1	0.1	0.1		
Clostridium botulinum	1	0.2	1.0		
Listeria monocytogenes	1	<4.8	10.6		

>No activity at maximum concentration tested.

Source: Yurchenco, Yurchenco, and Peipoli (1953).

The medicated feed is then sold to poultry and swine production facilities. Persons working in these areas could be exposed to nitrofuran drugs through dermal contact and inhalation. The extent of and effects that might be due to such exposure are not well known. Caplan (1969) reported a few cases of allergic contact dermatitis in workers exposed to nitrofurazone in animal medications and feed. To our knowledge, there has been no survey of the incidence of cancers, tumors, reproductive effects, etc. of workers exposed to NF-180, NF-7, and NF-260.

A description of the wastes generated by the synthesis and subsequent production of nitrofuran-medicated feeds are not available to the Bureau. Depending on the constituents of these wastes and the manner in which they are disposed, adverse environmental effects are possible.

2.6.2.3.2. Introduction into the Environment/ Metabolism and Excretion by Target Animals

The three nitrofuran drugs, NF-180, NF-7, and NF-260, undergo hydrolysis when fed to animals. The metabolite 5-nitro-2-furaldehyde is produced and may be further oxidized to produce 5-nitro-2-furoic acid. Additionally, metabolism of furazolidone (NF-180) yields 3-amino-2-oxazolidone (Paul et al., 1969). Numerous other metabolites, many of which are not completely identified and characterized, are also found (Swaminathan and Lower, 1978).

Paul and Paul (1964) concluded from their data that some incorporation of the nitrofuran carbon skeleton into normal body constituents might be occurring.

In swine, chickens, laboratory animals and man, furazolidone is absorbed through the gastrointestinal tract and rapidly metabolized. Some but not all of the parent compound and metabolites are rapidly excreted. Metabolites containing the 5-nitrofuran ring appear in the urine. Orally administered furazolidone in rats is detectable in the feces. However, furazolidone does not represent the major part of the dose excreted. Orally administered furaltadone in rats is detectable in urine but not in feces. Nitrofurazone administered orally to rats is found both in urine and feces. As with furazolidone, the major portion of the oral dose of nitrofurazone and furaltadone is excreted as metabolites (Ali, 1983; Craine and Ray, 1972; Tennent and Ray, 1971; Paul and Paul, 1964).

2.6.2.4. Environmental Fate

Given the limited metabolism data reviewed in 2.6.2.3., it is not possible to identify all the nitrofuran metabolites that enter the environment as a result of medicating food-producing animals nor determine the potential for these residues to be further transformed, bioaccumulated, and transported to other environmental components.

The parent compounds, NF-180, NF-7, and NF-260, are all metabolized within the medicated animals. Small amounts of the dose are excreted as the parent drug. Pathways for metabolic degradation summarized by Paul and Paul (1964) include reduction of the nitro group, acetylation of the resulting amino furan, and opening of the furan ring. Hydrolysis of the side chain (2-substituent) may also occur. This metabolic degradation pathway probably also occurs in the environment in the soil microorganisms utilizing animal wastes containing nitrofuran residues (Beckett and Robinson, 1956, 1957, 1959) and in any higher organisms that might ingest nitrofuran residues.

Paul and Paul (1964) also state that: (1) the nitrofurans in dilute solution are photosensitive and must be protected from daylight and fluorescent light, (2) solutions of certain nitrofurans decompose when in contact with certain metals such as iron and zinc. The relatively high water solubility of the nitrofurans (compared to those compounds that bioaccumulate rather than biodegrade) and their simple structure also suggest that degradation of nitrofuran drugs occurs in the environment at a fairly rapid rate.

The time required for degradation of nitrofuran residues to mineralized compounds (carbon dioxide, water, nitrogen, etc.) depends on the chemical structure of the residue, its concentration in the environment, the level of microbiological activity and physical/chemical factors, such as metals, organics, and sunlight present. None of these factors is known well enough to predict environmental half-lives

for the various identified nitrofuran residues. No studies measuring the time required for degradation of the nitrofuran drugs to mineralized compounds under conditions simulating environmental situations were submitted to the Bureau by the firms producing the drugs and no such studies are available in the scientific literature.

2.6.2.5. Environmental Effects

One objective of the hearings planned for NF-180, NF-7, and NF-260, is to examine the evidence in the scientific literature and in the NADA holders' submissions and determine the carcinogenic, tumorigenic, and other adverse biological effects possible in humans consuming residues of these drugs in their food supply. Thus, it is possible that hearings will place into perspective the potential for such effects to occur in other organisms exposed to nitrofuran residues in the environment.

The use of laboratory single-species, short-term toxicity tests to predict effects on populations in the environment is an accepted procedure, however, such data must be accompanied by knowledge of environmental concentrations of the test chemical, in order to predict an effect. For the nitrofurans and for other animal feed medications, such environmental concentration data are limited. Canton and van Esch (1976) tested thirteen feed additives for ability to inhibit the growth of the green unicellular alga Cholorella pyrenoidosa, and for acute toxicity to the crustacean Daphnia magna and the two fish

species Lebistes reticulatus (guppy) and Salmo gairdneri (rainbow trout). Furazolidone caused 50 percent growth inhibition in C. pyrenoidosa at 1.3 mg/l (ppm) after two days. D. magna was not affected by levels up to 30 mg/l in two days, as was the case for S. gairdneri. The four day LC_{50} for furazolidone to L. reticulatus was 25 mg/l. Furazolidone is used in fish culture in Japan in water concentrations of 2-5 mg/l (Arai, Aoki, and Egusa, 1976). These concentrations would be sufficient to cause growth inhibition in C. pyrenoidosa. Table 19, using the same format and code as for Table 16, attempts to summarize the environmental information available for the nitrofurans subject to the Bureau's proposals.

2.6.3. Conclusions

For the most part, the data for nitrofurans and alternate drugs are limited. However, the following general conclusions can fairly be made:

(1) Most of the alternate drugs and nitrofurans are excreted into the environment in some portion as parent compound or bioactive metabolites.

(2) The environmental effects which are presently attributable to the use of alternate drugs are probably limited to shifts in the composition of microbial populations which normally colonize fresh

Table 19. Summary: Environmental Information on Nitrofuran Drugs

Drugs	Introduction into Environment: % Oral dose excreted as active compound*			Resistant Bacteria: Transmissible (Plasmid-mediated)		Resistant Bacteria: Non-transmissible (Chromosomal)	Fate in Environment: Envir. half-life (days)	Soil mobility	Bioaccumulation potential	Effects upon Environment: Inhib. soil and fecal bact.	Algal and phyto toxicity	Fish toxicity	Mammalian & avian toxicity	Drug resistant non-enteric bacteria
	chicken	cattle	swine	G+	G-									
Furazolidone NF-180	D	N/A	D	0	+	++	<7?	?	Low?	+	+	+	C,T	?
Nitrofurazone NF-7	D	N/A	D	0	+	++	<7?	?	Low?	+	+?	?	C?,T	?
Furaltadone NF-260	N/A	N/A	N/A	0	?	?	<7?	?	Low?	0	0	0	C?,T	0

*All three NF's are also used as topical, ophthalmic, or intramammary drugs. There are not sufficient data to determine the proportion of NF's used in three dosage forms which reach the environment outside the treated animal as parent or bioactive metabolites.

animal excreta. While such a shift in the microbial community in animal wastes is probably not desirable from the standpoint of the problem of stabilizing and treating those wastes, the effect does not appear to be significant ecologically. It is not known whether a microbial population shift due to differing drugs present in wastes actually shifts the level of metabolic activity in the community outside its normal ranges.

(3) Based on the available data, nitrofuran drugs do not appear to present a significantly different hazard than alternate drugs in the locales where residues are introduced.

(4) The replacement of the nitrofuran feed additive market (less than 3% of the total market) and the topical, mastitis, and eye-ear pharmaceuticals containing nitrofuran (less than 4% of the total market including the non-food animal uses) with competing alternate drugs in food-producing animals will not have significant environmental effects attributable to increased environmental residues of alternate drugs, based on data currently available to the FDA.

2.7. Magnitude of Impacts Due to Proposed Nitrofuran Restrictions

Provided with the information in sections 2.4., 2.5., and 2.6., above, what can be said about the magnitude of potential environmental impacts associated with the proposed actions which were identified in the Bureau's original environmental assessment?

2.7.1. Event 1 - Reduced Manufacture and Use of Nitrofurans

Potential environmental impacts associated with the reduced manufacture and use of nitrofurans are perceived as beneficial in nature:

1. Reduced environmental introduction and consequent decreased environmental exposure of humans* and other organisms to agents with carcinogenic, tumorigenic and other toxic properties;

2. Reduced energy and natural resources utilized to manufacture nitrofuran drugs.

The magnitude of both these potential environmental impacts is probably not significant, based on consideration of the following factors:

*Not including exposure of humans to residues of nitrofurans in the edible tissue of treated animals and poultry. This exposure is the basis for the action under the FD&C Act and is the subject of the forthcoming hearings. NEPA supplements, but does not duplicate, the Agency's decisionmaking under the FD&C Act.

1. Nitrofurans sales represent less than 3% of the total feed additive antibacterials market and less than 4% of the animal pharmaceutical antibacterial market (Table 9). Most of the feed additive sales and part of the pharmaceutical sales of nitrofurans are affected by the Bureau of Veterinary Medicine proposals. Therefore, the level of overall exposure is currently low, with the possible exception of occupational exposures of pharmaceutic and feed industry workers.

2. Although no definitive data are available, nitrofuran metabolism and inactivation data (2.6.2.3.) suggest that degradation of 5-nitrofuran residues in the environment is rapid when conditions are suitable for microbial activity or inactivation by sunlight. Locations currently receiving frequent or continual input of nitrofuran residues are subject to long-term exposure to compounds with carcinogenic, tumorigenic, and other toxic effects potential, however. Examples of locations continually exposed are poultry ranges, swine feeding facilities, and pharmaceutical and medicated feed handling facilities with improper dust control where

nitrofurans and medicated feed are prepared, handled, or used. Humans and other organisms in these locations could expect beneficial effects from the Bureau's proposals. Environmental transfer from these locations would be limited, however, and no detectable change would be expected elsewhere.

2.7.2. Event 2 - Increased Manufacture and Use of Alternate Drugs and Animal Management Practices Instead of or to Compensate for Restricted Nitrofuran Uses.

Potential environmental impacts associated with the increased use of alternate drug products and animal management procedures are probably adverse in nature, since these products and procedures do, in general, have an environmental cost associated with their use. These impacts counterbalance the beneficial impacts of Event 1:

1. Increased environmental introduction of alternate drugs with consequent potential increased environmental exposure of humans and other organisms to alternate drug residues;

2. Increased environmental introduction of disinfectants, insecticides, and other

chemicals used in animal management to control or prevent disease;

3. Increased labor, energy, and natural resources associated within alternate animal management practices;

4. Increased drug-resistant microbial populations due to increased use of alternate drugs, with consequent potential increase in animal and human disease not amenable to drug treatment.

Available evidence summarized below, indicates that these potential environmental impacts as they relate to the Bureau's proposed nitrofuran prohibition will not be significant in magnitude.

1. There are many alternate drugs currently competing with nitrofurans in the marketplace (Tables 1-9). The small portion of the antibacterial feed additive and pharmaceutical market occupied by nitrofuran products which would be affected by the proposals (Table 9) would be divided among many products. It is doubtful that there would be detectable increases in the sales of most alternate products.

2. The environmental impacts associated with the use of alternate drug products do not seem to be different in a major way from those associated with the use of nitrofurans (Tables 16 and 19).

3. Given the alternate drugs available, poultry and swine growers would have to give only minimal additional attention to animal management practices that prevent or control disease as a result of the Bureau's nitrofuran proposals. Emphasis would probably center on preventing and treating paratyphoid in young turkey poults and prevention and treatment of chronic respiratory disease complicated by E. coli in broiler chickens and turkeys (2.4.3.2., 2.4.3.3. and 2.4.3.7.). Increases in disinfectant use, labor, energy, etc. associated with the Bureau's nitrofuran proposals are expected to be minimal.

4. Based on the limited available evidence (2.5), it appears that while nitrofuran drugs presently may be useful to control outbreaks of disease organisms resistant to other drugs, they are not significantly better,

in the long term, than other alternate drug products. Nitrofuran resistance appears in the microbial population in the continued presence of the drugs, just as is the case for alternate drugs. Nitrofuran resistance appears frequently in multiply drug-resistant bacteria. The major tool for the prevention and control of these outbreaks appears to be in providing sanitary, healthful conditions for animals with judicious use of drugs.

2.7.3. Event 3 - Decreased Swine and Poultry Productivity, Increased Animal Morbidity, Mortality, and Condemnation at Slaughter.

The extent to which this event occurs will affect the potential environmental impacts with which it is associated. The potential impacts include:

1. Increased use of animal feed and feed supplements and increased waste generated per amount of marketed meat/product (due to decreased growth rate, mortalities, and condemnations) with secondary impacts on land, fertilizer, energy and labor used to produce animals and animal feed;

2. Disposal of animal carcasses due to increased mortality on the farm and increased condemnations at the processing plant;

3. Decreased availability of meat products for humans.

Several factors indicate that the event, itself, will not occur:

1. Primary use of nitrofurans appears to be in the turkey industry for poults 0-8 weeks old. To the extent they are used in chickens, broiler chicks 0-8 weeks old are also the most likely age class to receive nitrofurans. Nitrofurans are not important to cattle and swine production.

2. Alternate drug products (Tables 1-3 and 8) and animal management measures (2.4.3.) exist for the nitrofuran claims affected by the Bureau's proposals. Paratyphoid and chronic respiratory disease complicated by E. coli appear to be the poultry diseases where preventative management techniques and shifts to other modes of drug administration (drinking water and subcutaneous injection) may be required (2.4).

3. Alternate drugs are equal to or more effective than nitrofurans as growth promotants in poultry and swine (Tables 4, 5, and 6).

It is therefore unlikely that decreased swine and poultry productivity or increased animal morbidity, mortality or condemnation at slaughter would occur as a result of the Bureau's proposed nitrofuran restrictions. If such effects were to occur, they would be expected to be temporary, localized, and restricted to one or a few flocks of young turkey poults or chicks. Assuming that a few poultry flocks were adversely affected by the nitrofuran restrictions, it is questionable that there would be consequent environmental effects on land use, energy, disposal of animal carcasses, or availability of meat for humans that would be significant within the meaning of the National Environmental Policy Act or the Council on Environmental Quality's NEPA implementing regulations (40 CFR 1508.27, Federal Register, November 29, 1978).

2.7.4. Conclusion.

Based on the available data discussed in 2.7.1.-2.7.3. above, the magnitude of the potential environmental impacts associated with the Bureau's proposals to prohibit the use of three nitrofuran drugs in food-producing animals does not appear to be significant. An environmental impact statement is therefore not required for the proposed actions.

2.8. Mitigation Measures.

Mitigation measures are those measures which, if taken, would avoid or minimize potential adverse environmental effects associated with the proposed actions. Because no significant adverse environmental impacts were expected, no mitigation measures were included at the time the actions to withdraw approval of the nitrofuran drugs from food-animal use were proposed.

2.9. Environmental Impacts of Regulatory Alternatives.

Regulatory alternatives as defined by the Council on Environmental Quality Regulations (40 CFR 1508.25) include: (1) no action, (2) other reasonable courses of action, (3) mitigation measures not included in the proposed action.

2.9.1. Regulatory Alternative 1 -- No action.

As pointed out in section 1.3.2., no action, i.e., abandonment of the Bureau's proposals, is not a lawful alternative within the present requirements of the Food, Drug and Cosmetic Act. Any drug subject to the Delaney Clause that does not meet its requirements -- here, furazaolidone -- must be withdrawn. Any drug subject to the Safety Clause and which evidence shows is not shown to be safe -- here, furazolidone, nitrofurazone and furaltadone -- is subject to action to remove the hazard to human health by withdrawing approval of the drug for use in food-producing animals.

In order for "no action" to occur, Congressional amendment of the FD&C Act or Congressional imposition of a "moratorium" on prohibiting the use of nitrofuran drugs pending further studies would be required.

2.9.1.1. Effects of No Action on the marketing and use of nitrofuran drugs.

Because Congress has at least two approaches for imposing the "no action" alternative, there are at least two possible effects of such action on the marketing and use of nitrofuran drugs.

A moratorium on the pending actions to prohibit the use of nitrofuran drugs would probably result in no increased marketing of the products. This hypothetical outcome of a moratorium presumes that while the actions are stayed by Congress, no further uses of the drugs in food-producing animals would be approved.

Congressional amendment of the FD&C Act to permit the continued marketing of nitrofurans subject to the proposed actions, however, would not necessarily result in no change in the marketing of and use of the nitrofuran drugs in food-producing animals.

When the Bureau proposed to prohibit the use of the nitrofurans, the compounds marketed under the approved new animal drug applications were protected by patents. Since the date of publication of the proposals, the patents have expired. This means that other firms could now seek approval to manufacture and market the drugs for the

previously approved claims. Data to support new indications for use of the drugs in food-producing animals would also be considered and could receive approval. Thus, "no action" due to Congressional amendment of the FD&C Act might ultimately result in new competitors marketing the drugs with consequent lower prices and, therefore, more widespread use.

2.9.1.2. Environmental impacts due to "no action."

Health effects due to the continued use of nitrofurans in food-producing animals are, for the most part, covered under the FD&C Act mandate and are, therefore, not considered under NEPA. NEPA supplements but does not duplicate considerations under the FD&C Act. FD&C Act health considerations cover the exposure of consumers to residues of nitrofurans in food. Occupational exposure and exposure to nitrofuran residues through other environmental routes are considered below.

As discussed in 2.6.2.3.1. above, little is known about occupational exposure and manufacturing wastes resulting from drug synthesis and subsequent production and use of nitrofuran medicated feeds. Where such exposure and environmental releases occur there is a strong possibility that these wastes and exposures would have carcinogenic, and tumorigenic results on exposed humans. The forthcoming hearing on NF-180, NF-7, and NF-260 will likely better define the potential for adverse health effects on humans. Nitrofuran drugs are not

specifically regulated under the Occupational Safety and Health Act, the Clean Water Act, or the Clean Air Act.

"No action" would result in continued or increased exposure of humans to nitrofuran drugs through occupational and, possibly, other non-food environmental routes. If studies were mandated as part of a temporary moratorium on restricting the use of these drugs, occupational exposures and impacts due to manufacturing and production of nitrofuran-medicated feed should be items examined.

As discussed in 2.6.2. above, NF-180, NF-7 and NF-260 administered to target animals are excreted as parent compound and a wide variety of metabolites. This extensive metabolism pattern, the high water solubility of the metabolites, and the sensitivity of the nitrofurans to light and certain metals suggest that environmental exposure to these drugs is limited to sites of introduction. Environmental transport and bioaccumulation of these compounds is probably limited.

Therefore, adverse effects on non-humans would probably be limited to organisms repeatedly exposed to fresh nitrofuran residues in swine and poultry wastes and to residues released as manufacturing wastes. In the confinement rearing generally practiced for poultry, with litter buildup within enclosed housing, relatively small quantities of microbially active nitrofuran residues are expected to be present at the time these wastes are treated, used as fertilizer, or recycled into animal feeds. For swine, where wastes are frequently treated in

lagoons or oxidation ponds, and for turkeys grown on ranges, soil and aquatic microbes are expected to be continually exposed to unknown, but probably low, levels of nitrofurans. Because it is not possible to calculate the concentration of parent or bioactive metabolites present in fresh animal wastes and information about such concentrations has not been submitted to the Bureau by the firms marketing the drugs, it is not possible to determine the extent of antimicrobial and mutagenic effects that occur on the bacteria, fungi, algae, and invertebrates generally present in animal wastes. Effects on the microbial populations present in sewage treatment facilities due to nitrofuran manufacturing wastes likewise cannot be predicted due to absence of data. On the positive side, the "no action" alternative would not result in adverse environmental effects due to the lack of ability to control two poultry diseases (C.R.D. and paratyphoid) that are possible for the proposed prohibition on the use of NF-180. There would, of course, be no opportunity to determine whether NF-180 did indeed prevent the occurrence of outbreaks of C.R.D. and paratyphoid.

In sum, "no action" would result in the continued or increased exposure of organisms in the immediate environment of animal rearing facilities to nitrofuran residues. If studies were mandated as part of a temporary moratorium on restricting the use of drugs, a study on environmental effects at the sites of manufacture and use of the three nitrofuran drugs is strongly suggested. In the total absence of such data, the need for or the approach to mitigating adverse effects cannot be determined.

2.9.2 Regulatory Alternative 2 --Controlled use of furazolidone for uses not completely covered by alternate drugs.

The analysis in sections 2.4.1., 2.4.2., and 2.4.3. found that there were adequate alternate drugs for all NF-7 and NF-260 claims. For NF-180 (furazolidone), however, it is possible that poultry managers may find that adequate alternate drugs are not presently available for (i) late-occurring chronic respiratory disease in turkeys and, to a lesser extent, chickens and (ii) paratyphoid occurring in turkeys after 4 weeks of age and occurring in chickens after the protection of antibiotic injections at day 1 declines.

One regulatory alternative worth consideration would be to permit only those NF-180 claims (late-occurring C.R.D. and late-occurring paratyphoid in turkeys and chickens) where adequate alternate drugs do not presently exist and control usage such that unsafe furazolidone residues do not enter the human food supply.

There are, however, a number of reasons why this alternative does not appear to be feasible.

1) It is unclear whether late-occurring C.R.D. and paratyphoid in turkeys and chickens will become a more significant problem due to the absence of furazolidone and whether it would cause economic losses in excess of the costs of a regulatory program;

2) It is unclear whether furazolidone provides major benefits in flocks when used <u>after</u> the conditions are diagnosed;

3) It would appear that the withdrawal time required to reduce furazolidone levels to effective zero cannot be determined based on available data; and

4) It does not appear that a procedure guaranteeing compliance with a

withdrawal period could be developed, in the absence of an adequate method to detect furazolidone residues, that would be consistent with the U.S. legal framework for monitoring drug residues in meat for human consumption.

There are unknowns involved with each of the four points above. First, with the current information available, it is not possible to predict the impact that a ban on furazolidone would have on the incidence and treatment of late-occurring C.R.D. and paratyphoid. Alternate drugs are available for the prevention and control of these diseases for early life stages of chickens and turkeys, when they are a greater problem. Management procedures to prevent the introduction of these diseases into flocks are also widely practiced and are presumably effective. While furazolidone is singular in its indication for use in later life stages of turkeys and chickens for these diseases, it is not at all clear that this is the time when it is predominantly used.

Second, any furazolidone limited use strategy would be expected to be predicated on the diagnosis and treatment of C.R.D. or paratyphoid at a time in the life of turkeys or chickens when no alternate drugs could be used. Furazolidone is approved for prevention and treatment of paratyphoid and for control of C.R.D. If furazolidone were allowed only for treatment of paratyphoid and C.R.D., it could not be confidently predicted that significant benefits would result.

Third, and potentially most limiting, is the length of the withdrawal period after treatment that would be necessary to reduce furazolidone residues to effective zero. Based on the information available to the agency, it is not possible to accurately determine the length of the withdrawal period necessary to reduce furazolidone residues to

effective zero. Thus, it does not appear to be feasible to permit even limited uses of furazolidone.

Fourth, it is doubtful that a procedure could be developed, in the absence of a regulatory method for detecting furazolidone residues, that would guarantee compliance with withdrawal periods and also with the Food, Drug and Cosmetic Act and the Federal Meat and Poultry Inspection Acts. It would appear that the Delaney clause does not permit the approval of a carcinogenic new animal drug in the absence of an approved regulatory method. Moreover, there is no precedent for such a program. FDA, USDA, veterinarians, and poultry producers would have to agree on a procedure acceptable to all. The procedure would probably have to include third-party control of treated flocks during the withdrawal period. Costs to the poultry producer and the federal government would be apt to exceed the benefits gained by the treatment, unless the diseases were occurring in epidemic proportions.

For these reasons, regulatory alternative 3--the proposed prohibition of use of the nitrofurans plus administrative measures to expeditiously review and approve alternate drugs--would be a more feasible and realistic alternative in view of the safety and legal problems presented by regulatory alternative 2.

Regulatory alternative 2 provides some increased protection against poultry diseases, when compared to the proposed action, but not as much as regulatory alternative 1 "no action." There is reduction in occupational exposures to nitrofuran drugs, when compared to "no action," but not as much as the proposed action. Impacts on environmental organisms are probably similar for the proposed action, "no action," and regulatory alternative 2.

2.9.3. Regulatory Alternative 3-Proposed actions plus mitigations.

The proposed actions would prohibit the use of NF-180, NF-7, and NF-260 in food-producing animals. Mitigation measures may be added which would minimize potential adverse environmental effects associated with the proposed actions.

Although none of the environmental effects examined appear to be significant, a prohibition on the drug furazolidone may have adverse environmental effects stemming from a possible reduction in the ability of poultrymen to treat late-occurring complicated chronic respiratory disease in broiler chickens and turkeys and to prevent and treat late-occurring paratyphoid in turkeys and chickens. That is, if these diseases occurred at a greater frequency or severity as a result of the proposed actions (due to the limited availability of alternate drug products or animal management procedures), there would be a loss of resources of the types required to rear these animals.

2.9.3.1. Mitigations

Mitigation 1. Encourage the development of new drugs or new claims for presently existing drugs for complicated chronic respiratory disease and paratyphoid in chickens and turkeys.

This measure is both feasible and consistent with present policy in the Bureau. New drug products for these claims may qualify for priority handling ("fast-track") which would result in faster approval and marketing of the new products. Given the competitive nature of

the animal drug industry, it is reasonable to expect that a major disease problem in poultry (a very large market) would be addressed by one or more firms before much time elapses, especially if the drugs had an excellent chance of rapid approval by the FDA.

Mitigation 2. If a severe problem developed with high losses due to one of these diseases, the Bureau could consider whether any investigational drugs were available that could be safely permitted for treatment of the disease on a short-term and/or localized basis under direct Federal supervision. Such a permit has been called approval of an emergency investigational new animal drug application (emergency INAD).

Assuming the Bureau successfully advances its proposal to withdraw approval of furazolidone, mitigation 1 could be initiated immediately and mitigation 2 instituted only if absolutely necessary.

2.9.3.2. Environmental Impacts of Regulatory Alternative 3

If there are drugs that may qualify for fast-track NADA or emergency INAD procedures, the mitigations provide for swift approval of alternate drugs for the two poultry diseases affected by the proposed furazolidone prohibition.

If the mitigations worked effectively, then regulatory alternative 3--the proposed actions plus mitigations would be the environmentally preferrable alternative. Adverse environmental impacts would be

minimized and some beneficial reduction in occupational exposure to carcinogenic and tumorigenic drugs would result. If there were delays in finding and approving alternate drugs for the furazolidone claims where alternates do not currently exist, the impacts expected would be similar to those anticipated for the proposed actions alone during the delay.

SECTION 3. PERSONS INVOLVED IN THE PREPARATION OF THIS DOCUMENT

The following persons were involved in the preparation and review of this assessment.

John C. Matheson, III, the preparer-editor has been an environmental scientist in the FDA for eight years where he is responsible for the analysis of the potential environmental impacts of actions proposed by the Agency, for providing guidance to petitioners on the types of environmental data needed to determine whether a proposed action requires the preparation of an environmental impact statement, and for the evaluation of environmental documents prepared by other agencies. He specializes in limnology and aquatic ecology and earned a MSPH in Environmental Sciences and Engineering (1975) and a BS in biology (1973), both from the University of North Carolina, Chapel Hill.

Thomas V. Raines, DVM, a contributor on the topic of avian diseases and their treatment and reviewer, has been a staff member of the Bureau of Veterinary Medicine for approximately fourteen years. He is a licensed veterinarian and specialist on poultry diseases. Dr. Raines obtained his degree in veterinary medicine in 1945 from Auburn University.

David Ducharme, DVM, a contributor on the subject of alternate drug products for nitrofuran claims and reviewer, is the former Director of the Bureau of Veterinary Medicine's Division of Drugs for Avian Species. He has recently retired after approximately 20 years with FDA. Dr. Ducharme received his degree from Michigan State University in 1957.

Charles Haines, DVM, a contributor on the subject of alternate drug products for nitrofuran claims in swine is Group Leader of the Antimicrobial Drug Products Group in the Bureau of Veterinary Medicine. He received his DVM from Kansas State University in 1954. Prior to coming to FDA in 1968, he was in a primarily large animal (swine and cattle) veterinary practice in Iowa for 14 years.

Judith Hauswirth, Ph.D., heads the Bureau's effort in the hearing action on nitrofurans. She is a Group Leader on the staff of the Bureau's Toxicology Staff within the Office of Human Food Safety.

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APPENDIX A

The following references were submitted by one firm (Norwich) in support of its arguments that the original 1976 environmental assessment was inadequate and that an environmental impact statement is required for the proposed actions to prohibit the use of nitrofurans in food-producing animals. The one other commentor addressing the environmental impact of the proposed actions did not provide any data in support of the arguments presented.

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References 1-7 were cited as studies which reported the finding of R-factor transmissible nitrofuran resistance but in which the firm suggests chromosomal rather than transferable resistance was actually observed. The reasons for the firm's conclusions in this regard were not specified.

The 1976 environmental assessment cites only the possibility of R-factor transferable drug resistance. The revised environmental assessment has been expanded to more fully discuss the roles of chromosomal and R-factor nitrofuran resistance in animal and human disease (sec. 2.5.) References 1-7 were not especially relevant to this discussion and therefore were not used. The Bureau makes no judgment as to whether the firm's suggestions regarding the findings of references 1-7 are correct.

Reference 8, the so-called Swann Report, was cited as proof that use of subtherapeutic antibiotics encourages the emergence of drug-resistant strains of pathogens.

The Bureau agrees that the Swann Report supports such a conclusion. It further notes in sec. 2.5.2. that the epidemic of drug-resistant salmonella in calves which was a major event that stimulated the formation of the Swann Committee included frequent isolations of multiply-resistant Salmonella typhimurium which included furazolidone resistance (Anderson, 1968).

References 9-13 were submitted to demonstrate the seriousness of Salmonella typhimurium infections in humans.

The Bureau does not dispute the seriousness of salmonellosis in humans or that S. typhimurium may be transferred from animals to man. At issue is the essentiality of furazolidone for controlling S. typhimurium infections (paratyphoid) in poultry. This is discussed in sections 2.4.3.2.3. and 2.5. in the environmental assessment and considered below.

The firm cited seven references (14-20 dated 1947-1959) which show bacterial reduction of nitrofurans to aminofurans in axenic cultures as proof that nitrofurans are readily degraded in the environment.

The 1976 environmental assessment stated that "biologically mediated inactivation of 5-nitrofurans is likely" and the Bureau does not dispute the bacterial degradation pathways hypothesized in the cited references. The Bureau believes, however, that such data cannot be used to predict with any confidence the persistence of nitrofurans and their metabolites under natural conditions. The studies cited used bacterial culture media as substrate for the growth of a single strain of bacterium. Bacterial culture media provide complete nutrient requirements in high concentrations and, therefore, support much greater populations of microorganisms growing and metabolizing at a far greater rate than is commonly observed in most soils. Considering only biodegradation processes, the Bureau would expect nitrofurans, as well as any other biodegradable material, to persist for greater periods in environmental conditions than in culture conditions. The Bureau is not aware of any directly applicable laboratory or field studies that have been performed that might indicate more realistically the persistence of nitrofurans and their metabolites in the environment. The environmental fate of nitrofurans is more fully discussed in sec. 2.6.2.4. Three of the more pertinent of the seven references cited by the firm are included in that discussion.

References 21-30 and the following references cited in an appendix were submitted relating to the effectiveness of furazolidone in treating Salmonella and E. coli infections when compared to other drugs. The firm claimed these studies show that furazolidone is the drug of choice for control and treatment of salmonellosis in swine and poultry.

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A number of the cited references do not address the issue of whether furazolidone is the drug of choice for control and treatment of salmonellosis in poultry and swine. In references 26, 28, A-1, A-3, A-7, A-8, A-9, A-10, A-15, A-17, A-19, A-21, A-22. A-23, A-27, A-28, A-29, A-30, A-32 and A-33, no drugs approved by FDA for the claims tested were compared with furazolidone. In references 22, A-4, A-11, A-16, A-20, A-31, A-34, A-35 and A-38, furazolidone and/or the drugs tested in comparison were/was not administered in the manner approved by FDA. In references A-2, A-12, A-26, A-28, and A-36, the effectiveness of furazolidone and other drugs was compared for fowl typhoid or pullorum disease, not paratyphoid (S. typhimurium). Reference A-24 addressed the effectiveness of furazolidone in treating S. choleraesuis in swine, not S. typhimurium. Therefore, these references will not be considered further.

References A-5 and A-13 addressed the effectiveness of furazolidone and other drugs in treating chronic respiratory disease complicated by E. coli and E. coli septicemia. They support the conclusion stated in the environmental assessment that furazolidone is presently the drug of choice for oral administration for this indication. The studies, though, do not address the comparative effectiveness of the available antibiotics administered by subcutaneous injection.

References A-14, A-18, A-25, and A-37 address the effectiveness of furazolidone and other drugs in treating paratyphoid (S. typhiumurium) in chickens. The studies do not clearly show furazolidone as the drug of choice for paratyphoid in chickens. In one study (A-14), better results were obtained with chlortetracycline. In another (A-25), there was not a significant difference between results obtained for the same two drugs. A-37 found furazolidone more useful than oxytetracycline for treating S. typhimurium infections. References 23, 24, 25 and A-18 addressed the shedding of salmonellae by chickens infected with S. typhimurium. While this is not an FDA-approved claim for furazolidone or alternate drugs, it is one valid parameter in determining activity of drugs against paratyphoid infections in poultry. Neither furazolidone nor the FDA-approved alternate drugs evaluated in Ref. A-18 (the only experimental data cited) prevented fecal shedding of S. typhimurium.

Reference A-6 addressed the effectiveness of furazolidone, chlortetracycline, and two drugs not approved by FDA for treating E. coli infections in swine. Furazolidone and chlortetracycline were found to be equally effective in this study.

In sum, references 21 through 30 and A-1 through A-38 point out the importance of chronic respiratory disease complicated by E. coli and paratyphoid in poultry and the usefulness of furazolidone and other drugs, such as chlortetracycline, in treating these diseases. The environmental assessment accurately reflects these conclusions. The

proposed actions may hamper the ability of poultry managers to treat these diseases when they occur late in the growing period of turkeys and chickens. Regulatory alternative 3 includes some mitigation measures which would reduce such adverse effects.

References 31-34 point out that tetracycline drugs (one group of existing alternate drugs for furazolidone) permit drug-resistant strains of bacteria to emerge when they are used subtherapeutically. The Bureau of Veterinary Medicine recognizes that emergence of tetracycline-resistant bacterial strains result from long-term subtherapeutic use of tetracyclines and that this emergence is a potential problem. The Bureau and the National Academy of Sciences have developed a research program to evaluate the problem. No action to limit the use of tetracyclines in animals is contemplated until the research program is completed. The drug resistance problem is discussed in section 2.5. of the environmental assessment and in the Bureau of Veterinary Medicine's draft environmental impact statement "Subtherapeutic Antibacterial Agents in Animal Feeds" (Feinman and Matheson, 1978).