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PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Medicated Poultry Composition

We, AMERICAN CYNAMID COMPANY, a corporation organized under the laws of the State of Maine, United States of America, of the Township of Wayne, State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention relates to a medicated poultry composition and more particularly is concerned with a novel medicated poultry drinking water composition containing a substance which induces the poultry consuming the same to consume above normal quantities of the medicament contained therein.

It has been standard practice for a number of years in the poultry industry to administer medicaments such as the broad-spectrum antibiotics chlorotetracycline, tetracycline, oxytetracycline and demethylchlorotetracycline to poultry as part of their diet, and usually in the drinking water, in order to control infectious diseases particularly those of sub-clinical nature, and for the purpose of stimulating the growth of poultry. The prophylactic and therapeutic use of such antibiotics has met with wide commercial acceptance. However, complete or even substantially complete utilization of the antibiotics has not heretofore been achieved when the antibiotics are orally administered. Apparently, this is due to incomplete absorption of the antibiotic by the poultry which is believed to be due at least in part to the presence of calcium and other metallic cations in the diet which form a complex with the antibiotic and prevents complete absorption thereof. Accordingly, full utilization of such antibiotics has not been achieved and any method which would permit maximum absorption of the antibiotic would be highly desirable.

Chronic respiratory disease is a respiratory infection of chickens and turkeys characterized by respiratory rales, coughing, and nasal discharge. The clinical manifestations are slow to develop and the disease has a long course. Chronic respiratory disease has become an important flock problem in all areas of the United States, and losses from this disease may be very costly to the producer. It is also present in Canada, Australia, Holland, South Africa and Brazil. *Mycoplasma gallisepticum* is the pathogenic avian pleuropneumonia-like organism (PPLO) causing chronic respiratory disease.

Chlorotetracycline, among other drugs, has been used to combat this infection. Another drug that has been found to be effective is the antibiotic known as tylosin. This antibiotic is described in British Patent No. 901,273.

Several methods of administration of these drugs may be used effectively, but the method found most practical for use in the field is administration in the drinking water at recommended levels of about two grams per gallon. While such drug levels are generally palatable to poultry and will usually control PPLO in a diseased flock, if the flock should become infected with PPLO and Coliform simultaneously, high levels of medication are required and such medication must be provided in the matter of a few days or it can be expected that from 20% to 30% of the flock will be lost either by death or condemnation at slaughter. It is therefore, necessary, when disease symptoms are recognized, to assure that high levels of medication are ingested by the entire flock as rapidly as possible. In the past this has been a very real problem, for sick birds lose their appetite for food and drink. Thus at the critical stage, the birds consume less, rather than more, medicament.

Another disease which plagues the poultry industry and which can claim from 50% to 100% of a flock in a matter of several days after infectious symptoms are noted is Blackhead disease, more accurately known as infectious enterroheptatis or histomoniasis. The

[*Price 4s. 6d.*]

disease is caused by a microscopic, single-cell, protozoan parasite, *Histomonas meleagrides*. The histomonads multiply rapidly in the cecum and cause severe damage such as enlargement of the cecum, ulceration, hemorrhage and thickening with hardening of the cecal walls. 2-Amino-5-nitrothiazole and 2-acetylamino-5-nitrothiazole have been found to be effective against the disease when used alone or in combination with the tetracycline antibiotics. However, as stated above, diseased birds tend to lose their appetite for food and drink at the time when medication is most essential. Therefore, when administering these drugs in the drink and feed, which is the only really practical method of administration for a large flock, it can be seen that the amount of medication ingested by the birds is reduced at the critical stage.

In accordance with the invention there is provided a medicated poultry composition for oral administration via drinking water comprising a mixture of a medicament selected from tetracycline antibiotics, tylosin, 2-amino-5-nitrothiazole, and 2-acetylamino-5-nitrothiazole, and a sulfate of a cation carrying a single positive charge, or a mixture of two or more such sulfates, present in an amount to provide from 0.5 to 50 g. of sulfate ion per gram of medicament. Preferably the sulfates are selected from the monovalent metallic sulfates, sodium sulfate, sodium bisulfate, potassium sulfate and potassium bisulfate; and also sulfuric acid; ammonium sulfate, ammonium acid sulfate; and mixtures thereof. The presence of sulfate ion has been found to bring about an increased consumption of water and thus an increased consumption of medicament. Also contemplated by the invention are the organic sulfates such as trimethyl ammonium sulfate, and dimethyl ammonium sulfate. Also, when the medicament is a tetracycline antibiotic the use of the described sulfate ion actually promotes increased absorption of the antibiotic and thus acts as a potentiating agent or adjuvant and thereby produces higher blood levels of the antibiotic than are obtainable from the use of the antibiotic alone.

In conformity with common usage in the poultry industry, the medicated compositions of this invention will generally be made, and also packaged, in concentrated form, often with a non-toxic carrier for addition to a given quantity of drinking water to produce the desired concentration of medicament. In use the quantity of the medicated composition added to the drinking water should often be such that the drinking water contains from 0.1 to 1.0 percent by weight of sulfate ion.

The invention will be described in greater detail in conjunction with the following specific examples.

EXAMPLE 1.

In the following tests 24 groups of 5 day-old chicks, 24 groups of 12 day-old chicks and 36 groups of 19 day-old chicks were selected from three flocks. Birds in each particular flock were of substantially the same weight and size and 12 birds were selected at random for each group.

Four combinations of prepared feed and drink were selected for testing in the 5 and 12 day-old chicks and two additional combinations were used in the tests with the 19 day-old chicks. The feed and drink combinations used in these tests were as follows:

Feed and Drink Combinations

	Feed	Water
Diet I	feed + 200 ppm CTC	H_2O
Diet II	feed + 200 ppm CTC	H_2O + 0.71% Na_2SO_4
Diet III	feed	H_2O + 500 ppm CTC
Diet IV	feed	H_2O + 500 ppm CTC + 0.71% Na_2SO_4
Diet V	feed + 200 ppm CTC	H_2O 500 ppm CTC
Diet VI	feed + 200 ppm CTC	H_2O + 500 ppm CTC + 0.71% Na_2SO_4

The diet used in all tests was ground yellow corn containing 1% calcium carbonate and supplemented with chlorotetracycline (CTC) as indicated in the feed and drink combination table.

After selection of the chicks for the various groups to be tested, each group was separately caged. All groups were fasted overnight and the following morning all of the various groups were permitted to feed and drink *ad libitum*

the diet selected. Each of the above-noted diets, III through VI, were given to six separate groups of chicks from the 19 day-old flock.

Two hours after feeding was begun fourteen groups of chicks, one group from each dietary group in each of the 5, 12 and 19 day-old flocks, were selected. All birds in each group were bled by cardiac puncture and 1½ ml. of blood taken and assayed microbiologically for chlorotetracycline blood levels. At 4, 6, 8, 16 and 24 hour periods after feeding was begun, additional groups (one from each dietary group in each of the 5, 12 and 19 day-old flocks) were bled and blood serum levels of CTC ascertained micro-biologically. The results obtained appear in the table below.

TABLE I

	Age of Chicks in Days	Hours	Blood CTC at 4	6	8	16	24
Diet I	19		0.14	0.18	0.16	0.17	0.13
Diet II	19		0.18	0.20	0.19	0.31	0.22
Diet III	5		1.53	2.25	1.78	1.98	1.03
	12		0.77	1.07	1.17	0.90	0.82
	19		0.28	0.34	0.46	0.30	0.27
Diet IV	5		5.45	3.19	4.05	2.78	3.63
	12		1.22	1.45	1.32	1.31	0.66
	19		0.33	0.55	0.99	0.68	0.39
Diet V	5		2.18	2.13	3.11	1.57	1.44
	19		0.27	0.48	0.34	0.33	0.28
	12		1.19	1.79	1.14	0.89	0.80
Diet VI	5		4.38	5.15	3.43	3.61	3.13
	19		0.35	0.33	0.50	0.69	0.55
	12		1.68	1.91	1.91	1.42	1.30

From these data it can be seen that (1) the CTC blood levels, from a given amount of CTC orally administered, are significantly increased in poultry of all ages when sodium sulfate is added to the poultry drinking water; (2) the blood levels obtainable from a given amount of CTC potentiated with a given amount of sodium sulfate are significantly higher in young chicks than in older birds. It is an advantage that CTC blood levels in young chicks are very high for while young chicks are susceptible to disease infection, rapid and effective treatment against disease is possible. High CTC blood levels in young chicks is also advantageous since rapid growth rate and control of diseases reduces the cost of raising poultry.

(3) These data demonstrate the potentiating effect of sodium sulfate on CTC blood levels when CTC is administered to poultry in the drinking water along with the sodium sulfate.

(4) These data also show the potentiating effect on CTC blood levels when sodium sulfate is administered in the drinking water and CTC is provided in both the drinking water and feed.

(5) Finally, the data show that addition of sodium sulfate to drinking water of poultry consuming a feed supplemented with CTC will produce an increase in CTC blood levels in the poultry.

EXAMPLE 2.

Twenty-six day-old chicks of substantially similar size and weight were randomly divided into thirty-six groups of twelve chicks each. The groups were separately caged and starved overnight. The following morning the tests were begun with all groups being permitted to eat and drink *ad libitum* the prepared diets and drink provided. The basal ration used for all groups comprised a ground yellow corn containing 1% calcium carbonate and specified quantities of chlorotetracycline (CTC). Water to which specified amounts of sodium sulfate and chlorotetracycline has been added was supplied to the chicks for drinking purposes.

Six combinations of prepared feed and drink were selected for the tests and the combinations used were as follows:

Feed and Drink Combinations

	Feed	Water
Diet I	feed + 200 ppm CTC	H_2O
Diet II	feed + 200 ppm CTC	H_2O + 0.71% Na_2SO_4
Diet III	feed	H_2O + 500 ppm CTC
Diet IV	feed	H_2O + 500 ppm CTC + 0.71% Na_2SO_4
Diet V	feed + 200 ppm CTC	H_2O + 500 ppm CTC
Diet VI	feed + 200 ppm CTC	H_2O + 500 ppm CTC + 0.71% Na_2SO_4

Each of the above-noted diets was given to six randomly selected groups of chicks. Two hours after feeding had begun one group of chicks from each dietary group was selected. All birds in each group were bled by cardiac puncture and 1½ ml. of blood taken and assayed microbiologically for CTC blood levels. At 4, 6, 8, 16 and 24 hour periods after feed was begun, additional groups (one from each dietary group) were bled and blood serum levels of CTC ascertained microbiologically. Results of these tests are provided below.

TABLE 2

	26-Day-old Chicks Blood CTC at				
Hours	4	6	8	16	24
Diet I	.12	.13	.10	.11	.07
Diet II	.09	.14	.17	.18	.16
Diet III	.28	.17	.15	.40	.18
Diet IV	.28	.19	.30	.17	.29
Diet V	.15	.30	.23	.32	.28
Diet VI	.31	.34	.42	.38	.27

From this data it can be seen that substantially higher CTC blood levels can be obtained from a diet containing a given amount of CTC when sodium sulfate is added to the drinking water of birds consuming such diet.

The results provided also indicate that the addition of sodium sulfate to drinking water containing a given amount of chlorotetracycline will produce an increase in antibiotic blood levels of chicks drinking the treated water. Finally, the data clearly demonstrate that increased CTC blood levels are obtained from a given amount of CTC furnished in both the fed and drinking water when sodium sulfate is added to the drinking water.

EXAMPLE 3.

The following tests were conducted to determine whether or not the addition of the described sulfate to a medicated poultry drinking water would increase consumption of treated water and thus increase consumption of medicament.

Chicks, five-days old, of similar size and weight were randomly selected for 36 test groups, 12 chicks per group. These groups were separately caged and starved overnight. The following morning a standard, commercial diet, comprising:

Diet	%
Ground yellow corn	40.7
Soybean oil meal	45.5
Menhaden fish meal	7.5
$CaCO_3$	2.4
Dicalcium phosphate	2.0
Brewers dried yeast	1.25
Iodized salt	0.250
Magnesium sulfate	0.025
Vitamin A (10,000 IU/gm.)	0.110
Vitamin D—3 (15,000 ICU/gm.)	0.009
Choline chloride — 25% supplement	0.125
Vitamin supplement 92	0.100
Proferm — 20 (vitamin B_{12} supplement)	0.025
Niacin	0.0044
D-alpha tocopherol acetate	0.00055
Parvo 3% (folic acid supplement)	0.0030

was provided for all groups of chicks. Water containing various medicaments and specified amounts of sodium sulfate was also provided. The groups of birds were weighed at the start of the test period and the average weights calculated and recorded. Weighed amounts of feed were also provided along with measured quantities of water. The chicks were permitted to feed and drink *ad libitum* for 3 hours. Then they were re-weighed and the amount of feed and drink consumed was determined. Every three hours thereafter for a 24 hour period the above procedure was repeated. At the end of the test period all results were tabulated and the findings appear in Table III below where it is clearly shown that the addition of sodium sulfate to a medicated drinking water produces a substantial increase in the consumption thereof.

TABLE III
Consumption of Medicated Drinking Water

Time (Hours)	H_2O	CTC.HCl 2 g/gal	CTC.HCl 2 g/gal + Na_2SO_4 0.71%	2-Amino-5-nitro-thiazole 2.36 g/gal	2-Amino-5-nitro-thiazole 2.36 g/gal + Na_2SO_4 0.71%	Tylosin Tartrate 2 g/gal	Tylosin 2 g/gal + Na_2SO_4 0.71%	$CTC.SO_4$ 2 g/gal	$CTC.SO_4$ 2 g/gal + Na_2SO_4 0.71%
				Average Water Consumption Ml/100 Grams Chick					
3	7.17	5.84	7.24	5.95	7.88	6.46	9.64	4.04	3.72
6	12.08	11.14	14.71	11.82	14.13	12.07	19.09	9.02	8.65
9	16.92	15.88	21.76	16.82	19.34	17.11	27.37	13.70	14.10
12	21.99	21.25	29.31	21.70	24.97	22.35	35.78	18.47	21.03
15	26.67	26.21	35.33	26.70	29.42	26.88	44.52	22.76	27.13
18	31.92	31.64	42.12	31.94	35.16	31.73	53.02	27.93	34.17
21	36.68	37.13	49.03	36.37	40.12	36.93	62.51	33.61	40.95
24	41.78	42.41	55.90	41.49	46.36	42.69	70.61	38.16	48.15
				Average Feed Consumption Gms/100 Grams Chick					
3	8.29	6.92	8.12	7.13	7.19	7.50	7.28	7.33	7.43
6	11.03	10.09	10.78	10.00	9.65	10.86	9.87	9.81	9.97
9	14.12	13.30	13.87	13.10	12.38	13.83	12.67	13.03	12.51
12	17.48	16.54	16.93	16.69	14.92	16.98	15.97	16.23	15.80
15	20.96	19.24	19.96	19.50	17.66	19.77	18.93	18.90	18.33
18	24.51	22.36	22.96	22.98	20.17	22.83	21.63	21.75	21.20
21	27.75	25.40	25.48	25.48	22.59	26.07	24.49	24.87	23.97
24	30.79	28.30	28.44	28.30	25.32	28.97	27.39	27.40	26.71
				Average Water to Feed Ratio					
3	0.81	0.85	0.90	0.84	1.08	0.86	1.35	0.54	0.50
6	1.10	1.11	1.39	1.20	1.46	1.11	1.94	0.91	0.86
9	1.21	1.20	1.59	1.30	1.56	1.24	2.17	1.06	1.13
12	1.26	1.28	1.76	1.31	1.67	1.32	2.24	1.14	1.34
15	1.27	1.36	1.80	1.39	1.67	1.36	2.36	1.21	1.48
18	1.30	1.41	1.86	1.40	1.75	1.39	2.47	1.29	1.62
21	1.33	1.46	1.94	1.44	1.78	1.42	2.57	1.36	1.71
24	1.36	1.50	1.98	1.48	1.84	1.47	2.59	1.40	1.80

CTC.HCl = Chlortetracycline hydrochloride
$CTC.SO_4$ = Chlortetracycline bisulfate

EXAMPLE 4.

Five day-old chicks of similar weight and size were randomly divided into 32 groups of twelve chicks each. These groups were weighed and the average weight of the chicks calculated and recorded. The groups were then placed in separate cages and starved overnight. The following morning weighed amounts of food and measured quantities of water were provided for each group. All groups received the same standard commercial diet set forth in Example 3 above. No medication or feed supplement was added to the diet. However, the drinking water supplied to quadruplicate groups of chicks contained various concentrations of sulfates, sweeteners or commercially available electrolytes.

Four control groups were run and they received the standard diet and untreated water. At 3, 6, 12, 21 and 24 hours after feeding was begun, all groups of chicks were weighed. The amounts of feed and water consumed were also determined by weighing and measuring and the average consumption of food and water calculated for each period. From Table IV below, it can here be readily seen that the addition of sodium and potassium sulfate to the drinking water noticeably increased the consumption of water without adversely affecting food consumption. Other additives tested produced little or no change in either water or feed composition.

At sodium sulfate levels of 1.42% in the drinking water, average water consumption increased measureably over that obtainable with 0.71%, but average feed consumption began to taper off. While the high levels, i.e., above 1.0% sodium sulfate in the drinking water, are very effective, such levels should be used for short duration. Low levels, i.e., below 1.0% and preferably about between 0.3% and 0.7% are recommended for continuous use.

TABLE IV
Drinking Water Consumption

Time (Hours)	H_2O	Na_2SO_4 0.355%	Na_2SO_4 0.71%	Sucrose 0.71%	Cerelose 0.71%	K_2SO_4 0.71%	Electrolyte 0.312% KCl 0.042% $Ca(OH)_2$ 0.01% $MgSO_4$
			Average Water Consumption—Ml/100 Gm Chick				
3	8.67	10.91	11.97	8.70	9.23	8.72	8.65
6	14.43	18.67	20.75	15.08	15.00	16.04	14.21
12	27.14	33.33	39.28	26.69	26.87	31.02	25.96
21	43.39	53.72	64.62	43.40	43.95	51.26	43.53
24	49.88	60.79	71.96	49.20	50.33	58.65	50.18
			Average Feed Consumption—Gms/100 Gm Chick				
3	6.70	6.45	7.43	6.31	6.67	4.95	7.23
6	10.52	10.37	10.88	10.03	10.53	9.24	10.60
12	17.78	17.09	17.83	17.13	17.53	15.99	18.55
21	27.01	26.34	27.73	26.07	26.02	24.46	27.81
24	30.78	29.69	31.24	29.27	29.84	28.00	31.50
			Average Water to Feed Ratio				
3	1.32	1.70	1.61	1.38	1.44	1.76	1.20
6	1.39	1.80	1.94	1.50	1.46	1.74	1.37
12	1.53	1.95	2.23	1.56	1.56	1.95	1.41
21	1.61	2.04	2.34	1.67	1.71	2.10	1.57
24	1.62	2.05	2.31	1.69	1.71	2.10	1.59

EXAMPLE 5.

Potentiation of chlorotetracycline blood levels in chicks fed a corn diet containing 200 ppm of CTC.HCl and 0.8% calcium ion from calcium carbonate is achieved with the addition of sulfuric acid or ammonium sulfate. Groups of chicks were starved overnight then permitted to feed and drink *ad libitum* for three hours. At the end of the three hour period, the chicks were bled by cardiac puncture and the CTC blood levels assayed microbiologically. Chicks receiving the control diet containing 200 ppm of CTC, but no added sulfate ion, were found to have 0.11 γ/ml. of CTC in the blood. Those receiving 1.03% dietary sulfate ion furnished from sulfuric acid had CTC blood levels of 0.26 γ/ml. Those receiving the same level of sulfate ion from ammonium sulfate had CTC blood levels of 0.21 γ/ml.

WHAT WE CLAIM IS:—

1. A medicated poultry composition for oral administration via drinking water comprising a mixture of a medicament selected from tetracycline antibiotics, tylosin, 2-amino-5-nitrothiazole, and 2-acetylamino-5-nitrothiazole, and a sulfate of a cation carrying a single positive charge, or a mixture of two or more such sulfates, present in an amount to provide from 0.5 to 50 g. of sulfate ion per gram of medicament.

2. A composition according to Claim 1 which also includes a non-toxic carrier.

3. A composition according to Claim 1 or Claim 2 wherein the sulfate is selected from sodium sulfate, sodium bisulfate, potassium sulfate, potassium bisulfate, ammonium sulfate, ammonium acid sulfate, sulfuric acid, trimethyl ammonium sulfate or dimethyl ammonium sulfate.

4. A medicated poultry composition according to Claim 1 substantially as hereinbefore described.

5. A package containing a medicated poultry composition according to any preceding Claim.

TREGEAR, THIEMANN & BLEACH,
Chartered Patent Agents,
Melbourne House,
Aldwych,
London, W.C.2.
Agents for the Applicants.

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TREGEAR, THIEMANN & BLEACH,
Chartered Patent Agents,
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