To whom it may concern:

I have reviewed various studies relevant to the safety of use of Z-103, an equimolar complex of carnosine (a dipeptide) and zinc, which is a proposed treatment for gastric mucosal ulcers. The first article reviewed provides basic information on Z-103, which is used for some of the statements I make in the introductory section of my review (ie the molecular composition of Z-103).

There are a number of lines of reasoning that can be employed to expect that the proposed human dose of Z-103 (75 mg per day) is safe even if given for a prolonged period of time. Most of this reasoning is derived from the papers reviewed below. However, there are also lines of reasoning that can be derived from general information on the intake levels of the individual components of Z-103 (carnosine and zinc). These are given in the beginning of my accompanying review.

In general, I do not see any red flags as to why this compound, at the dose proposed, should pose major health dangers.

Sincerely,

Dr Robert DiSilvestro
Professor
INTRODUCTION

I have considered safety issues for the proposed daily dose of Z-103 (75 mg). My conclusions are based on both reviews of individual papers (individual reviews given below) and reviews of the proposed daily dose of Z-103. In zinc, the proposed daily dose of Z-103 has about 15 mg of zinc per day. There is no reason to think that this dose poses any health risk. In fact, this dose is equal to that typically found in popular multivitamin-mineral supplements (e.g., Centrum, One-A-Day Complete). Even if someone were to take both Z-103 and a typical multivitamin-mineral pill, the 30 mg or so of total supplemental zinc is still below the Tolerable Upper Limit recently established for zinc in adults. Another consideration is that the zinc in many multivitamin-mineral supplements is zinc oxide, which is not very well absorbed. Therefore, whatever zinc is absorbed from the Z-103 is adding to just a limited amount of zinc that would be absorbed from most multivitamin-mineral supplements.

A potential concern with zinc administration is possible induction of copper deficiency (high doses of zinc are known to inhibit copper absorption). However, this should not be a major issue here. The 15 mg of zinc from Z-103, or the 30 mg of zinc from Z-103 plus a multi-vitamin-mineral supplement, are both well below the doses known to cause clinical copper deficiency. Moreover, my laboratory has had some trouble getting even 60 mg of zinc to diminish blood copper enzyme activities, which is a very early sign of mild copper deficiency. Another consideration about a combined effect of Z-103 plus a multi-vitamin mineral supplement is that if the latter has zinc, then it usually also has copper. Therefore, I see no practical risk for copper deficiency due to Z-103 ingestion, even if combined with a zinc-containing multivitamin-mineral supplement.

From the carnosine perspective, a daily dose of 75 mg of Z-103 provides about 60 mg/day of carnosine. This intake of carnosine, which is a dipeptide, is well below what millions consume daily in the form of another dipeptide, namely aspartame. Although there are some differences in the two dipeptides, given that most dipeptides are degraded readily in the body, some comparison of carnosine and aspartame is justified.

Another important issue here is that the 60 mg/day carnosine is not tremendously high compared to what can be obtained in a meat-containing diet. Although extensive data on carnosine intake is not available, there is enough data to say that many people already eat more than 60 mg/day. For example, there is 400-500 mg in one-fourth lb of pork (Reference: Pork meat quality affects peptide and amino acid profiles during the ageing processes. Meat Science 58:197-206, 2001). It is also noteworthy that carnosine content of pork is stable over time. I have not found a similar analysis of beef. However, in an analysis of soups, there is about 50 mg in half a small can of beef consomme, and about the same in one small can of Fiesta Chili with beans (Reference: HPLC determination of carnosine in commercial canned soups and natural meat extracts. Lebensmittel - Wissenschaft + Technologie 33:60-62, 2000). Since neither of these foods represents very large beef servings, it is reasonable that beef could easily provide people with far more carnosine than would derive from a 75 mg dose of Z-103.
Other safety considerations of Z-103 are derived from the papers reviewed below. The papers reviewed below are not exhaustive, but emphasize recent papers plus a series of detailed Japanese studies. When discussing the papers noted below, for simplicity's sake, I will always use the term "Z-103" to denote zinc-carnosine, even though the original paper may use other terms (i.e., Polaprezinc). Another note is that for animal or cell culture studies discussed below, I compare Z-103 doses to the proposed dose for humans in the USA (75 mg/day). I will assume that this translates to about 1 mg/kg (since a 70 kg human is often used as average).

**Review Articles**

This review article provides some of the basic information on Z-103 and its use for treating ulcers. This information was used for some of the statements I have already made as well as for some of the assumptions used to review the subsequent articles. This article states that Z-103 is a 1:1 complex of zinc to carnosine, that the complex does not dissociate rapidly in the stomach environment, that it can stick to mucosal ulcers specifically, and that this sticking can be followed by dissociation where the two components could then exert healing actions.

This review article summarizes information on the preparation and chemical properties of carnosine complexed with various metals or combinations of metals. Although much of this paper deals with issues not real important to my current purpose, there is one important point in this regard. The paper notes that Z-103 has a variety of antioxidant actions in vitro. Besides the potential contribution of these properties to anti-ulcer actions, most antioxidants tend to be relatively safe unless they possess other negative properties.

**Interactions between carnosine, zinc and copper: implications for neuromodulation and neuroprotection.** Biochemistry (Moscow) 65:807-816, 2000.
This review article speculates about how carnosine might interact with copper or zinc in the nervous system, particularly in the olfactory section. Data is presented from work in vitro showing interactions among these three agents in terms of amino acid receptor interactions and synaptic transmissions. How much of this would occur in vivo is uncertain since most of the copper and zinc in cells are bound to ligands other than carnosine. There is also data presented showing that carnosine reduces toxicity of copper or zinc to cultured cells. The main value of this paper for present purposes is as follows: since carnosine-zinc may protect against neurological injury, this implies that an oral dose of such a complex may be among the most "neuro-safe" ways to give zinc.

This review contains some of the same data as noted in the previous article. Again, the main point relevant to Z-103 for human applications is that complexes of zinc and carnosine may be one of the "neuro-safe" ways to give zinc.
This review article indicates that carnosine has antioxidant, buffering and immune enhancement properties, all which could all be important in treating ulceration. Further, there is the notation that carnosine is a naturally occurring compound in mammalian cells. This means that giving humans Z-103, which is a carnosine-zinc compound, does not introduce a foreign organic molecule to people. This paper also notes that muscle is particularly high in carnosine (at least compared to other body sites). This means that toxicological considerations of Z-103 should consider how Z-103 affects muscle carnosine (which is done in a paper reviewed below).

One safety concern about the oral use of Z-103 would be what happens due to the carnosine portion. Presumably, some should leave the GI tract and enter the rest of the body. This paper, though not written primarily to deal with safety issues, makes some points relevant to these issues. First, the paper notes that carnosine is a naturally occurring compound in the body. Second, based on studies in vitro, this compound could have functions which protect cells from damage. These studies include cell culture work where 1 mM carnosine protects certain cells from damage due to certain toxins. Thus, an increase in body levels of carnosine, due to oral ingestion, may confer benefit rather than harm. Lastly, and perhaps most importantly, the cell culture data gives no evidence that 1 mM carnosine harms cells. Such a result should mean that lower concentrations of the compound would also not harm the cells. It is doubtful that orally ingested carnosine could ever produce plasma concentrations even as high as 1mM. This contention is made based on an oral dose of 75 mg/day. This is only about 0.25 mMoles, not all of which is necessarily absorbed from the GI tract. In addition, what is absorbed would be broken down by the body. Although the breakdown rate may not be known, generally degradation rates for peptides are fairly rapid. Such a rapid breakdown rate should prohibit any large additive effect for the typical daily dose for Z-103. In summary, based on cell culture studies, any blood carnosine resulting from typical oral doses of Z-103 should not pose a health risk to cells. Although these studies are far from the last word on the subject of safety, they do make a contribution.

Studies in Cell Cultures and Other Studies In Vitro

Although this study is primarily written from a Z-103 efficacy perspective, it is relevant to a safety issue. This issue is how a compound may interact with other molecules it encounters in the body. This study considers how carnosine affects hydrogen peroxide-mediated oxidant stress. Although hydrogen peroxide is not a free radical, it can promote radical-mediated oxidant stress in two ways. First, hydrogen peroxide can be a free radical precursor. Second, hydrogen peroxide can inactivate copper-zinc superoxide dismutase, an enzyme which eliminates superoxide radical. This paper shows that
Carnosine can inhibit hydrogen peroxide inactivation of superoxide dismutase in vitro. This action could be relevant to protecting superoxide dismutase in vivo, plus it provides evidence that carnosine can protect against hydrogen peroxide injury to molecules in general. Both ideas are further supported by the next study. In other words, carnosine interactions with hydrogen peroxide do not enhance the latter's toxicity, but work against it.

Polaprezinc protects gastric mucosal cells from noxious agents through antioxidant properties in vitro. *Alimentary Pharmacology & Therapeutics* 13:261-269, 1999. This study adds to the just mentioned study by showing that Z-103 can protect against hydrogen peroxide-induced cell death in cultured gastric mucosal cells. The study also raises the possibility that carnosine interactions with another molecule, ethanol, results not in enhanced toxicity of that molecule, but protection. In specific, Z-103 inhibits ethanol-induced superoxide accumulation in these cells.

Polaprezinc down-regulates proinflammatory cytokine-induced nuclear factor-kappaB activation and interleukin-8 expression in gastric epithelial cells. *Journal of Pharmacology & Experimental Therapeutics* 291:345-352, 1999. A big safety concern for any drug is whether the drug causes inflammation. This would be especially problematic for an anti-ulcer drug since a lot of inflammatory processes in the stomach are already triggered. This study, done in cultured gastric epithelial cells, examines Z-103 in regard to certain processes involved in inflammation triggered by cytokines. These processes include gene expression for a pro-inflammatory mediator plus molecular activation of a different mediator. Z-103 does not enhance these molecular processes relevant to inflammation, but rather inhibits them. One concern with this study is the lack of justification for concentration of Z-103 used in the cell cultures. It is somewhat difficult to estimate a concentration in vivo since Z-103 can adhere to gastric mucosal layers, which can cause the cell surface concentrations to exceed those in gastric fluids. However, it can be stated that a dose of 75 mg Z-103 would likely not produce stomach concentrations that greatly exceed the concentrations used in this study. The 75 mg dose translates to 259 uMoles. If this is diluted in the GI tract with 2.5 L or less, the 100 uM concentration used in this cell culture study is not unreasonable.

**Effect of polaprezinc (N-(3-aminopropionyl)-L-histidinato zinc), a novel antiulcer agent containing zinc, on cellular proliferation: role of insulin-like growth factor I.** *Biochemical Pharmacology* 58:245-250, 1999. The effect of Z-103 on cellular proliferation is studied using three types of cultured cells. This agent increases cell proliferation in two cell types, at least partially via insulin-like growth factor mediation, but does not affect proliferation in gastric mucosal epithelial cells. The main value for safety evaluation is that there is no toxicity evident in terms of suppressing cell multiplication or causing cell death.

From this monolayer, a circular artificial wound with constant size is made. The restoration process is monitored by measuring wound size. The main goals of the paper deal with efficacy, but there is some importance for safety. If Z-103 is used to treat ulcers, ideally it would not harm normal epithelial structure, particularly if that structure already has some damage. This situation is simulated in this study. Z-103 does not injure the epithelial structure, but instead reduces wound size.

**Studies In Vivo-Nonhuman Species**


This is a pilot study of the toxicity of Z-103 in dogs using daily intake for 13 or 52 weeks. At the shorter time period, 50 mg/kg/day results in various non-specific toxicity signs such as diarrhea, elevated blood alkaline phosphatase values, reduced food intake, and GI tract lesions. For the longer time period, similar results are noted with the same dose, but the symptoms were actually milder, a result which suggests some adaptation. The longer study also examines lower doses which lead to a designation of 20 mg/kg as a "no effect dose." This dose is 20 times higher than the proposed human dose for Z-103.


Metal toxicity is often characterized by accumulation of the overloaded metal plus either low or high accumulation of other metals. For zinc overload, a classic symptom is copper depletion. The effects of zinc overload on iron can vary. High zinc intake can block iron absorption, which would lower tissue iron contents. However, if zinc overload causes copper deficiency, this can cause high iron accumulation in organs such as the liver. This study of rats and dogs is designed to see if administering high oral doses of Z-103 affects accumulation of zinc, copper and iron in the blood and various tissues. There are four study subsections: two species (rats and dogs) and two dosing times (13 or 52 weeks), the latter of which is about one-third the maximal life span of a laboratory rat.

The lowest dose for 3 of the 4 study subsections is 50 mg/kg/day, which is about 50 times the proposed human dose. For the other study subsection, 8 mg/kg is used (about 8 times the proposed human dose). The lowest doses in each study subsection have no effects. In each study subsection, doses 2.5-3 times higher than the lowest doses had either no effects, or relatively small effects (ie no effects on copper in any of 10 body sites, and a small percent change for zinc in 1 of 10 body sites). Dramatic effects are seen only at even higher doses. Thus, this study suggests that at the proposed human dose for Z-103, there is low risk of toxicity in the form of abnormal accumulation of zinc, copper or iron. One shortcoming of this study is the lack of information about the levels of various metals in the diet. Many rat and dog diets can have copper present at a level which has a safety marginal above that which is minimally adequate. Thus, if this study was repeated with a more marginal copper intake, which may be typical of many people, the effects of Z-103 on copper may have been more pronounced. However, this consideration must be balanced with the fact that the doses of Z-103 are many times higher than the proposed human dose.
High levels of dietary carnosine are associated with increased concentrations of carnosine and histidine in rat soleus muscle. Journal of Nutrition 131:287-90, 2001.

This study examines 8 weeks of carnosine consumption (0%, 0.1% or 1.8% of the diet) by young rats with various levels of vitamin E intake. The main end points are skeletal muscle contents of carnosine, vitamin E and histidine (a portion of the carnosine molecule). As noted above, muscle is relatively high in endogenous carnosine. After 8 weeks, in soleus muscle 1.8% carnosine produces a five fold increase in carnosine, a twofold increase in histidine, and no effect on vitamin E. The lower carnosine dose had no effect on any of these parameters in soleus muscle, and neither dose had any effect on these parameters in other muscle types. These studies suggest that orally ingested carnosine, at a typical dose for a human clinical application, will not affect muscle levels of carnosine, histidine or vitamin E. The lower dose, on a mg/body weight basis, can be conservatively estimated to be at least 20 times the proposed Z-103 dose (the exact rat intake of Z-103 depends on some details not provided in the paper). The higher dose is at least 360 times higher. This means that if rats and humans respond similarly to ingested carnosine, there is no chance that a typical human oral dose of Z-103 will alter muscle carnosine levels enough to have any toxic effects.


Z-103 labeled with both radioactive carbon and radioactive zinc is given to rats at a total Z-103 dose of 50 mg/kg (about 50 times the proposed human daily dose). The dietary concentration of zinc is considered a little above adequate. However, it is less than twice that in a standard semipurified diet, and less than that in many mixed feed commercial rat diets. The importance of this study for Z-103 safety is as follows:

Despite the lack of excessive dietary zinc intake, and the relatively high dose of Z-103, no major changes are seen for total zinc in any of several body sites examined;

The two radionuclides show different kinetics, implying that the zinc and carnosine dissociate within the body (thus, the toxicity of Z-103 won't be much different from each individual component, neither of which are overly toxic at the proposed human dose);

The patterns for radioactive carbon suggest that this compound is metabolized within the normal amino acid pool, as would be expected from histidine, a component of Z-103 (same importance as for the previous comment);

The radioactive zinc is found in the liver, kidney and prostate, the tissues where zinc would be expected to accumulate;

Little radioactive zinc is found in brain or testes (areas vulnerable to zinc toxicity).


As noted for a cell culture study above, a big safety concern for any drug is whether the drug causes inflammation, especially if the treatment target area is already inflamed. This paper is relevant to this issue, even though its main purpose is to test for efficacy of Z-103 in a model for a pre-ulcer type injury. This paper shows that in rats, a single dose of Z-103 does not increase, but inhibits acute aspirin-induced gastric injury. This
assertion is based on area of erosion plus 3 different biochemical/molecular biological parameters. The most effective dose is about 40 times higher than the proposed human dose. A dose 10 times higher than the proposed human dose also gives very strong inhibition of erosion area, plus complete inhibition for 2 of the 3 biochemical/molecular biological parameters studied (the high dose gave complete inhibition of the other of these 3 parameters). Thus, Z-103 does not appear to be pro-inflammatory in rat stomach, nor does it enhance inflammation initiated by another agent (instead, it reduces that inflammation).

What was said about the previous paper also applies to this paper, except that different irritant processes are studied. Z-103 is given at each of 3 doses (a dose slightly above the proposed human dose, 6 times the proposed dose, and 12 times the proposed dose). Once again, Z-103 does not add to stomach irritation/inflammation, but actually inhibits the ulcerogenic response.

This paper is similar to the last paper, except that Z-103 is also compared to another compound. Again, Z-103 does not add to stomach irritation/inflammation, but actually inhibits the ulcerogenic response. The Z-103 doses range from just over the proposed human dose up to over 20 times the typical dose.

Series of papers translated from Japanese

Discussed below are a series of articles translated from Japanese. These studies concern both safety and efficacy but only the former will be discussed here. All of the studies, except for the last one, deal with human clinical evaluations of Z-103. The last paper involves a rat study. Page numbers are not always given since the translated version would not necessarily fit to the same pages as the original. Generally, the number of authors for each study vary from three up to double digit numbers. However, the last of the papers dealing with a human study has just one author. Although there are certain authors that appear on many of the papers, and there is overlap of authors, no single author appears on every paper.

Z-103 at 150 mg/day (twice the proposed dose for patients in the USA) is studied in subjects 16 to 75 years of age with a single gastric ulcer. The study is completed by 44 subjects, all of which are used for safety evaluations. Safety is judged based partly on blood chemical chemistries and partly on numerical scoring systems for side effects. In addition, other numerical ratings for safety are based on self-reported subjective or objective symptoms (ie heartburn, or blood in stool). Finally, an overall numerical safety rating is derived from all the relevant measures/judgment scores. General blood clinical chemistries did show some changes in some people, though most of these are minor.
fluctuations. Based on side effects, all 44 cases are judged by the authors as being safe. Thus, this study supports the idea that Z-103 is safe when used to treat gastric ulcer.

The results are impressive but the study has some weaknesses. One is the lack of a placebo control. However, if anything, this would be make it tougher to get good safety results. In most drug studies, some negative safety results arise due to psychosomatic or coincidental factors. Since these would also happen in a placebo group, inclusion of this group normally makes it easier to rate a drug as generally safe. In this study, a good safety rating is obtained without that help. Thus, in one sense, the lack of a placebo actually strengthens the safety aspects of the results. However, in another sense, the lack of a placebo group is a drawback. This sense is that the evaluators may not have had any blinding. I say "may not" because there may have been overlap of subjects and evaluations with other studies. However, if there was no blinding, then this is problematic for the subjective evaluations. In specific, the evaluators may have been biased against poor safety ratings.

Another issue is subject number. Although the subject number is very large for a major pilot study, or for an intermediate level trial, the subject number is not that large considering the following: it is multi-center trial, other co-treatments are continued along with the Z-103, and there is a broad age range. In fact, for the multi-center aspect, there are only about half as many subjects as there are centers. In other words, at least half of the centers contributed no subjects. Possibly, this occurred because a whole series of studies were done, some with different subject requirements. In that case, a large number of centers may have participated in the umbrella project, but not in every subdivision of the project. However, in light of the subject number, the lack of a placebo group, and the uncertainty about blinding, I would not classify this study as a "final word" study on safety. Nonetheless, due to the dramatic effects obtained, I would say that this study very much raises the possibility of safety for Z-103. Moreover, when this study is combined with the other studies in this series, a strong case emerges.


This multi-center study evaluates subjects 16 to 75 years of age who had been diagnosed by endoscopy as having gastric ulcer which is internally treatable. Z-103 (150 mg/day) is compared to another drug, Cetraxate Hydrochloride (800 mg/day). Safety is evaluated by blood chemistries, a scoring of subjective and objective symptoms, and numerical scoring of adverse effects (severity and frequency). Finally, an overall numerical safety rating is derived from all the other measures/judgment scores. There are 148 cases in the Z-103 administration group (Group Z) and 151 cases in the Cetraxate Hydrochloride administration group (Group C). No significant biases are found between the groups. For safety scores and blood chemistries, both drugs seem safe. The strengths of this study are the large number of subjects and the blinded evaluation of Z-103, at least in comparison to another drug.
This paper presents the results of a multi-center, double-blind comparative study of 3 dosages of Z-103 (100, 150 or 200 mg/day). There are 225 subjects, 18 to 76 years of age, who had been diagnosed by endoscopy as having gastric ulcer where internal medical treatment is possible. Subject evaluation is similar to the previously described study. Overall safety ratings are very good for all three groups. Although no placebo group is included, the dramatic results in a large number of people make it likely that Z-103 is generally safe.

This is another multi-center study of Z-l 03. Subjects (N = 156) are 18-75 years of age, who had been diagnosed by endoscopy as having gastric ulcer. Evaluation criteria is similar to other studies in this series. The main point of the study is to look at different dosing patterns, such as timing around meals. Daily doses are 150 or 225 mg. Although each of the patterns show some good results for safety and efficacy, the authors conclude that the best regimen is Z-103 at 75 mg twice a day after breakfast and before bed. For the purpose of my review, the main value of this paper is that it gives another trial which shows safety for Z-103.

This study design is similar to the others in this series, but does not involve as many centers or subjects (28) as some of the previous publications. The main new wrinkle is that effects on endocrine hormones are considered. Safety results are similar to those of the other studies in the series. No major effects are reported for endocrine hormones (prolactin, cortisol, GH, TSH, T3, T4, insulin, LH, FSH, testosterone, and estradiol). Although I am not overly concerned that Z-103 would affect these hormone levels, the study rationale is that there are some interactions between zinc and hormones. This paper adds more bulk to reports of safety for Z-103, plus adds some new safety information.

This study examines 64 subjects, all of which are given 150 mg/day. This study is mostly the same in design as the 150 mg/day groups of the previous studies in the series. I am assuming this represents a final run through of the optimal dose and dosing schedule derived from the previous work. The results resemble those of the other studies in this series for a 150 mg/day group.

This is another study in this series but involves fewer subjects (28) and authors than most of the human studies in this series. This paper does include some pictures and the main emphasis is on endoscopy evaluations. The safety ratings are again strong.
This article is different from the previous articles in the series. It is written by a single author and is actually a combination of different designs and measures. The study examines only male subjects, all of which are under 40 years old. A single-dose study is conducted with 150, 300, and 600 mg of Z-103, and a 7-day continuous administration study is done with 150 mg x 3/day (450 mg total/day). In the single dose study, other than a few subjects showing temporary, minor GI symptoms, Z-103 shows no toxic abnormalities in subjective symptoms, objective indications, physical examination, or clinical study. Plasma and urinary zinc shows no major sustained changes, but more than half the single dose could be recovered in the feces within 48 hours. The main value of this paper is that it confirms that Z-103 does not produce an extremely high absorption rate of zinc (which would increase the chances of toxicity).

This study, unlike the previous ones cited for this series, examines rats. In rats receiving 75 mg/kg of Z-103 (about 75 times the proposed USA human dose) for 52 weeks (about a third of the maximal life span of a rat), no toxic signs are observed. Also, tissue zinc and copper concentrations are unaffected. At a dose of 150 mg/kg, animals show slightly increased Zn levels (blood, liver and kidneys), unaffected Cu level, but histopathological changes in the pancreas. At 300 mg/kg, there are more clinical pathological signs, increased blood and tissue Zn levels, and decreased Cu levels. All changes are reversed by 5 week withdrawal. Considering that copper deficiency, which is an early sign of zinc toxicity, is not apparent at 75 times the proposed USA human dose of Z-103, given for a very long time, it is not extremely likely that humans using Z-103 for ulcer treatment would experience zinc toxicity. However, one drawback to this study is that dietary copper information is not provided. It is possible that in this study, dietary copper intake has a safety margin above that which is normally adequate. Even so, the lack of effect for very large doses of Z-103 (compared to the proposed human dose) give good evidence for safety at the proposed human dose.

Other Human Clinical Studies

Although Z-103 is not mentioned in the title, this is the form of zinc given. The liver is a major body site for metal toxicity. Therefore, it would be helpful to study whether the liver is affected adversely by Z-103. Although that is not the intent of this study, this goal is still accomplished to some extent. Subjects with chronic hepatitis C are given either interferon or interferon + Z-103 (150 mg/day) for 24 weeks (N = 30 for the latter group). Z-103 enhances the therapeutic effect of interferon. Side effects with the combination treatment are no worse than interferon alone. Although this study does not totally predict how Z-103 would affect liver health in normal subjects, or even in hepatitis patients not given interferon, the results make it likely that this dose of Z-103 is not hepatotoxic.
Conclusions

At present, I can see no reason to expect toxicity from a daily dose of 75 mg of Z-103. The two individual constituents of Z-103 are already normal components of the human body, the amounts administered are not large compared to other ways of ingesting these constituents, and current research in vitro, in animals, and in humans all give evidence of safety. The Japanese studies in humans, though not perfect, examined a very large number of subjects, for a prolonged period, and found no major problems attributable to Z-103. At present, I see no safety concerns for the use of Z-103, even for a somewhat extended period.