



Method of treatment of Equine disease

Field of the Invention

This invention relates to a method for the treatment and prevention of the equine condition known as anhydrosis. The invention further includes a novel feed
5 formulation and feed supplement for provision to horses suffering from anhydrosis.

Background of the Invention

Normally, horses sweat to cool themselves during hot weather. Anhydrosis, also known as non-sweating syndrome, dry coat or puff/s disease is the term used to describe the condition in which horses develop either partial or complete inability
10 to sweat in the usual way. This condition was first recognised by the British when horses were shipped from Britain to their tropical colonies and some of the British horses developed an inability to sweat. This inability to sweat leads to the inability of the horse to maintain its normal body temperature in such a warm environment, which leads to panting, fever and often results in death of the horse. Anhydrosis is
15 very common today and is seen in numerous tropical countries including Hong Kong, Singapore, Malaysia, India, Sri Lanka, Burma, The Philippines, the West Indies including Puerto Rico and Trinidad, some parts of South America, northern Australia and the gulf states of the USA: Florida to Texas.

It was originally thought that anhydrosis only occurred when horses were
20 brought from a cool and temperate climate to a hot, humid climate, but it can also be seen in horses which have lived all their lives in such hot, humid climates. The condition appears to be more common in Thoroughbreds or part-Thoroughbreds than in cold-blooded breeds of horses. Generally, both high temperatures and high humidity are required for the condition to develop although it is seen in places
25 where only extremely high temperatures occur, eg Arizona.

While not all horses in hot, humid climates develop the disorder, its incidence is high enough to warrant concern. In Hong Kong an incidence of about 3 per cent is seen in horses imported from Britain, Australia and New Zealand for racing. These horses then have to be withdrawn from racing. It has also been suggested
30 that up to 20 per cent of horses in Miami, Florida, USA are affected by anhydrosis during the summer months, which makes anhydrosis of great concern financially as well as with regards to the welfare of the animal. In Katherine, Northern Territory, Australia it has been reported that the most common cause of death in horses is from 'the puffs' due to the high temperature and high humidity.

35 The major symptom associated with anhydrosis is the inability of the horse to sweat, even with the severest exercise. Early in the course of the disease, sweating is generally restricted to the throat region, the neck, the base of the ears, between the hind legs and under the saddle. As the condition progresses, the amount of sweat as well as the area over which sweating can be observed will



gradually diminish. In the most severe cases, there is a complete cessation of sweating.

High body temperatures are also observed, particularly after exercise. The body temperature of the horse generally remains slightly elevated, even when the horse is at rest. If forced exercise is carried out, the horse may drop dead with a very high body temperature (above 43.3°C). Horses suffering from this condition may be at risk if given even mild exercise. The disease has been thought to be related to or some how to contribute to heat stroke.

The signs associated with anhydrosis (other than absence of sweating) include a marked excessive breathlessness or panting/puffing, such as a resting panting rate of over 30 per minute. Whereas a normal respiration rate for horses is 10 per minute or thereabouts, for a horse suffering from anhydrosis, puffing can be up to 180 per minute on a hot day. The coat also becomes dry, harsh, and generally poor in condition and there may be alopecia, or loss of hair. A horse suffering from this condition will also tend to urinate a lot as they are not losing fluid by sweating. The horse will also tend to roll regularly, trying to get mud or dust on them as protection from the sun's rays. Some horses will also exhibit symptoms of fever including high temperature. Occasionally, the horse loses its appetite and starts to lose weight. In relation to horses losing weight, it has been postulated that the main contributing factor is their desire to be in the shade all day, out of the sun, and so the horses have reduced grazing time.

It has also been noted that horses which are suffering from anhydrosis develop a shifting lameness. Cracks appear on the coronary band and spread down the hoof. The wall above the shoe disintegrates and has the appearance of being moth-eaten or as if white ants are at work from the bottom up. Thus the sole is directly on the ground, and shoeing eventually becomes impossible or a waste of time. This pattern of hoof disintegration is diagnostic and the hoof normalises as the 'Puffs' ease.

Anhydrosis can start suddenly or gradually, and may or may not be associated with visible sweating beforehand. The horses feel so bad that they refuse to roll in water which would obviously save them. Racehorses do not generally die from anhydrosis as they are hosed down immediately after a race. However, working horses suffering from anhydrosis can die some hours after exercise if they have been ridden, as most are not hosed down and have no shelter to protect them from the sun.

Why horses become either partially or completely anhydrotic is at present unknown. In the past, the causes of anhydrosis have been thought to be an infectious organism such as a virus or a bacterial infection, arsenic toxicity and adrenal insufficiency. The condition has also been thought to result from

hypothyroidism. One hypothesis suggests that the blockage of the sweat gland ducts is a secondary symptom and that the basic disturbance is that of insensitivity of the sweat glands to adrenalin, with the sweat glands having been conditioned by persistent exposure to consistently high environmental temperatures. However, 5 another current hypothesis postulates that anhidrosis is probably due to many of the sweat glands losing their ability to function properly, because the cells producing the sweat have become exhausted and their internal structure changed. This suggests that an abnormal period of prolonged sweating must have occurred, leading to temporary damage to the glands.

10 Anhidrosis has been reported for over a hundred years as being a condition suffered by horses, but with no known cure. Accordingly, a number and variety of treatments have been tried on horses suffering from this condition. The main objective of these treatments has been to reduce the horse's temperature. Artificial cooling is the most favoured treatment, such as by hosing down or keeping 15 them wet in other ways in order to provide for evaporative cooling. Horses subject to anhidrosis should be held in a cooler environment, such as a well-ventilated stable with no sun and little exercise. Some reported treatments which have been tried on horses suffering anhidrosis outside Australia include:

- 1) The addition of salt to the diet or by intravenous injection of sodium chloride,
- 20 2) The clipping of long-coated horses, together with a diet with much green feed in it,
- 3) Thyroid gland extract, administered 50 g daily for 20 days,
- 4) Vitamin E, 1000-3000 units, has also been recommended,
- 5) 12g iodinated casein containing 0.72 per cent iodine, administered in daily doses 25 for a period of six days, and
- 6) Extreme measures such as air-conditioning stables or removal to a cooler climate.

Although a large number of treatments have been tried on horses suffering from anhidrosis, they have generally been unsuccessful and generally, the only 30 effective means of treatment is to remove the horse to a more temperate climate. In hot, humid environments the condition may be avoided by stabling horses in air-conditioned stables. In affected animals the sweat glands recover during the cooler months of the year, but the condition reoccurs the following summer.

It is unknown whether there is any genetic predisposition to the disorder, nor 35 is it known whether any test can be developed to predict if a horse is pre-disposed to it. Although development of the disorder has generally been associated with exercise, it has also been reported in resting stabled horses and brood mares.

The condition is a debilitating one and generally means that a work horse suffering from it is unable to perform any work. This therefore results in economic

loss to the owner. If the horse suffering from the condition is a race horse, the cost involved is often far more significant as the withdrawal of a horse from a race means a loss of potential winnings. In extreme cases of anhydrosis, the welfare of the animal can be of grave concern, with the potential loss of the horse being a
5 consideration for the owner.

There is therefore a need for a method for the treatment and prevention of equine anhydrosis which is cost effective and which has no toxicity to horses. The method must be one which is readily available and economically viable to use in those parts of the world where equine anhydrosis is prevalent. The method must
10 also preferably be one which is easily administered to horses and which is quickly effective.

Objects of the Invention

Accordingly, it is an object of this invention to provide a method for the treatment of equine anhydrosis which is cost effective and which has no toxicity to
15 horses.

It is another object of this invention to provide a method for the prevention of equine anhydrosis which is cost effective and which has no toxicity to horses.

It is a further object of the present invention to provide a feed formulation for administration to horses suffering from equine anhydrosis.

20 It is also an object of the invention to provide for a dietary supplement composition for administration to horses suffering from equine anhydrosis.

Summary of the Invention

Unexpectedly, it has now been found that administration of an effective amount of zinc to a horse suffering from equine anhydrosis reduces the symptoms
25 of anhydrosis and results in a complete cure of the horse

Accordingly, a first aspect of the present invention provides a method for the treatment of equine anhydrosis comprising the administration of an effective amount of zinc to an animal in need thereof.

A second aspect of the present invention provides a method for the prevention
30 of equine anhydrosis comprising the administration of an effective amount of zinc to an animal in need thereof.

A third aspect of the present invention provides an animal feed formulation including an above nutritional level of zinc per dose.

A fourth aspect of the present invention provides a dietary supplement
35 including an above nutritional level of zinc per supplement dose.

A fifth aspect of the present invention provides a method for the treatment and/or prevention of equine anhydrosis comprising the administration of at least

one dose per day of the animal feed formulation of the third aspect of the invention to an animal in need thereof.

A sixth aspect of the present invention provides a method for the treatment and/or the prevention of equine anhydrosis comprising the administration of at least
5 one dose per day of the dietary supplement of the fourth aspect of the invention to an animal in need thereof.

A seventh aspect of the present invention provides the use of an above nutritional level of zinc in the manufacture of a dietary supplement for use in the treatment and/or prevention of equine anhydrosis.

10 An eighth aspect of the present invention provides the use of an above nutritional level of zinc in the manufacture of an animal feed formulation for use in the treatment and/or prevention of equine anhydrosis.

A ninth aspect of the present invention provides the use of zinc in the manufacture of a dietary supplement for use in the treatment and/or prevention of
15 equine anhydrosis at a rate of administration of said zinc in an above recommended daily allowance amount per day.

A tenth aspect of the present invention provides the use of zinc in the manufacture of an animal feed formulation for use in the treatment and/or prevention of equine anhydrosis at a rate of administration of said zinc in an above
20 recommended daily allowance amount per day.

An eleventh aspect of the present invention provides a dietary supplement including an above nutritional level of zinc per dose when used in the treatment and/or prevention of equine anhydrosis.

A twelfth aspect of the present invention provides an animal feed formulation
25 including an above nutritional level of zinc per dose when used in the treatment and/or prevention of equine anhydrosis.

A thirteenth aspect of the present invention provides an above recommended daily allowance amount of zinc when used in the treatment and/or prevention of equine anhydrosis at a rate of administration of said zinc of an above
30 recommended daily allowance amount of zinc per day.

A fourteenth aspect of the present invention provides an effective amount of zinc when used in the treatment and/or prevention of equine anhydrosis at a rate of administration of said zinc of an above recommended daily allowance amount of zinc per day.

35 A fifteenth aspect of the present invention provides an animal feed formulation including an above recommended daily allowance amount of zinc per dose.

A sixteenth aspect of the present invention provides a dietary supplement including an above recommended daily allowance amount of zinc per supplement dose.

A seventeenth aspect of the present invention provides a method for the treatment and/or prevention of equine anhydrosis comprising the administration of at least one dose per day of the animal feed formulation of the fifteenth aspect of the invention to an animal in need thereof.

5 An eighteenth aspect of the present invention provides a method for the treatment and/or the prevention of equine anhydrosis comprising the administration of at least one dose per day of the dietary supplement of the sixteenth aspect of the invention to an animal in need thereof

A nineteenth aspect of the present invention provides a dietary supplement
10 including an amount of zinc above the recommended daily allowance of zinc per dose when used in the treatment and/or prevention of equine anhydrosis.

A twentieth aspect of the present invention provides an animal feed formulation including an amount of zinc above the recommended daily allowance of zinc per dose when used in the treatment and/or prevention of equine anhydrosis.

15 A twenty first aspect of the present invention provides a method for the treatment and/or prevention of equine anhydrosis comprising the daily administration of an above recommended daily allowance amount of zinc to an animal in need thereof.

A twenty second aspect of the present invention provides a method for the
20 treatment and/or the prevention of equine anhydrosis comprising the daily administration of an above daily nutritionally required amount of zinc to an animal in need thereof.

This invention is based on the surprising discovery hitherto previously unsuspected that the administration of zinc is an effective treatment for equine
25 anhydrosis. The recommended daily allowance for a horse ("Nutrient Requirements of Horses", National Research Council, National Academy Press, Washington, 1989) of zinc is 40mg/kg food per day. An average size horse (400-500kg) eating 2-2.5% of bodyweight food per day therefore has an allowance of 320-500mg zinc per day. It has been discovered by the present inventors that
30 administration to a horse in need of greater than the recommended daily allowance of zinc will cure anhydrosis.

As used herein, the phrase 'nutritional level of zinc' is defined to mean the same as the phrase 'recommended daily allowance of zinc' which is defined to mean an amount of zinc of about 320-500mg zinc per day.

35 As used herein, the phrase 'an above nutritional level of zinc' is defined to mean the same as the phrase 'an above recommended daily allowance of zinc' which is defined to mean an amount of zinc of greater than about 320-500mg zinc per day.

The zinc may be administered by any conventional method employed in animal health. Preferably the zinc is administered orally or parenterally, more preferably orally.

Also preferably the zinc is in the form of elemental zinc or in a pharmaceutically or orally acceptable form including a zinc salt, more particularly zinc chelate or zinc proteinate.

Preferably, the effective amount of zinc is administered at least once daily to an animal suffering from anhydrosis. Also preferably, the effective amount of zinc can be administered in one or more doses throughout a day.

Preferably, the zinc which is administered in the present invention is administered daily in an amount above the recommended daily allowance.

The zinc can be mixed with suitable carriers and standard dietary ingredients including minerals and vitamins to formulate the animal feed formulations and the dietary supplements of the present invention.

The formulations of the present invention can take the form of orally and parenterally acceptable forms including water dispersions, tablet and/or capsule formulations, sustained release formulations, emulsions and solutions.

Preferably, the animal feed and/or dietary supplement formulations of the present invention include an effective amount of zinc together with any one or more suitably acceptable carriers or excipients. Selection of the carrier is of course made on the basis of compatibility with zinc, including such considerations as pH, toxicity and stability.

In one preferred feed formulation of the present invention, the zinc takes the form of zinc chelate and is present in an above nutritional level amount per dose with the optional addition of other vitamins and minerals in standard animal feeds.

In one preferred dietary supplement formulation of the present invention, the zinc takes the form of zinc chelate and is present in an above nutritional level amount per dose with the optional addition of other vitamins and minerals in standard animal feeds.

In the methods of the present invention it is preferred that the amount of zinc administered to a horse is greater than 40mg/kg food per day.

More preferably, the total amount of zinc administered to a horse suffering from anhydrosis is greater than about 500mg zinc per day, preferably greater than about 600mg zinc per day, more preferably greater than about 700mg zinc per day, more preferably greater than about 800mg zinc per day, more preferably greater than about 900mg zinc per day, more preferably greater than about 1000mg zinc per day, even more preferably greater than about 1100mg zinc per day, even more preferably greater than about 1200mg zinc per day, even more preferably greater

than about 1300mg zinc per day, even more preferably greater than about 1400mg zinc per day, even more preferably greater than about 1500mg zinc per day.

It is also preferable that the methods of the present invention provide for the administration of 750-1350mg zinc per day to an animal in need thereof in addition
5 to the animal's normal diet (which includes approximately 320-500mg of zinc per day).

Accordingly, in a preferred treatment of equine anhydrosis, a horse suffering from that condition is administered a total amount of zinc of about 600-1700mg/day.

In another preferred treatment of equine anhydrosis, a horse suffering from
10 that condition is administered a total amount of zinc of about 700-1700mg/day.

In another preferred treatment of equine anhydrosis, a horse suffering from that condition is administered a total amount of zinc of about 800-1700mg/day.

In another preferred treatment of equine anhydrosis, a horse suffering from that condition is administered a total amount of zinc of about 900-1700mg/day.

15 In another preferred treatment of equine anhydrosis, a horse suffering from that condition is administered a total amount of zinc of about 1000-1700mg/day.

In another preferred treatment of equine anhydrosis, a horse suffering from that condition is administered a total amount of zinc of about 1100-1700mg/day.

In another preferred treatment of equine anhydrosis, a horse suffering from
20 that condition is administered a total amount of zinc of about 1200-1700mg/day.

In a one animal feed formulation embodiment of the present invention, there is included an effective amount of zinc of at least about 600mg per dose of formulation, said formulation being administered at least once per day to an animal in need thereof.

25 In another animal feed formulation embodiment of the present invention, there is included an effective amount of zinc of at least about 700mg per dose of formulation, said formulation being administered at least once per day to an animal in need thereof.

In another animal feed formulation embodiment of the present invention, there
30 is included an effective amount of zinc of at least about 800mg per dose of formulation, said formulation being administered at least once per day to an animal in need thereof.

In another animal feed formulation embodiment of the present invention, there
35 is included an effective amount of zinc of at least about 900mg per dose of formulation, said formulation being administered at least once per day to an animal in need thereof.

In another animal feed formulation embodiment of the present invention, there is included an effective amount of zinc of at least about 1000mg per dose of

formulation, said formulation being administered at least once per day to an animal in need thereof.

In another animal feed formulation embodiment of the present invention, there is included an effective amount of zinc of at least about 1100mg per dose of formulation, said formulation being administered at least once per day to an animal in need thereof.

In another animal feed formulation embodiment of the present invention, there is included an effective amount of zinc of at least about 1200mg per dose of formulation, said formulation being administered at least once per day to an animal in need thereof.

In another animal feed formulation embodiment of the present invention, there is included an effective amount of zinc of at least about 1300mg per dose of formulation, said formulation being administered at least once per day to an animal in need thereof.

In another animal feed formulation embodiment of the present invention, there is included an effective amount of zinc of at least about 1400mg per dose of formulation, said formulation being administered at least once per day to an animal in need thereof.

In another animal feed formulation embodiment of the present invention, there is included an effective amount of zinc of at least about 1500mg per dose of formulation, said formulation being administered at least once per day to an animal in need thereof.

In another animal feed formulation embodiment of the present invention, there is included an effective amount of zinc of at least about 1600mg per dose of formulation, said formulation being administered at least once per day to an animal in need thereof.

In a preferred dietary supplement of the present invention, there is included an effective amount of zinc of at least 300mg per dose of supplement, said supplement being administered at least once per day to an animal in need thereof, in addition to the animal's normal diet.

In another preferred dietary supplement of the present invention, there is included an effective amount of zinc of at least 400mg per dose of supplement, said supplement being administered at least once per day to an animal in need thereof, in addition to the animal's normal diet.

In another preferred dietary supplement of the present invention, there is included an effective amount of zinc of at least 500mg per dose of supplement, said supplement being administered at least once per day to an animal in need thereof, in addition to the animal's normal diet.

In another preferred dietary supplement of the present invention, there is included an effective amount of zinc of at least 600mg per dose of supplement, said supplement being administered at least once per day to an animal in need thereof, in addition to the animal's normal diet.

5 In another preferred dietary supplement of the present invention, there is included an effective amount of zinc of at least 700mg per dose of supplement, said supplement being administered at least once per day to an animal in need thereof, in addition to the animal's normal diet.

In another preferred dietary supplement of the present invention, there is
10 included an effective amount of zinc of at least 800mg per dose of supplement, said supplement being administered at least once per day to an animal in need thereof, in addition to the animal's normal diet.

In another preferred dietary supplement of the present invention, there is included an effective amount of zinc of at least 900mg per dose of supplement, said
15 supplement being administered at least once per day to an animal in need thereof, in addition to the animal's normal diet.

In another preferred dietary supplement of the present invention, there is included an effective amount of zinc of at least 1000mg per dose of supplement, said supplement being administered at least once per day to an animal in need
20 thereof, in addition to the animal's normal diet.

In another preferred dietary supplement of the present invention, there is included an effective amount of zinc of at least 1100mg per dose of supplement, said supplement being administered at least once per day to an animal in need thereof, in addition to the animal's normal diet.

25 In another preferred dietary supplement of the present invention, there is included an effective amount of zinc of at least 1200mg per dose of supplement, said supplement being administered at least once per day to an animal in need thereof, in addition to the animal's normal diet.

In another preferred dietary supplement of the present invention, there is
30 included an effective amount of zinc of at least 1300mg per dose of supplement, said supplement being administered at least once per day to an animal in need thereof, in addition to the animal's normal diet.

In a further preferred method of the present invention, there is administered 5-9g zinc proteinate (750-1350mg zinc) per day to an animal in need thereof, in
35 addition to that animal's normal diet.

Best Mode and Other Modes of Performing the Invention

A supplement composition containing zinc is administered to a horse suffering from anhydrosis. The horse is fed one or more daily doses of the supplement containing zinc, such that a horse receives a total daily amount of zinc of at least

about 800mg of zinc and preferably in the order of a total daily amount of zinc of 1000-1700mg. The number of doses of the supplement is not significant so long as the horse receives at least about 600-800mg of zinc per day in total, more preferably at least about 1000mg of zinc per day.

5 The zinc formulations and supplements of the present invention can be administered in any veterinarily acceptable oral or parenteral manner including in tablet, powder, capsule or pellet form. A powder supplement composition is generally preferred for its ease of addition to horse feed.

The formulation or supplement is administered until the animal's signs of
10 anhydrosis have disappeared. The formulation or supplement can continued to be administered for an extended time period, even though signs of anhydrosis have disappeared.

EXAMPLES

EXAMPLE 1

15 Eight horses suffering from anhydrosis were taken and their symptoms including exercise tolerance, sweating, puffing and coat appearance were recorded. The horses were then fed in addition to their normal diet, a daily dose of supplement containing greater than 300mg zinc. The supplement was given once daily in either the morning or evening feed. After at least 24 hours, the horses
20 began to show small signs of improvement. After daily dosage of the supplement continued, the horses had all significantly improved within 3-5 days after commencement of treatment.

Supplement Composition administered to horses

	Sugar Castor	352.44g/kg
25	Linseed Oil	24g/kg
	Monosodium Phosphate	182g/kg
	Potassium Chloride	78g/kg
	Zinc Proteinat 15%	180g/kg
	Magnesium oxide	171g/kg
30	Potassium iodide	0.06g/kg
	Aerosil 200	12.5g/kg

Exercise tolerated:

	walk in paddock	run in paddock	light work	full work
Before treatment	3	1	3	1
After treatment	0	0	4	4

Sweating:

	none	neck/poll only	under saddle only	most of body	All over

12

Before treatment	4	2	2	0	0
After treatment	0	1	1	4	2

Puffing:

	walk in paddock	light work	full work	no puffs
Before treatment	4	4	0	0
After treatment	0	2	3	3

Coat Condition:

	dull, hair loss	dull	dull in parts	normal
Before treatment	2	3	3	0
After treatment	0	0	4	4

- 5 The horses were fed 25g of the supplement described above for 60-120 days. Their condition did not recur after treatment.

Claims

1. A method for the treatment or prevention of equine anhydrosis comprising the administration of an effective amount of zinc to a horse in need thereof.
2. The method for the treatment or prevention of equine anhydrosis according to
5 claim 1 comprising the daily administration of above about 320-500mg of zinc to a horse in need thereof.
3. The method according to claim 1 comprising the daily administration of greater than about 1000mg of zinc to a horse in need thereof.
4. The method according to claim 1 comprising the daily administration of about
10 600-1700mg of zinc to a horse in need thereof.
5. A therapeutic horse feed formulation including above about 320-500mg of zinc per dose.
6. The feed formulation of claim 5 including at least about 800mg of zinc per dose
- 15 7. The feed formulation of claim 5 including at least about 1400mg of zinc per dose.
8. A dietary supplement for horses including above about 320-500mg of zinc per supplement dose.
9. The dietary supplement of claim 8 including at least about 700mg of zinc per
20 supplement dose.
10. The dietary supplement of claim 8 including at least about 1200mg of zinc per supplement dose.
11. The dietary supplement of claim 8 including about 750-1350mg of zinc per supplement dose
- 25 12. A method for the treatment or prevention of equine anhydrosis comprising the administration of at least one dose per day of the feed formulation of any one of claims 5-7 to a horse in need thereof.
13. A method for the treatment or prevention of equine anhydrosis comprising the administration of at least one dose per day of the dietary supplement of any one of
30 claims 8-11 to a horse in need thereof.
14. A dietary supplement according to any one of claims 8-11 when used in the treatment or prevention of equine anhydrosis.
15. A therapeutic horse feed formulation according to any one of claims 5-7 when used in the treatment or prevention of equine anhydrosis.
- 35 16. The use of above about 320-500mg of zinc in the manufacture of a dietary supplement for horses for use in the treatment or prevention of equine anhydrosis.
17. The use of above about 320-500mg of zinc in the manufacture of a therapeutic horse feed formulation for use in the treatment or prevention of equine anhydrosis.

18. The use of zinc in the manufacture of a dietary supplement for horses for use in the treatment or prevention of equine anhydrosis at a rate of administration of said zinc of above about 320-500mg per day.

19. The use of zinc in the manufacture of a therapeutic horse feed formulation for
5 use in the treatment or prevention of equine anhydrosis at a rate of administration of said zinc in of above about 320-500mg per day.

20. An effective amount of zinc when used in the treatment or prevention of equine anhydrosis at a rate of administration of said zinc of above about 320-500mg per day.