

ADVISORY COMMITTEE FOR NOVEL FOODS AND PROCESSES

BEE VENOM FOR ADDITION TO HONEY

ISSUE

An application has been submitted to the UK Competent Authority for authorisation of bee venom as an ingredient to be added to honey under the novel foods regulation (EC) No 258/97. The Committee is asked to advise whether the available data provide an adequate basis for a safety assessment of this novel ingredient, and if it recommends authorisation of the product.

Background

1. An application has been submitted by Nelson Honey and Marketing (New Zealand) Ltd., for authorisation of venom from the honey bee (*Apis mellifera*) as a novel ingredient to be added into honey, hereafter referred to as venom. The application was accepted by the UK Competent Authority on 19 June 2009. In accordance with Article 6(3) of Regulation (EC) No 258/97, the UK has 3 months to prepare an initial assessment report on the application. The initial assessment will then be circulated for review by the Competent Authorities in the other EU Member States.
2. The application dossier attached at **Annex 1** states that venom is intended to be added to Manuka honey. Manuka Honey is not a novel ingredient and Members are therefore advised to limit their review to bee venom, unless they view the use of honey as the sole food matrix as giving rise to an additional cause for concern.
3. Venom is harvested from bees before adding to honey at a concentration of 20 µg/g. The applicant states that honeybee venom is associated with beneficial effects such as alleviation of the symptoms of arthritis.
4. The present application for authorisation of 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. Venom has been classified as a complex novel food from non-GM source, the source of the novel food has a history of food use in the EU (class 2.1). The requirements for a submission for this class are as follows:

I	Specification of the NF	X
II	Effect of the production process applied to the NF	X
III	History of the organism used as the source of the NF	X
<i>IV</i>	<i>Effect of the genetic modification on the properties of the host organism</i>	-
<i>V</i>	<i>Genetic stability of the GMO</i>	-
<i>VI</i>	<i>Specificity of expression of novel genetic material</i>	-
<i>VII</i>	<i>Transfer of genetic material from GM microorganisms</i>	-

<i>VIII</i>	<i>Ability to survive in and colonise the human gut</i>	-
IX	Anticipated intake/extent of use of the NF	X
<i>X</i>	<i>Information from previous human exposure to the NF or its source</i>	-
XI	Nutritional information on the NF	X
XII	Microbiological information on the NF	X
XIII	Toxicological information on the NF	X

The information presented in the dossier is structured accordingly and is considered below under these schemes.

- The application dossier contains four appendices (A-D). A non-confidential version of the application dossier has been placed on the Committee's website to allow the public to contribute to the assessment. Any comments received will be tabled at the meeting.

I. Specification of the novel food

Annex 1, p 8-11

- The information provided by the applicant on the typical composition of venom is detailed in Annex 1, p 10. Data from compositional analyses are taken from a reference and 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 and phospholipase A₂ which the applicant states are of the most toxicological significance, and moisture content (illustrated in the following table).

Component	Concentration or Activity
Melittin	≤ 45%
Phospholipase A ₂	≤ 100 µmol/mg/min
Moisture content	≤5%

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

Annex 1, p 12-14

- Venom is harvested from healthy bees (*Apis mellifera*). Venom is harvested 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 states that the use of a latex film excludes contaminating substances. The venom is then gently air-dried to a final moisture content of 5% ($\pm 2.0\%$) (Note: there is a slight discrepancy with the above specification value). 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. Venom is added to honey at a final concentration of 20 $\mu\text{g/g}$.

Stability tests

8. The applicant has carried out stability tests and determined the concentration of venom in honey by Western blot analysis and states that data show a small decrease from 100% in the initial product to 94.9% after 1.5 years storage at 20° and 92.4% after 2.5 years. The applicant concludes that venom was stable over this period.

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

Annex 1, p 15-17

9. The applicant states 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.
10. The applicant describes that sublingual immunotherapy (introduction of bee venom under the tongue prior to swallowing) is used in many European countries. Systemic reactions have been reported as being rare, severe adverse events as exceptional and common local side effects as mild and self limiting.

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

Annex 1, p 18

11. The applicant suggests that consumers start with $\frac{1}{4}$ 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 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.

X. Information from previous human exposure

Annex 1, p 19

12. The applicant states that honey with venom has been marketed in New Zealand since 1996 and reported incidences of adverse reactions have been extremely low (see Section XIV below).

XI. Nutritional information on the novel food

Annex 1, p 21-22

13. The applicant has provided nutritional information in the dossier but this relates to honey and is not relevant. The Secretariat notes that venom component is consumed in very small amounts and is likely to have little or no nutritional value.

XII. Microbiological information on the novel food

Annex 1, p 23

14. The applicant states that the microbiological hazards associated with honey with added bee venom are no different from those associated with standard honey except that bee venom may impart increased antimicrobial properties to the product.
15. The applicant has provided a detailed account of various microbiological considerations relating to bacterial spores (*Clostridium* spp. and *Bacillus* spp.) and infant botulism but these relate to honey and not to venom. The applicant intends to label the product as a precautionary measure against infant botulism; as follows "*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.
16. The applicant has not provided data to show levels of any bacterial spores or vegetative cells in typical batches of venom.

XIII. Toxicological information on the novel food

Annex 1, p 25-30

17. The applicant has provided details in the dossier of two rodent studies (acute and sub-acute) commissioned with Auckland University and Nelson Apiaries and these studies are described below.

Acute toxicity study

18. 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 overt toxicity 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.

Sub-acute toxicity study

19. Venom (in either honey form or freeze dried form) was dissolved in drinking water to a final concentration of 100 µg/ml. This concentration was based on an expected water consumption of 2mL/day giving a daily dose of 200 µg venom. For a 30g mouse this is equivalent to 6.67 mg/kg/day (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.
20. The applicant describes a published rodent study (Kim *et al.*, 2004) where venom was administered to mice, rats and rabbits at doses up to 1000 µg/kg bw which the applicant states is 200 fold greater than the effective single clinical dose of 5 µg venom/kg bw when administered by intradermal or subcutaneous route to human patients. The applicant reports that no significant effects on the central nervous system, blood pressure, heart rate or respiratory rate were observed.

Human study

21. The applicant has provided details of a human clinical trial to determine the efficacy of venom in reducing the symptoms associated with rheumatoid arthritis and osteoarthritis. While this can be regarded as an efficacy study, the applicant has drawn out information relating to safety and side effects and presented this in the dossier (Annex 1, p27). A report of this clinical trial is attached as **Annex 4**.
22. 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 the honey with venom per day. Adverse effects were recorded for seven (7.4%) of the patients (four taking the venom and three taking placebo honey). The applicant states that no serious adverse events occurred. 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 states that venom is safe providing bee and bee product allergy is excluded and states that the side effect profile is similar to the placebo.

Lethal dose for bee venom

23. The applicant states that the median lethal dose (LD50) for bee venom has been reported in a number of reports as 2.8 mg venom/kg body weight for intravenous and 3.8 mg venom/kg body weight for intraperitoneal delivery in mice. Assuming a body weight of 75kg, the applicant states that the LD50 is approximately 530 times higher than the daily consumption of bee venom from 20g (two teaspoons) per day of honey with bee venom.

XIV. Allergenicity and labelling

Annex 1, p 30

24. The applicant has provided details of two additional studies that investigate the potency of venom and provide evidence that honey naturally contains venom. The first study used a bioassay to assess the ability of bee venom to induce the release of prostaglandins from a cultured cell line (WISH). The applicant states that honey with bee venom was only slightly more potent than control honey in inducing PGE₂ production. Other honey samples tested were also slightly more potent than the control honey sample. The second study used a liposome assay in which the rate of melittin-induced release of alkaline phosphatase encapsulated in phospholipid micelles (liposomes) was measured through release of a fluorescent product. The applicant states that honey containing venom was similar to or only slightly more potent than the honey control. Full details of these studies are attached as **Annex 3**.

25. Three adverse reaction reports have been made to the Centre for Adverse Reactions Monitoring (CARM) in New Zealand. Two reports were made in 1998 and one in 2005. The applicant states that honey with added bee venom is specifically implicated in only one of these reports and this is likely to reflect a strong causal association (the individual had a known allergy to bee products). In the other two reports a number of other products were co-administered. The applicant has provided a copy of the CARM report data (attached as **Annex 2**).

26. The applicant reports that low levels venom are found naturally in honey as illustrated in the following table:

Honey Variety	Bee venom concentration (µg venom/g honey)
Uncreamed Manuka	1.3
Creamed Manuka	1.7
Active Manuka	1.5
Multifloral	1.1

27. The applicant has acknowledged that consumption of venom may pose an allergenic risk to individuals allergic to bee products and proposes to reduce this risk by providing labelling information.
28. The applicant proposes that honey with venom will be labelled as “*Special Manuka Honey with added bee venom*”. The label will also read “*WARNING: people with allergies to honey or bee venom should seek medical advice prior to use*”. The applicant proposes that, to reduce the risk of side effects, the label will state the following: “*Directions for use: Start with ¼ teaspoon per day and increase to one to two teaspoons per day as required*”.

Consumer access and choice

29. The Secretariat has considered the issues of access and choice in relation to venom. If authorised, the venom would be available for use in products across the UK and subsequently in other EU Member States. In practical terms, access to products containing the venom could be limited by a high price or by limited geographic distribution, which are both driven by commercial considerations that cannot be predicted at this stage.
30. It is envisaged that the introduction of products containing the venom will increase existing consumer choice. The consumer would be aware of the presence of the venom through the ingredient list and, most likely through special marketing that highlights its contribution to the nutrient composition of foods.

COMMITTEE ACTION REQUIRED

31. The Committee is asked whether the available data provide satisfactory basis for evaluating the safety of this novel food ingredient.
32. If so the Committee is asked whether it is content to recommend approval of bee venom as an ingredient to be added to honey.
33. If not, the Committee is asked to indicate what additional data would be required.

**Secretariat
July 2009**

Annexes attached:

Annex 1- Application for the approval of bee venom for addition to honey

The application dossier is available via the ACNFP website www.acnfp.gov.uk

Annex 2- Copy of an apiarist and beekeeper statement for the harvest of honey or other bee products for human consumption.

Annex 3- Toxicological and potency assays as provided by the applicant

Annex 4 – Summary of a random, double-blind, placebo controlled cross-over study in osteoarthritis and rheumatoid arthritis.