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(54) ANTI-PROTOZOAL COMPOSITION

*(71) We, TAKEDA YAKUHIN KOGYO KABUSHIKI KAISHA, also known as Takeda Chemical Industries Ltd., of 27, 2-chome, Doshomachi, Higashi-ku, Osaka, Japan, a body corporate organised under the laws of 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 a method for the prevention or treatment of protozoiasis in domestic animals, and also to a composition administrable to animals for this purpose.

Protozoiasis, caused by protozoal infections in livestock and poultry, such as coccidiosis, leucocytozoon infections, toxoplasmosis and piroplasmosis, not only lowers the productive performance of the afflicted animals but sometimes kills them in large numbers.

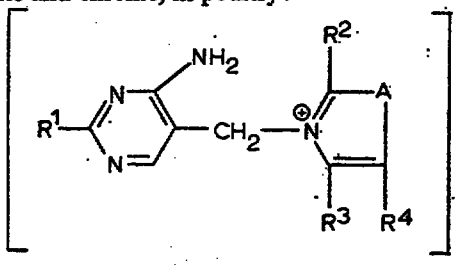
Of the protozoan infections, coccidiosis is the most important, and, while the use of some pyrimidine derivatives has proved fairly successful in the prevention and treatment of coccidiosis, the effects attainable still leave something to be desired. Stated differently, there are two types of coccidiosis: one is an acute disease accompanied by haemorrhagic lesions caused by such coccidia as *Eimeria tenella* and *Eimeria necatrix*, and the other is a chronic disease caused by such other coccidia as *Eimeria acervulina, E. maxima* and *E. brunetti*. Under field conditions, the hosts are often infected with both types of pathogenic organisms and such mixed infections frequently produce far more serious afflictions than do infections with a single species of the causative organisms.

While the aforementioned pyrimidine derivatives are fairly effective, although selectively, against acute coccidiosis, offering substantially symptomatic relief, they have no appreciable effects upon chronic coccidiosis.

Although outbreaks of chronic coccidiosis generally result in less serious damage than acute cases, the ravages played by the former in a meat-producing livestock and poultry such as broilers have been matters of great concern because the disease lowers their feed intake and accordingly makes them more vulnerable to other diseases.

White several sulpha drugs have been used for the treatment of these infections, none has proved completely effective. Moreover, many protozoan infections are actually caused by several species of protozoa and, therefore, a drug that will control a variety of infections has been awaited.

We have found that 3-sulphanilamidoisoxazole (hereinafter referred to as "3-SI") has excellent prophylactic and therapeutic effects upon protozoiasis in domestic animals, particularly upon chronic coccidiosis, and we have further found that 3-SI and a salt of a pyrimidine derivative of the general formula (I) or (II) as defined below or a mixture thereof, if used in conjunction, join forces to act effectively against all cases of coccidiosis, both acute and chronic, in poultry:

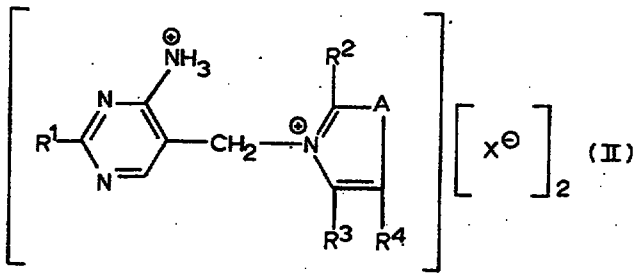


(I)

[*Price 25p*]

SEE CORRECTION SLIP ATTACHED

or



(II)

wherein the formula (I) represents the mono-salt and (II) the di-salt,
wherein
X represents a pharmaceutically acceptable acid anion
A represents —S— or —CH=CH—,
R^1 represents an alkyl group of up to 3 carbon atoms, and each of R^2, R^3 and R^4 represents H or an alkyl group of up to 3 carbon atoms.

Accordingly, the invention provides a method for the prevention or treatment of protozoiasis, which comprises administering to domestic animals an anti-protozoal amount of 3-sulphanilamidoisoxazole, a pharmaceutically acceptable salt thereof or a mixture of 3-sulphanilamidoisoxazole and its salt.

In a preferred embodiment the anti-protozoal amount is from 0.0005 to 0.3 percent by weight in terms of 3-sulphanilamidoisoxazole relative to a feedstuff for the animals.

In one embodiment of the method according to the invention an anti-coccidial amount of a pharmaceutically acceptable salt of a pyrimidine derivative of formula (I) or (II) as just defined or a mixture thereof is administered to the poultry, preferably in an amount of from 0.001 to 0.05 percent by weight in terms of the pyrimidine derivative base relative to the feedstuff fed to the poultry.

The invention also provides a composition for the prevention or treatment of protozoiasis in domestic animals, which comprises 3-sulphanilamidoisoxazole, a pharmaceutically acceptable salt or a mixture of 3-SI and its salt in a concentration of from 0.0005 to 0.3 percent by weight in terms of 3-sulphanilamidoisoxazole relative to the composition; and a major proportion of a physiologically acceptable carrier therefor.

According to another embodiment the invention provides a composition which comprises a) 3-sulphanilamidoisoxazole, a pharmaceutically acceptable salt or a mixture of 3-SI and its salt; b) a pharmaceutically acceptable salt of a pyrimidine derivative of the formula (I) or (II) as just defined or a mixture thereof; and c) a physiologically acceptable carrier of the ingredients a) and b).

It is often advantageous to first make the composition into a premix comprising, for example, from 1 to 30 percent by weight of ingredient a) in terms of 3-sulphanilamidoisoxazole and from 1 to 30 percent by weight of ingredient b) in terms of the pyrimidine derivative base, relative to the whole composition.

The composition when ready for use may contain ingredient (a) in an amount of from 0.0005 to 0.3 percent by weight in terms of 3-sulphanilamidoisoxazole and ingredient (b) in an amount of from 0.001 to 0.05 percent by weight in terms of the pyrimidine derivative base, relative to the composition.

The present invention provides an antiprotozoal composition which is not only effective and non-toxic, but also stable and palatable to the livestock or poultry, and a method for controlling (i.e. preventing or treating) protozoan infections in livestock or poultry more effectively and with greater ease than hitherto known methods.

The composition and method of the invention rely on the use of 3-SI or on the combined use of 3-SI and a salt of a pyrimidine derivative of the general formula (I) as the active ingredient or ingredients in the anti-protozoal composition to be administered to livestock, e.g. swine, dairy cattle, beef cattle, calf, lamp, horse, kid and dog, and to poultry, e.g. chick, layer, breeder, duck, turkey and quail.

3-SI can be prepared, for example, by the method described in British Patent No. 1,011,850, and may be used for the purposes of the present invention in its free form or in a pharmaceutically acceptable salt form or in a mixture thereof on the same molar basis. The salt of 3-SI is typically the alkali metal salt such as the sodium or potassium salt, being water-soluble.

Referring now to the above formulae (I) and (II), the alkyl group is methyl, ethyl or propyl. A partial listing of the pyrimidine derivatives of general formula (I) includes, for example:

3-(2-methyl-4-amino-5-pyrimidinylmethyl)-4,5-dimethylthiazolium salt (i.e. dimethialium);
3-(2-ethyl-4-amino-5-pyrimidinylmethyl)-4,5-dimethylthiazolium salt;
3-(2-ethyl-4-amino-5-pyrimidinylmethyl)-5-ethylthiazolium salt;
3-(2-methyl-4-amino-5-pyrimidinylmethyl)-2,4-dimethylthiazolium salt; or
1-(2-n-propyl-4-amino-5-pyrimidinylmethyl)-2-methylpyridinium salt (i.e. amprolium).

The salts of the above pyrimidine derivatives includes, as examples, the nitrate, hydrochloride, hydrobromide and thiocyanate, which may respectively be either the mono- or the di-salt.

Sulpha drugs are generally used as aqueous solutions, but they are so unpalatable to animals that, if given to them *ad libitum*, a sufficient intake cannot be expected. In contrast, 3-SI is quite palatable to animals and, moreover, even a continued administration of this compound yields no adverse effect upon growth of the livestock and poultry.

As an example, White Leghorn chicks, 3 days of age were battery-raised on a commercial feed for chicks, and meanwhile, the following test drugs were administered by way of drinking water to the chicks for a period of two weeks. This subacute toxicity test gave the following results.

Test Drug	Concentration of Drug (%)	Number of Birds	Livability (%)	Live Weight (g)	With Live Weight of Control as 100	Feed Requirement*
3—SI.Na	0.2	30	100.0	165.0	(97.5)	1.93
Sulphadimethoxine.Na	0.2	30	80.0	110.4	(65.2)	2.10
Sulphamonomethoxine.Na	0.2	30	96.7	134.5	(79.4)	1.99
Sulphaquinoxaline.Na	0.2	30	93.3	92.9	(54.9)	2.93
Control	—	30	100.0	169.3	(100.0)	1.93

$$\text{* Feed requirement (feed/gain)} = \frac{\text{Feed intake (g.)}}{\text{Increase in body weight (g.)}}$$

The safety of 3-SI is also demonstrated by the following test example using swine. Two groups of five young swine per group were raised for 60 days, Group A being fed with a normal feed and Group B being fed with the normal feed in admixture with 0.5 g/kg feed of 3-SI, to give the following results showing no statistically significant difference between Groups A and B. The feed requirement was calculated according to the above-mentioned equation.

Stage	Group	Mean Body Weight (kg.)	Feed intake kg./Head	Body Weight Index	Feed Requirement*
Initial	A	19.62 ± 4.53		100	
	B	19.60 ± 2.20		100	
1 Week	A	22.56 ± 5.57	7.14	115.0	2.43
	B	22.36 ± 2.25		114.1	2.59
2 Weeks	A	25.28 ± 5.74	7.86	128.8	2.89
	B	24.94 ± 2.85		126.4	3.05
3 Weeks	A	27.88 ± 6.38	9.06	142.1	3.49
	B	28.72 ± 3.00		146.5	2.40
4 Weeks	A	31.24 ± 7.24	8.52	159.2	2.54
	B	31.98 ± 3.10		163.2	2.61
5 Weeks	A	35.72 ± 7.90	11.92	182.1	2.66
	B	36.20 ± 3.58		184.7	2.82
6 Weeks	A	39.84 ± 8.16	11.04	203.4	2.68
	B	40.44 ± 3.64		206.3	2.60
Final (60 Days)	A	44.12 ± 9.43	14.96	224.9	3.50
	B	44.68 ± 3.58		228.0	3.53

The mixture of 3-SI and the pyrimidine derivative of general formula (I) is also palatable and non-toxic to poultry. Therefore, it can also be easily administered as a solution in drinking water to give an adequate control effect.

Sulpha drugs themselves are insoluble or hardly soluble in water and, therefore, have been used as water-soluble salts such as the salts of alkali metals, e.g. sodium and potassium. It follows, however, that the resulting aqueous solutions are stable only on the alkaline side and their solubilities decrease drastically on the acid side. In contrast, the pyrimidine derivatives of general formula (I) are stable on the acid side and will either precipitate or decompose on the alkaline side. It is for this reason that it has heretofore been considered difficult to secure a stable aqueous solution containing both a sulpha drug and a pyrimidine derivative.

However, 3-SI is soluble in water even on the acid side and its stability is not affected by the concomitant presence of pyrimidine derivatives. Thus, the mixed drug composed of 3-SI and the pyrimidine derivative according to this invention is also excellent in view of stability.

The solubility of 3-SI, in comparison with that of the conventional sulpha drugs, is shown below. The values of sulphisomezole, sulphadimethoxine and 3-SI in water at various pH levels are shown. It will be seen that 3-SI is soluble in excess of 0.2 percent over a wide pH range.

pH	Solubilities in Water (%)		
	Sulphisomezole	Sulphadimethoxine	3—SI
2.8	0.05	Insoluble	0.25
3.8	0.04	Insoluble	0.29
5.5	0.09	0.05>	1.54
6.5	0.32	0.01>	6.57

The above results show that 3-SI is far more readily soluble even in comparison with sulphisomezole which, in structure, bears a close resemblance to 3-SI.

The anti-protozoal drug of this invention can be administered, depending on the species of animal, symptoms and the age of the animal, for example, in varied forms such as powder, granule, tablet, capsule, oil solution, aqueous solution, emulsion, suspension or whatever is suitable, either with or without the use of a solid or liquid diluent. Alternatively, the drug may be administered as a feed additive. The drug may be directly dispersed in the feed or in the drinking water, or may be previously dispersed in a diluent and the resulting dispersion may be incorporated in the feed or drinking water.

The diluent mentioned above may be of various kinds, provided it does not spoil or reduce the anti-protozoal activity of 3-SI or the anti-coccidial activity of the pyrimidine derivative of general formula (I), although the diluent is preferably one which can be used as a feed or a feed additive. For example, use may be made of such diluents as barley flour, wheat flour, rye flour, corn meal, soybean meal, soybean cake, rapeseed meal, rice hull, rice-bran, solvent-extracted rice-bran, sweet potato powder, white potato powder, bean-curd refuse, various types of starch, lactose, sucrose, glucose, fructose, yeast, waste yeast, fish meal and fermentation broth residue. If desired, it is permissible to employ such supplements as various vitamins (e.g. vitamin B_2, fat-soluble vitamins), minerals (e.g. calcium sources), amino acids, proteins, carbohydrates, fats, as well as preservatives, germicides, enzyme preparations, enterostomachics, antipyretics, sedatives, antiphlogistics and purgatives..

The proportions of 3-SI in the anti-protozoal drug of this invention should vary with different species of animals, routes of administration, purposes (prophylactic or therapeutic), symptoms in the host, within the range of from 0.0005 to 0.3 per cent by weight, desirably from 0.002 to 0.2 percent by weight, relative to the feedstuff fed to the animals. Where the drug is incorporated in a feedstuff for controlling coccidiosis in poultry, the preferred concentrations are from 0.0005 to 0.3 percent by weight (desirably from 0.002 to 0.2 percent) for 3-SI and from 0.001 to 0.05 percent by weight desirably from 0.002 to 0.025 percent) for the pyrimidine derivative (I), relative to the feedstuff. When the present drug is used as a feed supplement, it may be directly added to the feed, but, for most practical purposes, it is first made into a premix containing from 1 to 30 percent by weight of the 3-SI or further containing from 1 to 30 percent by weight of the pyrimidine derivative (I) and then the premix is further diluted with the feed or drinking water.

The results of tests with the anti-protozoal drug of this invention are shown below. In the following, the various terms are used in accordance with the definitions given immediately below:

Rate of weight gain: The average weight of birds at the end of the experiment is divided by the average weight thereof at the time when the test was started, and, after the number 1 is subtracted from the product, the difference is multiplied by 100.

Weight gain ratio: The percentage of the rate of weight gain for each test group relative to the rate of weight gain for a normal control group, i.e. the group of uninfected and untreated individuals.

Number of bloody droppings: The total number of bloody droppings secreted by birds in each group.

*Pathological changes*H The pathological changes were investigated in the caeca for *Eimeria tenella* and in the small intestines for other species, and classified by the following criteria:

–	:	Normal, no pathological change,
+	:	Slight change,
+!+	:	Moderate change,
+!+!+	:	Serious change,
+!+!+!+	:	Pathological change all-over, very serious.

Pate of sporulation: A 2% aqueous solution of potassium dichromate is added to the faeces, the volume being 10 times as much as the contents, and the contents are then incubated at 28°C. for 3 days. The percentage of the sporulated oocysts bond on the total in the contents is calculated.

Oocyst output (*OPG*): The total number of oocysts occurring in one gram of caecal contents or faeces.

The number of oocysts per bird: Each bird is dissected and all the oocysts occurring in the entire intestinal tract are counted.

TEST 1

White Leghorn chicks, 12 days of age, were orally inoculated with 100 thousand sporulated oocysts of *Eimeria acervulina* and, at the same time, were fed with feeds which contained dimethialium, 3-SI and sulphadimethoxine, respectively. The results are summarised in Table 1, which clearly shows that 3-SI is far more effective against the chronic coccidiosis caused by *E. acervulina* than sulphadimethoxine and dimethialium.

TEST 2

White Leghorn hens, 200 days of age, were individually caged and continuously supplied with drinking water containing 0.2% of sulphadimethoxine sodium or 3-SI sodium. The results are summarised in Table 2, which indicates that, as contrasted with sulphadimethoxine, the administration of 3-SI causes no change in drinking water intake and results in a longer pre-moulting period as compared with the control group (untreated group).

TEST 3

(a) Of ten White Leghorn chicks, 10 days of age, five birds were orally inoculated with 25 thousand sporulated oocysts of *Eimeria tenella* each. The remaining five chicks were inoculated with 100 thousand sporulated oocysts of *Eimeria acervulina* each.

At the same time, the birds were fed with feeds containing dimethialium mononitrate and/or 3-SI. The results are summarised in Table 3(a), from which it will be seen that the combined administration of dimethialium and 3-SI provides better prophylaxis than the use of either one or the other of the same compounds.

(b) In the same manner as at (a) above, five White Leghorn chicks per group of 11 days old were inoculated with 100 thousand sporulated oocysts of *Eimeria acervulina* each, and were fed with feeds containing 3-(2-ethyl-4-amino-5-pyrimidinylmethyl)-4,5-dimethylthiazolium mononitrate (referred to herein as "DC-45") or of both DC-45 and 3-SI. The results are summarised in Table 3(b).

TEST 4

White Leghorn chicks, 10 days of age, were inoculated according to Table 4, using the sporulated oocysts of *Eimeria tenella*, *E. necatrix*, *E. acervulina* and *E. maxima*. At the same time, the chicks were fed with feeds containing dimethialium mononitrate and/or 3-SI. The results are summarised in Table 4.

TEST 5

Mice (dd-strain) were intraperitoneally infected with *Toxoplasma gongii* (RH-strain) to obtain inoculum. The intraperitoneal fluid of the infected mice was inoculated in an amount containing 12 thousand parasites each to nine sensitive mice (dd-strain) intraperitoneally. The mice were fed with a normal feed except that 0.12 percent by weight of 3-SI relative to the feed was administered in admixture with the feed to the test group, consisting of four mice among the nine, for the initial 5 days.

While the five mice of the control group survived only for an average of 7.4 days (7, 7, 7, 8 and 8 days, respectively) after the inoculation, the mice of the test group survived for an average of 12.5 days (12, 12, 13 and 13, days, respectively) after the inoculation.

TABLE 1

Drug and Concentration	Infection	Oocyst Output 4th Day	5th Day	6th Day	7th Day	Pathological Change in the small intestine (number of birds) +++	++	+	—	Weight Gain Ratio (%)
Uninfected, untreated group	—	0	0	0	0				5	100
Infected, untreated group	+	12,600	457,100	72,300	36,100	3	2			69
Dimethialium 0.006%	+	300	284,800	102,200	14,200	2	2	1		102
Sulphadimethoxine 0.05%	+	100	356,100	102,400	1,023,400	1	3	1		92
3—SI 0.05%	+	0	200	9,200	19,400		3	2		95
3—SI 0.025%	+	0	500	71,800	5,320	2	2	1		73

TABLE 2

Drug in Drinking Water (25 Birds Per Group)	Water Intake (Average per bird, control as 100) 1st Day	2	3	4	5	6	7	8	9	10	The Days After Administration Start Until Moulting	Egg Production Rate (%) Administration start	6th Day of Administration
Control, untreated	100	100	100	100	100	100	100	100	100	100	—	60.7	63.0
Sulphadimethoxine.Na	71.8	43.9	39.0	44.8	75.8	43.4	50.6	33.0	41.4	38.0	7 days	62.0	10.0
3—SI.Na	126.8	130.8	108.0	120.9	116.4	114.1	103.8	107.8	98.8	123.4	14 days	61.0	57.0

TABLE 3(a)

	Drug in Feed (%)		Infection	Number of Birds	Number of Bloody Droppings				Pathological Change in the Intestine					Number of Oocysts per Bird ($\times 10^4$)	
	Dimethialium	3—SI			4th	5th	6th	7th	++++	+++	++	+	−		
	0.006	0.005	+	5									5	0	10-day chicks 25 thousand oocysts per autopsied on 8th day
	0.006		+	5									5	0	
E. tenella	0.003		+	5			2				1	3	1	2.3	
	0.003	0.005	+	5			3				1	3	1	1.9	
		0.005	+	5	8	40	45	3	5					240.0	
			+	5	9	45	45	2	5					211.0	
	0.006		+	5					5					1571.0	10-day chicks 100 thousand oocysts per bird; autopsied on 6th day
	0.006	0.005	+	5									5	0	
E. acervulina	0.003		+	5					5					1920.0	
	0.003	0.005	+	5									5	0	
		0.005	+	5									5	0	
			+	5					5					2310.0	
			−	5									5		Healthy control

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TABLE 3(b)

Drug in Feed (%)			Pathological Change in the Intestine			Oocyst Output			Rate of Sporulation (%)	Weight Gain Ratio
DC—45	3—SI	Infection	++	+	—	4th Day	5th Day	6th Day		
0.003	0	+	4	1		$10^{6.5}$	$10^{6.9}$	$10^{6.9}$	79	97.6
0.003	0.003	+			5	0	0	0	0	93.4
0.003	0.0015	+			5	0	0	0	0	101.3
0.003	0.00075	+			5	0	0	0	0	100.8
None	None	+	5			$10^{6.7}$	$10^{7.2}$	$10^{7.0}$	96	95.5
None	None	—			5	0	0	0	0	100

TABLE 4

The combined effect (prophylactic) of dimethylialium and the sulpha drug against mixed coccidial infections

Coccidia (Number of Oocysts 10^4/Bird)				Drugs (% in Feed)		Number of Birds		Rate of Weight Gain %	Oocyst Output × 10^4			
E. tenella	*E. necatrix*	*E. acervulina*	*E maxima*	Dimethialium mononitrate	3—SI	Tested	Dead		5th Day	6th Day	7th Day	8th Day
2.0		20.0		0.006		10	1	89.6	4.0	121.0	205.0	90.0
2.0		20.0			0.005	10	2	62.6	0	0	0.2	15.0
2.0		20.0		0.006	0.005	10	0	100.0	0	0	0	0
2.0		20.0				10	7	59.3	8.0	250.0	171.0	521.0
	1.0	20.0		0.006		10	3	87.9	9.1	309.1	799.0	195.1
	1.0	20.0			0.005	10	4	68.3	0	0	0	2.1
	1.0	20.0		0.006	0.005	10	0	98.9	0	0	0	0
	1.0	20.0				10	9	52.5	12.0	311.3	982.9	291.1
2.0	1.0	20.0	20.0	0.006		10	3	88.9	27.3	1920.0	3010.5	613.0
2.0	1.0	20.0	20.0		0.005	10	3	64.1	0	0	3.0	81.5
2.0	1.0	20.0	20.0	0.006	0.005	10	0	101.0	0	0	0	0
2.0	1.0	20.0	20.0			10	9	58.4	28.0	1711.0	2190.2	711.0
				0.006		10	0	100.5				
					0.005	10	0	102.2				
						10	0	100.0				

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The present invention is further explained by way of Examples which are solely for the purpose of illustration. In the Examples, parts by weight bear the same relationship to parts by volume as do grams to millilitres.

EXAMPLE 1

The following components are mixed together:

3-SI	10 parts by weight
Wheat flour	90 parts by weight

0.1 Part by weight of the mixture is homogeneously added to 99.9 parts by weight of a conventional diet for chicks.
The resulting composition is fed to chicks.

EXAMPLE 2

The following components are mixed together:

3-SI	25 parts by weight
Soybean flour	75 parts by weight

0.4 Part by weight of the mixture is homogeneously added to 99.6 parts by weight of a conventional diet for swine.
The resulting composition is fed to swine.

EXAMPLE 3

The following components are homogeneously mixed together:

3-SI sodium	10 parts by weight
Lactose	85 parts by weight
Sucrose	5 parts by weight

One part by weight of the mixture is dissolved in 1000 parts by volume of drinking water. The resulting drinking water is given to layers.

EXAMPLE 4

The following components are mixed together:

3-SI	10 parts by weight
Dimethialium mononitrate	10 parts by weight
Fermentation residue	80 parts by weight

0.05 Part by weight of the mixture is homogeneously added to 99.95 parts by weight of conventional diet for breeders. The resulting composition is fed to breeders.

EXAMPLE 5

The following components are mixed together:

3-SI	2 parts by weight
3-(2-ethyl-4-amino-5-pyrimidinyl-methyl)-4,5-dimethylthiazolium mononitrate	3 parts by weight
Corn meal	95 parts by weight

0.1 Part by weight of the mixture is homogeneously added to 99.9 parts by weight of a conventional diet for chicks.
The resulting composition is fed to chicks.

EXAMPLE 6

The following components are mixed together to prepare a premix composition:

3-SI sodium	10 parts by weight
Lactose	85 parts by weight
Sucrose	5 parts by weight

On the other hand, the following components are admixed:

Dimethialium chloride hydrochloride	10 parts by weight
Lactose	85 parts by weight
Sucrose	5 parts by weight

0.5 Part by weight each of both premix compositions in mixed together. The resulting mixture is dissolved in 1000 parts by volume of drinking water, and is given to chicks.

WHAT WE CLAIM IS:—

1. A method for the prevention or treatment of protozoiasis, which comprises administering to domestic animals an anti-protozoal amount of 3-sulphanilamidoisoxazole, a pharmaceutically acceptable salt thereof or a mixture of 3-sulphanilamidoisoxazole and its salt.

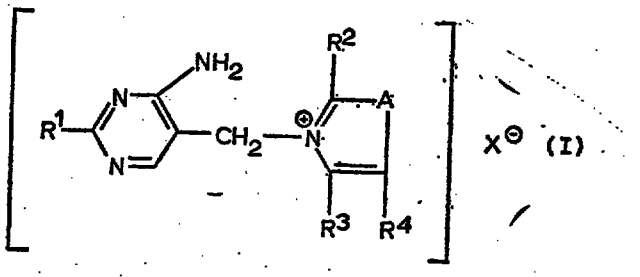
2. A method according to claim 1, wherein the anti-protozoal amount is from 0.0005 to 0.3 percent by weight in terms of 3-sulphanilamidoisoxazole relative to a feedstuff for the animals.

3. A method according to claim 1 or 2, wherein the anti-protozoal ingredient is administered in admixture with a feedstuff for the animals.

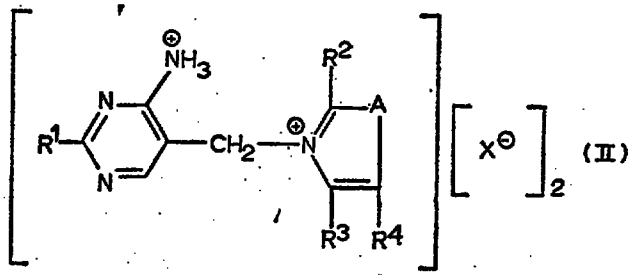
4. A method according to claim 1, wherein the anti-protozoal ingredient is administered together with drinking water.

5. A method according to any of claims 1 to 4 wherein the protozoiasis is coccidiosis in poultry.

6. A method according to claim 5, wherein an anti-coccidial amount of a pharmaceutically acceptable salt of a pyrimidine derivative of formula (I) or (II) or a mixture thereof:—



(I)



(II)

wherein the formula (I) represents the mono-salt and (II) the di-salt,
wherein
X represents a pharmaceutically acceptable acid anion,
A is —S— or —CH=CH—, R^1 is an alkyl group of up to 3 carbon atoms and each of R^2, R^3 and R^4 is H or an alkyl group of up to 3 carbon atoms, or of a mixture of two or more of the derivatives (I),
is administered to the poultry.

7. A method according to claim 6, wherein the anti-coccidial amount is from 0.001 to 0.05 percent by weight in terms of the pyrimidine derivative base relative to the feedstuff fed to the poultry.

8. A method according to claim 6, wherein the pyrimidine derivative salt is a 3-(2-methyly-4-amino-5-pyrimidinylmethyl)-4,5-dimethylthiazolium salt.

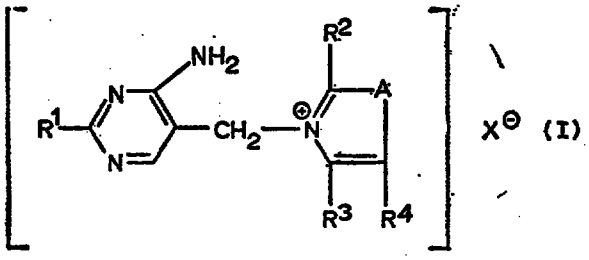
9. A method according to claim 6, wherein the pyrimidine derivative salt is a 3-(2-ethyl-4-amino-5-pyrimidinylmethyl)-4,5-dimethylthiazolium salt.

10. A method according to claim 6, wherein the pyrimidine derivative salt is 1-(2-*n*-propyl-4-amino-5-pyrimidinylmethyl)-2-methylpyridinium salt.

11. A method according to claim 1 substantially as herein described with reference to any of the specific Examples.

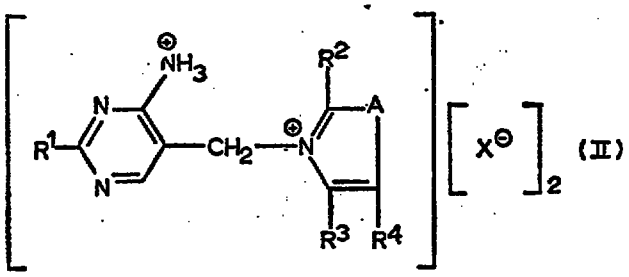
12. A composition for the prevention or treatment of protozoiasis in domestic animals, which comprises 3-sulphanilamidoisoxazole, a pharmaceutically acceptable salt or a mixture of 3-SI and its salt in a concentration of from 0.0005 to 0.3 percent by weight in terms of 3-sulphanilamidoisoxazole relative to the composition; and a major proportion of a physiologically acceptable carrier therefor.

13. A composition for the prevention or treatment of protozoiasis in domestic animals which comprises (a) 3-sulphanilamidoisoxazole, a pharmaceutically acceptable salt or a mixture of 3-SI and its salt; (b) a pharmaceutically acceptable salt of a pyrimidine derivative of the formula (I) or (II) or a mixture thereof:—



(I)

or



(II)

wherein the formula (I) represents the mono-salt and (II) the di-salt,
wherein X represents a pharmaceutically acceptable acid anion and A, R^1, R^2, R^3 and R^4 are as defined in claim 6; and
(c) a physiologically acceptable carrier for the ingredient (a) and (b).

14. A premix composition according to claim 13, wherein the amount of the ingredient (a) is from 1 to 30 percent by weight in terms of 3-sulphanilamidoisoxazole and the amount of the ingredient (b) is from 1 to 30 percent by weight in terms of the pyrimidine derivative base, relative to the whole composition.

15. A composition according to claim 13, wherein the amount of the ingredient (a) is from 0.0005 to 0.3 percent by weight in terms of 3-sulphanilamidoisoxazole and the amount of the ingredient (b) is from 0.01 to 0.05 percent by weight in terms of the pyrimidine derivative base, relative to the composition.

16. A composition according to any of claims 13 to 15, wherein the ingredient (b) is a 3-(2-methyl-4-amino-5-pyrimidinylmethyl)-4,5-dimethylthiazolium salt.

17. A composition according to any of claims 13 to 15, wherein the ingredient (c) is a 3-(ethyl-4-amino-5-pyrimidinylmethyl)-4,5-dimethylthiazolium salt.

18. A composition according to any of claims 13 to 15, wherein the ingredient (c) is a 1-(2-*n*-propyl-4-amino-5-pyrimidinylmethyl)-2-methylpyridinium salt.

19. A composition according to claim 12 substantially as herein described with reference to any of the specific Examples.

ELKINGTON AND FIFE,
Chartered Patent Agents,
High Holborn House,
52/54 High Holborn,
London, WC1V 6SH.
Agents for the Applicants.

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