Food Standards Agency
food.gov.uk

Mr Andreas Klepsch
European Commission
By Email

Reference
NFU 699

27 July 2010

Dear Mr Klepsch

INITIAL OPINION: BEE VENOM AS A NOVEL INGREDIENT TO BE ADDED TO HONEY.

Dear Mr Klepsch,

On 19 June 2009, the UK Competent Authority accepted an application from Nelson Honey and Marketing (New Zealand) Ltd. for bee venom as a novel food ingredient to be added to honey, in accordance with Article 4 of Regulation (EC) 258/97. The Advisory Committee on Novel Foods and Processes (ACNFP) reviewed this application and their opinion is attached.

The ACNFP was satisfied that consumption of the fortified honey did not present any general toxicological risk but it identified potential risks from allergic responses.

The ACNFP accepted that strong warning labelling could protect individuals who are allergic to bee venom and are aware of this from previous adverse

reactions to bee stings. However, the Committee was unable to quantify the potential risks relating to

- The risk of immediate and serious allergic reactions, including anaphylaxis, in individuals who are unknowingly allergic to bee venom (for example from sensitisation due to earlier bee stings) and who then become consumers of the novel ingredient.

- The possibility that low oral doses of bee venom may sensitise some genetically susceptible individuals so that they suffer serious allergic responses on later exposure to bee venom, for example via bee stings.

The ACNFP was therefore unable to conclude that venom is safe for consumers.

In view of the ACNFP's opinion, the UK Competent Authority does not consider that bee venom meets the criteria for acceptance of a novel food, as set out in Article 3 (1) of Regulation 258/97. The UK Competent Authority therefore recommends that bee venom is not approved as a novel ingredient in the EU, on the basis that we cannot be certain that the ingredient is safe for all consumers and we cannot identify any additional data that could be generated to remove this uncertainty.

Yours sincerely
(By email only)

Dr Manisha Upadhyay

For the UK Competent Authority

cc Grant MacDonald

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

OPINION ON AN APPLICATION UNDER THE NOVEL FOODS REGULATION FOR BEE VENOM FOR ADDITION TO HONEY

Applicant:	**Nelson Honey New Zealand Ltd.**
Responsible Person:	**Grant MacDonald**
EC Classification:	**2.1**

Introduction

1. An application was submitted to the Food Standards Agency in June 2009 by Nelson Honey New Zealand Ltd. for the authorisation of bee venom as a novel food ingredient. A copy of the application was placed on the Agency's website for public consultation.

2. Venom is harvested from honey bees (*Apis mellifera*) before adding to honey at a concentration of 20 µg/g. The applicant states that honeybee venom helps to relieve arthritic symptoms. The UK regulatory authority for medicinal products (the Medicines and Healthcare products Regulatory Agency) has confirmed that honey with added bee venom would not be regarded as a medicinal product. The marketing of such a product is therefore regulated under food law.

3. The application for authorisation of bee venom 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 the placing on the market of novel foods and novel food ingredients. Bee venom has been classified as a complex novel food from non-GM sources. The source of the novel food has a history of food use in the Community (class 2.1).

I. Specification of the novel food

Information on this aspect is provided on p. 8-11 of the application dossier

4. The applicant states that the composition of venom has been studied extensively and has been found to be reasonably consistent. Relating to the specification for dried venom, the applicant has addressed three main specification parameters, namely the concentrations of melittin (the principal

active component of bee venom) and the enzyme phospholipase $A_{2,}$ which in their view are of the most toxicological significance, and moisture.

Component	Concentration or Activity
Melittin	≤ 45%
Phospholipase A_2	≤ 100 µmol/mg/min
Moisture content	≤ 5%

Discussion*: The Committee noted the applicant's proposed specification for the novel ingredient and expressed concern about the idea of deliberately incorporating a known toxin into food, noting that the efficacy studies described by the applicant did not show sufficiently objectively any clear benefits for consumers (Section XIII.c).*

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

Information on this aspect is provided on p.12-14 of the application dossier

5. Venom is harvested from healthy bees (*Apis mellifera*). The harvesting of venom is achieved by using an electrical milking apparatus which is placed into hives and uses low amperage electrical impulses to stimulate worker bees to sting through a latex film onto a glass collector plate. The applicant proposes that the use of a latex film excludes contaminating substances. Harvested venom is then gently air-dried to a final moisture content of 5% (± 2.0%). Venom is added to a small amount of pre-warmed honey prior to slow addition of this concentrate to the bulk honey and thorough mixing for twenty four hours. The final concentration is 20 µg added bee venom per gram of honey.

Discussion*: A number of public comments were received expressing concern about the welfare of honey bees as a result of venom production and these concerns were also echoed by the Committee. The applicant has confirmed that venom production using an electrical milking apparatus does not confer any harm to bees.*

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

Information on this aspect is provided on p.15-17 of the application dossier

6. The applicant states that although for the purposes of this application, bee venom is intended to be added to honey (20 µg venom per gram of honey), ordinary honey can also contain small amounts of bee venom (see table below):

Honey variety	Bee venom (µg/ml)
Uncreamed Manuka	1.3
Creamed Manuka	1.7
Active Manuka	1.5
Multifloral	1.1

7. The applicant has explained that venom immunotherapy is practised in certain European countries and the US and it is effective in reducing allergic sensitivity (local and systemic) and can result in almost complete protection against allergic reactions from stings.

8. The applicant further states that sublingual immunotherapy (introduction of bee venom under the tongue prior to swallowing) is also used in many European countries.

***Discussion**: Members viewed it inappropriate to use evidence relating to venom immunotherapy (subcutaneous and sublingual) to demonstrate a history of use for bee venom. Members stated that when bee venom is given by subcutaneous injection there is a very high frequency of both local and systemic reactions meaning that bee venom can only be administered under careful supervision with at least one hour's observation after each dose. Members stated that even for sublingual immunotherapy there is a necessity for the first dose and any dose increases to be administered under observation. Therefore, the Committee concluded that the information in this section of the dossier provides a further reinforcement to the main concerns expressed in relation to those with bee venom allergy (Section XIV below).*

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

Information on this aspect is provided on p 18 of the application dossier

9. The applicant suggested that consumers start with ¼ teaspoon per day of honey with added bee venom and increase daily intake to one or two teaspoons per day as required (this information will appear on the product label). The Committee considered that it may be possible for certain individuals to exceed the recommended 20g of honey per day and were also concerned about the possible effects that consumption of honey may have on dental caries. The applicant estimates that two teaspoons are equivalent to 20g of honey with added bee venom, and the maximum consumption of venom would therefore be 400 µg per day. Honey with bee venom is not intended as a general replacement for ordinary table honey and is intended for use by individuals suffering from arthritic conditions.

***Discussion**: The applicant highlighted that honey (particularly Manuka honey) has been reported to reduce dental caries by inhibiting bacterial growth and acid and dextran production. Additionally, the applicant estimates that consumption of the suggested two teaspoons per day of honey with bee venom would provide approximately the same amount of sugar as many individuals would consume in two cups of tea or coffee per day. Members were not convinced by the applicant's response and noted that much of the available literature highlights the cariogenic properties of honey. The Committee advised that honey with bee venom should be labelled as a replacement for other dietary sugars so as not to increase total intake of sugars by consumers, in line with general dietary advice. The Committee additionally did not consider it acceptable to label a foodstuff in the way suggested by the applicant: "consumers start with ¼ teaspoon per day of honey with added bee venom and increase daily intake to one or two teaspoons per day as required".*

X. Information from previous human exposure

Information on this aspect is provided on p.19-20 of the application dossier

10. Honey with venom has been marketed in New Zealand since 1996 and the reported incidence of adverse reactions has been extremely low. Only one report, a case of anaphylaxis, has been solely attributed to bee venom (see Section XIV below).

***Discussion**: The Committee agreed that the reported incidence of adverse reactions during this thirteen year period is low but did express concerns that a more widespread use of bee venom, such as in the EU, may result in an increase in adverse effects. The Committee's comments relating to allergenicity are discussed further in section XIV below.*

XI. Nutritional information on the novel food

Information on this aspect is provided on p.21-22 of the application dossier

11. Venom when added to honey is consumed in very small amounts and is likely to have little or no nutritional value.

***Discussion**: The Committee did not raise any concerns or questions on this aspect of the application. Concerns over the potential increase in sugar consumption are discussed above.*

XII. Microbiological information on the novel food

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

12. The applicant suggests that venom may impart increased antimicrobial properties to honey but has not provided data illustrating levels of any

bacterial spores or vegetative cells in typical batches of venom. The applicant proposes to label the product "*honey should not be given to infants under 12 months of age*". This advice is consistent with that of the Food Standards Agency and many honey products in the UK already carry a similar warning, which is provided on a voluntary basis as a precautionary measure against infant botulism.

***Discussion**: The Committee did not raise any concerns or questions on this aspect of the application.*

XIII. Toxicological information on the novel food

Information on this aspect is provided on p. 4 and p.24-30 of the application dossier

13. Two rodent studies on bee venom (acute and sub-acute) and a human clinical trial were carried out by the applicant. The human study was primarily an efficacy-based study designed to measure the improvement of patients suffering from rheumatoid arthritis and osteoarthritis as a result of consuming honey with bee venom. These studies are summarised below.

(a) Acute toxicity study

14. Forty mice received venom in either a liquid honey or freeze-dried form (0, 5, 50 or 500 mg/kg) by gavage and were observed for 48 hours. The applicant states that no animals showed any signs of overt toxicity and inspection of internal organs did not reveal any abnormalities even at the highest dose tested.

(b) Sub-acute toxicity study

15. Venom (in either honey form or freeze dried form) was dissolved in drinking water to a final concentration of 100 µg/ml. Assuming the mice consume 2 ml water per day, this is equivalent to a daily dose of 200 µg venom or 6.67 mg/kg bodyweight/day for a 30 gram mouse (equivalent to 500 mg/day for a 75 kg human). Mice were allowed *ad libitum* access for three months. The applicant reports that animals gained weight, were observed to behave normally and showed no signs of change in internal organ form or function.

16. The applicant also refers to a published rodent study (Kim *et al*., 2004) where venom was administered by injection to mice, rats and rabbits at doses up to 1000 µg/kg body weight and no significant effects on the central nervous system, blood pressure, heart rate or respiratory rate were observed.

(c) Human study

17. Ninety four patients suffering from osteoarthritis or rheumatoid arthritis were treated in two six week treatment phases, separated by a four week wash out period. Patients took two teaspoons (20g) of honey with bee venom per day, or a placebo consisting of honey without added bee venom. No serious adverse events occurred and minor effects were recorded for seven (7.4%) of the patients (four taking the venom and three taking placebo honey). Skin rash occurred in both active and placebo patients but the overall occurrence of side effects was low and there were no abnormal laboratory findings. The applicant concludes that venom is safe, providing bee and bee product allergy is excluded, and that the side effect profile is similar to the placebo. In terms of efficacy, overall the trial indicated a small improvement only in pain score and only in patients with osteoarthritis.

***Discussion**: Although the evaluation of efficacy is not part of the risk assessment for novel foods, the Committee were not convinced of the proposed ability of bee venom to alleviate symptoms of arthritis (based on the data generated from the clinical study provided by the applicant) and noted that statistical significance in one or two endpoints does not necessarily signify clinical significance especially with such a heterogeneous patient population selected for the trial. The applicant acknowledged that the magnitude of the observed improvement lay within the expected placebo response range and is likely to be of marginal or no clinical significance. The applicant also explained that placebo honey used in the trial may also have contained a low level of bee venom, which could attenuate any positive result for the active product. The applicant highlighted that above all this human study showed that bee venom was safe for patients who are not allergic to bee products and the Committee agreed that the available data did not suggest that the proposed doses of bee venom would result in general toxicity. Allergenicity is discussed below.*

XIV. Allergenicity and labelling

Information on this aspect is provided on p.30 of the application dossier

18. Honey with bee venom has been marketed in New Zealand since 1996, during which time three adverse reaction reports have been made to the NZ Centre for Adverse Reactions Monitoring (CARM). The applicant states that honey with added bee venom is specifically implicated in only one of these three reports, where there is likely to be a strong causal association (the individual had a known allergy to bee products and suffered anaphylaxis after consuming honey with bee venom). In the other two reports a number of other products were co-administered and it was not possible to determine

whether the effects were due to the consumption of honey with added bee venom.

19. The applicant has acknowledged that consumption of venom may pose a risk to individuals allergic to bee products and proposes to manage this risk by appropriate labelling.

***Discussion**: Members expressed substantial concern that the consumption of bee venom has the potential to cause serious allergic reactions, including anaphylaxis as reported in the dossier, and that the dose proposed by the applicant (400 micrograms) is within the range that is associated with significant allergic responses to other ingested allergens. Public comments received during the consultation also expressed concerns relating to potential allergenicity of bee venom.*

The applicant acknowledges that bee venom, used as a food ingredient, has the potential to cause severe allergic reactions in a small proportion of the population and highlights that this also applies to ordinary honey which can naturally contain small amounts of venom. The Committee noted the applicant's view but remained concerned that levels of venom intended to be added to honey will be at least 12 times higher than those found in natural honey varieties (see paragraph 6 above), resulting in a substantial increase in the risk of allergic reactions.

The applicant reported that, since 1996, other bee products such as pollen, propolis and royal jelly have caused more allergic reactions in New Zealand than honey with added bee venom. Additionally, the New Zealand Authorities require these other products to carry mandatory warning labels but warnings are not required for bee venom products. Nonetheless, the applicant has proposed to label honey with bee venom products as "Special Manuka Honey with added bee venom" and to include a prominent statement: "WARNING: people with allergies to honey or bee venom should seek medical advice prior to use". The applicant also proposed that, to reduce the risk of side effects, the label will state: "Directions for use: Start with ¼ teaspoon per day and increase to one to two teaspoons per day as required".

Members considered that as medical advice to those with such allergies would inevitably be not to ingest the product, the applicant's proposed labelling was not appropriate. The Committee concluded that a stronger warning label along the lines "Not to be consumed by those with allergy to honey or bee venom" would be needed. Members viewed this warning to be more concise, clear and simple for consumers.

Members were also concerned that the consumption of bee venom may sensitise previously non-allergic but genetically susceptible individuals to allergens in bee venom.

The Committee advised that concerns relating to sensitisation are unlikely to be resolved by the provision of more data by the applicant and the issue is one of risk management.

The Committee also drew attention to reports of an increased incidence of allergic reactions to insect bites (in particular bee stings), possibly linked to population susceptibility.[1],[2],[3]

The Committee also considered the possibility that the novel ingredient may pose a risk for latex allergic individuals as a result of the carry-over of latex allergens from the production process, in which bee venom is harvested by stimulating worker bees to sting through a latex film onto a glass collector plate. However, the amount of bee venom consumed is likely to be around 0.4mg/day and the amount of latex allergen consumed would be extremely small and unlikely to pose an allergenic risk. In addition, research published by the Food Standards Agency has failed to detect residues of allergens in foods as a result of transfer from latex-containing food contact materials[4].

CONCLUSION

The Committee's main concerns about this novel ingredient were related to allergenicity, as the ingestion of bee venom demonstrably has the ability to cause anaphylaxis in individuals who have previously been sensitised to bee stings.

The Committee agreed that strongly worded warning labelling could minimise the risk to consumers who are aware that they are allergic to bee stings. The Committee was concerned, however, that a proportion of the population with this allergy may be unaware of it (it was noted that it is an uncommon occurrence for

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[1] Liew *et al*., 2009. Anaphylaxis fatalities and admissions in Australia. J Allergy Clin Immunol. 2009 Feb;123(2):434-42.

[2] Sheikh *et al*.,2008. Trends in national incidence, lifetime prevalence and adrenaline prescribing for anaphylaxis in England. J R Soc Med. 2008 Mar;101(3):139-43.

[3] Sheikh *et al*., 2000. Hospital admissions for acute anaphylaxis: time trend study. BMJ. 2000 May 27;320(7247):1441).

[4] http://www.food.gov.uk/science/research/researchinfo/contaminantsresearch/contactmaterials/a03prog/a03projlist/a03056/

most people to be stung by a bee) and warning labelling would not protect these consumers.

Members also noted that the consumption of bee venom may have the ability to sensitise previously non allergic but genetically susceptible individuals to allergens in bee venom and it is unlikely that this uncertainty could be addressed by additional studies.

The Committee therefore concluded its initial assessment of bee venom as an ingredient to be added to honey and stated that it was unable to advise with any certainty that bee venom, used as a food ingredient, is safe for consumers. It was unable to quantify the likelihood of potential risks relating to the two issues described above, namely:

- The risk of immediate and serious allergic reactions, including anaphylaxis, in individuals who are unknowingly allergic to bee venom (for example from earlier bee stings) and who later become consumers of the novel ingredient.

- The possibility that the ingredient may sensitise some genetically susceptible individuals so that they suffer serious allergic responses on later exposure to bee venom, for example via bee stings.

If, notwithstanding this initial assessment by the Committee, bee venom were to be authorised for addition to honey, the Committee remained concerned about the cariogenic properties of honey and that the proposed use of the novel ingredient in honey could lead to an increased risk of dental caries. Therefore, the Committee stated that honey with bee venom would need to be labelled with advice that it should be consumed as a replacement for other sugars, so as not to increase total sugar intake by consumers of the product.

The Committee reviewed the numerous public comments received during the public consultation on its draft opinion. These comments reported the efficacy of bee venom in the management of arthritic symptoms but the Committee emphasised that its remit is to assess novel ingredients for safety and not to provide a judgement on efficacy. The Committee's assessment is carried out in the context of the EU regulation on novel foods (Regulation (EC) 258/97), which requires that any novel food ingredient does not present a danger for the consumer and does not allow for the type of risk/benefit analysis that would be undertaken for a medicinal product.

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