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FOOD STANDARDS AGENCY

Mr Andreas Klepsch
European Commission, DG SANCO
By email

5 January 2006 Reference: NFU 471

Dear Mr Klepsch,

INITIAL OPINION: CLINOPTILOLITE

On 5 January 2004, the UK Competent Authority accepted an application from Euremica Environmental Ltd for authorisation of clinoptilolite as a novel food ingredient to be used as a food supplement, in accordance with Article 4 of regulation (EC) 258/97. The Advisory Committee on Novel Foods and Processes (ACNFP) has now completed its review of this application and an opinion is attached.

I apologise for the delay in submitting this opinion as the ACNFP's evaluation was extended while we awaited additional safety information from the applicant. However the applicant has indicated that they do not intend to respond to the questions and concerns raised by the ACNFP and the Committee has therefore concluded that the safety data provided by Euremica Environmental for the approval of clinoptilolite as a novel food ingredient is inadequate.

In view of the ACNFP's assessment, the UK Competent Authority considers that clinoptilolite does not meet the criteria for acceptance of a novel food defined in Article 3(1) of regulation 258/97.

I am copying this letter and the ACNFP's opinion to the applicant.

Yours sincerely,

[By email]

Michelle Gardner
For the UK Competent Authority

INVESTOR IN PEOPLE

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POSITIVE ABOUT DISABLED PEOPLE

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

OPINION ON AN APPLICATION UNDER THE NOVEL FOODS REGULATION FOR CLINOPTILOLITE AS A FOOD INGREDIENT

Applicant	**Euremica Environmental Ltd**
Responsible Person	**Mr Rob Sampson**
EC Classification	**2.2**

INTRODUCTION

1. An application has been submitted by Euremica Environmental Ltd. for authorisation of clinoptilolite as a novel food ingredient to be used as a food supplement in the EU, on 5 January 2004. A copy of this application dossier was placed on the Food Standards Agency web-site for public consultation and no comments were received.

2. Clinoptilolite is the geological term for a naturally occurring zeolite aluminosilicate mineral. Clinoptilolite is formed by the devitrification (the conversion of glassy material to crystalline material) of volcanic ash in lake and marine waters millions of years ago. As with other zeolites, clinoptilolite has a cage-like structure consisting of SiO_4 and AlO_4 tetrahedra joined by shared oxygen atoms. The negative charges of the AlO_4 units are balanced by the presence of exchangeable cations – notably calcium, magnesium, sodium, potassium and iron. These ions can be readily displaced by other substances, for example heavy metals and ammonium ions. This phenomenon is known as cation exchange and is the major property of clinoptilolite to be utilised by the applicant. The applicant wishes to market clinoptilolite as a dietary supplement intended to carry out this ion-exchange process in the GI tract thus helping to remove commonly consumed heavy metals such as lead and cadmium from the body.

3. The Medicines and Healthcare products Regulatory Agency were consulted on the status of this product and they were of the view that clinoptilolite is not a medicinal product.

4. Several mineral-derived products are currently permitted in foods in the EU. Many of these are silicate minerals, such as calcium silicate, talc and kaolin that are widely used as additives in the processing of cheese, including pre-packed grated cheese.

5. The application for the authorisation of clinoptilolite was prepared pursuant to Commission Recommendation (97/618/EC) of 29 July 1997 concerning the scientific aspects and presentation of information necessary to support applications for placing on the market of novel foods and novel food ingredients. Clinoptilolite has been classified as a complex novel food ingredient from a non-GM source (class 2.2). This opinion presents the information provided in the dossiers under the schemes outlined in the Commission Recommendation which was considered by the ACNFP in February 2004, but it does not investigate or comment on the perceived nutritional effects that the applicant attributes to the consumption of clinoptilolite.

I. Specification of the novel food

Information on this aspect is provided in the application dossier, p. 6-13

6. Euremica Environmental Ltd. proposes to market clinoptilolite as a novel food ingredient (NI) in food supplements, which will be sold in capsule form. It is proposed that each capsule will contain 250mg of clinoptilolite and 340g of rice flour together with the anticaking agents magnesium stearate (E470b) - 6mg and silicon dioxide (E551) - 6mg. The NI has an approximate empirical formula $(Ca,Fe,K,Mg,Na)_{3-6}Si_{30}Al_6O_{72}.24H_2O$ and CAS number 12173-10-3.

7. Deposits of clinoptilolite can be found throughout the world. The applicant has stated that their NI will be obtained from a single mine in Queensland, Australia. According to the applicant, this deposit is of very high purity and contains very low levels of lead. In addition the applicant proposed to analyse each batch to check the composition. Any batch found to contain an unacceptable level of any element likely to cause harm would be rejected and not used for human consumption.

8. Most elements will be quantified using Inductively Coupled Plasma Mass Spectrometry (ICP-MS). This method is not suitable for elements such as silicon, sulphur and the halogens and these elements will be quantified using other methods, which are described in detail in the dossier, (page 10). Should the applicant be obliged to source their product from another mine, the same stringent tests and safety procedures will be used.

9. Five samples from one batch of clinoptilolite were analysed for elemental content (Table 1 of the dossier, pages 7-9). The low levels of heavy metals in the product suggest that consumers will be are well below the Provisional Tolerable Weekly Intake levels as set by JECFA[1]. The applicant notes that this analysis assumes that all the heavy metals present in clinoptilolite are totally absorbed in the GI tract whereas in reality only low levels of these metals are likely to be solubilised and absorbed through the gut wall.

[1] **JECFA:** the Joint FAO/WHO Expert Committee on Food Additives

10. The applicant stated that they will screen each batch of product before encapsulation for heavy metal content, dioxins, micro-organisms and protein to ensure that the product does not exceed acceptable levels for these impurities. The applicant however, has not indicated what the acceptable levels might be.

Discussion: *The Committee noted that the production process for the NI was basic and raised some concerns over the high silicon content of the NI, which could induce crystalluria in people who are susceptible to renal calculi, and concluded that there was insufficient information regarding the levels of impurities.*

II. Effect of the production process applied to the novel food ingredient

Information on this aspect is provided in the application dossier, p. 13

11. The NI is obtained from Supersorb Environmental NL, who are owners of a mine in Duaringa, Queensland, Australia. The NI is removed from the mine using a bulldozer and transferred to the crushing and screening plant. The rock is crushed and milled to achieve a particle size of 30-50 microns. The clinoptilolite is then bagged and shipped to the UK.

12. The supplement capsules will be manufactured within an approved facility in accordance with Good Manufacturing Practice (GMP) guidelines.

13. The applicant has stated that the production process will not confer any adverse toxicological or microbiological properties to the product. However, as a precaution, the applicant will heat their product to above 100°C to kill any micro-organisms or denature any protein as outlined in section XII. The Applicant will also test each batch for a variety of impurities as outlined in section I.

Discussion: *Members considered the proposed heat treatment of the NI to* 100°C *was insufficient to ensure denaturation of the protein and requested characterisation of the protein present in the NI in order to evaluate potential allergenicity.*

III. History of the organism used as a source of the novel food ingredient

Information on this aspect is provided in the application dossier p. 14

14. The applicant has not supplied information under this heading, noting that clinoptilolite is a mineral. However, the dossier describes previous human exposure to clinoptilolite outside of the EU. As far as the applicant is aware, no adverse effects have been noted from this exposure (Section X).

15. Clinoptilolite is currently used within the EU in drinking water purification, although not in the UK. Clinoptilolite from volcanic and sedimentary sources is authorised in the EU for use as a binder, emulsifier or thickener in animal food for pigs, poultry and rabbits.

Discussion*: Members noted the information provided by the applicant.*

IX. Anticipated intake/extent of use of the novel food ingredient

Information on this aspect is provided in the application dossier p 21-27

16. The applicant intends to use the NI only as a dietary supplement and is not seeking to incorporate the product into any other foodstuffs. The availability of this product will not be restricted geographically and there are no plans to target the product at specific sectors of the public. Based on its established ability to bind heavy metals, the applicant anticipates that the NI will also be purchased by companies who handle toxic and/or radioactive metals or by hospitals and/or public authorities who may wish to stock the NI in case of possible contamination by radioactive materials.

17. The dosage will be four capsules per day, two in the morning and two in the evening; the equivalent of one gram of clinoptilolite per day.

***Discussion**: The Committee noted that the proposed use of clinoptilolite was limited to supplements but considered that the information provided by the applicant on the human consumption of the NI provided insufficient reassurance that the proposed levels of consumption would not be harmful.*

X. Information from previous human exposure to the novel food ingredient or its source

Information on this aspect is provided in the application dossier, p 17-18

18. The applicant has not provided any information pertaining to the sale of dietary supplements containing the NI outside the EU but has supplied details of medicinal products containing clinoptilolite consumed in other parts of the world. In Bulgaria pills and biscuits were prepared for human consumption with added clinoptilolite to help absorb heavy metal radioisotopes present in food after the Chernobyl disaster.

19. Clinoptilolite has also been approved by the Cuban Drug Control Agency as an anti-diarrhoeic drug. The Cuban drug is called Enterex and consists of purified natural clinoptilolite. The applicant has outlined four clinical trials carried out for the Cuban Drug Control Agency. These trials included a dose determination trial and a study consisting of 73 volunteers with acute diarrhoea who were given a dose of 2-6 tablets each containing 900 mg of clinoptilolite every 4 hours. The final two studies involved treatment of over 400 diarrhoea patients with Enterex. No adverse effects of clinoptilolite were demonstrated and no drug interactions were found between Enterex and Tetracycline, Chloramphenicol, Metronidazole and Sulphamethoxazole. A low level of adsorption of aspirin, theophylline, propanolol and phenobarbital was demonstrated. The applicant has not investigated the effect of this product on the efficacy of these drugs but the labelling suggestion they have provided includes a warning about consumption of clinoptilolite when taking medication.

***Discussion:** The Committee considered the information relating to previous human consumption of clinoptilolite as a medicine to be supporting data only, as these uses fall outside the scope of the Novel Foods Regulation (EC) 258/97.*

XI. Nutritional information on the novel food ingredient

Information on this aspect is provided in the application dossier p. 19-22

20. The applicant wishes to utilise the purported ion exchange, heavy metal and mycotoxin binding properties of the NI and have provided studies that they believe demonstrate the adsorption of mycotoxins and heavy metals by clinoptilolite and their subsequent removal from the body.

21. Clinoptilolite has been found to bind only weakly to the essential micronutrients copper, zinc, cobalt and manganese. The applicant is of the opinion that the aluminium present in the product will only be poorly absorbed into the bloodstream, as the product will mostly pass through the body unaltered except for the ion-exchange process.

***Discussion**: Members did not comment on the proposed functionality of the NI as this is outside the scope of (EC) Regulation 258/97. Members were also concerned that the product might affect the absorption and activity of some medicines, nutrients (such as beta-carotene) and gut hormones and requested further data in these areas. Finally, Members would like to see more human studies carried out on the product, in particular to address concerns that the product may remove essential trace elements from the gut. This effect would not be evident in animal studies, as these use standard diets supplemented with trace elements that may be present only at low levels in the human diet.*

XII. Microbiological information on the novel food ingredient

Information on this aspect is provided in the application dossier, p.23

22. Clinoptilolite is an aluminosilicate mineral of volcanic origin, which contains a very low water content and would not be expected to harbour bacterial contamination. The applicant has tested two samples of the NI for microbiological safety and has found that *E. coli*, *S. aureus* and Salmonella were undetectable in both samples. The aerobic colony count and yeast were <10 cfu/g and mould count was 100 cfu/g for one sample and <10 cfu/g for the other. Certificates for the microbiological analysis of the clinoptilolite samples have been provided. As stated in the dossier (page 12), the applicant intends to heat the product to temperatures >100°C before encapsulation to ensure that any micro-organisms present will be killed.

***Discussion**: Members considered that the proposed heat treatment may not be sufficient to kill bacterial spores that may be present in the NI and asked for analyses to be carried out to demonstrate that these were absent from the NI.*

XIII. Toxicological information on the novel food ingredient

Information on this aspect is provided in the application dossier, p.24-25

23. The applicant has provided details of several toxicology studies carried out using clinoptilolite. Apart from the studies on cation exchange, these studies were carried

out on clinoptilolite from other producers.

Exchangeable Cations

24. To demonstrate the low level of exchangeable cations present in the product the applicant has included an *in vitro* study which uses ammonium ions, for which clinoptilolite has a very high affinity, to give the maximal exchange. The table below shows the results obtained for those metals that were present in measurable quantities.

Element	Total quantity in clinoptilolite (% or ppm)	Proportion of element exchanged after exposure to ammonium ions (%)
Sodium	0.39%	50%
Magnesium	0.69%	10%
Aluminium	4.3%	0%
Calcium	2.0%	43%
Titanium	0.21%	0.7%
Manganese	520ppm	0.5%
Strontium	0.11%	35%
Yttrium	32ppm	2.3%
Barium	0.18%	24%
Lanthanum	38ppm	1.8%
Praseodymium	14ppm	3.8%
Neodymium	45ppm	4.3%

25. The table above indicates that elements which are present within the body such as sodium, magnesium and calcium will be most likely to undergo ion exchange within the GI tract and be deposited into the gut whereas only very low levels of metals such as yttrium and lanthanum will be exchanged and deposited within the gut. Levels of exchangeable zinc, cadmium, lead, nickel and copper were below the limit of detection.

Gastric Fluid Extractable Elements

26. A further *in vitro* experiment was carried out using synthetic gastric fluid to quantify key elements that are particularly extractable from the NI in the human stomach. Five replicates were analysed and the results are shown in the table below.

Element	Concentration in gastric fluid on completion of study (mean ± SD)	% extraction *
Antimony	Not detected	-
Mercury	Not detected	-
Cadmium	0.5 ± 0.31ppb	13.9
Chromium	4.1 ± 0.9ppb	2.5
Arsenic	12.5 ± 0.28ppb	15.6

Element	Concentration in gastric fluid on completion of study (mean ± SD)	% extraction *
Copper	19.5 ± 6.1ppb	7.0
Nickel	20.6 ± 1.0ppb	64.4
Cobalt	21.8 ± 0.6ppb	34.1
Titanium	62.5 ± 1.7ppb	0.1
Lead	91.8 ± 8.1ppb	14.8
Zinc	164.7 ± 5.8ppb	15.0
Phosphorus	4.4 ± 0.2ppm	70.0
Silicon	20.2 ± 0.6ppm	0.4
Manganese	4.6 ± 0.1ppm	44.2
Barium	3.7 ± 0.4ppm	10.3
Strontium	5.6 ± 0.2ppm	25.5
Iron	7.4 ± 0.3ppm	2.7
Potassium	6.8 ± 1.0ppm	3.1
Magnesium	30.5 ± 1.0ppm	22.1
Aluminium	147 ± 5.0ppm	17.1
Calcium	158 ± 4.0ppm	39.5

* calculated from the total of each element in the sample, based on previous analysis

27. The table above indicates the levels of elements detectable in the synthetic gastric fluid solution after incubation at 38° for 2 hours. Elements commonly utilised by the body such as calcium, manganese and phosphorus are shown to dissolve in the gastric fluid solution more readily than elements which are not used in the body such as titanium. The table also shows the proportion of the total of each element that has been dissolved in the gastric fluid solution.

Acute, Subchronic and Chronic Toxicology Studies

28. Three studies were performed by Pavelic *et al* (2001): an acute toxicity study (1 month), a sub-chronic toxicity study (3 months) and a chronic toxicity study (6 months). Mice fed 25% clinoptilolite were monitored daily for phenotypic changes, behavioural changes and survival. Body weight changes were monitored on a weekly basis. Food and water consumption levels were checked twice during the study. Haematological and serum clinical chemistry parameters were tested after 1, 3 and 6 months and urine clinical chemistry parameters were tested after each month. Pathohistological analyses were carried out on liver, spleen, kidney, brain, lung, testes, ovary, duodenum, eye, stomach, large and small intestine, muscles, myocardium, pancreas, thymus and axillary lymph node. No statistically significant changes were observed for any of these 3 tests.

29. Pavelic also carried out a similar study on Wistar rats using a variable ratio of cliniptilolite in their diet. The rats were monitored daily, over periods of 1, 3, and 6 months, for phenotypic changes and changes in food consumption, behaviour and survival and every four days were monitored for changes in body weight and water

consumption. Changes in haematological and serum clinical chemistry parameters were tested once a month and pathohistological analysis of liver, spleen, lung, kidney, testes, ovaries, and brain were performed at necropsy. No statistically significant changes were noted for any of these parameters.

Carcinogenicity

30. Carcinogenicity of respirable clinoptilolite particles (5μm) has been investigated in Wistar rats administered intratracheally with single doses of 0, 30 or 60 mg. None of the experimental groups showed a significant increase in the incidence of any specific tumours compared to the corresponding control groups and no positive trend was noted in the occurrence of tumours. Anatomical sites and histopathological characteristics of tumours were similar in control and test groups. The authors of the study were of the opinion that clinoptilolite has no carcinogenic activity in rats when administered intratracheally.

Reproductive and Developmental Toxicity

31. Three separate reproductive toxicity tests have been carried out using a diet of clinoptilolite administered in the diet of rats, mice and pigs.

32. Pond and Yen (1983) concluded that the addition of clinoptilolite to the rat diet at 5% had no apparent adverse effect on growth or reproduction. No evidence of toxicity or teratogenicity was found and the offspring grew normally and reproduced normally.

33. Pavelic *et al* (2001) reported on a study using a diet containing 25% clinoptilolite given for 50 days (males) and at least 14 days (females) before mating. The animals and their offstring were observed through 4 reproductive cycles (4-5 months). The test group had increased litter sizes, which the authors considered was responsible for observed changes in the offspring, which had a reduced gain in body weight until weaning and the higher mortality between days 8 and 21. The authors concluded that there were no adverse effects on reproduction that were attributable to clinoptilolite administration.

34. A reproductive toxicity study (Kyriakis *et al* 2002*)* was carried out on pigs given a diet containing 2% clinoptilolite. No adverse effects were noted in the sows of the experimental group and they showed normal oestrus behaviour during the breeding period. The sows had a slightly improved farrowing rate when compared to the control group. No teratogenic effects were reported.

35. Kyriakis *et al* carried out a further study on crossbred sows fed a diet containing 2% clinoptilolite. This study was carried out for a complete reproductive cycle and a number of serum parameters (P, K, Cu, Zn and vitamins A and E) were monitored. The authors of the study were of the opinion that the administration of clinoptilolite did not significantly change the levels of these parameters, with the exception of a reduction in the levels of vitamin E.

Repeated Dose Dermal Toxicity

36. In a study from Pavelic *et al* (2001) clinoptilolite was applied to the skin of male Wistar rats and male BALB/c mice either as a powder, a mixed neutral cream in a ratio of 1:1 or mixed with paraffin oil at a ratio of 1:1. No dermal toxicity or allergenicity was observed.

Animal Nutrition Applications

37. Several studies have been carried out in animals to investigate agricultural uses for clinoptilolite. The studies suggest that the addition of clinoptilolite to the diets of poultry, pigs and ruminants helps to improve weight gain and feed conversion as well as milk yields. Incidence of scours, enteritis and other intestinal diseases also seemed to be reduced in the test groups when compared to the control groups. No obvious adverse effects were noted and no necropsy was carried out.

38. The applicant has also provided studies that they believe demonstrate that the addition of clinoptilolite into the diet helps to protect the animals from the effects of mycotoxins such as aflatoxins, which are thought to bind to the clinoptilolite and are subsequently excreted from the body. The authors of these studies state that addition of clinoptilolite to animal feed has resulted in measurable improvements in the health of pigs, sheep and chickens.

Zeolite A: Toxicology Studies.

39. The applicant has provided data that relates to zeolite A, a type of synthetic zeolite very similar in structure to clinoptilolite and has many uses in household detergents. No developmental or carcinogenic effects have been observed during studies with zeolite A.

Discussion: *Members noted that the available toxicity studies on clinoptilolite products did not indicate any adverse effects but highlighted that these were primarily acute studies, often with non-oral administration. However, it is anticipated that the NI will be consumed as a dietary supplement on a chronic basis and the Committee considered that the information provided did not provide sufficient reassurance of safety.*

The Committee noted that the majority of studies did not provide information relating to particle sizes of the test materials, but some such as those conducted by Pavelic et al (2001) indicated that the particle size ranged from 1- 3 µm. The Committee considered that further information was needed to confirm the relevance of these studies to the NI, which has a particle size of 30-50 microns

*Also, a paper by Martin-Kleiner et al (2001)[2], not mentioned in the application dossier, reported on the effects of clinoptilolite on hematopoiesis and serum chemistry in mice given 12.5% or 25% in the diet (uniformed particle sizes with an average diameter of 2.68*µm*). The animals were studied at 10-day intervals up to 40 days and the authors*

[2] Martin-Kleiner I, Flegar-Mestric Z, Zadro R, Breljak D, Stanovic Janda S, Stojkovic R, Marusic M, Radacic M, Boranic M. The effect of the zeolite clinoptilolite on serum chemical and hematopoiesis in mice. Food Chemistry Toxicology 39 (2001) 717-727

observed leukocytosis accompanied by bone marrow changes in the treated animals. This effect was attributed to intestinal irritation and inflammation elicited by rough zeolite particles and was less marked when clinoptilolite was administered in a more finely powdered form. The significance of these findings for the clinoptilolite preparation described by the applicant should be determined.

Labelling

40. The applicant has indicated that the label will state the following:

> "Zeolife®, part of the Euremica Environmental range, is a natural supplement that contains micronised zeolite. Taken regularly as part of a balanced diet, it helps to maintain a healthy body.
>
> **Ingredients** Rice Flour, Zeolite, Capsule Shell (Gelatine, Water), Magnesium Stearate, Silicon Dioxide.
>
> **Warning** if you are pregnant, nursing, taking medication or have a medical condition, consult your doctor before taking this product. Discontinue use if you notice any unusual effects. KEEP OUT OF REACH OF CHILDREN
>
> **Directions for use** Swallow four capsules per day with liquid, two in the morning and two in the evening. This container provides 30 days' supply. DO NOT EXCEED THE RECOMMENDED DAILY INTAKE"

Discussion: *The Committee also requested that applicant should either indicate a dose on the label for children or recommend that the product is not suitable for consumption for this population group. Members also noted that advisory warning should be placed on the packaging to address the concerns regarding silicon consumption by individuals who are susceptible to renal calculi (see para 10 Discussion above).*

Overall discussion

41. The risk assessment for the use of clinoptilolite in food supplements cannot be completed, as the information provided by applicant does not offer sufficient reassurance of safety. In particular, the applicant would need to provide additional data to address the concerns highlighted in this opinion.

CONCLUSION

42. The Advisory Committee on Novel Foods and Processes has concluded that, the safety data provided by Euremica Environmental for the approval of clinoptilolite as a novel food ingredient are inadequate and does not support the approval of this novel food ingredient in accordance with Regulation (EC) 258/97.

January 2006