

PATENT SPECIFICATION

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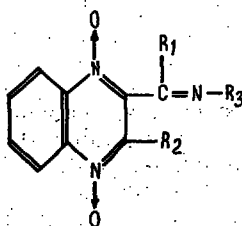
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(54) PROCESS FOR THE PREPARATION OF DUSTLESS QUINOXALINE-1,4-DIOXIDE ANIMAL FEED SUPPLEMENT PREMIXES

(71) We, PFIZER INC. a Corporation organized under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York, State of New York, 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 process for the preparation of substantially dustless quinoxaline-1,4-dioxide animal feed supplement premixes.

Many quinoxaline-1,4-dioxides administered to animals are effective in the control of urinary tract and systemic infections, chronic respiratory disease in poultry and infectious sinusitis in turkeys such as disclosed in United States Patent Specification No. 3,371,090. Of special interest is their use in the control of swin dysentery. These anti-bacterial agents are useful in both prophylaxis and therapy. By controlling or eliminating many common bacterial infections which afflict animals, these agents also function as both growth and feed efficiency promoters. Quinoxaline-1,4-dioxide anti-bacterial agents hereinafter referred to have the formula:—



wherein each of R₁ and R₂ is a hydrogen atom or a lower alkyl group, R₃ is a group of the formula:—

NH—CO—NH₂

NH—CS—NH₂

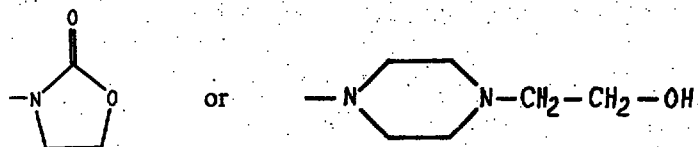
NH—C(NH)—NH₂

NHR₄

NHCOOR₅

NHCOR₆

OR₇



wherein R_1 is a lower alkyl, phenyl or benzyl group or a hydroxyalkyl group containing 2, 3 or 4 carbon atoms, R_2 is a lower alkyl group a hydroxyalkyl group containing 2, 3 or 4 carbon atoms or a haloalkyl group containing 2, 3 or 4 carbon atoms, R_3 is a lower alkyl or phenyl group and R_4 is a hydrogen atom or a lower alkyl group.

The term "lower alkyl" as used herein means alkyl groups containing 1 to 6 carbon atoms and includes branched-chain as well as straight-chain groups of those alkyl groups having three to six carbon atoms.

A particularly preferred anti-bacterial compound is 2-formyl-quinoxaline-1,4-dioxide carbomethoxy-hydrazone known by the common name of carbadox.

Carbadox is supplied to the consumer as a premix which is further blended with an animal feed to produce an ultimate product containing a pharmaceutically effective concentration of carbadox. The composition of the premix varies depending upon the part of the world in which it is intended for consumption. The carrier also may be varied so that the material used, usually farinaceous, is one which is readily available in the area in which it is to be consumed. Typical carbadox premixes contain 85 to 98 percent by weight of the total weight of the premix of carrier and from 2 to 12 percent carbadox. Up to 1% by weight of the final premix of silicon dioxide or 10% by weight of the final premix of calcium carbonate may be used in addition to farinaceous materials. Also an effective amount of calcium propionate as a preservative, usually 0.2% by weight of the final premix, is sometimes added. Examples of farinaceous carriers are rice bran, corn germ meal, soybean meal, soybean grits, wheat middlings, corn gluten feed, soft phosphate rock, cornmeal, rapeseed meal and soybean mill run.

Because of the physical nature of carbadox crystals, a nature it shares with other quinoxaline-1,4-dioxides, difficulties are encountered in the formulation of a dustfree premix containing a uniform amount of carbadox. Processes for producing carbadox usually yield an extremely fine crystalline material with typically 3% by weight smaller in size than 5 micrometres, 23 percent between 5 and 10 micrometres and 74 percent larger than 10 micrometres. However, this particle size distribution may be deceiving since carbadox crystals are very friable and tend with abrasion to be reduced greatly in size.

Because of the small particle size of carbadox relative to the carrier, any dust escaping from the blender in which the premix is formulated would be expected to be composed mostly of carbadox. Measurements have in fact shown that such escaped dust is 93 percent carbadox. Though particles smaller than 10 micrometres are usually regarded as respirable, this presents no problem in the current application because all mixing is done in closed systems with dust collectors. Nevertheless, the escaping dust does create difficulty in producing a uniform formulation. The carbadox which is trapped in a dust collector, which in most instances is a bag, is recycled back to the mixer. However, 6 or 7 batches may be run before the collected material is removed, weighed, and recycled. As a result the initial mixtures will tend to be low in carbadox content and the batch containing the recycled material high in carbadox concentration. Uniformity of composition requires, therefore, that even in a closed system the amount of dust generated in blending process be an absolute minimum.

The premix remains dusty even after it is removed from the blender and packaged for shipment. It is believed that some carbadox may actually be lost in shipment and it is known that some is definitely lost when the premix is formulated into a feed by the ultimate user. Again, uniformity of composition requires a stable, that is dustless blend of carbadox and carrier. Furthermore, it is generally undesirable to market a product which contains or generates respirable dust even though no medical hazard may be immediately apparent.

Dustless quinoxaline-1,4-dioxide premises are also extremely desirable because of their safety. The tendency of carbadox to explode is great. Its minimum ignition energy is extremely low and the crystals are highly flammable and self-sustaining in the absence of air. In stable, dustless premixes these dangers are not encountered. However, a hazard does exist whenever carbadox separates from its

carrier. Stable premixes eliminate the possibility of baghouse fires and explosions in transit. Dusty premixes may not be shipped by air freight whereas the product of the present invention is sufficiently safe to be shipped by any mode of transportation.

In accordance with the present invention there is provided a process for the preparation of a substantially dustless animal feed supplement premix containing an anti-bacterial quinoxaline-1,4-dioxide, which process comprises (a) blending 0.5 to 2.0 percent and preferably 1.0 to 1.25%, by weight based on the total weight of supplement premix of a non-toxic oil, usually one with some nutritive value, such as soybean oil, corn oil, mineral oil or a mixture thereof with 80 to 95 percent by weight based on the total weight of supplement premix product of an edible carrier, (b) mixing the said blend with 2 to 12% by weight based on the total weight of supplement premix product of a pharmaceutically-acceptable quinoxaline-1,4-dioxide anti-bacterial agent, and (c) adding to and blending into the mixture in step (b) another 0.75 to 6.0%, preferably 3.0 to 3.75%, by weight based on the total weight of supplement premix product of the said oil, so that the total amount of oil added is in the range of 1.25 to 8%, preferably 4 to 5%, by weight of the premix.

The edible carrier is usually farinaceous in nature, such as soybean mill run, rice brans, soybean meal, soybean grits, corn meal, corn germ meal, corn gluten feed, wheat middlings, rapeseed meal or a mixture thereof. Soft phosphate rock may be also used as well as blends of all the above with silicon dioxide or calcium carbonate. The non-toxic oil frequently contains an appropriate antioxidant such as calcium propionate.

Of particular interest as an anti-bacterial agent is 2-formyl-quinoxaline-1,4-dioxide carbomethoxyhydrazone.

It has been found that stable premixes of quinoxaline-1,4-dioxide anti-bacterial agent used as animal feed supplements which have substantially no tendency to segregate, are free of respirable dust and are without the flammable and explosive properties of pure quinoxaline-1,4-dioxides may be formulated by the sequential oil addition process described above.

Particularly preferred are those premixes wherein the non-toxic oil is soybean oil or mineral oil, and the oil contains a suitable antioxidant such as calcium propionate with soybean mill run, rapeseed meal, rice brans or soybean meal as carrier.

The addition of oil to reduce the amount of dust in animal feed supplements is known in the art. United States Patent Specification No. 3,468,667 describes a product containing dicalcium orthophosphate diammonium orthophosphate, ammonium dihydrogen phosphate and mixtures thereof also containing glyceryl lactopalmitate and a fatty acid or fatty acid salt wherein an oily liquid is added for the purpose of binding the mixture. Furthermore, increasing the amount of oil in a feed supplement reduces the amount of dust contained therein. However, the addition of large amounts of oil for this purpose may yield a product with many undesirable properties, such as poor flowability, which makes the product difficult to mix and package.

It has now been discovered that in the preparation of premixes, especially those containing quinoxaline-1,4-dioxide anti-bacterial agents, the addition of oil in two portions, approximately 20 to 30 percent by weight of the total amount of oil added before the anti-bacterial agent is added to the carrier and the balance of the oil after the anti-bacterial agent is added is significantly more effective in producing a dustless feed supplement premix than the addition of oil in a single batch either before or after the introduction of the anti-bacterial agent. In particular, it has been found that the addition of 1.25 to 8 percent and preferably 4 to 5 percent by weight of the final premix product of oil in such a fashion that 10 to 60, and preferably 20 to 30 percent by weight of the total amount of oil added of the oil is coated onto the carrier before the addition of the anti-bacterial agent and the balance after the anti-bacterial agent is added is exceptionally effective in eliminating respirable dust from the feed supplement premix. In a similar experiment with a premix containing 10% by weight of the final premix of carbadox it was found that the addition of 0.75% by weight of the final premix of oil before and an equal amount after the addition of carbadox was nine times more effective than adding 1.5% by weight of the final premix of oil before the addition of the carbadox. In one experiment with a supplement wherein the ingoing premix contained 2.2% by weight of the final premix of carbadox, it was found that the addition of 0.75% by weight of the final premix of oil before the carbadox and 2.25% by weight of the final premix of oil after the carbadox addition was up to

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forty times as effective in reducing the amount of respirable dust than the addition of the same amount of oil before the carbadox was added. Also it can be estimated from these experiments that the single step addition of 3 percent by weight of the final premix of oil is up to 50 times more effective than the addition of 1.5 percent by weight of the final premix of oil in the elimination of respirable dust. The product containing 5 percent by weight of the final premix of oil has good flow properties. The addition of amounts of oil in excess of 8% by weight of the final premix reduces the flowability of the premix which makes it difficult to blend and package. It is believed that the first increment of oil added forms a coating on the surface of the carrier to which the carbadox adheres and that the second increment of oil then covers the carbadox and prevents the firable crystal from breaking down due to abrasion thus preventing segregation of the mixture. However, the present invention is not bound by this interpretation.

The Examples I to III, V and VI illustrate the invention and the manner in which it may be performed. Example IV is included to illustrate the influence of increased oil addition on the dustiness and flowability of the resulting premix.

EXAMPLE I.

Direct Formulation of Carbadox Premix

Pre-milled soybean mill run (7,583.7 lbs) is weighed and added to a mixer. Soybean oil (60 lbs) is added and the mixer run until the soybean mill run is uniformly coated with oil. Feed grade carbadox (176.3 lbs) is then added and the mixer run again to uniformly blend the carbadox into the mixture. Soybean oil (180 lbs) is then added and the batch mixed for a pre-set time until homogeneous to yield a carbadox premix which is substantially dust free having a concentration of 10 grams of carbadox per pound.

This premix formulation is suitable for use in the United States of America. In similar fashion the following carbadox premixes shown in Table 1 may be formulated for ultimate consumption in other countries, the differences being in typical carrier materials most available at the cheapest price in the respective countries. Soybean oil (3% by weight of the final premix) is incorporated in each of these with 0.75% added before the carbadox and 2.25% after.

Premixes other than those listed in the table which contain quinoxaline-1,4-dioxide anti-bacterial agents may also be formulated in similar fashion.

TABLE 1

	Carbadox (%) *	Carrier	Amount (%) *	Other Ingredients
1. Japan	11.0	Rice Brans	89.0	None
2. Korea	2.20	Corn germ Meal	97.8	None
3. Taiwan	11.0	Soybean Meal	89.00	None
4. Germany	4.0	Soybean Grits	96.0	None
5. France	5.00	Soybean Meal	94.0	SiO ₂ 1.0%*
6. Greece	10.00	Soybean Meal	89.0	SiO ₂ 1.0%*
7. Spain	4.00	Soybean Meal	95.0	SiO ₂ 1.0%*
8. Brazil	5.00	Soybean Meal	95.0	None
9. Argentina	2.10	Wheat Middlings	97.90	None
10. Canada	2.43	Corn Gluten Feed	97.57	None

* The percentages shown here are by weight of the supplement premix excluding the amount of oil used.

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EXAMPLE II.

Formulation of Carbadox Premix Through a Pre-Blend

Pre-milled soybean mill run (645.2 lbs) is placed in a mixer. Soybean oil (60.0 lbs) is added and the mixer run for a pre-set time until the soybean oil uniformly coats the soybean mill run. Feed grade carbadox (176.3 lbs) is then added and the mixer run for a pre-set time until the blend is homogeneous. This product, known as a pre-blend, is then stored until such time as it is desired to make the premix.

To make the premix, said pre-blend (881.5 lbs) is added to a mixer along with pre-milled soybean mill run (6938.5 lbs) and the mixer run for a pre-set time until the blend is homogeneous. Soybean oil (180.0 lbs) is then added and the mixer run for a pre-set time until the oil uniformly coats the carrier and the carbadox. This premix (8,000 lbs) is substantially dustless, contains 10 grams of carbadox per pound and is a formulation suitable for use in the United States of America.

In similar fashion the premixes of Example I may be prepared through pre-blends.

EXAMPLE III.

Determination of the Percentage of Carbadox in Dust

An apparatus was constructed consisting of a 20 gallon drum with a 6" x 4" elliptical hole cut in one end resting in a cradle which could be rocked by an electric motor at various rates. When the drum is charged with the carbadox premix, this apparatus simulates the dust generated as a bag of premix is emptied. The drum itself empties into a bin hopper similar to that used by feed manufacturers.

A premix (45 kilos) prepared by the method of Example II containing 10% carbadox and no oil was placed in the drum and the cover fastened on. Three Bendix (Registered Trade Mark) Model C115 Air Sampling Probes were placed at a distance of 4 inches from the centre of the anticipated dust cloud. This probe simulates human inspiration rates and velocities. The total inspiration rate is 22 litres per minute. They also separate particles less than and greater than 10 microns; those smaller than 10 microns being generally regarded as respirable. The air sampling probes were turned on as was the rocking cradle and the sample dumped over a 45 minute period. The dust was collected from each of the probes weighed and the carbadox concentration determined by differential pulse polarography. The lowest limit of easily detected carbadox in this assay procedure is 0.1 micrograms. The results obtained are shown in Table 2.

TABLE 2

Probe	Respirable Dust Carbadox Weight/Dust Weight	%* Carbadox	Non Respirable Dust Carbadox Weight/Dust Weight	%* Carbadox
1	No sample collected, probe obstructed			
2	4.1 mg/4.3 mg	95.5%	31.2 mg/33.1 mg	94.3%
3	2.8 mg/2.9 mg	96.5%	26.0 mg/28.4 mg	92.3%

* The percentages are by weight of the dust collected.

EXAMPLE IV.

Effect of Oil Addition on Various Premixes

The premixes of this experiment were formulated in 100 pound batches in an AMF Glen mixer by first adding an appropriate amount of carrier to the mixer, blending it with the indicated amount of oil and carbadox and running the mixture until a homogeneous blend was obtained.

The dustiness of the mixtures were determined by the method of Example III with the Bendix air samplers placed at a distance of 4, 20 and 30 inches from the centre of the visible dust cloud formed at the dumping site.

A plus sign indicates that a positive analytical response was obtained but that

the concentration was less than 0.1 μ gm. ND indicates that no analytical response whatsoever was observed.

The data indicate that the decrease in dustiness with increasing oil concentration is non-linear and that virtually optimum results are obtained at about a 3% oil concentration. Above this percentage, the flowability of the premix is impaired. The results are shown in Table 3.

TABLE 3

%* Carbadox	Carrier	%* Oil**	Probe $\rightarrow$	Carbadox Dust (Micrograms)					
				Respirable			Non-Respirable		
				1	2	3	1	2	3
1%	Soybean Meal	0		36	6.9	5.2	138	69	51
10%	Soybean Meal	0		30	26	5	1300	56	188
10%	Soybean Meal	1.5		5.2	2.7	1.7	146	74	32
10%	Soybean Meal	3.0		+	+	+	3.8	1.9	1.2
2.2%	Soy Mill Run	0		.6	.4	.1	49	20	9
2.2%	Soy Mill Run	0.75		+	ND	ND	8	2	12
2.2%	Soy Mill Run	1.5		.3	.2	.1	3.2	1.6	1.2
2.2%	Soy Mill Run	3.0		+	.12	+	1.5	.3	4.0
2.43%	Corn Gluten	0		5.5	2.0	2.5	238	120	114
2.43%	Corn Gluten	3.0		.1	.1	.1	4.2	1.3	1.1

* percentages are by weight of final premix.

** Oil is added in a single step.

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EXAMPLE V.

Effect of Incremental Oil Addition on Premixes

The dustiness of premixes formulated in 100 lb batches by the method of Example I was measured by the method of Example IV. The results shown in Table 4 were obtained.

TABLE 4

%* Carbadox	Carrier	%* Soybean Oil	Probe →	Carbadox Dust (Micrograms)					
				Respirable			Non-Respirable		
				1	2	3	1	2	3
(Comparative) 10	Soybean Meal	1.5		5.2	2.7	1.7	146	74	32
10	Soybean Meal	0.75+0.75		0.7	0.2	0.3	83	26	42

* percentages are by weight of the final premix.

EXAMPLE VI.

The following premixes were prepared by the method of Example I. In each instance, one-fourth by weight of the oil was added to the carrier before the carbadox and three-fourths after the addition of the carbadox.

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INGREDIENT	%**	%**	%**
Carbadox (wet cake)*	13.33	3.33	6.67
Soybean oil	5.00	5.00	5.00
Calcium propionate	0.50	0.125	0.25
Rapeseed meal	81.17	91.54	88.08
INGREDIENT	%**	%**	%**
Carbadox (wet cake)*	6.67	3.33	3.33
Soybean oil	4.00	4.00	5.00
Calcium propionate	0.25	0.125	0.125
Soybean mill run	89.08	92.54	91.54

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*Approximately 75% by weight carbadox; 25% by weight water. Dry carbadox equivalent may be calculated with the following formula: grams carbadox/lb activity = % carbadox wet cake $\times$ 0.75 $\times$ 454 grams.

**Percentages are by weight of the final premix.

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WHAT WE CLAIM IS:—

1. A process for the preparation of a substantially dustless animal feed supplement premix containing an anti-bacterial quinoxaline-1,4-dioxide, which process comprises (a) blending 0.5 to 2.0% by weight based on the total weight of supplement premix product of a non-toxic oil with 80 to 95% by weight based on the total weight of supplement premix product of an edible carrier, (b) mixing the said blend with 2 to 12% by weight based on the total weight of supplement premix product of a pharmaceutically-acceptable quinoxaline-1,4-dioxide anti-bacterial agent, and (c) adding to and blending into the mixture obtained in step (b) another 0.75 to 6.0% by weight based on the total weight of supplement premix product of the said oil, so that the total amount of oil added is in the range of 1.25 to 8% by weight of the premix.

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2. A process according to claim 1, wherein the amount of oil added in step (a) is from 1.0 to 1.25% by weight based on the total weight of the supplement premix product.

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3. A process according to either one of claims 1 to 2, wherein the amount of oil added in step (c) is from 3.0 to 3.75% by weight based on the total weight of the supplement premix product.

4. A process according to any one of claims 1 to 3, wherein the anti-bacterial agent is 2-formyl-quinoxaline-1,4-dioxide carbomethoxy-hydrazone.

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5. A process according to any one of claims 1 to 4, wherein the oil is soybean oil, corn oil, mineral oil or a mixture thereof.

6. A process according to claim 5, wherein the oil is soybean oil.

7. A process according to any one of the preceding claims, wherein the edible carrier is soybean mill run, rice brans, soybean meal, soybean grits, rapeseed meal, corn meal, corn germ meal, corn gluten feed, wheat middlings, soft phosphate rock or a mixture thereof with silicon dioxide or calcium carbonate.

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8. A process for the preparation of a substantially dustless animal feed supplement premix according to claim 1 and substantially as hereinbefore described with reference to Examples I and II.

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9. A substantially dustless animal feed supplement premix whenever prepared by a process according to any one of the preceding claims.



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	INGREDIENT	%**	%**	%**	
	Carbadox (wet cake)*	13.33	3.33	6.67	
	Soybean oil	5.00	5.00	5.00	
	Calcium propionate	0.50	0.125	0.25	
5	Rapeseed meal	81.17	91.54	88.08	5
	INGREDIENT	%**	%**	%**	
	Carbadox (wet cake)*	6.67	3.33	3.33	
	Soybean oil	4.00	4.00	5.00	
	Calcium propionate	0.25	0.125	0.125	
10	Soybean mill run	89.08	92.54	91.54	10

*Approximately 75% by weight carbadox; 25% by weight water. Dry carbadox equivalent may be calculated with the following formula: grams carbadox/lb activity = % carbadox wet cake $\times$ 0.75 $\times$ 454 grams.

**Percentages are by weight of the final premix.

- 15 WHAT WE CLAIM IS:— 15
1. A process for the preparation of a substantially dustless animal feed supplement premix containing an anti-bacterial quinoxaline-1,4-dioxide, which process comprises (a) blending 0.5 to 2.0% by weight based on the total weight of supplement premix product of a non-toxic oil with 80 to 95% by weight based on the total weight of supplement premix product of an edible carrier, (b) mixing the said blend with 2 to 12% by weight based on the total weight of supplement premix product of a pharmaceutically-acceptable quinoxaline-1,4-dioxide anti-bacterial agent, and (c) adding to and blending into the mixture obtained in step (b) another 0.75 to 6.0% by weight based on the total weight of supplement premix product of the said oil, so that the total amount of oil added is in the range of 1.25 to 8% by weight of the premix. 20
2. A process according to claim 1, wherein the amount of oil added in step (a) is from 1.0 to 1.25% by weight based on the total weight of the supplement premix product. 25
3. A process according to either one of claims 1 to 2, wherein the amount of oil added in step (c) is from 3.0 to 3.75% by weight based on the total weight of the supplement premix product. 30
4. A process according to any one of claims 1 to 3, wherein the anti-bacterial agent is 2-formyl-quinoxaline-1,4-dioxide carbomethoxy-hydrazone. 35
5. A process according to any one of claims 1 to 4, wherein the oil is soybean oil, corn oil, mineral oil or a mixture thereof. 35
6. A process according to claim 5, wherein the oil is soybean oil.
7. A process according to any one of the preceding claims, wherein the edible carrier is soybean mill run, rice brans, soybean meal, soybean grits, rapeseed meal, corn meal, corn germ meal, corn gluten feed, wheat middlings, soft phosphate rock or a mixture thereof with silicon dioxide or calcium carbonate. 40
8. A process for the preparation of a substantially dustless animal feed supplement premix according to claim 1 and substantially as hereinbefore described with reference to Examples I and II.
9. A substantially dustless animal feed supplement premix whenever prepared by a process according to any one of the preceding claims. 45



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