

**Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies
on a request from the Commission related to a notification from DSM on
fish gelatine for use as a formulation aid (carrier) in vitamin and carotenoid
preparations pursuant to Article 6 paragraph 11 of Directive 2000/13/EC**

(Request EFSA-Q-2004-121)

(adopted on 2 December 2004)

SUMMARY

Fish is one of the most important allergenic foods, and allergic reactions to fish can be severe. The major allergen of fish is the muscle protein parvalbumin. Gelatine is made by denaturation of collagen. The present application concerns fish gelatine produced from fish skin for use as a formulation aid (carrier) in vitamin and carotenoid preparations.

The information provided by the applicant indicates that the production process of gelatine from fish skins is well standardized. However, no analytical data regarding possible residual levels of the major fish allergen parvalbumin in fish gelatine preparations are provided. Daily fish gelatine intake from vitamin preparations intended for use in food supplements, colourings and beverages is in the low milligram range. Based on vitamin preparations available on the market, a maximum concentration of fish gelatine of 30 mg per litre is estimated, or 7.5 mg per typical 250-mL serving.

There is published evidence that some fish allergic individuals have specific serum IgE reactive with fish collagen and its denatured form gelatine, but only two clinical provocation studies with fish gelatine have been reported. In one single-blind oral provocation study, three patients with IgE reactivity to fish gelatine did not react upon ingestion of 5 g gelatine. In a double-blind placebo-controlled food challenge (DBPCFC) study of 30 patients with clinical allergy to fish, no patient reacted to a cumulative dose of 3.6 g of fish gelatine.

On the basis of the data provided by the applicant, the Panel considers that it is not likely that fish gelatine, under the conditions of use specified by the applicant, will cause a severe allergic reaction in fish allergic individuals.

However, appropriate analytical methods to determine residual levels of parvalbumin in fish gelatine preparations are needed to support the above conclusion. More clinical studies in fish allergic individuals sensitised to fish gelatine are needed to exclude the likelihood of adverse reactions in these individuals.

KEY WORDS

Fish gelatine, carrier, vitamin preparations, carotenoid preparations, food allergy.

BACKGROUND

In November 2003, the European Parliament and the Council adopted Directive 2003/89/EC¹ amending Directive 2000/13/EC, as regards indication of the ingredients present in foodstuffs.

Annex IIIa of the Directive specifies a list of ingredients that are known to trigger allergic reactions or intolerances for which no labelling exemptions are allowed. Whenever the listed ingredients or their derivatives are used in the production of foodstuffs, they must be labelled.

Article 1, paragraph 11 of the Directive establishes a procedure allowing for temporary labelling exemption of derivatives from ingredients listed in Annex IIIa for which it has been scientifically established that it is not possible for them to cause adverse reactions. In accordance with this provision, submissions of request for temporary labelling exemption were notified to the Commission before 25 August 2004. The Commission shall, not later than 25 November 2004, and after consultation with the European Food Safety Authority, adopt a list of those ingredients which shall be temporarily excluded from Annex IIIa, pending the final results of the notified studies, or at the latest until 25 November 2007. Therefore, the European Food Safety Authority is asked to provide scientific opinions on the submissions in accordance with the present terms of reference.

TERMS OF REFERENCE

In accordance with Article 29 (1) (a) of Regulation (EC) N° 178/2002, the European Commission requests the European Food Safety Authority to evaluate the scientific data submitted by DSM Nutritional Products in the framework of the procedure laid down for temporary labelling exemptions in Article 6 paragraph 11 of Directive 2000/13/EC. On the basis of that evaluation, EFSA is requested to issue an opinion on the information provided, and particularly, pending the final results of the studies undertaken, to consider the likelihood of adverse reactions triggered in susceptible individuals by the consumption of the following ingredients/substances used under the conditions specified by the applicant: Fish gelatine for use as a formulation aid (carrier) in vitamin and carotenoid preparations.

ASSESSMENT

1. Manufacturing process

Gelatine is produced by extraction and hydrolysis of fibrous, insoluble collagen from fish skin. The applicant provides information which indicates that for fish gelatine in general there may be considerable variations in the production process, to achieve products with different properties suitable for specific applications. However, for the use specified in the application, the manufacturing process appears to be standardized with most, if not all, gelatine obtained from one producer. According to the applicant, the manufacturing process uses only the skins of edible, food-grade cold water fish such as cod, pollock, haddock, hake, cusk, flatfish and redfish. The skins are supplied as fresh, frozen or salted from approved suppliers. They are washed in large quantities of fresh water with agitation to remove loose scales, flesh, salt, and odour-forming materials, typically for 3 hours or more. Completion of the washing-step is

¹ Directive 2003/89/EC of the European Parliament and of the Council amending Directive 2000/13/EC as regards indication of the ingredients present in foodstuffs. OJ L 308. 25.11.2003, p. 15.

determined by the decrease in conductivity of the discharge water to a set endpoint. After draining, water and acetic acid are added to the skins to reach a defined pH. The acidified water is circulated continuously through the skins and heated to reach a certain temperature, which is maintained until the gelatine solids have been extracted from the skins. The liquor contains between 4-7% gelatine solids. It is transferred to a holding tank and kept at 60°C while a second shorter extraction is performed on the skins to remove any remaining gelatine. The two extractions are then combined and filtered to clarify the gelatine and filter out any particles and traces of fish oil. Soluble salts are removed, and the purified liquor is concentrated to 44-46% solids. The liquid concentrate is blended while hot to ensure batch uniformity.

Dry gelatine is produced by coating a belt with a thin film of liquid concentrate and passing it under infrared heaters. The dried film is thereafter peeled off mechanically, ground and stored in bulk bags. Representative samples are taken during the grinding process and sent to an independent laboratory for testing to comply with specification parameters. Upon approval, bulk bags are blended into lots and packaged. Although the manufacturing process with the main supplier of gelatine appears to have a considerable degree of standardisation, information is also provided which indicates that there is large variation between productions of different fish gelatines, giving the gelatines different properties.

2. Characterisation of the products and their use

2.1 Characterisation of fish gelatine

Gelatine is denatured collagen. Fish gelatine, according to the applicant's statement, is a protein which has an approximate molecular weight of 60,000 Da. The CAS (Chemical Abstract Services) number is the same for all gelatines including fish gelatine: CAS # 9000-70-8. The applicant provides specifications of the product they use, and states that they are in compliance with EU specifications, European Pharmacopoeia, US Pharmacopoeia and Japanese Pharmacopoeia. Fish gelatine can be identified as gelatine by tests as specified in the European Pharmacopoeia.

2.2 Conditions of use and exposure levels

2.2.1 Conditions of use

Under the present application, fish gelatine is used for the micro-encapsulation of oil soluble substances, specifically vitamins A, D, E and carotenoids (e.g. β -carotene, canthaxanthin, lutein, lycopene) to bring the substances into suitable use for incorporation into processed foods like fruit-based beverages (so-called ACE drinks) and multivitamin drinks. Carotenoids are also used as food colours. The encapsulation process is described by the applicant. The products are water-dispersible and the nutrients are bioavailable. The use of fish gelatine as a formulation aid (carrier) in vitamin/carotenoid preparations is protected by a patent owned by DSM Nutritional Products.

2.2.2 Exposure levels

The applicant claims that the amount of fish gelatine in the final products introduced by vitamin and carotenoid preparations is very low and far below the NOAEL (No Observed Adversed Effect Level) observed in a double-blind placebo-controlled food challenge

(DBPCFC) study (see below). The highest amounts of fish gelatine will approximately correspond to the amount of pure active substance present in the preparation, which according to the applicant means that in fortified/coloured foods or beverages the amount of fish gelatine typically will be between 2 and 20 mg/kg. To achieve an orange-coloured soft drink, a maximum of 5 mg/kg of β -carotene is necessary.

Fish gelatine intake calculated on the basis of typical reference values for vitamins - Reference values for nutrition labelling are currently laid down for vitamins and minerals (Council Directive 90/496/EEC). Relevant for this application are reference values for vitamins A (β -carotene), D and E. For a set of product forms listed by the applicant, estimated potential intakes of fish gelatine per day are as follows: 2.0-7.2 mg fish gelatine for vitamin A/ β -carotene preparations, 6.0 mg fish gelatine for vitamin E and 1.5 mg fish gelatine for vitamin D preparations. Based on these calculations, the applicant states that the intake of fish gelatine per day will be far below the claimed NOAEL of 3.6 g (see below).

Fish gelatine intake calculated on the basis of existing products on the European market - German data are used, as this country has the highest consumption of the relevant products and this also is where the highest-dosed products can be found. According to the applicant, ACE and multivitamin beverages contain maximum 20 mg β -carotene per litre (self-limitation of the German industry). The applicant estimates that the maximum concentration of fish gelatine is 30 mg per litre, or 7.5 mg per typical 250-ml serving. An extreme consumption of 1.5 litres per day would result in maximum of 45 mg fish gelatine over the day. Additional calculations based on seven different beverages on the German market give fish gelatine content per 250 mL serving over a range from 6.3 to 7.2 mg/250 mL, which are below the claimed NOAEL. However, it must be taken into consideration that a number of sources may contribute to the total fish gelatine intake.

3. Evidence of non-allergenicity

3.1 History of non-allergenicity of the product

3.1.1 Literature search strategy

No formal literature search is reported by the applicant.

3.1.2 Historical evidence of safe use

The applicant claims that a history of safe use is established. Fish gelatine-containing vitamin and carotenoid preparations have been on the market since 1992. The applicants state their unawareness of any documented report about allergic reactions due to the presence of fish gelatine in the products in question.

It should, however, be mentioned that lack of clear labelling, may be the reason for the absence of reporting as the consumers and health professionals would not be aware of the constituents of the products consumed, and therefore would not have suspected or reported fish gelatine as a cause for an allergic reaction if it occurred.

3.2 *Laboratory-based tests*

3.2.1 *Residual amounts of known fish allergen (parvalbumin) in gelatine*

The major fish allergen is the protein parvalbumin (NDA, 2004), a protein structurally different from collagen and gelatine. At least 14 fish parvalbumins have been described, and mostly they have been isolated from fish muscle. However, there is one report in which parvalbumin was detected in the brain and kidney, and it is uncertain whether parvalbumin has been looked for in fish skin and fish scales. Some minor fish allergens have also been reported.

The applicant claims that parvalbumin is not found in the skin, bones, connective tissue or scales of fish, and further states that “the manufacturer that uses a collagen source with low amounts of meat or removes excess meat will be able to wash the collagen to substantially reduce any allergens”. It is stated that “large fish processors use efficient, mechanical equipment that leave only traces of flesh attached to the skins. Some hand processing is performed in small plants...”. It is argued that since the major income comes from fish fillets, it is economical to leave as little meat as possible attached to the skin. The applicant claims that during washing “the water-soluble allergens are substantially reduced”.

However, no analytical data are provided to support this claim and to indicate what residual levels of parvalbumin can be found in fish gelatine, if any. The allergenicity of fish parvalbumin is not easily destroyed by heat, proteolytic activity or denaturation with chemicals.

3.2.2 *Allergenicity of fish gelatine*

3.2.2.1 *Serological and immunochemical studies of fish collagen and gelatine*

3.2.2.1.1 Collagen and gelatine

Experimental studies (Hamada *et al.*, 2001 and 2003) found that the IgE reactivity of fish collagen was very thermostable and was preserved also in peptide fragments. When collagen was denatured to gelatine by heating in boiling water for 120 minutes, the collagen (gelatine) retained 90% of its original binding ability to the IgE in three human sera (Hamada *et al.*, 2001). Collagen allergenicity must, therefore, be considered in the discussion of gelatine allergenicity.

3.2.2.1.2 Mammalian and fish gelatines

Allergic reactions to mammalian (bovine, porcine) gelatines used in vaccines and medical devices are well documented. Also, a few cases of food allergic reactions to mammalian gelatine can be found in the literature. These cases (Wahl and Kleinhans, 1989; Kawahara *et al.*, 1998; Mullins *et al.*, 1996; Sakaguchi *et al.*, 1996 a and b; Patja *et al.*, 2001) may often be a consequence of sensitisation due to medical applications of gelatine.

Mammalian and fish gelatines have some similarities, and the possibility of allergic cross-reactivity must be considered. Sakaguchi *et al.* (1999) reported a single case of a child with IgE reactivity to fish (salmon and cod) gelatine with no IgE cross-reactivity to bovine gelatine. The absence of serological cross-reactivity between mammalian and fish gelatines is supported by the findings of André *et al.* (2003), Hamada *et al.* (2001 and 2003) and by two cases from the study of Sakaguchi *et al.* (2000) who also demonstrated strong cross-reactivity among fish

gelatines (cod, tuna, saurel, mackarel and salmon). Also Hamada *et al.* (2001 and 2003) concluded that collagen is commonly allergenic and cross-reactive regardless of fish species. Thus, there appears to be little or no IgE cross-reactivity between mammalian and fish collagens, whereas fish collagens from different species appear to be broadly cross-reactive. It seems reasonable to treat fish collagens from different species as one entity. No data have been found regarding cross-reactivity between collagens from different organs (e.g. skin and muscle) from the same species of fish.

3.2.2.1.3 Serological and immunochemical evidence for fish collagen and gelatine allergenicity

Sakaguchi *et al.* (1999) reported a single case of a child IgE reactive to fish (salmon and cod) gelatine. No information was provided with regard to clinical reactivity to fish.

Shiomi *et al.* (1999) investigated the reactivity of sera from five subjects with clinical fish allergy against specimens from nine species of fish. The most significant finding was that the major allergens in Japanese eel and bigeye tuna for two of the subjects were higher molecular weight substances distinguishable from parvalbumins, aggregates of parvalbumin or complexes of parvalbumin with some high molecular weight substance.

Hamada *et al.* (2001) tested sera from eight subjects with a clinical history of immediate hypersensitivity to fish, and identified the high molecular weight allergen detected in bigeye tuna muscle as collagen based on findings with SDS-PAGE, immunoblotting and amino acid analysis. Two sera showed reactivity only to parvalbumin, two sera were almost specific for the high molecular weight allergen, and one serum showed about equal reactivity to parvalbumin and the high molecular weight allergen (collagen). The finding of two sera almost specific for collagen in subjects with clinical fish allergy might suggest that IgE reactivity to fish collagen could lead to clinical fish allergy. However, the clinical significance of collagen as a fish allergen was not tested by oral challenge of fish allergic individuals. Also Yamada *et al.* (1999) and Hamada *et al.* (2000 and 2003) presented immunochemical data indicating that collagen can cause allergic sensitization.

Sakaguchi *et al.* (2000) demonstrated IgE antibodies to fish skin gelatine in three different categories of subjects. Specific IgE to fish gelatine was found in 3/10 patients with fish allergy and specific IgE to fish meat; 2/2 patients with fish meat and bovine gelatine allergy and specific IgE to fish meat and to bovine gelatine; and 5/15 patients with atopic dermatitis and specific IgE to fish meat. All patients with specific IgE to gelatine also had specific IgE to fish meat. This could be due to reactivity against collagen/gelatine which according to the paper comprises up to 12% of the protein in fish meat, or it could be due to concomitant reactivities against different allergens. It is somewhat unclear how several of the gelatines used by Sakaguchi *et al.* were prepared, and therefore also whether they may have been contaminated by fish flesh allergen.

In one study (Hamada *et al.*, 2003) using sera from 15 clinically fish allergic individuals, 10/15 sera demonstrated IgE binding only to parvalbumin, 2/15 demonstrated binding both to parvalbumin and collagen, and also in this study 2/15 sera interestingly showed binding only to collagen. One patient appears to be identical to one of the two donors of sera with almost collagen-specific IgE referred to in the paper cited above (Hamada *et al.*, 2001). One serum did bind to neither parvalbumin nor collagen. However, although the presence of specific IgE is a strong warning sign in relation to the possibility of clinical allergy, it is possible and common to have specific IgE to a particular food without exhibiting clinical symptoms. In addition,

again, there are technical uncertainties, in particular the possibility of contamination of the collagen used with parvalbumin.

It must be emphasised that the presence of IgE-binding to gelatine does not mean that clinical allergy is present, and food challenges with gelatine or collagen were not performed in the studies cited above.

3.3 *Clinical studies*

3.3.1 *DBPCFC (Double-blind placebo-controlled food challenge) study with fish gelatine*

The applicant refers to a DBPCFC study by *Hansen et al.* (2004) with fish gelatine from the same supplier as the one used by the applicant, performed in Denmark.

Patients: Thirty fish allergic patients aged 9 to 50 years were included. All were fish allergic according to the European Academy of Allergology and Clinical Immunology (EAACI) Guidelines. Fifteen patients had reacted in DBPCFC with codfish (no information regarding how long before testing with gelatine), 12 of the remaining patients had experienced “classical systemic type 1 reactions to ingestion of very small amounts of codfish within few weeks to less than 24 months prior to this study”, and the last 3 patients all had experienced “relevant reaction to fish more than two years ago” and “still had a large skin prick test (SPT) to codfish and all had recently experienced rhinoconjunctivitis and asthma due to vapour from preparation of fish meals”. These latter patients considered highly sensitive had not been challenged with fish for ethical reasons.

Protocol: SPT and histamine release tests (HR) were performed with fish gelatine made from codfish skin and with fresh raw codfish. Codfish specific IgE was measured. All patients underwent DBPCFC (seven dose steps increasing from 10 mg to 7 g with a cumulative dose of 14.61 g fish gelatine).

Results: In all 30 patients SPT, HR, and specific IgE to codfish were positive. In SPT with fish gelatine 3/30 were positive, and in HR with fish gelatine 7/30 were positive. One patient showed a mild objective reaction to placebo and no reaction to active substance challenge. Two patients reported mild subjective reactions to active challenge. They were re-challenged, and one patient with positive SPT/HR to fish gelatine and a high level of codfish-specific IgE (477 kUA/L) described subjective symptoms to active challenge with no reaction to placebo, while the other patient experienced mild subjective symptoms to placebo and nothing to active challenge. Thus, one strongly fish allergic patient showed a mild subjective reaction (“irritation in the throat” of which the patient according to the investigators was unsure [1st challenge], and “itching in the mouth” [2nd challenge]) to a cumulative dose of 7.61 g of fish gelatine, but without reappearance of the symptoms with the final dose (cumulative 14.61 g dose) in any of the two challenges. None of the 30 patients reacted adversely to the ingestion of 3.61 g cumulative dose of fish gelatine.

Conclusions: One patient had a confirmed subjective reaction at a cumulative dose of 7.61 g of fish gelatine at DBPCFC, without reaction to the following higher dose. The investigators conclude that the NOAEL for fish gelatine was a cumulative dose of 3.61 g. However, the applicant claims with reference to the study protocol (“reaction to fish gelatine not present at the maximal dose given” to be regarded as “no reactions”) that the NOAEL observed was 14.61 g fish gelatine. Statistically, the results according to the investigators indicate that there is 90%

certainty that 95% of fish allergic consumers will not react to the ingestion of a cumulative dose of 3.61 g of fish gelatine. The applicant claims that “(the) results demonstrate that fish gelatine is unlikely to trigger adverse reactions when used as a formulation aid (carrier) in vitamin and carotenoid preparations”.

3.3.2 *Other clinical studies*

A study by André *et al.* (2003) analysed serum samples from 100 consecutive adults and children (age 1 to 76 years) with documented fish allergy or sensitisation without clinical allergy and tested for IgE antibodies to hydrolysed and non-hydrolysed (gelforming) tuna (yellowfin) skin-derived gelatine, tuna skin, tuna flesh, and bovine and porcine gelatines. In SDS-PAGE and immunoblotting, three of 100 serum samples showed evidence of reactivity to tuna skin-derived gelatine. Pre-incubation of the serum with gelatine, tuna skin or tuna flesh all removed the band corresponding to gelatine in immunoblotting. There was no evidence for cross-reactivity between fish gelatine and the bovine and porcine gelatines. The three patients with IgE binding to tuna skin-derived gelatine had negative skin prick tests for the gelatine, and did not react clinically upon ingestion of 5 g of tuna skin-derived gelatine (single-blind testing with one dose).

3.3.3 *Proposed clinical studies*

The applicant does not indicate any ongoing or planned studies.

CONCLUSIONS AND RECOMMENDATIONS

The information provided by the applicant concerning fish gelatine for use as a formulation aid (carrier) in vitamin and carotenoid preparations indicates that the production process of gelatine from fish skins is well standardized. However, no analytical data regarding possible residual levels of the major fish allergen parvalbumin in fish gelatine preparations are provided.

Daily fish gelatine intake from vitamin preparations intended for use in food supplements, colourings and beverages is in the low milligram range. Based on vitamin preparations available on the market, a maximum concentration of fish gelatine of 30 mg per litre is estimated, or 7.5 mg per typical 250-mL serving.

There is published evidence that some fish allergic individuals have specific serum IgE reactive with fish collagen and its denatured form gelatine, but only two clinical provocation studies with fish gelatine have been reported by the applicant. In one single-blind oral provocation study three patients with IgE reactivity to fish gelatine did not react upon ingestion of 5 g gelatine. In a DBPCFC study of 30 patients with clinical allergy to fish, no patient reacted to a cumulative dose of 3.6 g of fish gelatine.

On the basis of the data provided by the applicant, the Panel considers that it is not likely that fish gelatine, under the conditions of use specified by the applicant, will cause a severe allergic reaction in fish allergic individuals.

However, appropriate analytical methods to determine residual levels of parvalbumin in fish gelatine preparations are needed to support the above conclusion. Clinical studies in fish

allergic individuals sensitised to fish gelatine are needed to exclude the likelihood of adverse reactions in these individuals.

DOCUMENTATION PROVIDED TO EFSA

Dossier submitted by DSM Nutritional Products to the European Commission pursuant to Article 6 Paragraph 11 of Directive 2000/13/EC as amended by Directive 2000/89/EC, on 23 August 2004.

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