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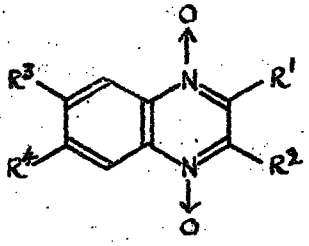
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(54) GROWTH PROMOTION

(71) We, IMPERIAL CHEMICAL INDUSTRIES LIMITED of Imperial Chemical House, Millbank, London, S.W.1., a British Company, 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 of promoting the growth of domestic animals, that is it relates to a method of accelerating the rate of growth of domestic animals over and above the rate of growth normally achieved by such animals when fed on a nutritionally-balanced diet.

According to the invention there is provided a method of promoting the growth of domestic animals which comprises feeding such animals on a nutritionally-balanced diet which additionally contains a quinoxaline derivative of the formula:—



wherein, when R^1 and R^2 stand for hydrogen, R^3 stands for a hydrogen or halogen atom, or a methyl radical, and R^4 stands for hydrogen or a methyl radical; or when R^1 and R^2 stand for methyl radicals, then R^3 stands for a halogen atom and R^4 stands for hydrogen.

A preferred value for R^3 when it stands for a halogen atom is a chlorine or bromine atom.

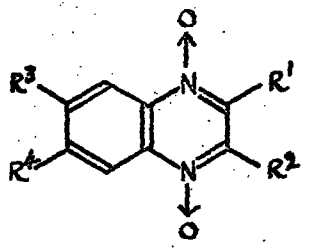
The method of the invention is applicable to all domestic animals, for example poultry, pigs, sheep and cattle.

The nutritionally-balanced diet should contain from 0.0001% 20 w/w (1g. per metric ton) to 0.025% w/w (250g. per metric ton) of a quinoxaline derivative as defined above, or from 0.0001% w/w (1g. per metric ton) to 0.0025% w/w (25g. per metric ton) of the preferred quinoxaline derivative. The animals may be fed on such a supplemented diet for substantially the whole of their growing period, or they may be fed on the diet for only a part, preferably the earlier part, of their growing period, in order to achieve the desired increase in the rate of growth of the animals. Such an increase in the rate of growth of the animals enables the animals to be brought to a desired market weight in a shorter growing period than previously employed, or it enables heavier animals to be produced at the end of the previously employed growing period. In addition, it has been found that the method of the invention leads to improved food conversion ratios, that is animals fed on a diet containing a quinoxaline derivative as defined above are found to attain a given weight after the consumption of less food than animals fed on a diet not containing such a quinoxaline derivative.

Specific quinoxaline derivatives which may be used in the method of the invention are, for example, quinoxaline - 1,4 - dioxide, 6 - methylquinoxaline - 1,4 - dioxide, 6-chloro - 2,3 - dimethylquinoxaline - 1,4-dioxide, 6 - bromo - 2,3 - dimethylquinoxaline - 1,4 - dioxide, 6,7 - dimethylquinoxaline - 1,4 - dioxide and 6 - chloro - 7-methylquinoxaline - 1,4 - dioxide, and of these, the preferred compound is quinoxaline-1,4-dioxide itself.

In order to carry out the method of the invention, a quinoxaline derivative as defined above may be fed to domestic animals in the form of a supplemented foodstuff, and such a foodstuff may be prepared by diluting a concentrated pre-mix.

According to a further feature of the invention there is provided an animal foodstuff composition which comprises a quinoxaline derivative of the formula:—



wherein, when R^1 and R^2 stand for hydrogen, R^3 stands for a hydrogen or halogen atom, or a methyl radical, and R^4 stands for hydrogen or a methyl radical; or when R^1 and R^2 stand for methyl radicals, then R^3 stands for a bromine atom and R^4 stands for hydrogen, together with a substantially solid edible carrier therefor.

A preferred value for R^3 when it stands for a halogen atom when R^1 and R^2 stand for hydrogen, is a chlorine or bromine atom.

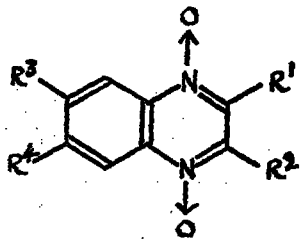
As indicated above, the composition may be in the form of a concentrated pre-mix suitable for dilution with a nutritionally-balanced foodstuff to provide a supplemented animal foodstuff, or it may be in the form of an animal foodstuff suitable for direct feeding to domestic animals to increase their rate of growth.

A suitable pre-mix is, for example, a mixture of a quinoxaline derivative defined immediately above with an inert edible carrier, for example kaolin, talc, calcium carbonate, fuller's earth, attapulgus clay, ground oyster shells, starch or lactose, or with a nutritionally-balanced edible carrier, for example a standard broiler chicken diet of ground grain and grain by-products, animal protein supplemented by vitamins and minerals, or other conventional animal foodstuff.

Such a pre-mix may contain from 0.2% w/w to 50% w/w of quinoxaline derivative or from 0.2% w/w to 5% w/w of the preferred quanoxaline derivative, and may be diluted with a nituritionally-balanced foodstuff to produce an animal foodstuff containing from 0.0001% w/w to 0.025% w/w of quinoxaline derivative or from 0.0001% w/w to 0.0025% w/w of the preferred quinoxaline derivative. In diluting the above pre-mixes, it is convenient to incorporate 500g. of pre-mix in 1 metric ton of animal foodstuff.

The animal foodstuff intended for direct feeding to domestic animals, and the pre-mixes, may also contain other compounds of known veterinary utility, for example an anthelmintic, for example tetramisole, pyrantel tartrate, thiabendazole or piperazine, a coccidiostat, for example methyl benzoquate, meticlorpindol, 3,5-dinitro-*o*-toluamide, 3,5-dinitrobenzamide, amprolium or decoquinate, or an antibiotic, for example bacitracin, oleandomycin or virginamycin.

According to a further feature of the invention there is provided a process for the manufacture of an animal foodstuff composition as hereinbefore defined which comprises uniformly mixing a quinoxaline derivative of the formula:—



wherein, when R^1 and R^2 stand for hydrogen, R^3 stands for a hydrogen or halogen atom, or a methyl radical, and R^4 stands for hydrogen or a methyl radical; or when R^1 and R^2 stand for methyl radicals, then R^3 stands for a bromine atom and R^4 stands for hydrogen, together with a substantially solid edible carrier therefor.

The growth promoting properties of the quinoxaline derivatives defined above as being suitable for feeding to domestic animals in accord with the method of the invention, and of compositions containing those quinoxaline derivatives, have been demonstrated by feeding groups of domestic animals on a diet containing the quanoxaline derivative for a standard time, and then comparing the increase in weight of those animals with the increase in weight of a control group of animals fed on the same basic diet but not containing such a quinoxaline derivative.

The invention is illustrated but not limited by the following Examples:—

Example 1

Pre-mixes suitable for dilution with an animal foodstuff may be obtained by incorporating 5, 10, 25, 50 or 100g. of quinoxaline-1,4-dioxide in a standard broiler chicken diet comprising ground maize and fishmeal, with added lysine, methionine, vitamins and minerals, so that the final weight of pre-mix is 500g.

Other pre-mixes may be obtained by replacing the quinoxaline - 1,4 - dioxide by 6 - methylquinoxaline - 1,4 - dioxide, 6-bromo - 2,3 - dimethylquinoxaline - 1,4-dioxide, 6,7 - dimethylquinoxaline - 1,4-dioxide or 6 - chloro - 7 - methylquinoxaline - 1,4 - dioxide.

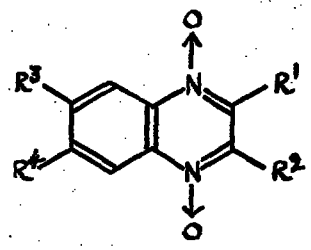
EXAMPLE 2

An animal foodstuff intended for direct feeding to poultry may be obtained by intimately mixing 500g. of a pre-mix obtained as described in Example 1 with 1 metric ton (1000kg.) of standard broiler chicken diet.

EXAMPLE 3

Groups of 60 7-day-old chickens were weighed and kept in cages in which 10 chickens were present in each cage. One group of chickens was fed for 6 days on a basic nutritionally-balanced diet containing no compound known to possess growth promoting properties, and fourteen other groups were fed for 6 days on the same basic diet but containing amounts of a quinoxaline derivative varying from 0.01% w/w to 0.0005% w/w. At the end of the 6 days, all the chickens were weighed, and the increase in weight of each group was recorded. A compound showing growth promotion properties caused the birds in the treated group to show a greater increase in weight than the increase in weight shown by the control group. The difference between these increases in weight, expressed as a percentage of the increase in weight of the control group was considered to be significant if it was equal to or greater than 11% more than the increase in weight of the control group.

The following results were obtained with test quinoxaline derivatives:—



R^1	R^2	R^3	R^4	% of test compound in the food	% difference between increases in the weights of the treated and control groups
H	H	H	H	0.01	+34.6
				0.005	+33.0
				0.0025	+20.9
				0.001	+18.2
				0.0005	+19.0
H	H	Me	H	0.01	+34.6
Me	Me	Cl	H	0.01	+25.2
Me	Me	Br	H	0.01	+33.8
H	H	Me	Me	0.01	+42.5
H	H	Cl	Me	0.01	+41.3

EXAMPLE 4

In an essentially similar procedure to that described in Example 3, a group of 360 1-day-old chickens, kept in pens each containing 60 chickens, was fed on a diet containing quinoxaline-1,4-dioxide and the rate of growth over 8 weeks observed relative to a similar control group of 360 chickens. The following result was obtained at the end of 8 weeks. Mean weight of birds in the control group—1.60kg. Means weight of birds fed on a diet containing 0.001% w/w of quinoxaline-1,4-dioxide—1.82 kg. Ratio of food eaten/weight of bird in the control group—2.18. Ratio of food eaten/weight of bird in the treated group—2.02.

EXAMPLE 5

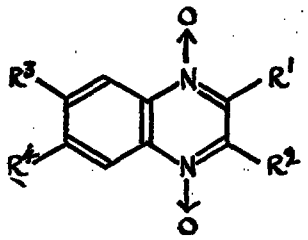
In a test on pigs, in which each group contained 6 pigs, the following results were obtained after 7 weeks feeding.

Hogs: mean increase in weight per pig of the pigs in the control group—21.8kg. mean increase in weight per pig of the pigs in the group fed on a diet containing 0.001% w/w of quinoxaline-1,4-dioxide—24.2kg.

Gilts: mean increase in weight per pig in the control group—22.9kg. mean increase in weight per pig in the group fed on a diet containing 0.001% w/w of quinoxaline-1,4-dioxide—25.1kg.

WHAT WE CLAIM IS:—

1. A method of promoting the growth of domestic animals which comprises feeding such animals on a nutritionally-balanced diet which additionally contains a quinoxaline derivative of the formula:—



wherein, when R^1 and R^2 stand for hydrogen, R^3 stands for a hydrogen or halogen atom, or a methyl radical, and R^4 stands for hydrogen or a methyl radical; or when R^1 and R^2 stand for methyl radicals, then R^3 stands for a halogen atom and R^4 stands for hydrogen.

2. A method as claimed in claim 1 wherein R^3 stands for a chlorine or bromine atom.

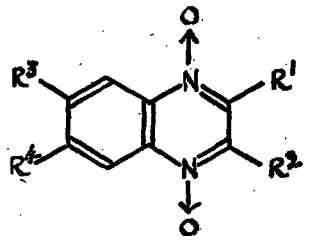
3. A method as claimed in claim 1 wherein the quinoxaline derivative is quinoxaline-1,4-dioxide.

4. A method as claimed in claim 1 wherein the quinoxaline derivative is 6-methylquinoxaline - 1,4 - dioxide, 6 - chloro - 2,3 - dimethylquinoxaline - 1,4 - dioxide, 6 - bromo-2,3 - dimethylquinoxaline - 1,4 - dioxide, 6,7 - dimethylquinoxaline - 1,4 - dioxide or 6 - chloro - 7 - methylquinoxaline - 1,4-dioxide.

5. A method as claimed in any preceding claim wherein the nutritionally-balanced diet contains from 0.0001% w/w to 0.025% w/w of the quinoxaline derivative.

6. A method as claimed in claim 3 wherein the nutritionally-balanced diet contains from 0.0001% w/w to 0.0025% w/w of the quinoxaline derivative.

7. An animal foodstuff composition which comprises a quinoxaline derivative of the formula:—



wherein, when R^1 and R^2 stand for hydrogen, R^3 stands for a hydrogen or halogen atom, or a methyl radical, and R^4 stands for hydrogen or a methyl radical; or when R^1 and R^2 stand for methyl radicals, then R^3 stands for a bromine atom and R^4 stands for hydrogen, together with a substantially solid edible carrier therefor.

8. A composition as claimed in claim 7 wherein when R^1 and R^2 stand for hydrogen, R^3 stands for a chlorine or bromine atom.

9. A composition as claimed in claim 7 wherein the quinoxaline derivative is quinoxaline-1,4-dioxide.

10. A composition as claimed in claim 7 wherein the quinoxaline derivative is 6-methylquinoxaline - 1,4 - dioxide, 6 - bromo - 2,3-dimethylquinoxaline - 1,4 - dioxide, 6,7-dimethylquinoxaline - 1,4 - dioxide or 6-chloro - 7 - methylquinoxaline - 1,4 - dioxide.

11. A composition as claimed in any of claims 7 to 10, wherein the edible carrier is an inert edible carrier, for example kaolin, talc, calcium carbonate, fuller's earth, attapulgus clay, ground oyster stells, starch or lactose.

12. A composition as claimed in any of claims 7 to 10, wherein the edible carrier is a nutritionally-balanced edible carrier, for example a standard broiler chicken diet.

13. A composition as claimed in any of claims 7 to 12, which is in the form of a concentrated pre-mix and contains from 0.2% w/w to 50% w/w of quinoxaline derivative.

14. A composition as claimed in any of claims 7 to 10 and 12 which is in the form of an animal foodstuff intended for direct feeding and contains from 0.0001% w/w to 0.025% w/w of quinoxaline derivative.

15. A composition as claimed in claim 13 or 14 which additionally contains other compounds of known veterinary utility, for example an anthelmintic, a coccidiostat, or an antibiotic.

16. A process for the manufacture of an animal foodstuff as claimed in claim 7 which comprises uniformly mixing a quinoxaline de-

EXAMPLE 5

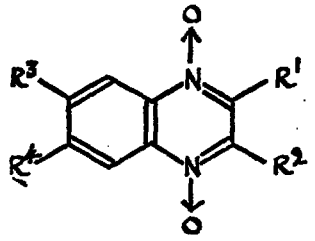
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Gilts: mean increase in weight per pig in the control group—22.9kg. mean increase in weight per pig in the group fed on a diet containing 0.001% w/w of quinoxaline-1,4-dioxide—25.1kg.

WHAT WE CLAIM IS:—

1. A method of promoting the growth of domestic animals which comprises feeding such animals on a nutritionally-balanced diet which additionally contains a quinoxaline derivative of the formula:—



wherein, when R^1 and R^2 stand for hydrogen, R^3 stands for a hydrogen or halogen atom, or a methyl radical, and R^4 stands for hydrogen or a methyl radical; or when R^1 and R^2 stand for methyl radicals, then R^3 stands for a halogen atom and R^4 stands for hydrogen.

2. A method as claimed in claim 1 wherein R^3 stands for a chlorine or bromine atom.

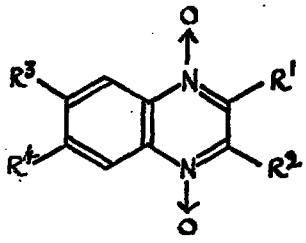
3. A method as claimed in claim 1 wherein the quinoxaline derivative is quinoxaline-1,4-dioxide.

4. A method as claimed in claim 1 wherein the quinoxaline derivative is 6-methylquinoxaline - 1,4 - dioxide, 6 - chloro - 2,3 - dimethylquinoxaline - 1,4 - dioxide, 6 - bromo-2,3 - dimethylquinoxaline - 1,4 - dioxide, 6,7 - dimethylquinoxaline - 1,4 - dioxide or 6 - chloro - 7 - methylquinoxaline - 1,4-dioxide.

5. A method as claimed in any preceding claim wherein the nutritionally-balanced diet contains from 0.0001% w/w to 0.025% w/w of the quinoxaline derivative.

6. A method as claimed in claim 3 wherein the nutritionally-balanced diet contains from 0.0001% w/w to 0.0025% w/w of the quinoxaline derivative.

7. An animal foodstuff composition which comprises a quinoxaline derivative of the formula:—



wherein, when R^1 and R^2 stand for hydrogen, R^3 stands for a hydrogen or halogen atom, or a methyl radical, and R^4 stands for hydrogen or a methyl radical; or when R^1 and R^2 stand for methyl radicals, then R^3 stands for a bromine atom and R^4 stands for hydrogen, together with a substantially solid edible carrier therefor.

8. A composition as claimed in claim 7 wherein when R^1 and R^2 stand for hydrogen, R^3 stands for a chlorine or bromine atom.

9. A composition as claimed in claim 7 wherein the quinoxaline derivative is quinoxaline-1,4-dioxide.

10. A composition as claimed in claim 7 wherein the quinoxaline derivative is 6-methylquinoxaline - 1,4 - dioxide, 6 - bromo - 2,3-dimethylquinoxaline - 1,4 - dioxide, 6,7-dimethylquinoxaline - 1,4 - dioxide or 6-chloro - 7 - methylquinoxaline - 1,4 - dioxide.

11. A composition as claimed in any of claims 7 to 10, wherein the edible carrier is an inert edible carrier, for example kaolin, talc, calcium carbonate, fuller's earth, attapulgus clay, ground oyster stells, starch or lactose.

12. A composition as claimed in any of claims 7 to 10, wherein the edible carrier is a nutritionally-balanced edible carrier, for example a standard broiler chicken diet.

13. A composition as claimed in any of claims 7 to 12, which is in the form of a concentrated pre-mix and contains from 0.2% w/w to 50% w/w of quinoxaline derivative.

14. A composition as claimed in any of claims 7 to 10 and 12 which is in the form of an animal foodstuff intended for direct feeding and contains from 0.0001% w/w to 0.025% w/w of quinoxaline derivative.

15. A composition as claimed in claim 13 or 14 which additionally contains other compounds of known veterinary utility, for example an anthelmintic, a coccidiostat, or an antibiotic.

16. A process for the manufacture of an animal foodstuff as claimed in claim 7 which comprises uniformly mixing a quinoxaline de-

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rivative as defined in claim 7 together with a substantially solid edible carrier therefor.

17. A method of promoting the growth of domestic animals as claimed in claim 1, substantially as described in Example 3 or 4.

18. An animal foodstuff composition as claimed in claim 7 substantially as described in Example 1 or 2.

A. H. LAIRD,
Agent for the Applicants.

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