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Environmental Assessment
for Dimetridazole
Notice of Opportunity for Hearing

1. Description of the Proposed Action

a. Proposed action and regulatory authority.

The Food and Drug Administration's (FDA's) Center for Veterinary Medicine (Center) is providing an opportunity for hearing on a proposal to withdraw approval of the new animal drug applications (NADA's) for dimetridazole and to revoke the new animal drug regulations reflecting approval of the NADA's (21 CFR 520.680, 558.240 and 556.210). This action is being taken in accordance with section 512(e)(1)(B) of the Federal Food, Drug, and Cosmetic Act (the act), 21 U.S.C. 360b(e)(1)(B). That section requires FDA to withdraw approval of an NADA if the agency finds

> that new evidence not contained in such application or not available to the [FDA] until after such application was approved, or tests by new methods, or test by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the [FDA] when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved ****

The Center has determined that dimetridazole is not shown to be safe for use within the meaning of section 512(e)(1)(B) of the act because (a) new evidence provides a reasonable basis from which serious questions about the ultimate safety of dimetridazole and the residues that may result from its use may be inferred, (b) new evidence shows that the drug is no longer shown to be safe by adequate tests by all methods reasonably applicable, and (c) new evidence shows that the labeled directions for use have not been followed in practice and are not likely to be followed in the future.

Under 21 CFR 25.31b, FDA is required to prepare an environmental assessment of the proposed action to determine whether the action may significantly affect the quality of the human environment under the criteria in 40 CFR 1508.14 and 1508.27.

b. Underlying purpose and need for the proposed action.

Dimetridazole (1,2-dimethyl-5-nitroimidazole) belongs to a class of compounds called 5-nitroimidazoles, some of which are used to treat protozoal diseases in man and other animals. Dimetridazole is approved for use in turkeys (1) for the prevention and treatment, and as an aid in the control of histomoniasis (blackhead, infectious enterohepatitis), (2) for growth promotion, and (3) for improved feed efficiency (21 CFR 558.240 and 520.680). Section 558.240 provides for continuous use at 0.015 to 0.02 percent (136 to 182 grams per ton) in feed and for use for not more than 7 days at 0.06 to 0.08 percent (544 to 725 grams per ton) in feed. Section 520.680a provides for continuous use at 0.01 or 0.02 percent in drinking water and for use for 5 days only at 0.04 percent in drinking water. Section 520.680b provides for the use of one 125-milligram tablet for 1 to 10 pound birds and for use of two 125-milligram tablets for birds weighing more than 10 pounds. The regulations specify a 5-day withdrawal period. In the FEDERAL REGISTER of November 13, 1964 (29 FR 15255) FDA established a tolerance of zero for residues of dimetridazole in uncooked edible tissues and eggs of turkeys (current 21 CFR 556.210). Dimetridazole has also been widely misused for the prevention and treatment of dysentery in swine, a species in which use of the drug has not been approved.

Data presented in the notice of opportunity for hearing (NOOH; copy attached) for dimetridazole demonstrate (1) that there are serious questions about the safety of dimetridazole and the residues that may result from its use, (2) that the data in the NADA's for dimetridazole no longer show, by all tests by all methods reasonably applicable, that dimetridazole is safe, and (3) that dimetridazole is widely misused in swine and that such misuse is likely to continue unless approval of the NADA's is withdrawn. For these reasons, the Center is proposing to withdraw the approval of the NADA's for dimetridazole.

c. How the proposed action addresses the problem.

Withdrawal of approval of the NADA's for dimetridazole will remove the drug from the market and eliminate the potential for the drug to be used in food-producing animals. This action will consequently eliminate human exposure to potentially carcinogenic residues of dimetridazole in edible turkey tissues, and because the drug is misused in swine, in edible swine tissues as well.

2. Environmental Introductions as a Consequence of the Proposed Action

a. Approved uses for which the approval would be withdrawn.

Marsden (1971) describes turkey rearing practices for ranges (pasture), in confinement, or by a combination of range and confinement. Range rearing provides benefits from direct sunlight, exercise, fresh air, and reduced feed costs. However, range rearing may become unprofitable because of losses from soilborne diseases, insects, predators, and adverse weather conditions. Turkeys are generally moved to the range from the brooder house when they are about eight weeks old. One range rearing method, the Minnesota Plan, involves moving birds to a clean location once every 7-14 days and the use of a range once every 2-4 years. This method stipulates the use of 1 acre of range per 250 birds per year and is generally restricted to rearing a maximum of 4,000 birds at a time. The Minnesota Plan is often effective in preventing soilborne diseases and parasites, although contamination by soilborne diseases organisms can occur. Confinement rearing in houses requires the use of bedding and eliminates access to a yard or range. It is a rearing practice that has been widely adopted because it offers protection against losses from predators, adverse weather, soilborne disease, and insects, it lowers land and labor costs, and it provides for better control of turkey production. Disadvantages include higher costs of housing and equipment, increased risk from respiratory disease and cannibalism, and more danger from overcrowding. A combination of range and confinement rearing is provided through the use of a confinement house with a range or yard on either side of the house. Turkeys are confined at night and during adverse weather, and left outside

in one of the yards during the day. The combination rearing method offers the benefits of protection from predators and adverse weather, as well as access to sunlight, exercise, and fresh air. Yards are used in alternate years to help minimize contamination of soil. One acre per 250 birds is the space specified for yards. However, once soil has been contaminated by disease-causing organisms, preventative medication is often utilized to prevent disease occurrence.

One of the major soilborne diseases of turkeys is histomoniasis. Histomoniasis is a parasitic disorder of the digestive system of many gallinaceous birds. The turkey is one of the most susceptible birds to histomoniasis, especially from its 4th or 5th week (Lund, 1972), but turkeys of all ages are susceptible to the disease (The Merck Veterinary Manual, 1979). Chickens are not as susceptible to the disease but remain carriers leading to the basic management rule that turkeys should not be reared with chickens or on range where chickens have been produced during the previous several years (McDougald, 1984). The disease syndrome was first described by Smith (1895). It is characterized by necrotic foci of the liver and ulceration of the ceca (McDougald, 1984). Histomoniasis is caused by the protozoan Histomonas meleagridis, which is principally transmitted from host to host by Heterakis gallinarum, a common cecal worm of domestic and several species of wild galliform birds (McDougald, 1984; Lund, 1972; Lund and Chute, 1971, 1972, & 1974). H. gallinarum alone may not cause appreciable harm in the host (Lund and Chute, 1974). H. gallinarum depends heavily on earthworms for its transmission and survival outside a host bird (Lund, 1974), although arthropods including flies, grasshoppers, sowbugs and crickets, may serve as mechanical vectors (McDougald, 1984).

Dimetridazole is approved for the prevention and treatment, and as an aid in the control of histomoniasis (blackhead, infectious enterohepatitis) in turkeys (21 CFR 520.680 and 558.240). These approvals will be withdrawn if the proposed action becomes final. Besides dimetridazole, several other animal drugs including ipronidazole, nitarsone, and carbarsone have been approved for use in the treatment, prevention, or as an aid in the control of histomoniasis in turkeys.

Dimetridazole is also approved for improved growth promotion and improved feed efficiency in turkeys. These approvals will be withdrawn if the proposed action becomes final. Other animal drugs including bacitracin, bambermycins, arsanilic acid, ipronidazole, chlortetracycline, erythromycin, oleandomycin, penicillin, roxarsone, and carbarsone in combination with bacitracin are also approved as growth promotants in turkeys.

The NADA's for dimetridazole known to the Center and affected by the proposed notice of opportunity for hearing are:

FIRM	NADA NO.	DATE APPROVED
Salsbury Laboratories, Inc.	14-145	01/21/64
Salsbury Laboratories, Inc.	14-345	11/13/64
Salsbury Laboratories, Inc.	14-613	03/19/65

The approval of NADA 36-826 for dimetridazole, held by Albers Milling Company (Division of Carnation Company), was voluntarily withdrawn and will not be considered further in this document.

b. Magnitude of uses for which the approval would be withdrawn.

The Center is unaware of any non-proprietary information respecting the exact magnitude of the production and use of dimetridazole. The largest single contribution to total production and use of dimetridazole probably results from its use in the prevention of histomoniasis because of the high dosage, the extended duration of use, and the prevalence of histomoniasis in the U.S. The contribution to total production and use resulting from the use of dimetridazole for the treatment and control of histomoniasis is not expected to be significant because of limited duration of use and because animal management practices emphasize prevention of disease rather than treatment or control. The contribution to total production from the use of dimetridazole in growth promotion and feed efficiency could be significant, but it is not possible to reliably separate production for uses in growth promotion and feed efficiency from production for use in prevention of histomoniasis. The contribution to the total production of

dimetridazole from its use in swine dysentery cannot be estimated with any precision for two reasons. First, there are numerous drugs approved and used for swine dysentery. Second, the use of dimetridazole in swine dysentery is illegal, as a result of which there is no reliable information that would provide a means of estimating the portion of the use in swine which could be attributed to the production of dimetridazole. Therefore, in order to obtain a reasonable estimate of the magnitude of the total production and use of dimetridazole, the Center has considered the size of a yearly turkey crop, an estimate of the extent of drug usage to prevent histomoniasis, and the portion of this usage which could be attributable to dimetridazole.

The 1985 turkey crop totaled 185 million birds (USDA, 1986). Although the turkey crop has fluctuated over the years and has had a general upward trend, this value provides a reasonable basis for subsequent calculations. Potter (1986) estimated that, averaged over the last twenty years, about 30% of turkeys received an antihistomonal drug. Current use could be as low as 10% (Davidson, 1986), but the 30% value will be used in the following calculations in order to determine the potential environmental impacts based on the liberal use of antihistomonal drugs. Thirty percent of the total turkey crop in 1985 is 55,500,000 birds. Of the 55,500,000 turkeys which could receive an antihistomonal drug, no more than 50% (27,750,000) would be expected to receive dimetridazole because other drugs, particularly ipronidazole (see section 2.d.), are available for use in turkeys for histomoniasis.

Because turkeys are susceptible to histomoniasis at any age (The Merck Veterinary Manual, 1979), turkeys will probably receive an antihistomonal drug from hatching until market age. (A 5-day withdrawal period is required for dimetridazole, but will not be considered in the calculations because it will not significantly alter the estimated total production and use.) Slaughter of turkeys will often occur at approximately 23 weeks of age, by which time each turkey will have consumed 70.4 pounds of feed (Marsden, 1971). Dimetridazole is approved for continuous use to prevent histomoniasis at a finished-feed level of 136 to 182 grams per ton of feed (21 CFR 558.240). Proportionately, at the 182 grams per ton level, one

bird will have consumed 6.4 grams of dimetridazole by the age of 23 weeks. Multiplying the number of birds estimated to be treated with dimetridazole (27,750,000 birds) by the grams of dimetridazole consumed per bird (6.4 g) gives an estimate of 1.78×10^8 grams or 178,000 kg of dimetridazole produced in 1985 and used for the prevention of histomoniasis. This estimate is high relative to the amount actually produced, as reported to FDA.

c. Misuse and magnitude of misuse and approved substitutes for swine dysentery for which the drug product would no longer be available.

Data presented in the NOOH on the proposed withdrawal of the NADA's for dimetridazole show that it is widely used for the treatment and prevention of dysentery in swine, a species in which use of the drug has not been approved.

Swine dysentery (bloody scours, vibrionic dysentery, hemorrhagic dysentery, black scours, mucohemorrhagic diarrhea) is a common, important mucohemorrhagic diarrheal and exudative disease which occurs in most swine-producing countries (The Merck Veterinary Manual, 1979). In its early stages the disease is characterized in most herds by the appearance of yellow-to-gray, soft feces combined with a slight reduction in appetite. Progression of the disease is noted by changes in feces which become watery and contain blood, mucus, and a whitish mucofibrinous exudate. Eventually, dehydration, weakness, emaciation, rough coat, incoordination and increased thirst occur. Lesions appear in the large intestines, cecum, and rectum (The Merck Veterinary Manual, 1979). The only known agent involved in the transmission of swine dysentery is the spirochete, Treponema hyodysenteriae (The Merck Veterinary Manual, 1979). Glock (1984) reports that the incidence of swine dysentery in the Midwest is high and that a survey found an average of 39.5% of the swine herds in Iowa, Illinois, and Missouri were infected.

As noted in section 2.b., the Center cannot estimate with any precision the magnitude of the production of dimetridazole which might be allocated to misuse in the prevention and treatment of swine dysentery. However, numerous alternative animal drugs are approved for use in the prevention or treatment of swine dysentery and the Center expects that increases in their production would be distributed among a number of approved animal drug products and would not be significant for any one approved product. Among the animal drugs approved for use in the prevention or treatment of swine dysentery are the following: lincomycin (21 CFR 520.1263 and 558.325); roxarsone (21 CFR 520.2087, 520.2088 and 558.530); tiamulin (21 CFR 520.2455); tylosin (21 CFR 520.2640 and 558.625); carbadox (21 CFR 558.115); virginiamycin (21 CFR 558.635); bacitracin (21 CFR 558.76); and gentamicin (21 CFR 520.1044).

d. Uses and magnitude of uses of approved substitutes for histomoniasis in turkeys.

As noted above, besides dimetridazole, ipronidazole (21 CFR 520.1162 and 558.305), nitarsone (21 CFR 558.369), and carbarsone (21 CFR 558.120), are approved for use in the treatment or prevention, or as an aid in the control of histomoniasis in turkeys. Ipronidazole is approved as (1) a soluble powder for addition to drinking water at 0.0125% for the treatment of histomoniasis, (2) as a medicated feed at 0.00625% (56.75 grams/ton) for continuous use as an aid in the prevention of histomoniasis, for increased weight gain and improved feed efficiency and (3) as a medicated feed at 0.025% (227 grams/ton) to be fed for 7 days for the treatment of histomoniasis. Additionally, ipronidazole (56.75 grams/ton) may be combined with sulfadimethoxine (56.75 grams/ton) and ormetoprim (34.05 grams/ton) in feed for use as an aid in the prevention of histomoniasis, coccidiosis caused by specified pathogens, and bacterial infections caused by Pasteurella multocida.

Carbarsone is approved for use as an aid in the prevention of blackhead at 227-340.5 grams/ton and in combination with specified doses of bacitracin, zoalene, amprolium, and bambermycin as an aid in the prevention of histomoniasis and for increased weight gain.

Nitarsone is approved for use in feed as an aid in the prevention of histomoniasis at 170.5 grams/ton.

It is expected that turkey producers currently using dimetridazole would switch primarily to the use of ipronidazole to treat, prevent, or control histomoniasis and for increased rate of weight gain and feed efficiency. There are at least two reasons for this expectation. First, ipronidazole and dimetridazole are chemically and pharmacologically related and ipronidazole would be expected to provide the same results and actions as experienced with dimetridazole. Second, ipronidazole may be used in combination with sulfadimethoxine and ormetoprim to treat coccidiosis and bacterial infections.

Therefore, in this document the Center has estimated the potential increase in the production and use of ipronidazole under the assumption that it will be the only substitute product used when dimetridazole is no longer available. If data become available indicating that the other substitute drugs are utilized to a large extent, revisions of the estimate will be necessary and estimates will be made for the other alternatives.

Utilizing the estimate provided in section 2.b. for the production of dimetridazole (178,000 kg/year), the comparable dose of ipronidazole (56.75 grams per ton), and the assumption that ipronidazole will be used as the only substitute for dimetridazole, the production of ipronidazole would increase by 55,500 kilograms (56.75 g x 178,000 kg) / 182 g). Because of the assumptions that (1) dimetridazole is used in 50% of turkeys receiving some form of antihistomoniasis drug, (2) ipronidazole will be the substitute drug used to replace dimetridazole, (3) ipronidazole is already used in 50% of the turkeys receiving an antihistomonal drug, and (4) ipronidazole is approved for use only in turkeys for histomoniasis, weight gain and feed efficiency, the estimated increase in the production of ipronidazole would represent as much as a 100% increase in the production and use of this product. This would be a significant increase in production and use of ipronidazole.

e. Use and extent of use of management practices as substitute for approved uses of dimetridazole.

Turkey growers were reported to have fairly effective means of controlling histomoniasis before the discovery of satisfactory antihistomonal drugs (Lund, 1972). The primary means of management was and remains the isolation of poults from chickens and older turkeys and confinement rearing (Lund, 1972). On range, sandy well-drained soil may provide good rearing conditions, provided the previous history of the range is known, (i.e., free of previous contamination) and contamination of the soil does not occur. Total confinement rearing of turkeys offers the best means of controlling soilborne diseases and appears to be the method being utilized more extensively as time passes. Although no figures exist to support management as a sole control for histomoniasis, with recent increases in the knowledge of the etiology of histomoniasis, implementation and strict adherence to existing management practices could provide a good means of controlling the disease without the use of drugs. However, because dimetridazole would be replaced by a comparable drug product, changes in management practices as a result of the proposed action would not be anticipated or necessary to maintain current turkey production rates.

f. Uses for which no substitute product or management practice is available.

All of the current uses of dimetridazole can be covered by substitute drug products. In particular, ipronidazole is indicated for the same uses as dimetridazole and will provide complete substitute use in turkeys. Additionally, numerous products are available as substitutes for use for swine dysentery.

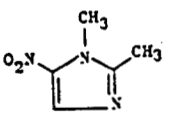
3. Environmental Impact as a Consequence of the Proposed Withdrawal of Dimetridazole

a. Environmental data for dimetridazole.

The following paragraphs summarize the environmental data available to the Center on dimetridazole. These data will be used to assess the potential

environmental impact of the removal of dimetridazole and the increased use of substitute drugs. No environmental assessment of the use of dimetridazole was conducted at the time the NADA's were approved because the approvals preceded FDA implementation of the National Environmental Policy Act (NEPA), and the Center is unaware of environmental data submitted for proposed new uses of the drug. Therefore, the environmental information available to the Center is limited to that available in the scientific literature.

(1) Chemical identity: Dimetridazole is the active chemical component of the products marketed under the trade names Emtryl®, Emtylvet®, and Unizole®. Its chemical name is 1,2-dimethyl-5-nitroimidazole (USAN, 1984). Its CAS registration number is CAS-551-92-8. Its chemical and structural formulas as provided in The Merck Index (1983) are as follows:



$C_5H_7N_3O_2$

Dimetridazole's molecular weight is 141.13 (The Merck Index, 1983; USAN, 1984). The Merck Index (1983) reports that dimetridazole is sparingly soluble in water, but that it is freely soluble in water as the hydrochloride and the dihydrogen phosphate. Its melting point is reported to be 138-139°C (The Merck Index, 1983). Stone and Hobson (1974) report that it demonstrates maximum light absorption at 320 nm.

(2) Introduction into the environment through manufacturing: No information is available concerning the manufacture of dimetridazole. Like other nitroimidazoles, however, dimetridazole is synthesized through chemical means. Wastes from the manufacturing facility would be expected to contain at least some finished drug product and a number of reaction products, as well as solvents, emulsifiers, and other chemicals used in its production. Some adverse environmental effects could occur from manufacturing wastes, but the extent of any impact would depend upon the

effluent treatment processes utilized at the manufacturing facility. Occupational exposures and effects at the manufacturing facility could also occur.

The withdrawal of approval of the NADA's for dimetridazole should result in the elimination of the manufacture of this product in the U.S. The reduction would be expected to consist of the amount of drug estimated to be used in turkeys, i.e., 178,000 kg/year. Wastes containing dimetridazole, its reaction products, and any associated chemicals would no longer enter the environment and occupational exposures would no longer occur. Subsequently, any adverse environmental and occupational health impacts associated with the production of dimetridazole would be eliminated.

Dimetridazole is marketed to turkey production facilities as a premix for use in the preparation of medicated feed, as a soluble powder for use in drinking water, and in the form of tablets. The premix is combined with feed by licensed feed mill personnel to provide a finished feed for turkeys. The soluble powder is combined with water at the turkey-growing facility to provide medicated drinking water. Personnel preparing medicated feed and drinking water could be exposed to dimetridazole through topical or inhalation routes. Toxic effects, including carcinogenicity, to these persons as well as to those persons in the primary manufacturing facility could occur.

(3) Introduction into the environment through the use of dimetridazole: As noted in section 2.a., turkeys may be grown on ranges, in confinement, or by a combination of these methods. In 1971, Marsden reported that turkey flocks could range from 1000 to 10,000 birds with as many as 50,000 to 100,000 birds raised per year on some farms and ranches. Dimetridazole would be introduced into the environment via turkey waste which would be directly excreted onto ranges by range-reared birds or added to soil following the cleanout of confinement rearing facilities. Turkeys given access to range, either for total rearing or for a combination of range and confinement rearing, are given 174.2 square feet per bird (1 acre per 250 birds). No bedding is used on ranges, but birds are moved every 7-14

days and it is recommended that a range be used only every 2-4 years. The amount of space given each bird, as well as the movement and alternating use of ranges, aids in reducing contamination of soil with disease organisms, but these birds are susceptible to soilborne diseases. Therefore, they are most likely to receive an antihistomonal drug to prevent outbreaks of disease. Those birds held in confinement, either for complete confinement rearing, or during confinement when a combination of confinement and range rearing is used, are given 5.5 square feet per bird. In confinement areas, heavy bedding is required to provide good ground cover and to prevent excessive dust and waste buildup. Those birds raised totally in confinement would be least susceptible to outbreaks of soilborne diseases and preventative use of an antihistomonal drug might not be necessary, but turkeys may, nonetheless, receive a drug such as dimetridazole or ipronidazole for growth promotion and feed efficiency. Turkeys reared by a combination of confinement and range would be susceptible to soilborne diseases.

Although higher spot concentrations of wastes and excreted residues of drugs may occur from range-reared birds where wastes are directly introduced onto soils, the most extensive and widespread environmental introduction of drug residues into the environment would be expected to occur from the introduction of waste from a confinement area into soils. Therefore, environmental introductions of dimetridazole will be calculated based on concentrations of the drug contained in waste from confinement areas.

Utilizing ^{14}C-labeled dimetridazole, Law, et al. (1963) reported that 90% of a single 32 mg/kg dose of dimetridazole administered to turkeys was excreted in the urine, feces, and expired air within 72 hours and that 97% of this was present in a metabolized form. The main metabolic pathway involved oxidation of the 2-methyl group to the 2-hydroxymethyl which could then conjugate as the hydroxysulfate, glucuronide, or oxidize further to the 2-carboxyl derivative. Turkeys were also administered dimetridazole (0.05%) in water for six days (200 mg/day). These birds were killed at 0, 1, and 2 days after dosing. At the detection limits of the test, excreted dimetridazole products consisted of parent and six metabolites, 4 of which

were identified as follows:

	Excreted Dimetridazole Products	Percent of Excreted
I	conjugated glucuronide probably of the nitroimidazole 2-hydroxymethyl derivative	not provided
IV	1-methyl-5-nitroimidazol-2-carboxylic acid	25.8
V	urinary metabolite 1-methyl-5-nitroimidazol-2-ylmethyl hydrogen sulfate	44.4
VI	2-hydroxymethyl-1-methyl-5-nitroimidazole	9.4
VII	unchanged dimetridazole	3.2

Because turkeys are susceptible to histomoniasis at any age (The Merck Veterinary Manual, 1979) and slaughter of turkeys often occurs at 23 weeks of age, turkeys could be given an antihistomonal agent for 23 weeks for the prevention of the disease. For the 23-week period, a turkey will consume 70.4 pounds of feed (Marsden, 1971). Dimetridazole is recommended for use at a level of 182 grams/ton for the prevention of histomoniasis, growth promotion and feed efficiency. During the 23-week period a turkey will consume approximately 6.4 g of dimetridazole (70.4 lbs. X 182 g/2000 lbs.). Based on data presented by EPA and USDA (1979), a ten-pound turkey will produce 0.255 kg wet waste/day. Although turkeys weighing more or less than ten pounds will produce proportionately more or less waste, utilizing the figure of 0.255 kg waste/day, in 161 days (23 weeks) a turkey will produce 41.1 kg of waste. An initial estimate, based on an assumption that 100% of the administered dimetridazole will be excreted, gives a concentration of dimetridazole in turkey wet waste of 0.156 g dimetridazole/kg waste (6.40 g / 41.1 kg) or 156 ppm.

As previously indicated, Law et al. (1963) report that of the excreted product only 3.2% is parent dimetridazole, while three of the metabolic products, 1-methyl-5-nitroimidazol-2-ylmethyl hydrogen sulfate 1-methyl-5-nitroimidazol-2-carboxylic acid, and 2-hydroxymethyl-1-methyl-5-nitroimdidazole, make up 44.4%, 25.8%, and 9.4%, respectively, of excreted product. The concentrations of parent and metabolites expected in wet wastes are therefore, 4.99, 69.26, 40.25, and 14.66 ppm respectively.

Poultry waste is used as a source of fertilizer on agricultural fields where it may be spread and incorporated into soil at rates ranging from 3.6 to 8.9 tons dry weight per acre depending on climate, soil type, land use, and application methods (Fuller and Warrick, 1985). The moisture content of poultry waste at the time of application will vary considerably. Perkins and Parker (1971) report that upon removal of poultry waste from a poultry growing facility, the waste contained on average about 25% moisture. At the maximum application rate of 8.9 tons dry weight per acre and using a 25% moisture content, a comparable wet weight is 11.9 tons per acre. Following application, waste is typically incorporated into the top six inches of soil. Assuming the top six inches of soil weighs 909,000 kg per acre, incorporation of waste into soil at a rate of 11.9 tons (10,818.2 kg) per acre gives a concentration of dimetridazole plus metabolite of 1.86 mg/kg (ppm) in soil (156 mg/kg X 10,818.2 kg/acre) / 909,000 kg).

Of the 1.86 ppm in soil, 0.06 ppm (3.2%) could be parent dimetridazole, while 0.83 ppm (44.4%) could be the sulfate metabolite, 0.48 ppm (25.8%) may be the carboxylic acid metabolite, and 0.18 ppm (9.4%) could be the nitroimidazole metabolite.

If it rains before the incorporation into soil of manure containing dimetridazole, the concentration of dimetridazole which could be in 2 inches (205,500 kg) of runoff is 8.21 mg/kg (ppm) (156 mg/kg X 10,818.2 kg/acre / 205,500 kg water).

Of the 8.21 ppm in runoff, 0.26, 3.65, 2.12, and 0.77 ppm could, respectively, be parent dimetridazole and the sulfate, carboxylic acid, and nitroimidazole metabolites.

It should be recognized that these estimated concentrations of dimetridazole in soil and runoff are high relative to the amounts which may actually be present in the environment. This is because (1) a high initial concentration was utilized, (2) the initial concentration did not include the mass of bedding which is normally utilized by poultry producers, (3) wastes are usually stored for a period before spreading onto soils resulting in degradation of waste residues, and (4) it is unlikely that all of the dimetridazole residue would be present in either soil or runoff, instead, the residues would be distributed between these two compartments.

(4) Fate of dimetridazole in the environment: There is only limited information relevant to the fate of dimetridazole or its metabolites in the environment. The Merck Index (1983) reports that dimetridazole is sparingly soluble in water, while the hydrochloride and the dihydrogen phosphate are freely soluble in water. Based on this report, dimetridazole will be found in runoff and soil-water. It could, therefore, be found in surface and ground water, and could be absorbed by plants.

Chemicals with log P (log of the octanol/water partition coefficient) values of less than 1 are not expected to significantly bioconcentrate or sorb to organic matter in soil, whereas those with log P of 4 or greater may bioconcentrate or sorb to organic matter in soil (EPA, 1985; Veith et al., 1985). Guerra (1981) reported log P values for the 5-nitroimidazoles, metronidazole, ipronidazole, carnidazole, and ronidazole, ranging from -0.38 to 1.06. The log P for ipronidazole was reported as 1.06. The log P of 1.06 for ipronidazole indicates that it would not be expected to significantly bioconcentrate or sorb to organic matter in soil. Structurally, dimetridazole closely resembles ipronidazole. Therefore, dimetridazole presumably will not significantly bioaccumulate or sorb to soil organic matter.

Additional data on ipronidazole and its identified 5-nitroimidazole metabolite indicate that they are stable in acid but subject to hydrolysis in bases (MacDonald et al., 1971). They also report that 80% or more of ipronidazole and its identified metabolite decompose after 7 hours of exposure to direct sunlight. Stone and Hobson (1974) report that

dimetridazole and ipronidazole demonstrate maximum absorption of light at 320 nm. Because dimetridazole is structurally similar to ipronidazole, these data indicate that dimetridazole and possibly its metabolites could be subject to hydrolytic and photolytic degradation in the environment. The data presented by Law et al. (1963), demonstrating that dimetridazole is extensively metabolized, also suggest that biological degradation is another potential pathway for the elimination of dimetridazole from the environment.

(5) Effects of dimetridazole in the environment: Muller, Lindmark, and McLaughlin (1976) and Edwards (1980) report that the activity of nitroimidazoles appears to require an organism that contains enzyme systems which use ferredoxin or flavodoxin as electron acceptors or donors. Edwards (1980) states that any ferredoxin-linked system of the correct potential (redox potential = -450 mV) should be capable of reducing nitroimidazoles. The reduced nitroimidazole appears to be the active component which causes cell death. The reduction of nitroimidazoles and subsequent cell death even occurs in some photosynthetic plant systems where ferredoxin-linked systems are present. Information presented by Muller, Lindmark, and McLaughlin (1976) also suggest that the compound(s) responsible for nitroimidazoles' toxic biological activity may not be present in turkey excreta and, therefore, that the metabolites might not be expected to cause toxic effects in environmental organisms.

Several studies comparing the toxic effects of nitroimidazoles on pathogenic microorganisms have been conducted. Edwards et al. (1973) report minimum inhibitory concentrations (MICs) for six nitroimidazoles against eight species of Clostridia and Trichomonas vaginalis. They report MICs for dimetridazole ranging from 0.2 ug/ml (ppm) for C. butyricum to 3.2 ug/ml (ppm) for C. welchii. They also report that tests with dimetridazole in solution cultures had little effect on evolution of bacterial CO_2, but did inhibit evolution of hydrogen. The pH of the test solution was unchanged, indicating that no accumulation of H ions occurs and, further, that the reduction of the nitro group is irreversible. Edwards et al. (1973) considered these results to be compatible with

Hoffmann (1953) and Rabinowitz and Pincer (1956), who Edwards et al. (1973) report found that reduced nitroimidazoles are unstable and that the reduction causes fragmentation of the heterocyclic ring.

Jokipii and Jokipii (1985) compared seven nitroimidazole compounds, including dimetridazole, against Bacteroides fragilis and other bacteria of the Bacteroides fragilis group. They report that the MICs of each drug against 17 strains of B. fragilis varied within a 10-fold range, with the exception of tinidazole with two extreme MICs with a 20-fold difference. Dimetridazole demonstrated the least amount of activity based on MICs as molar concentrations, and with the exception of carnidazole activity against B. fragilis, the activity of nitroimidazoles seemed to increase with molecular weight. The geometric mean MIC for dimetridazole against B. fragilis was reported at 10.0 uM or 1.41 ug/ml (ppm) and against 16 clinical isolates of B. fragilis the MIC range was 2.0-20 uM or 0.28-2.82 ug/ml (ppm). Reynolds (1981) reports an MIC of 0.001 mmol/l or 0.14 mg/l (ppm) for dimetridazole against B. fragilis.

Fernie et al. (1977) report MICs ranging from 0.1-10.0 ug/ml (ppm) for dimetridazole against 44 strains of Campylobacter coli and C. fetus. They also report that dimetridazole at 100 ug/ml (ppm) did not inhibit 4 strains of Escherichia coli when grown under aerobic or anaerobic conditions.

Edwards (1980) states that no resistant organisms of clinical significance have arisen during 20 years' use with any nitroimidazole, suggesting that a single gene change conferring resistance is, itself, lethal. Meingassner and Mieth (1976), however, conducted studies which produced a resistant strain of Trichomonas foetus in mice treated with metronidazole. The resistant strain also demonstrated a marked cross-resistance to several other nitroimidazole derivatives tested, including dimetridazole.

There is only a limited amount of information regarding the toxicity of dimetridazole to larger animals. Plisek (1977) reports an LD50 in white mice of 1300.0 mg/kg (ppm) and an LD50 of 1550.0 mg/kg (ppm) for male white

leghorn chicks. An LD50 could not be established in 1-week old turkey poults administered up to 1000 mg/kg (ppm) dimetridazole in single oral doses via gelatin capsules (Hoffer et al., 1971).

Riddell (1984) reports that he did not find mortality in Rouen ducklings and goslings at dimetridazole levels of 0.5 g/l (500 ppm) administered in drinking water for five and eight days, but he found 100% mortality in Rouen ducklings and 67% mortality in groups of goslings administered 1.0 g/l (1000 ppm) via the same route. The first abnormality observed was unusual behavior in all birds on the second day of the trials. Behavior abnormalities included excessive purposeless running, abnormal head attitude and movement, ataxia, much vocalization, and recumbency. A reduced weight gain was also noted in birds administered 0.5 and 1.0 g/l dimetridazole for eight days. Microscopic lesions were noted in the congested tissues of brain, kidney, liver, and spleen tissues, and atrophy of the Bursa of Fabricius, thymus and spleen were also noted.

The mutagenicity of nitroimidazoles including dimetridazole, is documented in the NOOH on the proposed withdrawal of approval of the NADA's for dimetridazole.

As already noted, nitroimidazoles exert toxic effects associated with ferredoxin-linked systems (Edwards et al., 1973; Edwards, 1980; Muller, Lindmark, and McLaughlin, 1976). The effects apparently occur even in photosynthetic systems. Edwards (1980) reports on a study (Edwards and Schoolar, 1971) in which metronidazole inhibited sugar synthesis in sugar cane leaves as a consequence of inhibiting Photosystem I, where ferredoxin is involved, but had no effect on Photosystem 2. Edwards (1980) also reports on a study (Edwards et al., 1973) where metronidazole produced inhibition of the ferredoxin-linked nicotinamide adenine dinucleotide phosphate reduction in chloroplasts of spinach. In another study (Edwards et al., 1974), also reported by Edwards (1980), metronidazole had no effect on the chemo-organotrophic growth of Rhodopseudomonas acidophila in the dark but killed it when grown in light, when the ferredoxin-linked systems are operative. In a preliminary report by Sinha and Mohan (1978), ronidazole and metronidazole exerted algicidal effects on the blue-green

algae Anacystis nidulans with increasing drug concentration, while dimetridazole stimulated algal growth with concomitant increases in its concentration up to 100 ug/ml (ppm). Higher concentrations were reported to be lethal.

(6) Summary of potential environmental impact of dimetridazole on the environment: Based on the limited amount of information available, dimetridazole would not be expected to exert a significant adverse impact on the human environment. Dimetridazole is reported to be extensively metabolized, with a limited amount of parent dimetridazole and several metabolic by-products contained in the turkey waste. Because of this metabolism, if the waste is totally incorporated into agricultural soils, only 0.06 ppm of parent dimetridazole, 0.83 ppm of sulfate metabolite, 0.48 ppm of carboxylic acid metabolite and 0.18 ppm of nitroimidazole metabolite could be present in soil. Similarly, if all of the parent and metabolites are contained in runoff, 0.26 ppm, 3.65 ppm, 2.12 ppm and 0.77 ppm of parent and sulfate, carboxylic acid, and nitroimidazole metabolites could be present. However, as noted in 3.a.(3), these estimated concentrations are high. Realistic environmental concentrations would be lower because (1) the estimated concentrations do not include the weight of litter which is generally used in turkey production, (2) storage, which normally occurs before the spreading of waste, would allow for degradation of dimetridazole and metabolites and (3) parent dimetridazole and metabolites would not be totally present in either soil or runoff, but would be distributed between these two compartments.

Based on the limited data presented in section 3.a.(5), the estimated concentrations of dimetridazole in soil would not be expected to cause adverse environmental effects in microorganisms, blue-green algae, or mammalian or avian species. Estimated concentrations of parent dimetridazole in runoff suggest that some toxicity to aquatic microorganisms could occur. The limited amount of information available concerning plants suggests that adverse effects could occur upon exposure to parent dimetridazole, but the concentration at which such effects could occur and the nature and extent of the effects are not known.

No data are available concerning the toxicity of dimetridazole in aquatic invertebrate or vertebrate species. Additionally, no direct information is available concerning acute toxic effects which could result from the exposure of environmental organisms to the metabolites of dimetridazole, but some information (Edwards et al., 1973; Muller, Lindmark & McLaughlin, 1976) suggests that metabolites contained in turkey waste might not be acutely toxic to environmental organisms.

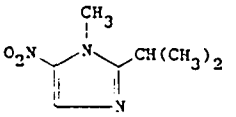
Dimetridazole is not expected to bioaccumulate. Additionally, it would be expected to degrade in the environment from biological, hydrolytic, and photolytic mechanisms. Therefore, any effects which could occur would be expected to be limited to organisms exposed to dimetridazole in fresh turkey waste.

Data concerning the concentrations of dimetridazole which could be present at the manufacturing and final mixing sites are not available. But data on a mammalian species indicate that dimetridazole might not be acutely toxic to employees provided reasonable occupational safety precautions are utilized. However, data presented in the NOOH on the Center's proposal to withdraw approval of the NADA's for dimetridazole indicate that carcinogenicity is a concern for those involved in manufacturing dimetridazole and those preparing the final formulations of the drug.

b. Environmental data on ipronidazole.

The following paragraphs summarize the environmental data available to the Center on ipronidazole, the drug expected to be the substitute for dimetridazole in turkeys. These data will be used to assess the potential impact on the human environment of the increased production and use of ipronidazole. No environmental assessment of the use of ipronidazole was conducted at the time the NADA's were approved because the approvals preceded FDA's 1973 implementation of NEPA. The Center is unaware of other sources of environmental data except the literature.

(1) Chemical identity: Ipronidazole is the active chemical component of the products marketed under the trade name Ipropan (The Merck Index, 1983). Its chemical name is 1-methyl-2-(1-methylethyl)-5-nitro-1H-imidazole (The Merck Index, 1983). Its CAS registration number is CAS-14885-29-1. Its chemical and structural formulas as provided in The Merck Index (1983) are as follows:



$C_7H_{11}N_3O_2$

Ipronidazole's molecular weight is 169.18 (The Merck Index, 1983; USAN, 1984). The Merck Index (1983) reports that the hydrochloride is water-soluble and has a melting point of 177-182°C (Merck, 1983). Stone and Hobson (1974) report that ipronidazole demonstrates maximum light absorption at 320 nm, while Hoffer et al. (1971) report a maximum absorption at 310 nm.

(2) Introduction into the environment through manufacturing: As with dimetridazole, no information is available concerning the manufacture of ipronidazole. Like other nitroimidazoles, however, ipronidazole is synthesized through chemical means. Waste from the manufacturing facility would be expected to contain at least some finished drug product and a number of reaction products, as well as solvents, emulsifiers, and other chemicals used in its production. Some adverse environmental effects could occur from manufacturing wastes, but the extent of any impacts would depend on the treatment processes utilized at the manufacturing facility. Occupational exposures at the manufacturing facility could occur. If the approvals of the NADA's for dimetridazole are withdrawn, the production of ipronidazole would increase. The increase would be expected to consist of the amount of drug estimated to be used in place of dimetridazole in turkeys. As estimated in section 2.d., ipronidazole's production would be expected to increase by 55,500 kg. This increase in production could represent a doubling of the production of ipronidazole.

Ipronidazole is marketed as a feed premix and as a water-soluble powder. The premix is combined with feed by licensed feed mill personnel to provide a finished feed for turkeys. The soluble powder is combined with water by turkey production facility personnel to provide medicated drinking water. Personnel preparing these products could be exposed to ipronidazole through topical or inhalation routes. There is a potential for toxic effects to occur in these persons as well as persons in the primary manufacturing facility.

(3) Introduction into the environment through the use of ipronidazole: As with dimetridazole (see 3.a.(3)), environmental introductions of ipronidazole will be calculated based on a liberal estimate of the concentration of the drug contained in waste from a confinement facility. Additionally, for the same reasons given for dimetridazole (see section 3.a.(3), it should be recognized that the estimated concentrations calculated for ipronidazole in soil and runoff are high relative to the concentrations which might actually be expected to occur in the environment.

MacDonald et al. (1971) report that Fellig et al. (1969) identified 1-alpha-alpha-trimethyl-5-nitroimidazole-2-methanol as a metabolite of ipronidazole. In a later study, Weiss et al. (1981) report that in rats this metabolite together with unchanged parent compound accounted for about 40% of the excreted dose of ipronidazole. They indicated that the remaining metabolites were highly water-soluble and could not be extracted into organic solvents before enzymic hydrolysis occurred. Upon analysis of water extractable fecal metabolites they identified 2,3-dihydro-2-(-hydroxypropyl)-3-methyl-4-nitro-1H-imidazol-5-ol as an additional metabolite of ipronidazole. From the information available in Weiss et al. (1981), it appears that this metabolite represented 12.4% of the administered dose.

Because turkeys are susceptible to histomoniasis at any age and slaughter often occurs at 23 weeks of age, turkeys could be given an antihistomonal agent for 23 weeks for prevention of the disease. For the 23-week period a turkey will consume 70.4 pounds of food (Marsden, 1971). Ipronidazole is

recommended for use at a level of 56.75 grams/ton for the prevention of histomoniasis, growth promotion, and feed efficiency. During the 23-week period a turkey will consume approximately 2.0 g of ipronidazole (70.4 lbs. X 56.75 g/2000 lbs.). Based on data presented by EPA and USDA (1979), a ten-pound turkey will produce 0.255 kg wet waste/day. Although turkeys weighing more or less than ten pounds will produce proportionately more or less waste, utilizing the figure of 0.255 kg wet waste/day, in 161 days (23 weeks), a turkey will produce 41.1 kg of waste. An initial estimate, based on an assumption that 100% (2.0 g) of the administered ipronidazole will be excreted, gives a concentration of ipronidazole in turkey waste of 0.049 g ipronidazole/kg waste (2.0 g / 41.1 kg) or 49 ppm. Based on the report of Weiss et al. (1981), less than 40% (19.6 ppm) of this waste would be expected to be parent ipronidazole.

As stated in section 3.a.(3), poultry waste could be spread on agricultural fields at a rate of 11.9 tons wet waste per acre and incorporated into soil to a depth of six inches. Assuming the top six inches of soil weighs 909,000 kg per acre, incorporation of waste into soil at a rate of 11.9 tons (10,818.2 kg) per acre will give a concentration of ipronidazole plus metabolites of 0.58 mg/kg (ppm) (49 mg/kg X 10,818.2 kg/acre / 909,000 kg). Of this concentration, less than 0.23 ppm (40%) could be parent ipronidazole.

If it rains before the incorporation into soil of manure containing ipronidazole, the concentration of ipronidazole which could be in 2 inches (205,500 kg) of runoff is 2.58 mg/kg (49 mg/kg X 10,818.2 kg/acre / 205,500 kg water). Of this concentration, less than 1.03 ppm (40%) could be parent ipronidazole.

(4) Fate of ipronidazole in the environment: There is only limited information relevant to the fate of ipronidazole or its metabolites in the environment. The Merck Index (1983) reports that ipronidazole is soluble in water. Based on this report, ipronidazole would be found in runoff and soil-water. Therefore, it could leach into surface and ground waters and be absorbed by plants.

Chemicals with log P values of less than 1 are not expected to significantly bioconcentrate or sorb to organic matter in soil, whereas those with log P of 4 or greater may bioconcentrate or sorb to organic matter in soil (EPA, 1985; Veith et al., 1985). Guerra (1981) reports a log P of 1.06 for ipronidazole, which indicates that ipronidazole would not be expected to significantly bioaccumulate or sorb to organic matter in soil.

MacDonald et al. (1971) reports that ipronidazole and its identified 1-alpha, alpha-trimethyl-5-nitroimidazole-2-methanol metabolite are stable in acid but subject to hydrolysis in bases. They also report that 80% or more of the parent ipronidazole and its identified 2-methanol metabolite decompose after 7 hours of exposure to direct sunlight. Weiss et al. (1980) report that other metabolites of ipronidazole are subject to enzymatic hydrolysis. Stone and Hobson (1974) report that ipronidazole absorbs light at a maximum of 320 nm. These data, as well as ipronidazole's relatively high water solubility, indicate that ipronidazole would be present in an aquatic solution in the environment and be subject to hydrolytic degradation. Additional degradation would also be expected from exposure to sunlight and possibly from biological actions.

(5) Effects of ipronidazole in the environment: Considerable data have been presented regarding the mode of action, MICs, and toxicity of dimetridazole (see section 3.a.(5)). Ipronidazole, like dimetridazole, is a 5-nitroimidazole, and they are chemically, structurally, and pharmacologically related. It is reasonable therefore to apply the information presented for dimetridazole toward a consideration of the effects of ipronidazole on the environment. Based on the available information, both drugs would be expected to exhibit the same effects relative to their expected concentrations in the environment.

Hoffer et al. (1971) and Marusich et al. (1970) report that the LD50 for ipronidazole in 1-week old turkey poults is 640$\pm$25 mg/kg. Marusich et al. (1970) also report that the onset of clinical signs of toxicity was rapid with birds appearing lethargic with wings dropped, bodies resting on hocks and head arched backwards. In those eventually dying, death occurred

within 24 hours. Marusich et al. (1970), also report that surviving birds recovered rapidly and subsequently showed essentially the same growth rate and feed conversion as controls except in birds where group mortality was 50% or more. In dead birds, gross pathological lesions were observed with nephromegaly and hepatomegaly and scattered foci of necrosis. These pathological observations are similar to those reported by Riddell (1984) as occurring in Rouen ducklings and goslings treated with dimetridazole. Weiss et al. (1981) report the LD50 of ipronidazole in adult rats to be 920±48 mg/kg.

(6) Summary of the environmental impact of ipronidazole: Based on the limited amount of information available for dimetridazole and ipronidazole, any increase in the production and use of ipronidazole resulting from the removal of dimetridazole from the market would not be expected to significantly effect the quality of human environment.

Ipronidazole is chemically, structurally, and pharmacologically similar to dimetridazole. Therefore, any environmental impacts from the increased production and use of ipronidazole would be anticipated to be similar to those already resulting from the manufacture and use dimetridazole. Adverse effects from soil concentrations on microorganisms, blue-green algae, and avian or mammalian species are not expected. Adverse effects could occur in aquatic microorganisms. The limited amount of information concerning plants indicates that adverse effects on plants could occur, but the nature of the effects and the level of exposure necessary for such effects to occur are not known.

As with dimetridazole, no data are available concerning the toxicity of ipronidazole to aquatic invertebrate or vertebrate species, nor are data available relevant to the toxicity of its metabolic products. However, as previously noted for dimetridazole, some data (Edwards et al., 1973; Muller, Lindmark and McLaughlin, 1976), suggest that metabolites contained in turkey waste might not cause acute toxic effects in environmental organisms.

Ipronidazole is not expected to bioaccumulate and could be subject to biological, hydrolytic, and photolytic degradation in the environment.

Therefore, any effects which could occur would be expected to be limited to organisms exposed to ipronidazole in fresh turkey waste.

Acute occupational toxicity would not be anticipated provided reasonable occupational safety precautions are utilized at the manufacturing sites and at the sites of final formulation preparation.

c. Environmental data on the most likely substitutes for misuse in swine.

As noted above (see section 2.c.), lincomycin, roxarsone, tiamulin, tylosin, carbadox, virginiamycin, bacitracin, and gentamicin are approved for use in the prevention or treatment of swine dysentery. Therefore, if dimetridazole were no longer available for misuse in swine, swine producers would have a number of approved products to use as substitutes for dimetridazole. It is not possible to estimate the amount of dimetridazole which is currently being misused for swine dysentery, nor is it possible to estimate the increases in production and use of approved products which would result from the removal of dimetridazole from the market. However, increases in the production and use of the approved products may represent only a small portion of their current production and use because of the number of approved products available and because many of the approved products are currently approved for uses other than swine dysentery and for use in other species. For example, lincomycin is approved for use in chickens for control of respiratory disease and in broilers chickens for improved weight gain, feed efficiency, and necrotic enteritis. It is also approved for use in dogs, cats, and swine for conditions other than swine dysentery. Roxarsone is approved for use in chickens and turkeys for improved weight gain and feed efficiency as well as in swine for improved weight gain and feed efficiency. Virginiamycin is approved in both swine and poultry for weight gain.

The potential environmental impacts of lincomycin, roxarsone, tylosin, carbadox, virginiamycin, and bacitracin have been considered with respect to their use as substitutes (1) for subtherapeutic uses of tetracyclines and penicillins in animal feeds and (2) for several nitrofuran drug

products (Matheson, 1984; Feinman and Matheson, 1978). In those analyses, no significant environmental impacts were expected from potential increases or decreases in the production and use of these substitute drugs. Following environmental analysis of the use of tiamulin and gentamicin in swine dysentery, the Center found that no significant environmental impact would be expected from their production and use (NADA's 139-472 and 133-836, respectively).

In view of (1) the number of approved products available for the treatment or prevention of swine dysentery, (2) the limited increases in production and use expected for approved products, and (3) previous environmental assessments of these products, which found no significant environmental impacts from their production and use, no further consideration of the environmental impacts of the use of approved products to replace the misuse of dimetridazole in swine dysentery is warranted.

d. Environmental impact of the proposed action from the use of substitute products in turkeys.

The Center has considered the available environmental information for dimetridazole and ipronidazole. These new animal drugs are related, structurally, chemically, and pharmacologically, and potential environmental impacts associated with increased production and use of ipronidazole are likely to be the same as those which occur with the current use of dimetridazole. No change in the production of turkeys or in morbidity and mortality of turkeys is anticipated from the substitution of ipronidazole for the existing uses of dimetridazole. Therefore, the Center concludes that any increases in the production and use of ipronidazole resulting from the proposed withdrawal of approval of the NADA's for dimetridazole would not be expected to significantly effect the quality of the human environment.

e. Conclusions.

The withdrawal of approvals of the NADA's for dimetridazole, subsequent removal of dimetridazole-containing drug products from the market, and

increases in the use of substitute products in turkeys and swine would not be expected to have any significant adverse impact on the quality of the human environment.

4. Mitigation Measures to Offset Any Adverse Environmental Effects

No adverse environmental effects associated with the proposed action are expected. Therefore, no mitigation measures are necessary.

5. Regulatory Alternatives to the Proposed Action and Any Expected Environmental Impacts

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, and (3) mitigation measures not included in the proposed action.

Dimetridazole is approved for use only in food-producing animals and data presented in the proposal to withdraw approval of the NADA's for dimetridazole (NOOH; copy attached) demonstrate that it is not shown to be safe within the meaning of Section 512(e)(1)(B) of the act because (a) new evidence provides a reasonable basis from which serious questions about the ultimate safety of dimetridazole and the residues that may result from its use may be inferred, (b) new evidence shows that the drug is no longer shown to be safe by adequate tests by all methods reasonably applicable, and (c) new evidence shows that the labeled directions for use have not been followed in practice and are not likely to be followed in the future. Any known alternative to or mitigation of the proposed action would result in the exposure of humans to residues of a drug which has not been shown to be safe within the meaning of 512(e)(1)(B) of the act. In view of the seriousness of the questions surrounding the safety of dimetridazole and the residues that may result from its use, including the questions of the carcinogenicity of dimetridazole and its metabolites, such an alternative or mitigation would therefore be in conflict with the basic statutory requirements of the act and cannot be considered reasonable.

Congressional imposition of a "moratorium" on the proposal to withdraw approval of the NADA's for dimetridazole pending further studies or Congressional amendment of the act would be necessary before alternatives could be considered. Such a Congressional moratorium or amendment could result in the Center taking no action with regard to the NADA's for dimetridazole.

The Center will consider regulatory alternatives if identified, provided the questions concerning dimetridazole's human food safety are resolved in favor of the compound.

6. Comparison of the Environmental Impacts of the Proposed Action with those of Regulatory Alternatives

As indicated in section 5, no reasonable regulatory alternatives to the proposed action are known to exist. Therefore, no comparisons of impacts are possible. However, as stated in section 3.d., the Center has considered the available environmental information for dimetridazole and ipronidazole, and concluded that because they are chemically, structurally, and pharmacologically similar, the potential environmental impacts associated with their production and use are likely to be the same. In section 3.e., the Center also states that any impacts which could occur are not expected to be significant. Therefore, any regulatory alternative to the proposed action, congressional moratorium, or congressional amendment to the act which would result in continued production and use of dimetridazole, decreases in its production and use, or increases in the production and use of ipronidazole, would not be expected to significantly effect the quality of the human environment.

7. Conclusions

The proposed withdrawal of the NADA's for dimetridazole is not expected to significantly effect the quality of the human environment. Therefore, an environmental impact statement will not be prepared for this proposed action.

8. Persons Involved in the Preparation of this Document

Charles E. Eirkson III prepared and edited this document. Mr. Eirkson has been an environmental biologist with the Center's Environmental Staff for two years. He is responsible for the analysis of the potential environmental impacts of actions proposed by the Center, for providing guidance to applicants 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 or by individuals. Mr. Eirkson earned his B.S. degree in biology with specialization in biogeography and environmental science at the University of Pittsburgh, Pittsburgh, Pennsylvania (1975) and is currently preparing a thesis for fulfillment of the requirements for his Masters Degree in Environmental Science at Hood College, Frederick, Maryland.

John C. Matheson III contributed to, reviewed, and provided editorial assistance during the development of this document. Mr. Matheson has served as an environmental scientist at FDA for eleven years, the last six as FDA's NEPA focal point and as Chief of the Center's Environmental Staff. Mr. Matheson earned his MSPH in Environmental Sciences and Engineering (1975) and a B.S. in Biology (1973) at the University of North Carolina-Chapel Hill, Chapel Hill, NC.

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