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PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Compositions for Stimulating Growth of Domestic Animals

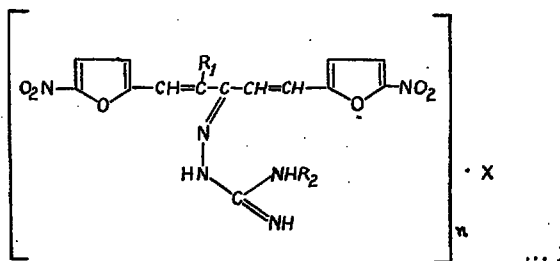
We, TOYAMA KAGAKU KOGYO KABUSHIKI KAISHA, a Corporation organized under the laws of Japan, of 9, Nihonbashi-Honcho-2-Chome, Chuo-Ku, Tokyo, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to an improved animal feed, particularly for young domestic animals, in which is included chicks, turkey poult and ducklings. It is also useful for young cattle, horses, swine, dogs and sheep.

A considerable problem has been raised in accelerating the growth of young domestic animals, and also in protecting against diseases. The economic importance of a rapid growth rate is very great, especially in chicks, turkey poult and ducklings. The more rapid the growth, the greater the proportion of feed which is transformed into meat. It is also desirable to prevent diseases, for example, coccidiosis in chickens. For both of these purposes it has been proposed in the past to use various narrow-spectrum antibiotics such as penicillin, bacitracin, streptomycin, and broad-spectrum antibiotics such as tetracycline, oxytetracycline, or chlorotetracycline. When mixed with animal feeds in suitable amounts these compounds do in fact aid in weight gain under some circumstances, and the drugs also assist in protection against infection. However, there is always room for improvement and it is with such an improved animal feed that the present invention deals.

The present invention comprises an animal feed composition containing the conventional nutritionally balanced feed ingredients and an effective amount of a novel growth promoting additive as more particularly hereinafter defined. In addition, the animal feed composition may contain one or more of the useful broad-spectrum antibiotics chlortetracycline, tetracycline or oxytetracycline.

The novel additive is a bis-(5-nitrofurfurylidene)-acetoneguanylylhydrazone and its addition salts such as the hydrochloride. The formula is as follows:



where R_1 is hydrogen, lower alkyl or halogen, R_2 is hydrogen or lower alkyl, and X is a mono-, di-, or tribasic acid, either inorganic or organic, n is 1, 2, or 3 with the proviso that when X is monobasic, n is 1, when X is dibasic n is 1 or 2, and when X is tribasic n is 1, 2 or 3. The unsubstituted derivative in which R_1 and R_2 are hydrogen and X is chlorine is sold in the trade under the name "Panazon" and

[Price 4s. 6d.]

for simplicity in the remainder of this specification the short term will be used, it being understood that it is used only in the above meaning.

The additives to the feeds of the present invention may be used over a broad range, for example from about 5 to 500 ppm. Optimum results are obtained, particularly with chicks, at a concentration nearer 25 ppm.

The present invention may be considered from two aspects, one as an improved animal feed in which the Panazon or its derivatives is mixed with the feed in the proportions given above, or as a process of increasing the growth of young animals. When considered as a process the administration of the Panazon may be in an already prepared feed stuff as referred to above, or it is possible to mix it with the drinking water, for example, in the case of chicks. In such a case the amounts used should be comparable to those which would be ingested if the premixed feed were used.

It is an advantage of the present invention that in its optimum concentrations it shows a growth stimulating effect greater than the antibiotics which have been used in the past, and it is a further advantage that the drug need not be used alone, as it is useable with antibiotics such as chlortetracycline, and such combined mixed feeds are included within the scope of the present invention. It is also an advantage of the present invention that Panazon and its derivatives exert marked protection against certain infectious diseases such as coccidiosis in chickens, and thus combine both the desirable economic effect of enhancing growth rate and the protection against loss by disease.

The invention will be described in greater detail in conjunction with specific examples in which various amounts of Panazon are incorporated in various animal feeds.

EXAMPLE 1

A typical commercial feed was used having the following composition:

Ingredient	Per Cent
Ground yellow maize	51.4
Soybean oil meal solvent (44%)*	30.0
Menhaden fish meal (60%)	5.0
Maize gluten meal (41%)	5.0
Dehydrated alfalfa meal (17%)	2.0
Stabilized fat**	4.0
Dicalcium phosphate	1.2
Ground calcite limestone (33% Ca)	0.5
Sodium chloride	0.3
Trace minerals (Delamix plus 2% Zn)***	0.1
Vitamin-amino acid premix****	0.5

*Solvent extracted soybean oil meal which contains 44% crude protein.

**Animal and vegetable fat stabilized with butylated hydroxy toluene.

***manganese 6.0%, iodine 0.12%, iron 2.0%, copper 0.2%, zinc 2.0%, cobalt 0.02%, calcium 25.5%.

****Vitamin-amino acid premix — Amount per Kg. feed: 125 mg butylated hydroxy toluene, 500 mg. DL-methionine, 3300 I.U. vitamin A, 1100 I.C.U. vitamin D₃, 2.2 I.U. vitamin E, 11 mcg. vitamin B₁₂, 4.4 mg. riboflavin, 27.5 mg. niacin, 8.8mg. pantothenic acid, 500 mg. choline chloride, 1.43 mg. folic acid, 1.1 mg. menadione sodium bisulfite to 5 g. of ground yellow-maize.

The diet alone was used as a control and various amounts of Panazon were added as were various amounts of procaine penicillin and chlortetracycline hydrochloride. In each group Peterson-cross broiler chicks were used, six males and six females per group. Feed and water were supplied *ad libitum*. The results are shown in the following table 1.

TABLE 1

Supplement	Growth response per cent of control			
	Age in Weeks			
	1	2	3	4
Control	100	100	100	100
100 ppm Panazon	118	109	109	106
110 100 ppm procaine penicillin	97	98	100	97
100 ppm chlortetracycline hydrochloride	109	104	103	100

It will be seen that at 100 ppm Panazon gives better results at all periods than did either of the antibiotics.

EXAMPLE 2

5 The effect of varying amounts of Panazon and procaine penicillin was tested; the diet used in Example 1 was used as a control; and the drugs were added in separate tests in amounts of 12.5, 25, 50 and 100 ppm. The following table shows the results:

TABLE 2

Compound	Age	Growth response per cent of control ppm				
		0	12.5	25	50	100
Panazon	1 week	100	116	127	111	120
	2 weeks	100	105	116	106	107
	2 weeks	100	105	112	102	104
	4 weeks	100	105	110	103	103
Procaine penicillin	1 week	100	111	119	107	131
	2 weeks	100	100	107	103	116
	3 weeks	100	97	103	102	105
	4 weeks	100	98	101	103	104

10 It will be seen that the optimum amount of Panazon is about 25 ppm and at this concentration there was markedly better results than with any concentration of the antibiotic after four weeks. Even when 100 ppm of Panazon is compared with penicillin at the same figure, their optimum, the results were not significantly different at the end of four weeks. In other words, Panazon is as effective as penicillin and in its preferred concentration, which is lower, is more effective.

EXAMPLE 3

20 The procedure of Example 2 was followed, except that there was a control test and tests of each concentration of Panazon were of other concentrations of chlortetracycline hydrochloride. Table 3 shows the results, the control being designated as 100% as in Example 2.

TABLE 3

Growth response per cent of control

		Panazon			
		ppm			
	Age	0	25	50	100
0	1 week	100	108	118	107
	2 weeks	100	109	115	108
	3 weeks	100	106	111	108
	4 weeks	100	110	113	112
50	1 week	114	123	111	115
	2 weeks	106	115	108	110
	3 weeks	103	110	106	108
	4 weeks	106	111	111	111
Chlortetra- cycline-hy- drochloride ppm 100	1 week	113	126	129	116
	2 weeks	108	112	109	109
	3 weeks	105	113	107	105
	4 weeks	108	115	110	107
200	1 week	110	109	101	113
	2 weeks	106	111	101	109
	3 weeks	103	108	100	107
	4 weeks	106	112	106	111

It will be seen that the combined drugs gave useful results, and that Panazon was highly effective as a chick growth promoter. Statistical analysis of these data indicates that the chlortetracycline growth effect was augmented by the addition of Panazon. It appears that Panazon and chlortetracycline hydrochloride function differently in stimulating chick growth.

EXAMPLE 4

The following test was made to show that Panazon is also useful with other animal feeds. For this test a purified casein-sucrose feed was used having the following composition:

Ingredient	Per Cent
Sucrose	60.4
Casein	20.0
Gelatin	8.0
Calcium gluconate	5.0
Salt mixture No. 1*	2.0
Bone ash	2.0
Vitamins in cerelose**	1.0
Cystine	0.4
Choline chloride	0.2
Vitamins A, D and E in maize germ oil	1.0
Folic acid	5 mg/kg
Biotin	0.2 mg/kg
Vitamin B ₁₂	50 mcg/kg

*600 mg. sodium chloride, 600 mg. dipotassium phosphate, 450 mg. monopotassium phosphate, 250 mg. magnesium sulfate monohydrate, 38 mg. manganese sulfate, 50 mg. ferric citrate, 2 mg. cupric sulfate, 0.6 mg. potassium iodide, 0.08 mg. potassium bromide, 1.4 mg. zinc acetate, 1.6 mg. aluminium sulfate, 0.4 mg. cobalt acetate tetrahydrate, 0.2 mg. nickel sulfate, 0.05 mg. sodium molybdate, 0.055 mg. sodium selenite. Water to dissolve trace minerals up to 2 gm.

**1 mg. thiamine hydrochloride, 1 mg. riboflavin, 5 mg. niacinamide, 1 mg. pyridoxine, 5 mg. calcium pantothenate, 0.5 mg. folic acid, 0.5 mg. vitamin K, 0.02 mg. biotin, 5 mcg. vitamin B₁₂, 100 mg. inositol, glucose up to 1 gm.

The following table shows the gain in weight as a percentage of the control:

	TABLE 4			
	Control (diet)	100	100	100
100 ppm Panazon	154	136	127	108

EXAMPLE 5

The effectiveness of feeds containing Panazon in preventing infection was tested with four groups of 80 male Leghorn chicks. A standard diet was used and the feeding period was extended for nine weeks under conditions which did not involve any attempt to protect the chicks from coccidiosis infection. The large numbers in each group were used because the incidence of coccidiosis is not so high that one could be sure that there would be cases in a smaller group. The results appear in the following table:

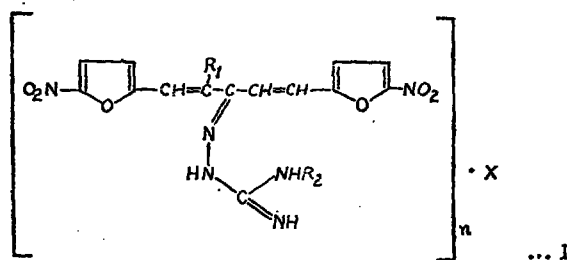
TABLE 5

Group	Number of chicks tested	Period after treatment started (weeks)				total	Per cent of symptomatic chicks (%)
		3	5	7	9		
Control	(80)	0	1	2	0	3	3.75
10 ppm	(80)	0	0	0	0	0	0
20 ppm	(80)	0	0	0	0	0	0
40 ppm	(80)	0	0	0	0	0	0

It will be seen that beginning at the fifth week the controls showed occurrence of coccidiosis, but the chicks which were fed the feeds with varying amounts of Panazon showed no cases. It is apparent, therefore, that substantial protection against infection is obtained.

WHAT WE CLAIM IS:—

1. An animal feed or drink for animals, characterized by the fact that it contains bis-(5-nitrofurfurylidene)-acetone guanylhyazone or its acid addition salt having the formula:



in which R₁ is hydrogen, lower alkyl or halogen, R₂ is hydrogen or lower alkyl, X is an acid, and when X is a monobasic acid n is 1, when X is dibasic n is 1 or 2 and when X is tribasic n is 1, 2 or 3.

2. A feed or drink according to claim 1, characterized by the fact that the bis-(5-nitrofurfurylidene)-acetone guanylhyazone or its acid addition salt of formula I is present in an amount of from 5 to 500 ppm.

3. A feed or drink according to claim 1 or 2, characterized by the fact that the bis-(5-nitrofurfurylidene)-acetone guanylhyazone or its acid addition salt of formula I is present in an amount of from 10 to 100 ppm.

4. A feed or drink according to claim 1, 2 or 3, characterized by the fact that it is a poultry feed.



characterized



**1 mg. thiamine hydrochloride, 1 mg. riboflavin, 5 mg. niacinamide, 1 mg. pyridoxine, 5 mg. calcium pantothenate, 0.5 mg. folic acid, 0.5 mg. vitamin K, 0.02 mg. biotin, 5 mcg. vitamin B₁₂, 100 mg. inositol, glucose up to 1 gm.

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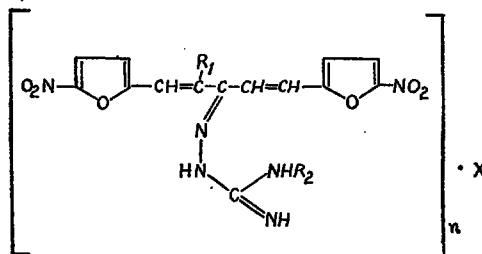
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10 ppm	(80)	0	0	0	0	0	0
20 ppm	(80)	0	0	0	0	0	0
40 ppm	(80)	0	0	0	0	0	0

It will be seen that beginning at the fifth week the controls showed occurrence of coccidiosis, but the chicks which were fed the feeds with varying amounts of Panazon showed no cases. It is apparent, therefore, that substantial protection against infection is obtained.

WHAT WE CLAIM IS:—

1. An animal feed or drink for animals, characterized by the fact that it contains bis-(5-nitrofurfurylidene)-acetone guanyldrazone or its acid addition salt having the formula:



in which R₁ is hydrogen, lower alkyl or halogen, R₂ is hydrogen or lower alkyl, X is an acid, and when X is a monobasic acid n is 1, when X is dibasic n is 1 or 2 and when X is tribasic n is 1, 2 or 3.

2. A feed or drink according to claim 1, characterized by the fact that the bis-(5-nitrofurfurylidene)-acetone guanyldrazone or its acid addition salt of formula I is present in an amount of from 5 to 500 ppm.

3. A feed or drink according to claim 1 or 2, characterized by the fact that the bis-(5-nitrofurfurylidene)-acetone guanyldrazone or its acid addition salt of formula I is present in an amount of from 10 to 100 ppm.

4. A feed or drink according to claim 1, 2 or 3, characterized by the fact that it is a poultry feed.

5. A feed or drink according to claim 4, characterized by the fact that the compound of formula I is bis-(5-nitrofurfurylidene)-acetone guanyldrazone hydrochloride.

6. A feed or drink according to claim 5, characterized by the fact that the amount of the compound of formula I is approximately 25 ppm.

7. A feed or drink according to any one of the preceding claims, characterized by the fact that there is also present in the feed chlortetracycline, tetracycline and/or oxytetracycline.

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