FOOD STANDARDS
Australia New Zealand
Te Mana Kounga Kai – Ahitereiria me Aotearoa

1 October 2008
[17-08]

DRAFT ASSESSMENT REPORT

APPLICATION A490

EXEMPTION OF ALLERGEN DECLARATION FOR ISINGLASS

DEADLINE FOR PUBLIC SUBMISSIONS: 6pm (Canberra time) 12 November 2008
SUBMISSIONS RECEIVED AFTER THIS DEADLINE
WILL NOT BE CONSIDERED
(See 'Invitation for Public Submissions' for details)

For Information on matters relating to this Assessment Report or the assessment process generally, please refer to http://www.foodstandards.gov.au/standardsdevelopment/

Executive Summary

Food Standards Australia New Zealand (FSANZ) received an unpaid Application from the Beer, Wine and Spirits Council of New Zealand (BWSCNZ) in 2003 seeking to amend the Table to clause 4 of Standard 1.2.3 – Mandatory Warning and Advisory Statements and Declarations, of the *Australia New Zealand Food Standards Code* (the Code). Specifically, the Applicant is seeking an exemption from the requirement to declare isinglass (a processing aid commonly derived from dried swim bladders of certain tropical and subtropical fish) on the label, when present in beer and wine as a result of its use as a clarifying agent.

The exemption was initially sought on the basis that isinglass has a long history of use as a fining agent in the production of beer and wine and has not been known to cause adverse reactions in susceptible individuals. The Applicant has now provided evidence that dietary exposure to isinglass through beer and wine consumption is extremely low. Results of oral challenge studies have also been provided indicating that isinglass does not cause an allergic reaction to fish sensitive individuals when consumed at levels substantially higher than the potential exposure levels that may be encountered through the consumption of beer and wine. A new isinglass manufacturing protocol designed to minimise the allergen parvalbumin in the final product has also been established.

At Draft Assessment, FSANZ has undertaken a robust and extensive assessment of the public health and safety implications of this Application. A summary of the key risk assessment findings and risk management issues are detailed below. The proposed draft Standard is provided at Attachment 1.

This Draft Assessment Report has been reviewed by an allergy expert, Dr Rob Loblay, Director of the Allergy Unit at the Royal Prince Alfred Hospital in Sydney. Dr Loblay has endorsed the FSANZ preferred regulatory approach.

Risk Assessment

At Draft Assessment, the key risk assessment findings include:

- the three main components of isinglass (collagen, elastin and gelatin) are not major fish allergens;
- parvalbumin is the major allergenic fish protein, and possibly the sole allergen for most individuals with IgE-mediated allergy to fish;
- the levels of parvalbumin in isinglass manufactured using the new protocol has been shown to be extremely low and well below the limit of determination of the analytical method;
- the Code specifies the use of Good Management Practice in regulating the maximum amount of the isinglass which may be present in the food (i.e. beer and wine in this instance);

- a significant amount of isinglass introduced for clarifying purposes in beer and wine is removed allowing only a residual amount of isinglass to remain in these alcoholic beverages;

- parvalbumin co-sediments with isinglass and is unlikely to be present in the bulk of the beer or wine after the completion of the precipitation process; and

- the residual amounts of isinglass that are shown to remain in beer and wine are well below the isinglass dosage used in oral challenge tests that did not provoke an allergic reaction.

Therefore taking into account of all of the above, FSANZ considers that isinglass fined beer and wine are not likely to present a risk of allergic reactions in fish allergic consumers.

The key risk assessment issues are discussed in Section 8 of this Report. Additional information is provided at Attachment 2 – Risk Assessment Report and Attachment 3 – Food Technology Report.

Risk Management

This Draft Assessment Report considers, in the context of the findings from the Risk Assessment, issues relevant to the exemption from the requirement to declare isinglass on the label when present in beer and wine as a result of its use as a clarifying agent, including potential changes to conditions that provide the current high level of safety.

In addition, other issues raised by submitters in response to the Initial Assessment Report have been addressed in this Report. A summary of submissions to the Initial Assessment Report is at Attachment 4.

Preferred Approach

The preferred regulatory approach is to prepare a draft variation to the Table to clause 4 of Standard 1.2.3 to grant an exemption from the requirement to declare isinglass on the label, when present in beer and wine as a result of its use as a clarifying agent.

Reasons for Preferred Approach

FSANZ supports the regulatory approach to grant exemption from the requirement to declare isinglass on the label, when present in beer and wine as a result of its use as a clarifying agent as it:

- does not raise any safety concerns for fish allergic consumers;

- provides fish allergic consumers with increased choice of beer and wine products;

- supports industry with an added choice of clarifying agent that does not require allergen declaration;

- does not undermine provision of adequate information on the product label to make an informed choice by fish allergic consumers; and

- the impact analysis concludes that exemption from the requirement to declare isinglass on the label, when present in beer and wine as a result of its use as a clarifying agent provides a net benefit to affected parties.

Consultation

FSANZ is seeking comment on this Draft Assessment Report from all interested parties, particularly in relation to the expected impact(s) of the preferred regulatory approach. Comments received will assist in the preparation of a Final Assessment, including a recommended regulatory approach to isinglass labelling, when used in beer and wine production.

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INVITATION FOR PUBLIC SUBMISSIONS

FSANZ invites public comment on this Draft Assessment Report based on regulation impact principles and the draft variation to the Code for the purpose of preparing an amendment to the Code for approval by the FSANZ Board.

Written submissions are invited from interested individuals and organisations to assist FSANZ in preparing the Final Assessment of this Application. Submissions should, where possible, address the objectives of FSANZ as set out in section 18 of the FSANZ Act. Information providing details of potential costs and benefits of the proposed change to the Code from stakeholders is highly desirable. Claims made in submissions should be supported wherever possible by referencing or including relevant studies, research findings, trials, surveys etc. Technical information should be in sufficient detail to allow independent scientific assessment.

The processes of FSANZ are open to public scrutiny, and any submissions received will ordinarily be placed on the public register of FSANZ and made available for inspection. If you wish any information contained in a submission to remain confidential to FSANZ, you should clearly identify the sensitive information, separate it from your submission and provide justification for treating it as confidential commercial material. Section 114 of the FSANZ Act requires FSANZ to treat in-confidence, trade secrets relating to food and any other information relating to food, the commercial value of which would be, or could reasonably be expected to be, destroyed or diminished by disclosure.

Submissions must be made in writing and should clearly be marked with the word 'Submission' and quote the correct project number and name. While FSANZ accepts submissions in hard copy to our offices, it is more convenient and quicker to receive submissions electronically through the FSANZ website using the Standards Development tab and then through Documents for Public Comment. Alternatively, you may email your submission directly to the Standards Management Officer at submissions@foodstandards.gov.au. There is no need to send a hard copy of your submission if you have submitted it by email or the FSANZ website. FSANZ endeavours to formally acknowledge receipt of submissions within 3 business days.

Submissions need to be received by FSANZ by 6pm (Canberra time) 12 November 2008.

Submissions received after this date will only be considered if agreement for an extension has been given prior to this closing date. Agreement to an extension of time will only be given if extraordinary circumstances warrant an extension to the submission period. Any agreed extension will be notified on the FSANZ website and will apply to all submitters.

Questions relating to making submissions or the application process can be directed to the Standards Management Officer at standards.management@foodstandards.gov.au.

If you are unable to submit your submission electronically, hard copy submissions may be sent to one of the following addresses:

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Canberra BC ACT 2610
AUSTRALIA
Tel (02) 6271 2222
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INTRODUCTION

In 2003, Food Standards Australia New Zealand (FSANZ) received an unpaid Application from the Beer, Wine and Spirits Council of New Zealand (BWSCNZ) seeking to amend the Code to provide an exemption from the allergen labelling requirements for isinglass when used in the production of beer and wine. BWSCNZ ceased operations in December 2006, and the Application was taken over by the Brewers Association of New Zealand (BANZ). In referring to 'the Applicant' this Draft Assessment Report refers to BWSCNZ for activities prior to December 2006 and BANZ thereafter.

This Draft Assessment Report discusses matters in relation to providing an exemption from the allergen labelling requirements for isinglass, addresses issues raised in submissions to the Initial Assessment Report, and proposes a preferred regulatory approach.

FSANZ is seeking comment on this Draft Assessment Report from all interested parties, particularly in relation to the expected impact(s) of the preferred regulatory approach. Comments received will assist in the preparation of a Final Assessment, including a recommended regulatory approach to isinglass labelling when used in the production of beer and wine.

1. Nature of the Application

1.1 Background to the Application

On 12 August 2002, the BWSCNZ, on behalf of the Brewing Industry of New Zealand wrote to FSANZ requesting that an exemption be granted for isinglass from the mandatory declaration requirements in clause 4 of Standard 1.2.3 – Mandatory Warning and Advisory Statements and Declarations. In the accompanying documentation that was provided to FSANZ, the BWSCNZ requested a permanent exemption, although if this was not possible, a temporary exemption, to allow further scientific evidence to be obtained regarding the non-allergenicity of isinglass.

On 20 September 2002, FSANZ responded to this request, advising that, in the absence of substantial scientific evidence on the relationship between residual levels of isinglass in beer and associated allergenicity, it was not in a position to favourably consider exemptions to the requirements in clause 4 of Standard 1.2.3. However, FSANZ advised that it would consider an application to amend the Standard should further research provide persuasive new evidence in this area.

On 6 January 2003, the BWSCNZ resubmitted the document dated 12 August 2002 and requested that it be considered as an application. It was formally accepted and placed in Group 2 (unpaid) on the FSANZ Work Plan, on 7 February 2003, and estimated to commence in the 4th Quarter 2003.

On 15 October 2003, the Applicant requested that wine also be considered within the scope of their Application. Additionally, the Applicant requested a four-year exemption from the requirement to label for isinglass, in line with the European Commission's proposed amendment to Directive 2000/13/EC.

Under this amendment, the European Commission proposed to consider temporary exemptions from allergen labelling until November 2007, for derivatives of allergens that are unlikely to cause allergic reactions, while awaiting further scientific evidence for a permanent exemption.

On 19 December 2003, FSANZ agreed to expand the scope of the Application to include wine. However, FSANZ did not agree to the request for a temporary exemption and sought further information from the Applicant under subsection 34(1) of the *Food Standards Australia New Zealand Act 1991* (FSANZ Act) (as was in force prior to 1 July 2007). A response to this request was received on 28 June 2004. However, further information provided by the Applicant was considered to be insufficient and a subsequent request for information under subsection 34(1) of the FSANZ Act (as was in force prior to 1 July 2007) was sent in December 2004.

Meanwhile in October 2004, the Applicant provided FSANZ with a copy of the dossier that was submitted to the European Commission by the Brewers of Europe and the Brewing, Food and Beverage Industry Suppliers Association (BE/BFBi) under the requirements of Commission Directive 2003/89/EC. This dossier, titled 'Notification for the temporary exemption from labelling for isinglass used as a clarifying agent in brewing' (the BE/BFBi notification) was used by FSANZ in the assessment of this Application.

On 16 May 2005, FSANZ received further information from the Applicant, and proceeded to the Initial Assessment of Application A490. The Initial Assessment Report for Application A490 was advertised for public comment from 5 October to 16 November 2005. Following an assessment of submitters' comments, together with the information provided by the Applicant, FSANZ concluded that sufficient information was not available to progress the Application to the Draft Assessment stage.

In March 2006, FSANZ requested the Applicant to provide further information under subsection 34(1) of the FSANZ Act. On February 2008, FSANZ received further information from the Applicant, and has now proceeded to the Draft Assessment.

1.2 Basis of the Application

The Applicant is seeking to amend the Table to clause 4 of Standard 1.2.3. Clause 4 of Standard 1.2.3 requires fish and fish products must be declared when present in food as an ingredient, an ingredient of a compound ingredient, a food additive or component of a food additive, or a processing aid or component of a processing aid.

Specifically, the Applicant is seeking an exemption from the requirement to declare isinglass on the label, when present in beer and wine as a result of its use as a clarifying agent. Isinglass is a permitted processing aid commonly derived from dried swim bladders of certain tropical and subtropical fish. A statement such as 'Produced with isinglass (fish product)' is used to declare isinglass on the label. The exemption was initially sought on the basis that isinglass has a long history of use as a fining agent in the production of beer and wine and has not been known to cause adverse reactions in fish allergic individuals.

1.3 Scope of the Application

This Application is specific to the use of isinglass in the production of beer and wine only. Isinglass for the purpose of this Application is defined as a piscine collagen derived exclusively from the dried swim bladder of tropical and sub-tropical fish species for use as a fining/ clarifying agent in beer and wine. Collagen derived from other parts of fish has not been considered in this Application.

1.4 Additional information provided by the Applicant since Initial Assessment

During Initial Assessment in 2005, FSANZ was aware of a number of scientific studies in progress in Europe, USA and Australia aimed at addressing outstanding questions on the allergenic potential of isinglass. Results of these studies have now been made available to FSANZ as detailed below.

In February 2008, the Applicant provided FSANZ with a copy of the dossier that was submitted to the European Commission in October 2006 jointly by the BE and the BFBi in support of a request for an extension of the exclusion from Annex IIIa of Commission Directive 2005/26/EC beyond 25 November 2007, and thus, from the requirement to label isinglass used as a clarifying agent in brewing. This dossier contains analytical studies and clinical trials on isinglass co-ordinated by FARRP (Food Allergy Research and Resource Program), University of Nebraska, USA. Further investigations related to residues of isinglass in beer have been carried out by Brewing Research International.

Additionally in April 2008, the Australian Wine Research Institute and Wine Federation of Australia provided relevant scientific information in relation to the use of isinglass in wine.

These documents have answered the outstanding questions on the allergenic potential of isinglass.

2. The Issue

Currently, clause 4 of Standard 1.2.3 requires that fish and fish products must be declared when present in food as an ingredient, an ingredient of a compound ingredient, a food additive or component of a food additive, or a processing aid or component of a processing aid. This declaration enables fish allergic consumers to be aware of the presence of any potential allergenicity in the food and provides for informed choices.

The exemption was initially sought on the basis that isinglass has a long history of use as a fining agent in the production of beer and wine and has not been known to cause adverse reactions in susceptible individuals. The Applicant has now provided evidence that dietary exposure to isinglass through beer and wine consumption is extremely low. Results of oral challenge studies have also been provided indicating that isinglass does not cause an allergic reaction to fish sensitive individuals when consumed at levels substantially higher than the potential exposure levels that may be encountered through the consumption of beer and wine. A new isinglass manufacturing protocol designed to minimise the allergen parvalbumin in the final product has also been established.

The issue is whether granting an exemption from the requirement to declare isinglass on the label, when present in beer and wine as a result of its use as a clarifying agent can have an impact on the health and safety of fish allergic consumers. That is, are isinglass fined beer and wine likely to present a risk of allergic reactions in fish allergic consumers?

3. Objectives

The specific objectives for the assessment of this Application are to:

- consider the granting of an exemption from the mandatory requirement to declare isinglass on the label;
- ensure the protection of the public health and safety of consumers who are allergenic to fish; and
- ensure product label information provided to fish allergic consumers to make an informed choice is not undermined.

In developing or varying a food standard, FSANZ is required by its legislation to meet three primary objectives which are set out in section 18 of the FSANZ Act. These are:

- the protection of public health and safety;
- the provision of adequate information relating to food to enable consumers to make informed choices; and
- the prevention of misleading or deceptive conduct.

In developing and varying standards, FSANZ must also have regard to:

- the need for standards to be based on risk analysis using the best available scientific evidence;
- the promotion of consistency between domestic and international food standards;
- the desirability of an efficient and internationally competitive food industry;
- the promotion of fair trading in food; and
- any written policy guidelines formulated by the Ministerial Council.

4. Historical Background

The current mandatory declaration requirements in Standard 1.2.3 were developed during the review of the Code, as part of Proposal P161 – Review of Specific Labelling Statements and was gazetted in December 2000. The list of substances included in the Table to clause 4 of Standard 1.2.3 is based on the recommendations of an Expert Panel commissioned by the then Australia New Zealand Food Authority (ANZFA).

To qualify for mandatory declaration, the substance(s) needed to be recognised by medical experts as a frequent cause of severe systemic reactions resulting in significant morbidity or mortality.

The justification for the mandatory declaration requirements in Standard 1.2.3 was based on the requirement to protect the health and safety of those individuals who are susceptible to adverse reactions from certain foods or substances in foods.

Currently, among the substances included in the Table to clause 4 of Standard 1.2.3, the Code grants exemption from mandatory labelling declaration for beer and spirits made using cereals containing gluten.

5. Current Regulations

5.1 Current Domestic Regulations

5.1.1 Australia New Zealand Food Standards Code

Alcoholic Beverages meet the definition for food in the FSANZ Act and are therefore required to comply with the General Food Standards set out in Part 1 of the Code. In addition, beer and wine are further regulated by Part 2.7 – Alcoholic Beverages of the Code and are defined in Standard 2.7.2 and Standard 2.7.4 respectively. The Table to clause 6 of Standard 1.3.3 – Processing Aids, permits Isinglass to be used as a processing aid in food. This Standard defines a processing aid as a permitted substance used in the processing of raw materials, foods or ingredients, at the lowest level necessary irrespective of any maximum permitted level specified, to fulfil a technological purpose relating to treatment or processing, but does not perform a technological function in the final food. The Table to clause 6 of Standard 1.3.3 specifies the use of Good Management Practice (GMP) in regulating the maximum amount of the isinglass which may be present in the food. The relevant GMP criteria are:

(a) the quantity added to food shall be limited to the lowest possible level necessary to accomplish its desired effect;
(b) the quantity that becomes a component of food as a result of its use in the manufacture, processing or packaging of a food and which is not intended to accomplish any physical, or other technical effect in the finished food itself, is reduced to the extent reasonably possible; and
(c) the material is prepared and handled in the same way as a food ingredient.

The Standard in the Code most relevant to this Application is Standard 1.2.3.

Clause 4 of Standard 1.2.3 requires that the presence of fish or fish products in a food must be declared on a label (or declared in connection with the display of food or provided to the purchaser on request when a food is not required to bear a label). This requirement is irrespective of the fish or fish product being used as an ingredient; a compound ingredient; a food additive; or a processing aid.

5.2 Overseas and International Regulations

5.2.1 Codex Alimentarius

The Codex general standard for the labelling of pre-packaged foods [Codex Stan 1-1985 (Rev. 1-1991)] requires the mandatory declaration of substances that are known to cause adverse reactions. The list of substances that are required to be declared includes 'fish and fish products', in addition to other major food allergens. There are no exemptions to these labelling requirements.

5.2.2 United States of America

In the US, the Food and Drug Administration's (FDA) Food Allergen Labelling and Consumer Protection Act of 2004 (FALCPA) applies to most domestic and imported food and beverage products. However, it is the responsibility of the Alcohol and Tobacco Tax and Trade Bureau (TTB) to issue regulations with respect to the labelling of wine, distilled spirits and malt beverages. In July 2006, the TTB proposed mandatory labelling of major food allergens used in the production of alcohol beverages. The proposition of mandatory allergen labelling parallels amendments to the Federal Food, Drug and Cosmetic Act contained in the FALCPA.

These proposed regulations were published as an interim rule which allows producers, bottlers and importers of alcoholic beverages to voluntarily declare the presence of major allergens (including fish and proteins derived from fish). The interim regulations set forth mandatory requirements for how such labelling must be applied should an industry member choose to do so. The purpose of introducing interim regulations was to allow adequate time for consultation on the proposed final regulations whilst encouraging the alcohol beverage industry to introduce allergen labelling alongside the introduction of the FALCPA. The aim of this action was to minimise confusion to consumers who may not realise that alcoholic beverages are not included in the FALCPA.

Notice No. 62 published in the Federal Register of 26 July 2006 proposes that fining agents used in the production of alcohol beverages be labelled in the same way as any other major food allergen. The TTB's rationale for this position is the lack of scientific or clinical evidence to show "virtually no risk" to susceptible individuals. At present the only exemption to the proposed regulations are highly refined oils and ingredients derived from these oils, this is consistent with exemptions in the FALCPA. The proposed regulations and interim rule establishes a petition process (as set out in the FALCPA) through which a food ingredient may be exempt from the labelling requirements if the ingredient does not cause an allergic response that poses a risk to human health or if the ingredient does not contain allergenic protein.

5.2.3 Canada

In February 2004, Health Canada proposed amending the Food and Drug Regulations to enhance allergen labelling requirements on pre-packaged foods for specific allergens. This proposal included the requirement for mandatory labelling of fish by species name. In September 2004, Health Canada amended its original proposal such that fining agents derived from fish, milk and egg, used during the manufacture of standardised alcoholic beverages, would be exempt from the allergen labelling requirements.

This exemption was based on a history of use of such fining agents and the lack of documented clinical evidence of allergic reactions caused by consumption of these products.

Health Canada published its proposed regulatory amendments for allergen labelling (including the exemption from labelling for isinglass and other fining agents) in *Canada Gazette, Part I* in July 2008 to allow for public comment. Any comments received during the 90-day consultation period will be considered before Health Canada publishes the final regulations in the *Canada Gazette, Part II*, this is expected to happen later in 2008. Health Canada has expressed that it may reconsider its position on a labelling exemption for fining agents used in the production of standardised alcoholic beverages should scientific evidence become available suggesting that residues of these substances remaining in the final beverage could cause a health risk to susceptible individuals.

European Union

Commission Directive 2000/13/EC provides for the possibility of an exclusion from the allergen labelling requirement for substances derived from allergenic ingredients, for which it has been scientifically established that such substances are unlikely to cause an adverse reaction in susceptible individuals. As a result, Commission Directive 2005/26/EC granted a temporary allergen labelling exemption for specific derivatives of allergenic ingredients or substances until 25 November 2007. This provisional list of exemptions included 'fish gelatine or isinglass used as a fining agent in beer, cider and wine'.

During the period of this temporary labelling exemption, industry sectors wishing to make an application for a permanent labelling exemption were responsible for submitting research to the European Food Safety Authority (EFSA). EFSA received and considered an application for a permanent labelling exemption for isinglass used as a fining agent in beer and wine production. Based on the consideration of research submitted by the applicant, EFSA then gave an opinion to the Commission regarding the appropriateness of a permanent labelling exemption for isinglass (under specific circumstances of use). In the case of beer, EFSA's opinion was that "it is not very likely that isinglass used as a clarifying agent in beer will trigger a severe allergic reaction in susceptible individuals under the conditions of production and use specified by the applicant". EFSA concluded that there was insufficient evidence to enable a similar assessment for isinglass use in wine production.

The Commission considered EFSA's opinions alongside all other available information relating to derivatives from allergenic processing aids in the production of beer and wine. It was concluded that a permanent exemption from allergen labelling should apply to isinglass used in the production of both beer and wine. Annex IIIa of Commission Directive 2000/13/EC was amended by Commission Directive 2007/68/EC as of 27 November 2007. This amendment stipulates a revised regulatory approach to allergen labelling and includes the requirement that fish and products thereof must be declared on a label except fish gelatine and isinglass used as a fining agent in beer and wine.

5.2.5 Japan

Japan's current allergen labelling requirements became enforceable in April 2002 and divides allergen labelling into two categories, mandatory and recommended, according to the number of cases and degree of seriousness of allergic reactions.

Fish is not included on the list of allergens requiring mandatory labelling (these are eggs, milk, wheat, buckwheat and peanuts) and only specific species of fish (salmon and mackerel) are recommended for allergen labelling. Furthermore, alcohol beverages and related products are not subject to the allergen labelling requirements. Hence labelling of isinglass and other fining agents used in the production of alcoholic beverages is not required in Japan.

5.3 Regulatory differences and its impact

As stated above labelling exemption for isinglass has already been granted in some countries. Therefore beverage manufacturers supplying to these countries may require the maintenance of two labelling strategies to satisfy the requirements of the different markets. This regulatory difference to labelling may have an impact on trade and increase the costs to manufacturers.

6 Matters of Relevance

This section provides summarises of key information extracted from the documents provided by the Applicant, Australian Wine Research Institute, and Wine Federation of Australia to date. Further details of analytical data are provided in the Risk Assessment Report in Attachment 2 and the Food Technology Report in Attachment 3.

6.1 Information on substances relevant to this Application

6.1.1 Isinglass definition used by the Applicant (submission 16 May 2005)

Isinglass is a pure form of collagen, which is derived from the dried swim bladders of certain tropical and subtropical fish. In brewing, only isinglass from catfish, croakers and threadfins is used.

6.1.2 Isinglass definition from the BE/BFBi notification

Isinglass is the usual term for piscine collagen. Within the BE/BFBi notification, the term is used exclusively to mean the collagen obtained from the dried swim bladders and does not include collagen from fish skins. This notification states that the isinglass used in brewing is a pure form of collagen derived from the dried swim bladders of a restricted range of specific tropical and subtropical fish species. These species are specific catfish, croakers and threadfins.

The BE/BFBi notification provides an example of typical specifications for commercial isinglass. The specifications include microbiological and heavy metals as well as protein and moisture parameters. The BE/BFBi notification also addresses metabisulphite, which is added to isinglass paste and liquid formulations as a preservative. The notification states that at the dilutions of isinglass used in beer production, the amount of resulting sulphur dioxide does not reach 10 mg/litre.

6.1.3 Collagen

Collagen is a protein with a molecular weight of approximately 300 kDa and is present in fish muscle, skin and swim bladder. Intact collagen has a triple helical structure stabilised by cross linkages.

Soluble collagen exists mainly as trimers and tetramers with a molecular weight of 800-1300 kDa. The large size of collagen contrasts with known allergenic proteins, which are usually small, compact proteins with molecular weights ranging between 10 kDa and 80 kDa.

Collagen is thermally labile and denatures to gelatin, where the triple helix is unwound to form random coils. Collagen from tropical fish species is most suitable for isinglass production because it remains intact in temperatures up to 29ºC, while collagen from coldwater fish species denatures at about 5ºC.

6.1.4 Parvalbumin

Parvalbumin is identified as the major food allergen associated with isinglass. Parvalbumins have molecular weights of approximately 10-13 kDa, and acidic pI values[1]. Parvalbumins are water soluble and resistant to heat treatment and enzymatic degradation (Aas and Elsayed, 1975 [as cited in Chen et al. 2006]).

6.2 Development of tests to quantify isinglass and parvalbumin

A method has been developed whereby residual isinglass present in fined beers can be concentrated using rabbit polyclonal antibodies raised to pure isinglass. The separated isinglass can then be hydrolysed to its constituent acids and quantified by measuring the content of hydroxyproline, an amino acid characteristic of animal collagens. The limit of detection (LOD) of this method is 0.17 mg isinglass/ L of beer.

Enzyme-linked immunosorbent assay (ELISA) for fish parvalbumin has been used to measure parvalbumin levels in swim bladders, isinglass and beer. Using monoclonal antibody directed against carp parvalbumin, a competitive ELISA has been developed and found to be capable of detecting 0.05 μg/ml of carp parvalbumin (or 1 μg/g).

A further improved method has been developed based on anti-cod parvalbumin polyclonal antibodies to detect parvalbumins from a wider range of fish species. The sensitivity of the anti-cod parvalbumin ELISA has shown to be 0.20 μg/g. However, the measurement uncertainty of this method is considered relatively high.

6.3 Commercial production of isinglass

The swim bladders of tropical and subtropical fish are used to produce isinglass on a commercial scale for use in the alcohol beverage industry. Swim bladder is an air sac, located in the dorsal part of the body cavity quite separate from the fish muscle tissue. The adherence between the bladder and the body cavity is minimal and as such it can be readily detached without significant contamination with the fish muscle tissue which mainly contains the allergen parvalbumin. Results of ELISA test have shown low but variable levels of parvalbumin in unprocessed swim bladders in the range of 7-30 μg/g carp parvalbumin equivalent. These data have also shown variation in parvalbumin levels between species. Approximately 250 tonnes of swim bladders per year are required for the manufacture of isinglass worldwide.

[1] The pH at which the protein is least soluble.

6.3.1 Traditional processing method

The traditional basic production process has been reported to vary between manufacturers, which can also depend on the source and species of the fish. However, a number of steps are considered standard practice. Dried swim bladders are blended according to specific quality and other criteria, followed by granulation, washing, sterilisation with dilute hydrogen peroxide and rinsing. A temperature of less than 15ºC is maintained throughout the wet steps. The product is then sold as powder, paste or liquid. The paste and liquid forms include a source of sulphur dioxide as a preservative.

As a result of the traditional processing method the final parvalbumin levels in isinglass have shown to be reduced by about a half compared to the starting material.

6.3.2 New manufacturing protocol

In 2007, an EFSA scientific panel reported that the traditional manufacturing process did not have a high level of standardisation and as a consequence, the residual levels of the major fish allergen, parvalbumin, may possibly be affected. However, in considering the latest research findings, the three major European manufacturers (AB Vickers, Kerry Bioscience and Murphy & Son Ltd) have come together in developing a common code of GMP for the sourcing and manufacturing of isinglass. This new protocol, which was developed with the aim of reducing the parvalbumin content in isinglass, includes the following additional steps.

- The fish species with high parvalbumin level in the swim bladder have been excluded.

- A granulation stage to ensure that swim bladder wall particle size does not exceed 25 mm has been introduced. This step increases the surface area thus ensuring adequate sterilising during peroxide wash and improving the extent of washing out of the parvalbumin in the subsequent buffer wash.

- Additional washing steps using phosphate buffer and further water washing have been introduced. Phosphate buffer wash has shown to have the greatest effect in reducing parvalbumin levels in samples containing the highest initial parvalbumin levels.

Data presented by the Applicant show that parvalbumin residues in eight samples of commercial isinglass, prepared using the new protocol, are below 1 µg/g. Taking into account the uncertainties associated with the parvalbumin detection methodologies, the concentration of parvalbumin in isinglass prepared using the new protocol could be approximately 4 µg/g.

6.3.3 Products used by the Applicant

Based on the information received from the Applicant nearly 100% of the isinglass used in Australia and New Zealand is manufactured by AB Vickers, Kerry Bioscience and Murphy & Son Ltd using the new manufacturing protocol.

FSANZ has also been made aware of the existence of other European companies who are not manufacturers of isinglass but resellers or blenders of fining agents who source the raw material from the above mentioned manufacturers. In Australia and New Zealand isinglass is predominantly sourced through a local supply network, from the European manufacturers, blenders and resellers.

6.4 Isinglass as a Processing Aid/ Clarifying Agent

6.4.1 History of usage

At Initial Assessment, the Applicant stated that isinglass has been used in the clarification of beer and wine for over a hundred years. The dossier submitted by BE/BFBi in 2004 made a similar statement and, based on a rigorous literature search, concluded that no isinglass-related allergy cases have been reported. A further literature search has been completed by BE/BFBi to identify any reports which might have been published since 2004. No reports of allergenic responses to beer or isinglass by fish sensitive individuals have been found.

A comprehensive literature search has also shown no reports of any adverse reactions to wine ingestion that is attributable to consumption of isinglass.

6.4.2 Usage levels in beer and wine

The rod-like structural integrity of the collagen triple helix was hypothesised to be crucial for efficient clarification (Hickman *et al*., 2000). However, a more popular hypothesis of the fining activity is based upon charge interactions. The isinglass is assumed to electronically attract yeast cells with negatively charged cell wall and other suspended charged polyphenolic and protein components. These aggregated complexes would then settle to the bottom of the container. In the sediment, further interactions may take place resulting in firm sediment that is resistant to disturbance when the clear beverage is drawn off.

The Table to clause 6 of Standard 1.3.3 specifies the use of Good Management Practice in regulating the maximum amount of the isinglass which may be present in the food (i.e. beer and wine in this instance).

In the brewing process isinglass is typically added after fermentation and cooling of the beer. The typical usage level is 15 mg/L for brewery conditioned beer and 35-60 mg/L for cask-conditioned beer. Isinglass is subsequently removed by sedimentation followed by filtration or centrifugation. Cask-conditioned beer does not undergo filtration or centrifugation and relies on gravity settling.

In the wine production process isinglass is added prior to fermentation to remove phenolic compounds from white juice or immediately post fermentation to remove yeast, phenolic and tannin compounds from white wine. The typical usage level is 10-25 mg/L for white wines. It is assumed that isinglass is seldom used in red and rose wines. Isinglass is removed by sedimentation and filtration. The information provided by Australian Wine Research Institute states that a laboratory trial is undertaken on individual batches of wine prior to the addition of isinglass to accurately determine the amount of isinglass to be added so as not to result in an over-fined wine.

6.5 Residues of isinglass and parvalbumin.

The majority of isinglass added to beer and wine for clarification is removed by sedimentation, filtration or centrifugation.

6.5.1 Residues of isinglass and parvalbumin in beer

Results indicate that residual amounts of isinglass in bottled and canned beer are below the limit of detection and where detectable, do not exceed 1 mg/L. For kegs the residues are reported to be up to 3 mg/L and for cask beer, isinglass residues are found to not exceed 5 mg/L.

Since a significant amount of the isinglass added to beer for clarifying purposes is removed, parvalbumin residues in beer are considered too low to measure. Therefore an estimate of potential parvalbumin has been calculated.

Based on this information, parvalbumin levels in beer are calculated to be 0.001 µg/L for bottled and canned beer, and 0.005 µg/L for cask-conditioned beer when using isinglass prepared according to the new protocol. For traditionally prepared isinglass, the levels are estimated to be 10 times higher at 0.01µg/L and 0.05 µg/L for can and cask beer, respectively.

6.5.2 Residues of isinglass in wine

No residual isinglass has been detected in a small sample of commercially available wines fined with isinglass (detection limit 1 mg/L) and made following Good Manufacturing Practice. Therefore it has been concluded that the concentration of isinglass is likely to be less than 1 mg/L. Results of subsequent analysis of isinglass fined wines have supported this conclusion.

6.6 Interaction between parvalbumin and isinglass in beer

Consideration has been given to a situation where a significant proportion of the parvalbumin present in the isinglass could migrate out into the bulk of the beer or wine and be carried through to the final food without undergoing sedimentation and removal. In theory, based on the structure of collagen and the nature of parvalbumin, such a partitioning is not seen as possible due to the following reasons:

- Fish collagen entraps and removes materials such as protein in alcoholic beverages. Therefore it can be expected that the parvalbumin residues present in isinglass would remain entrapped to a certain degree.

- Parvalbumin is not very soluble in acidic conditions. Therefore even if it migrates out into the bulk of the liquid it is very likely to precipitate in wine and beer, which are acidic. The precipitated parvalbumin would then settle with the sediment with isinglass-protein complexes and be filtered out by the filtration processes used to clarify beer and wine.

The above theory has been confirmed with scientific experiments. These are given below:

- Isinglass which was commercially prepared using the old protocol was added to beer at a dose of 36 mg/L (0.36 µg parvalbumin/ L assuming a typical parvalbumin content of 10 µg/g). The concentration of parvalbumin in the sediment was found to be 120 µg parvalbumin/ L using carp ELISA. This shows the segregation of a significant amount of parvalbumin in the beer sediments rather than in the bulk of the beer.

- Three types of beer were fined using isinglass dosed at 10 mg/L, 40 mg/L, and 156 mg/L. The beer was freeze dried, which increased the concentration around twenty-two folds, and tested for parvalbumin. No parvalbumin could be detected in the beer using cod ELISA.

Therefore it can be concluded that under current beer and presumably wine processing conditions, parvalbumin co-sediments with isinglass and is unlikely to be present in the bulk of the beer or wine.

6.7 Toxicological Assessment

Isinglass is a natural product derived from swim bladders of tropical and subtropical fish. FSANZ is not aware of any toxicity concerns related to the use of isinglass as a clarifying agent. The BE/BFBi notification reports that in addition to being a source of isinglass, the fish swim bladders (also known as fish maws) are consumed as food in many parts of the world. More than 2750 metric tons are accounted for by such consumption.

6.8 Allergenicity Assessment

Allergy to fish is well documented in the scientific and clinical literature, including double-blind-placebo-controlled food challenge (DBPCFC) studies. Fish muscle, skin and roe have been reported to cause allergic reactions, the latter only rarely. Fish allergy appears to be common in coastal communities where fish is a major component of the diet, such as Japan and Scandinavia and is more common among adults than children. There are currently no data on the prevalence of fish allergy in the Australian and New Zealand populations.

The major component of isinglass is type 1 collagen and its denaturation product, gelatin. Isinglass also contains small quantities of elastin, a highly hydrophobic, 72 kDa protein. Collagen, gelatin and elastin constitute about 95% of the dry weight of isinglass.

There is some evidence indicating the occurrence of sensitisation to fish collagen in only a small percentage of individuals but the clinical relevance of collagen/gelatin allergenicity has not been shown. There is no evidence to suggest that elastin is allergenic. Therefore, the three main components of isinglass (collagen, elastin and gelatin) are not major fish allergens.

Parvalbumins are the major allergenic fish proteins, and possibly the sole allergens for most individuals with IgE-mediated allergy to fish. They are small, calcium-binding proteins abundant in the muscle tissue of various fish species. One parvalbumin, named Gad c 1, is present in muscle tissue of most fish species. This is why fish sensitised individuals are likely to react to many types of fish.

Isinglass has been shown to be highly susceptible to pepsin digestion in comparison to peanut allergen. As allergenic proteins are generally resistant to pepsin digestion, the susceptibility of isinglass to enzyme digestion would suggest that it is unlikely to be allergenic.

Clinical studies testing the allergenicity of isinglass in fish allergic individuals have also been completed. These studies include skin prick tests and oral challenge tests.

6.8.1 Skin prick testing

Skin prick testing (SPT) provides information about the presence of IgE antibody specific to a given allergen. Although SPT for food allergy is valid, interpretation can be complex and positive tests often occur without clinical allergy (ASCIA-SPT Manual 2006).

Skin prick tests have been performed on 8 fish allergic individuals using flesh and swim bladder extracts of the fish species that are used in the manufacture of commercial isinglass. All eight patients tested were positive when skin tested with fish flesh extracts. Seven of eight patients were positive with fish swim bladder extracts.

A separate study has been conducted in France where six patients with verified fish allergy were challenged with commercial isinglass. Two of the six patients were skin-test positive, but all six patients were negative in the oral challenge test (see below).

These skin prick test results, when considered in conjunction with the oral challenge results conducted on the same patients, do not appear to be clinically relevant. This is because individuals may have allergen-specific IgE which leads to positive skin prick test, but do not react to oral challenge with the same allergen. This is a well-acknowledged and commonly encountered response in food allergy testing.

6.8.2 Oral challenge tests

Controlled oral food challenges are the gold standard in diagnosing food allergy. However, the targeted nature of the recruitment and the strict qualifying criteria, including convincing clinical history, limits the number of subjects available to participate in such studies.

Oral challenges have been conducted using a protocol developed by Food Allergy Research and Resource Program, University of Nebraska, USA to determine whether or not the test samples (isinglass used as a fining agent) can provoke an allergic reaction in fish allergic individuals.

Fish allergic patients were dosed every half an hour with isinglass starting from a low dose and gradually increasing over a period of two hours. The doses used were 0.5, 5, 15 and 30 mg of isinglass in mashed potatoes. In this study, 15 fish allergic patients were tested but none reacted to the oral challenge with isinglass, even at the very highest dose used. Since most of the isinglass is removed from beer or wine through sedimentation and filtration achieving a cumulative dosage of 50.5 mg of isinglass within two hours would require a significant amount of beer or wine to be ingested. Such consumption patterns are uncommon.

Another study was conducted separately in France using isinglass containing 10 µg/g (manufactured using traditional method) parvalbumin which is a typical sample of commercially available isinglass. Six patients with allergy to fish, as determined by oral food challenge or by a convincing clinical history at the time of the study, were included. Each patient received a total of 20 mg of isinglass (three doses of 2, 6, 12 mg), mixed with cooked potato, over two hours. None of the patients had positive reactions to the oral challenge (while two of the six patients showed positive reactions in the skin prick test using the same material).

These two studies, conducted by experts in the field using rigorous protocols, provide supporting evidence that isinglass does not pose a safety concern for fish allergic consumers.

6.9 Dietary Exposure to isinglass from beer

An average drinker of beer may consume about 1.5 L of beer within a single drinking session, while a heavy drinker of beer may consume up to 3 L. Research data show that the dose of isinglass tolerated by fish-allergic individuals in the oral challenge studies far exceeds isinglass levels that may be expected in the volume of beer that could be consumed by an individual within 2 hours.

In light of the normal constraints on the volume that can be consumed by an individual within a few hours, FSANZ considers that potential exposure to parvalbumin through the consumption of beer (and presumably wine) fined with isinglass is likely to be extremely low.

7. Key Assessment Questions

What is the evidence in relation to the allergenicity of isinglass?

What is the level of isinglass residue present in beer and wine? Is there a risk of an adverse reaction occurring in susceptible individuals from this residual isinglass?

What is the potential of parvalbumin partitioning out into the bulk liquid and then being carried into the final product?

RISK ASSESSMENT

8. Risk Assessment Issues

This section assesses the allergenicity of isinglass. The full details of the risk assessment are presented in Attachment 2.

8.1 Allergenicity of isinglass

8.1.1 What is the evidence in relation to the allergenicity of isinglass?

As stated previously, the three main components of isinglass (collagen, elastin and gelatin) are not major fish allergens. Parvalbumin present in isinglass is the major allergenic fish protein, and possibly the sole allergen for most individuals with IgE-mediated allergy to fish. The Applicant has provided the following information:

- There is a long history of safe use of isinglass as a fining agent in the production of beer and wine.

- A comprehensive literature search has been conducted. This literature search shows the absence of published reports of any adverse reaction to wine or beer ingested that is attributable to the consumption of isinglass.

- Twenty-one fish allergic patients have been used in two separate oral challenge tests. In one study isinglass produced using the new protocol has been tested up to a cumulative dosage of 50.5 mg in mashed potato and given to fish allergic patients over two hours. In the other study each patient received a total of 20 mg of isinglass (produced using the old protocol), mixed with cooked potato, over two hours. None of the patients had positive reactions to the oral challenge tests.

- The levels of parvalbumin in isinglass manufactured using the new protocol has been shown to be extremely low and well below the limit of determination of the analytical method.

- This new manufacturing protocol is now widely adopted by the isinglass manufacturers supplying the Australia and New Zealand markets.

These findings suggest that the ingestion of isinglass within the limits specified above (depending on the processing method) is unlikely to pose a risk to fish allergic consumers. The isinglass levels beer and wine drinkers are exposed to are well below these limits.

8.2 Presence of isinglass in beer and wine

8.2.1 What is the level of isinglass residue present in beer and wine? Is there a risk of an adverse reaction occurring in susceptible individuals from this residual isinglass?

- The Table to clause 6 of Standard 1.3.3 specifies the use of Good Management Practice in regulating the maximum amount of the isinglass which may be present in the food (i.e. beer and wine in this instance).

- The typical isinglass usage level is 15 mg/L for brewery conditioned beer and 35-60 mg/L for cask-conditioned beer. In the wine production process the typical isinglass usage level is 10 mg/L to 25 mg/L for white wines.

- The majority of isinglass added to beer and wine for clarification is removed by sedimentation, filtration or centrifugation.

- The results indicate that residual amounts of isinglass in bottled and canned beer are below the limit of detection and where detectable, do not exceed 1 mg/ L. For kegs, the residues are reported to be up to 3 mg/ L and for cask beer, isinglass residues are found to not exceed 5 mg/ L.

- No residual isinglass has been detected in a small sample of commercially available wines fined with isinglass (detection limit 1 mg/L) and made following GMP. Therefore it has been concluded that the concentration of isinglass is likely to be less than 1 mg/L. Results of subsequent analysis of isinglass fined wines have supported this conclusion.

- Since a significant amount of the isinglass added to beer for clarifying is removed parvalbumin residues in beer are too low to measure. Therefore an estimate of potential parvalbumin has been calculated.

- Parvalbumin levels in beer are calculated to be 0.001 µg/L for bottle and can beer, and 0.005 µg/L for cask-conditioned beer using isinglass prepared according to the new protocol. For traditionally prepared isinglass, the levels are estimated to be 10 times higher at 0.01µg/L and 0.05 µg/L for can and cask beer, respectively.

These findings suggest that only a very low amount of isinglass residue remains in beer and wine. These levels are well below the isinglass dosage used in oral challenge tests and therefore provide a reasonable safety margin and are unlikely to pose a risk to fish allergic consumers. The new manufacturing protocol has shown to achieve a further reduction of parvalbumin in isinglass providing a greater safety margin in comparison to the traditionally produced isinglass.

8.3 Potential of parvalbumin partitioning out into the bulk liquid.

8.3.1 What is the potential of parvalbumin partitioning out into the bulk liquid and then being carried into the final product?

If parvalbumin in the isinglass used for fining separates out into the beer or wine and is not sedimented and removed the risk of an adverse reaction occurring in susceptible individuals may increase significantly.

The information provided by the Applicant indicates the following.

- Due to the inherent entrapment property of collagen, it can be expected that the parvalbumin residues present in isinglass would remain entrapped to a certain degree.

- Parvalbumin is not very soluble in acidic conditions. Therefore even if it migrates out into the bulk of the liquid it is very likely to precipitate in wine and beer, which are acidic. The precipitated parvalbumin would then be removed with the rest of the sediments.

The above theory has been confirmed with scientific experiments given below.

- Analysing isinglass (produced using traditional method) fined beer for parvalbumin has indicated a significant concentration of parvalbumin in the beer sediments.

- No parvalbumin could be detected in three types of beer fined using isinglass.

Therefore it can be concluded that parvalbumin co-sediments with isinglass and is unlikely to be present in the bulk of the beer or wine.

In summary a high level of safety is achieved due to the following conditions.

- The new protocol for isinglass manufacturing results in further reduction of parvalbumin.

- The Code specifies the use of Good Management Practice in regulating the maximum amount of the isinglass which may be present in the food (i.e. beer and wine in this instance).

- A significant amount of isinglass introduced for clarifying purposes in beer and wine is removed allowing only a residual amount of isinglass to remain in these alcoholic beverages.

- Parvalbumin co-sediments with isinglass and is unlikely to be present in the bulk of the beer or wine after the completion of the precipitation process.

- The residual amounts of isinglass that are shown to remain in beer and wine are well below the isinglass dosage used in oral challenge tests that did not provoke an allergic reaction.

Therefore taking into account all of the above, FSANZ considers that isinglass fined beer and wine, are not likely to present a risk of allergic reactions in fish allergic consumers.

RISK MANAGEMENT

9. Risk Management Issues

On the basis of FSANZ's risk assessment, the following sections discuss approaches to managing any public health and safety risks in the event of a change in some of the conditions that are currently contributing to a high level of safety. Other broader issues relevant to the exemption from the requirement to declare isinglass on the label, when present in beer and wine as a result of its use as a clarifying agent, and issues raised in submissions have also been discussed.

9.1 Potential changes to conditions that provide the current high level of safety

As specified above the current high level of safety has been achieved due to the cumulative effect of several conditions. However a change to one or more conditions could impact on the level of safety. The new protocol for isinglass manufacturing results in low levels of parvalbumin. This manufacturing protocol is now widely adopted by the isinglass manufacturers which supply the Australia and New Zealand markets. Therefore the safety and quality of the isinglass is not likely to deteriorate. Changes to the remaining conditions are also not likely to happen since it affects the quality of the final product (i.e. beer or wine). FSANZ therefore believes the deterioration of the current high level of safety is not likely to happen as a consequence of potential changes to the conditions mentioned above.

9.2 Issues raised in submissions

During Initial Assessment several arguments were put forward in relation to the Application. The key arguments have been listed and addressed below.

9.2.1 Arguments in relation to safety concerns

The following safety related arguments were put forward.

- Studies into the safety of residual levels of isinglass in beer and wine in fish allergic individuals are incomplete.

- There are no data on the prevalence of fish allergy in the Australian and New Zealand populations and the threshold dose of the allergen for fish allergic individuals is unknown.

- Consumers need to be aware of all sources of allergens in foods, particularly as it is not known how much protein is needed to cause an allergic reaction.

The Applicant has provided a dossier of information addressing the safety concerns related to isinglass. This includes analytical studies determining the residual levels of isinglass and parvalbumin in beer and wine, clinical testing, exposure assessment, and the development of an improved isinglass manufacturing method. This information was originally submitted to the European Commission in October 2006 and was used in the Commission's evaluation process to conclude that a permanent exemption from allergen labelling should apply to isinglass when used in the production of both beer and wine. Even though the data on the prevalence of fish allergy in the Australian and New Zealand populations and the threshold dose of the allergen for fish allergic individuals are unknown, FSANZ is satisfied that the data provided by the Applicant addresses the safety concerns (in the context of the use of isinglass as a fining agent for beer and wine) and enables a decision to be made with regard to this application.

9.2.2 Arguments in relation to current regulations

The following arguments were put forward in relation to the current regulations relevant to this application.

- Standard 1.2.3 should be reviewed so that there is no requirement to declare products of allergens where it can be demonstrated that they do not contain the allergenic protein.

- Possible exemptions from the allergen declaration should be dealt with in a systematic and broader fashion and not through individual applications.

- There is growing body of evidence demonstrating that threshold doses for food allergens are finite, measurable and detectable. The requirement that the presence of allergens be declared even when undetectable leads to consumer confusion and an unnecessarily restrictive diet for allergic consumers.

- Due to the increasing number of disclaimers on food packages, food allergic consumers are questioning the validity of disclaimers, potentially leading to increased risk taking.

FSANZ considers the above raised issues to be outside the scope of this Application. However, at the request of the Australia and New Zealand Food Regulation Ministerial Council (Ministerial Council), FSANZ has commenced a review of the regulatory management of food allergens. The overall aim of the review is to determine whether regulatory and non-regulatory measures are meeting the needs of allergic consumers in a manner that is practical for industry to implement, and that is effective in achieving the objectives of food regulatory measures outlined in the FSANZ Act. A number of issues relevant to the regulatory management of food allergens are being considered. One of the issues being considered as part of this review and relevant to this application is the exemption of non-allergenic ingredients derived from allergenic foods.

FSANZ will consider whether there are other derivatives of foods, which currently require labelling, that are not likely to pose a risk to allergic consumers.

9.2.3 Arguments in relation to provision of adequate information

Further arguments were put forward in relation to the application based on the provision of adequate information to make informed choices. Specifically the following were mentioned.

- Consumers have a right to know what they are consuming. If approval is granted, the ingredient may be replaced with a GM ingredient at a future date and could be exempt from labelling under current GM labelling laws.

- Allowing an exemption for labelling could conceal the non-vegetarian nature of the product.

The available scientific evidence shows that isinglass is not likely to cause an allergic reaction to fish allergic consumers. Therefore the current requirement for mandatory declaration of isinglass on product labels of beer and wine can be considered as not providing accurate information for fish allergic consumers to make an informed choice.

There is no requirement to declare non allergenic processing aids in the label. Specifically, clause 3 of Standard 1.2.4 does not require the declaration of a substance (other than those mentioned in Table to clause 4 of Standard 1.2.3) used as a processing aid in accordance with Standard 1.3.3.

This Application deals specifically with the labelling requirement in the context of the requirement for allergen declaration and therefore the informed choices arguments raised above fall beyond the scope of this Application.

FSANZ is currently considering a separate Application (A545) on vegetarian labelling.

9.2.4 Other arguments specific to isinglass declaration

The submissions specified the following arguments.

- there is little opportunity to enforce the Standard, given the lack of reliable tests for isinglass residues in wine and the lack of significant food safety risk related to this issue; and

- international trade implications due to different labelling requirements.

FSANZ is aware that since the publication of the Initial Assessment Report, isinglass detection methodologies have improved significantly. FSANZ also notes the requirement for the implementation of different labelling regimes specific to isinglass when beer and wine are traded internationally. FSANZ has given due consideration to these issues in considering this application.

10. Options

Two options are presented for addressing this Application:

10.1 Option 1 – Reject the Application

Reject the Application, thus maintaining the *status quo* – this would not allow the exemption from the requirement to declare isinglass on the label when present in beer and wine as a result of its use as a clarifying agent.

10.2 Option 2 – Prepare a draft variation to the Table to clause 4 of the Standard 1.2.3

Prepare a draft variation to the Table to clause 4 of the Standard 1.2.3 for exemption from the requirement to declare isinglass on the label, when present in beer and wine as a result of its use as a clarifying agent.

11. Impact Analysis

11.1 Affected Parties

The parties likely to be affected by this Application and preferred approach include:

- **Consumers** of beer and wine who are allergic to fish;
- **Industry** – Australian and New Zealand manufacturers and importers of beer and wine and isinglass manufacturers and distributors supplying to the Australian and New Zealand markets ; and
- **Government,** including the enforcement agencies of Australia States/Territories and New Zealand.

11.2 Benefit Cost Analysis

The Benefit Cost Analysis assesses the immediate and potential impacts of each regulatory option on the affected parties.

11.2.1 Option 1 – Reject the Application

Under this Option, the *status quo* would be maintained and the Code would not be amended to allow the exemption from the requirement to declare isinglass on the label, when present in beer and wine as a result of its use as a clarifying agent.

11.2.1.1 Benefits and Costs

It is unlikely that maintaining the *status quo* will greatly impact the identified parties. As beer and wine will continue to be produced and consumed in the current environment, there will be no additional benefits or costs to consumers, industry and government.

11.2.2 Option 2 – Prepare a draft variation to the Table to clause 4 of the Standard 1.2.3

11.2.2.1 Benefits

Industry

Granting an exemption from the requirement to declare isinglass on the label, when present in beer and wine as a result of its use as a clarifying agent, would provide the industry with an added choice of clarifying agent that does not require allergen declaration. This provides greater technical flexibility without creating negative consumer perceptions. FSANZ has been made aware that currently the brewing industry does not use isinglass as a clarifier mainly due to the mandatory declaration requirement. Isinglass is considered a clarifying agent superior in functionality. The presence of international trade obstacles due to different labelling requirements may also be eased.

Consumers

Generally, fish allergenic consumers will benefit in terms of increased choice of beer and wine products. Since isinglass is not likely to cause an allergic reaction, exemption from labelling increases the accuracy of product information that is specifically provided to fish allergic consumers. This enhanced accuracy in information and the increase in product choice may also ease the risk taking behaviour of some of the consumers.

Government

The impact on health care expenditure of government is likely to be negligible, since isinglass fined beer and wine, that are exempt from labelling are not likely to present a risk of allergic reactions in fish allergic consumers. There may be further enhancement in consumer confidence in the regulatory system as a consequence of the improved accuracy in labelling information due to the proposed changes. Enforcement agencies may benefit from this increase in consumer confidence. Also, enforcement agencies would no longer require to enforce the mandatory allergen declaration for isinglass.

11.2.2.2 Costs

Industry

As the use of isinglass in beer and wine would be a voluntary choice, no additional costs would be imposed on industry.

Consumers will continue to have a broad choice in terms of quality and price points across the range of beer and wine in the market place.

Consumers

Costs are expected to be neutral to consumers.

Government

Costs are expected to be neutral to government.

11.3 Comparison of Options

Options 1 and 2 would continue to protect the health and safety of allergic consumers of beer and wine clarified using isinglass. Option 2 will provide fish allergic consumers an increased choice of beer and wine products without undermining the provision of adequate information on the product label to enable fish allergic consumers to make an informed choice. This option will also provide the industry with greater technical flexibility.

Overall, a comparison of the options at draft assessment suggests option 2 provides greater net benefit to the affected parties.

COMMUNICATION AND CONSULTATION STRATEGY

12. Consultation

12.1 Public Consultation

The Initial Assessment Report for Application A490 was advertised for public comment from 5 October to 16 November 2005. In response, FSANZ received 20 submissions, with eleven submissions from industry, six from government, and three from consumers. A summary of these submissions is at Attachment 3.

Overall, eleven of the submitters provided support for the exemption, six objected to providing an exemption and one did not provide a preferred option. Out of the remaining two submitters, one indicated cautious support awaiting results of safety assessment. The other indicated support based on a condition that only isinglass derived from the swim bladders of (tropical and subtropical) fish should be exempt.

All the key issues raised in submissions to the Initial Assessment Report are addressed in the main body of this Report.

FSANZ is now seeking further public comment through this Draft Assessment Report to assist in undertaking a Final Assessment of this Application.

12.2 World Trade Organization

As members of the World Trade Organization (WTO), Australia and New Zealand are obligated to notify WTO member nations where proposed mandatory regulatory measures are inconsistent with any existing or imminent international standards and the proposed measure may have a significant effect on trade.

There are relevant international standards and amending the Code to grant exemption from the requirement to declare isinglass on the label, when present in beer and wine as a result of its use as a clarifying agent is unlikely to have a significant effect on international trade as the proposed permission has already been granted in some international markets and products with similar allergen labelling exemption are marketed internationally.

Therefore at Draft Assessment, FSANZ does not consider it necessary to notify WTO member nations of the proposed amendment under either the Technical Barriers to Trade or the Sanitary and Phytosanitary Agreements.

13. Communication Strategy

FSANZ does not intend to undertake specific communication strategies outside of the two statutory public consultation periods. Initial feedback indicates general support from fish allergic consumers and the food industry for the proposed exemption. Any concerns raised by stakeholders have been assessed and risk management strategies identified, as required.

CONCLUSION AT DRAFT ASSESSMENT

14. Conclusion and Preferred Approach

Preferred Approach

At Draft Assessment, the preferred regulatory approach is to prepare a draft variation to the Table to clause 4 of Standard 1.2.3 to grant an exemption from the requirement to declare isinglass on the label, when present in beer and wine as a result of its use as a clarifying agent.

FSANZ supports the preferred regulatory approach to grant exemption from the requirement to declare isinglass on the label, when present in beer and wine as a result of its use as a clarifying agent as it:

- does not raise any safety concerns for fish allergic consumers;
- provides fish allergic consumers with increased choice of beer and wine products;
- supports industry with an added choice of clarifying agent that does not require allergen declaration;
- does not undermine the provision of adequate information on the product label for fish allergic consumers to make an informed choice; and
- the impact analysis concludes that exemption from the requirement to declare isinglass on the label, when present in beer and wine as a result of its use as a clarifying agent provides a net benefit to affected parties.

The amended Standard to provide the exemption from the requirement to declare isinglass on the label, when present in beer and wine as a result of its use as a clarifying agent is at Attachment 1.

The Draft Assessment Report has been reviewed by an allergy expert, Dr Rob Loblay - Director Allergy Unit at the Royal Prince Alfred Hospital in Sydney. Dr Loblay has endorsed the FSANZ preferred regulatory approach.

15. Implementation and Review

Following the consultation period for this Report, a Final Assessment of the Application will be completed and considered for approval by the FSANZ Board. The FSANZ Board's subsequent decision on the draft variation to the Standard will then be notified to the Ministerial Council.

Following notification, the proposed draft Standard is expected to come into effect on gazettal, subject to any request from the Ministerial Council for a review of FSANZ's decision.

ATTACHMENTS

1. Draft variation to the *Australia New Zealand Food Standards Code*
2. Risk Assessment Report
3. Food Technology Report
4. Summary of Submissions to the Initial Assessment Report

Attachment 1

Draft Variation to the *Australian New Zealand Food Standards Code*

Standards or variations to standards are considered to be legislative instruments for the purposes of the Legislative Instruments Act (2003) and are not subject to disallowance or sunsetting.

To commence: on gazettal

[1] ***Standard 1.2.3*** *of the Australia New Zealand Food Standards Code is varied by omitting from the* Table to clause 4, *the entry for* Fish and fish products, *substituting* –

Fish and fish products, except for isinglass derived from swim bladders and used as a clarifying agent in beer and wine.

Attachment 2

Risk Assessment Report

Definition: Isinglass is a processing aid derived from the swim bladder of tropical and sub-tropical fish species for use as a fining/ clarifying agent.

Risk Assessment

1. General

1.1 Fish allergy - parvalbumin

Allergy to vertebrate fin fish is well documented in the scientific and clinical literature, including double- blind placebo-controlled food challenge (DBPCFC) studies. Fish muscle, skin and roe have been reported to cause allergic reactions, the latter only rarely (Sicherer et al., 2000; Escudero et al., 2007). Allergic reactions to the consumption of fish/fish products may include life-threatening anaphylaxis. Fish allergy reportedly affects 0.4% of the US adult population (Sampson, 2004); but there are currently no data on the prevalence of fish allergy in the Australian and New Zealand adult population.

Parvalbumins are a class of calcium-binding proteins found at highest concentration in fast contracting/ relaxing muscle fibres of vertebrates. In fish, parvalbumins are generally associated with skeletal muscle. Parvalbumins have molecular weights of approximately 10-13 kDa, and acidic pI values[2]. Parvalbumins are water soluble and resistant to heat treatment and enzymatic degradation (Aas and Elsayed, 1975-[as cited in Chen et al. 2006]).

Parvalbumins are the major allergenic fish proteins, and possibly the sole allergens for most individuals with IgE-mediated allergy to fish. Parvalbumin is the major allergen in several fish species including cod, salmon, carp, mackerel and tuna. Parvalbumin sequences from commonly consumed fish species are highly homologous. This would indicate a high likelihood of IgE cross-reactivity to a range of fish species for at least some fish-allergic individuals (Swoboda et al., 2002; Hilger et al., 2004; Van Do, 2005).

There is limited information on the potential allergenicity of fish collagen. In a double-blind, placebo-controlled food challenge (DBPCFC) study, a mild, subjective reaction was reported by one out of 30 fish-allergic patients given 7.6 g codfish skin gelatine (Hansen et al., 2004).

1.2 Fish swim bladder – anatomical location and tissue composition

The swim bladder is an air sac located in the dorsal part of the body cavity of most fish species. As such, it can be readily detached without significant contamination with the fish muscle tissue. The swim bladders from certain tropical and sub-tropical fish species are used to prepare commercial isinglass.

The major component of isinglass is type 1 collagen and its denatured product, gelatin. Isinglass also contains small quantities of elastin, a highly hydrophobic, 72 kDa protein. Collagen, gelatin and elastin constitute about 95% of the dry weight of isinglass.

[2] The pH at which the protein is least soluble.

There is no evidence to suggest that elastin is allergenic and, as mentioned above, the clinical relevance of collagen/gelatin allergenicity has not been shown.

Collagen is a protein with a molecular weight of approximately 300 kDa and is present in fish muscle, skin and swim bladder. The fish swim bladder is the source of collagen, known commercially as isinglass. Intact collagen has a triple helical structure stabilised by cross linkages. Soluble collagen exists mainly as trimers and tetramers with a molecular weight of 800-1300 kDa. The large size of collagen contrasts with known allergenic proteins, which are usually small, compact proteins with molecular weight ranging between 10 kDa and 80 kDa.

Collagen is thermally labile and denatures to gelatin, where the triple helix is unwound to form random coils. Collagen from tropical fish species is most suitable for isinglass production because it remains intact in temperatures up to 29ºC, while collagen from coldwater fish species denatures at about 5ºC. There is no evidence that gelatin is a clinically important allergen in fish-allergic individuals.

1.3 The hazard and the risk

For fish-allergic consumers, fish parvalbumin is the relevant allergen of significance i.e. the hazard. The FSANZ risk assessment process considers that the hazard is the potential to cause an adverse reaction and the risk is the likelihood of the adverse reaction actually occurring within the conditions of exposure. In the context of this Application, the overall risk to fish allergic consumers is dependent on the level of exposure to parvalbumin through the consumption of isinglass-fined beer and wine.

2. Beer-related data

Information in this section is mainly extracted from documents provided by the Applicant to FSANZ in 2008 (originally submitted by the Brewers of Europe and the Brewing, Food and Beverage Industry Suppliers Association to EFSA in 2006).

2.1 Analytical methods used in beer studies

2.1.1 Isinglass detection

A method has been developed whereby residual isinglass present in fined beers can be concentrated using rabbit polyclonal antibodies raised to pure isinglass. The separated isinglass can then be hydrolysed to its constituent acids and quantified by measuring the content of hydroxyproline, an imino acid characteristic of animal collagens. The limit of detection (LOD) of this method is 0.17 mg isinglass/ L of beer. Information provided by the Applicant indicates this method was used to quantify the concentration of isinglass residues which could be present in beer.

2.1.2 Parvalbumin detection

Enzyme-linked immunosorbent assay (ELISA) for fish parvalbumin was used to measure parvalbumin levels in swim bladders, isinglass and beer. Using monoclonal antibody directed against carp parvalbumin, a competitive ELISA was developed and found to be capable of detecting 0.05 µg/ml of carp parvalbumin (or 1 µg/g).

An improved method was developed based on anti-cod parvalbumin polyclonal antibodies which would have broader specificity to detect parvalbumins from a wider range of fish species. The ELISA is specific for parvalbumin and does not substantially cross-react with common food ingredients. The sensitivity of the anti-cod parvalbumin ELISA was shown to be 0.20 µg/g. However, using the sandwich ELISA to measure parvalbumin levels in isinglass samples suggests the possibility of matrix inhibition of 2 to 4 fold. Therefore, quantitative estimates of parvalbumin levels need to take this into account.

2.2 Parvalbumin in fish swim bladder and in isinglass preparations

Although parvalbumin is not a major component of the swim bladder, it has been identified in the swim bladder tissue of a western Atlantic fish (*Opsanus tau* or the oyster toadfish), a species not used in isinglass production. This information raised the question whether parvalbumin may also be present in the swim bladders of some fish species that are used in the commercial production of isinglass. The Applicant provided analytical data on parvalbumin levels in eight isinglass samples from three commercial manufacturers. Using the anti-cod parvalbumin ELISA, six samples were below 10 µg/g, one sample at 34µg/g and one below 1 µg/g. Various levels of parvalbumin were detected in the swim bladder of seven fish species. According to this information, it is possible to minimise the level of parvalbumin in isinglass by identifying and eliminating fish species with high levels of parvalbumin.

Parvalbumin is soluble in water and dilute salt solutions, at neutral or slightly alkaline pH, making it possible to further minimise residual levels of parvalbumin in isinglass by incorporating a washing step in the manufacturing process. The Applicant provided analytical data which indicates that significant reduction of residual parvalbumin in isinglass is achieved after washing with a phosphate buffer. The effect of different washing procedures on parvalbumin levels was tested. The most effective washing process appears to reduce parvalbumin level by about four-fold.

To ensure minimum parvalbumin content in isinglass, the Applicant indicated that a new Code of Good Manufacturing Practice (GMP) for the manufacture of isinglass low in parvalbumin has been developed and agreed by the industry. However, it is not clear how widely the new GMP is adopted by isinglass manufacturers world-wide. The new GMP Code incorporates an additional washing step using phosphate buffer, the introduction of a sieving step in the granulation stage to ensure that swim bladder wall particle size does not exceed 25 mm, and the exclusion of fish species with high parvalbumin levels in the swim bladder. Data presented by the Applicant shows that parvalbumin residues in eight samples of commercial isinglass, prepared using the new GMP, are below 1µg/g.

2.3 Residues of isinglass and parvalbumin in fined beer

Information provided by the Applicant states that residual amounts of isinglass in bottle and can beer are below the LOD and where detectable, do not exceed 1 mg/ L. For keg and cask beer, isinglass residues are at 3 - 5 mg/ L.

Experiments were conducted using ELISA methods in order to determine whether detectable parvalbumin remained in the fined beer. Samples of beer fined with isinglass, containing various levels of parvalbumin, was freeze-dried and tested. Data provided indicates that no parvalbumin could be detected in the beer samples, which included lager and cask ale.

Theoretical calculations suggest that parvalbumin levels would be below the level of detection of the ELISA method used in these tests.

Since parvalbumin residues in beer are too low to measure, the Applicant provided an estimate of potential parvalbumin based on the following information:

- The dose of isinglass during fining is 50 mg/L. This is around the highest dose which would be used commercially for cask beers and is 2-3 times higher than the dose used for most brewery-conditioned beers.
- Residual levels of isinglass in beer, when detectable, range from 1 mg/L for can and bottle beer to 5 mg/L for cask beer. Even in cloudy beer, the level is not reported to exceed 5 mg/L.
- Residual parvalbumin in commercial isinglass products currently on the market (old protocol) is 10 µg/g (cod equivalent) on a dry weight basis.
- Residual parvalbumin in commercial isinglass products using the new GMP protocol is 1µg/g.
- Parvalbumin most likely co-sediments with isinglass residue and does not partition into the fluid part of the beer (see section 2.4 below).

Based on this information, parvalbumin levels in beer are calculated to be 0.001 µg/L for bottle and can beer, and 0.005 µg/L for cask-conditioned beer using isinglass prepared according to the new protocol. For traditionally prepared isinglass, the levels are estimated to be 10 times higher at 0.01µg/L and 0.05 µg/L for can and cask beer, respectively. These estimated levels of parvalbumin are considered, together with oral challenge studies, in the exposure assessment.

2.4 Parvalbumin levels in beer sediments

Parvalbumin is soluble in water and dilute salt solutions at neutral and alkaline pH. Data provided by the Applicant indicates that the level of parvalbumin in isinglass can be minimised by washing in buffer solution. For any residual parvalbumin, which is not eliminated from isinglass, there are two potential scenarios. Parvalbumin residues would either end up in the sediment or in the fluid. In the acidic environment of beer brewing, parvalbumin would be expected to precipitate with the isinglass to form the sediment. Analytical data provided by the Applicant suggests this to be the case.

Isinglass commercially prepared using the old protocol (which assumes a typical parvalbumin content of 10 µg/g as determined by cod parvalbumin ELISA) was added to beer at a dose of 36 mg/L (0.36 µg parvalbumin/ L) of beer. The sediment was collected and tested for parvalbumin content using the cod parvalbumin ELISA. The results suggest that parvalbumin content in isinglass is concentrated in the sediment and therefore, is unlikely to be present in the clear portion of the beer.

2.5 Clinical testing

2.5.1 Skin prick tests

Skin prick testing (SPT) provides information about the presence of IgE antibody specific to a given allergen. Although SPT for food allergy is valid, interpretation can be complex and positive tests often occur without clinical allergy (ASCIA-SPT Manual 2006).

The Applicant provided information on skin prick tests performed using extracts from a number of the fish species that are used in the manufacture of commercial isinglass. Flesh and swim bladder extracts were prepared from six fish species, and checked for microbial contamination to eliminate false positive due to non-allergic inflammation. SPT was performed on 8 fish allergic individuals according to a protocol developed at the Food Allergy Research and Resource Program (FARRP). Samples of blood are also taken from the individuals and tested for IgE antibodies to fish. All eight patients tested were positive when skin tested with fish flesh extracts. Seven of eight patients were positive with fish swim bladder extracts.

Information was also provided by the Applicant on a separate study conducted in France where six patients with verified fish allergy were challenged with commercial isinglass. Two of the six patients were skin-test positive, but all six patients were negative in the oral challenge test (see below).

These skin prick test results, when considered in conjunction with the oral challenge results conducted on the same patients, do not appear to be clinically relevant. This is because individuals may have allergen-specific IgE which leads to positive skin prick tests, but do not react to oral challenge with the same allergen. This is a well-acknowledged and commonly encountered response in food allergy testing.

2.5.2 Oral challenge tests

Controlled oral food challenges are the gold standard in diagnosing food allergy. However, the targeted nature of the recruitment and the strict qualifying criteria, including convincing clinical history, limits the number of subjects available to participate in such studies.

In the context of this Application, oral challenges are conducted to determine whether or not the test samples (isinglass used as a fining agent) can provoke an allergic reaction in fish allergic individuals.

A protocol for DBPCFC tests were developed by FARRP using isinglass prepared according to the new protocol. Fish-allergic patients were dosed every half an hour with isinglass starting from a low dose and gradually increasing over a period of two hours. The doses used were 0.5, 5, 15 and 30 mg of isinglass in mashed potatoes. In this study, 15 fish allergic patients were tested but none reacted to the oral challenge with isinglass, even at the very highest dose used. Based on parvalbumin content of 1 µg/g isinglass, the total of the challenge doses is equivalent to over 50 L of beer (or 10 L of cask beer) exceeding the volume that is possible to consume in a single sitting.

Another study was conducted separately in France using isinglass containing 10 µg/g parvalbumin. According to information provided by the Applicant, this is a typical sample of commercially available isinglass. Six patients with allergy to fish, as determined by oral food challenge or by a convincing clinical history at the time of the study, were included. Each patient received a total of 20 mg of isinglass, mixed with cooked potato, over two hours. None of the patients had positive reactions to the oral challenge (while two of the six patients showed positive reactions in the skin prick test using the same material).

These two studies, conducted by experts in the field using rigorous protocols, provide supporting evidence that isinglass does not pose a safety concern for fish allergic consumers.

2.6 Exposure assessment

The data suggest that levels of isinglass that may remain in beer do not exceed 1 mg/L for bottle or can beer, and 5 mg/L for cask beer. The level of parvalbumin is isinglass is likely to vary according to the manufacturing protocol (from 1μg/g for the new protocol to 10 μg/g for old protocol). No data are available on the level of parvalbumin in beer because it is below the LOD for current methodologies. As parvalbumin is known to be insoluble in the acidic environment of fermentation, it is expected to co-sediment with isinglass which is removed during the beverage production and is not consumed.

FSANZ notes that currently there are no agreed thresholds for any food allergen including parvalbumin. A threshold is the lowest dose of the allergen (parvalbumin) that can trigger an allergic reaction in fish allergic individuals. However, the levels of parvalbumin that may be consumed in isinglass-fined beer are likely to be very low (estimated to be 0.001-0.005 μg/L for new protocol isinglass and ten fold higher at 0.01-0.05 μg/L for old protocol isinglass).

The oral challenge studies indicate that isinglass prepared according to either the old or the new protocol did not provoke allergic reactions in any of the 21 fish allergic individuals. The isinglass doses used in these studies and corresponding volumes of beer are as follows:

Isinglass prepared according to:	**The cumulative oral challenge dose (no reactions observed):**	**Equivalent volume of beer**
New manufacturing protocol	50.5 mg isinglass (isinglass was given in increasing dose of 0.5 mg, 5 mg, 15 mg and 30 mg in about 40 grams in mashed potato over 2 hours)	50 L of bottle/can beer 10 L of cask beer
Old manufacturing protocol	20 mg isinglass	20 L of bottle/can beer 4 L of cask beer

An average drinker of beer may consume about 1.5 L of beer within a single sitting, while a heavy drinker of beer may consume up to 3 L of beer within a single sitting. Clearly the dose of isinglass tolerated by fish-allergic individuals in the oral challenge studies, as reported by the Applicant, far exceeds isinglass levels that may be expected in the volume of beer that could be consumed by an individual within a single sitting.

In light of the normal constrains on the volume that can be consumed by an individual within a few hours, FSANZ considers that potential exposure to parvalbumin through the consumption of beer fined with isinglass is likely to be extremely low.

3. Wine-related data

Information in this section is derived from documents provided to FSANZ by the Australian Wine Research Institute (AWRI) in April 2008; and from EFSA opinion (Request N^{o} EFSA-Q-2006-154 – published in the EFSA Journal 2007, 533:1-8).

3.1 Usage of isinglass in wine

Information provided to FSANZ by the AWRI indicates that isinglass is used under GMP (as required in the Code under Standard 1.3.3) as a fining agent mainly in the production of white wine.

The amount of isinglass used is determined for individual batches to avoid overuse, but typically falls between 10-25 mg isinglass/L of wine. Isinglass is removed by sedimentation followed by racking, which may include high performance centrifugation or filtration.

3.2 Residual amounts of isinglass in wine

Analytical data, commissioned by the AWRI, is provided for two commercial samples of isinglass-fined wine produced according to GMP (Hofman et al., 2002). The analytical method is based on partial purification of collagen from the test sample followed by analysis using sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) technique. The wine samples had been fined with 0.42 and 4.4 mg isinglass/L wine, respectively. No collagen bands were detected in the wine samples. Using the same method, collagen residues could be recovered and detected in beer samples spiked with collagen at concentration of 1.0 mg/L or more. The AWRI concludes that the concentration of residual isinglass in the commercial wine samples is likely to be less than 1 mg/L.

In a recently published study, 16 wines were tested for residues of isinglass (Weber et al 2007). The wines were fined with four commercially available isinglass preparations at 50 or 250 ml isinglass/100 L wine. No residual isinglass could be detected in any of the wines when a competitive ELISA with LOD $\leq$ 5 µg/L was used. These findings further support results of undetectable isinglass in two samples of isinglass-fined Australian wines.

3.3 Potential allergenicity of isinglass-fined wine

An investigation of potential food allergens in fined wine was reported, including full details of the double-blind placebo-controlled clinical trial and basophil activation analysis (Rolland et al., 2006). The scope of the study included wine fined with isinglass as well as egg and milk-derived processing aids. The data relevant to isinglass is outlined below.

3.3.1 Literature review

A search of the medical literature was conducted by the AWRI on PubMed using the terms ‘wine AND allergy’. The most commonly reported adverse reactions among alcoholic beverage consumers appear to be associated with sulphite additives. However, the search was unable to identify any documented cases of adverse reactions specifically associated with isinglass.

3.3.2 Double-blind placebo-controlled trial - Exposure to isinglass in fined wine

The clinical study included ten fish allergic subjects recruited from the Allergy Clinics, Alfred Hospital in Melbourne. The patients (five females and five males) were diagnosed by a clinical allergist with IgE-mediated food allergy, based on a history of anaphylaxis and corresponding demonstration of specific IgE to allergens of fish or by skin prick testing. The exception was one individual who had negative tests for IgE but a positive oral fish challenge. Clinical characteristics of the ten fish allergic individuals are included in the published study (Rolland et al., 2006).

Control subjects, with no IgE to any of the allergens including fish, were also included in the study.

All subjects avoided antihistamine medications for three days, short-acting bronchodilator therapy for four hours, and long-acting bronchodilator therapy for twelve hours before each visit. Alcohol ingestion was avoided for at least three days before challenge, with subjects fasted for at least eight hours.

Samples from 23 isinglass-fined wines were used in the study. Controls wines were clarified using other non-food protein-processing aids and/or filtration.

Each subject consumed 100 mL (approximately one standard drink) over 10-15 minutes and completed a symptom questionnaire by using a visual analogue scale and repeated it at 15 minute intervals for two hours after challenge. Over the next six days, subjects abstained from alcoholic beverages and recorded any possible late reactions in a diary.

The study reported that one fish-allergic subject developed mild lip numbness, which resolved spontaneously, after ingestion of a control unfined wine. No subjects developed a typical IgE-mediated allergic reaction requiring medical treatment and no diary card abnormalities were noted during follow-up.

3.3.3 Basophil activation analysis

An analysis using a modified basophil activation assay was described in the study by Rolland et al. (2006). The study reported that one isinglass-fined wine caused weak basophil activation for two out of ten fish-allergic subjects, but this same wine was also reported to have caused weak activation of basophils from a peanut-allergic subject (who is not allergic to fish). The two fish allergic subjects showed no clinical adverse reactions to another wine made using isinglass. One of the two fish-allergic subjects showed weak basophil activation to a wine made using non-grape tannin but this subject was not allergic to peanuts or tree nuts.

4 Conclusion

The Table to clause 6 in the Standard 1.3.3 requires that isinglass is used according to GMP. Adherence to GMP in the use of isinglass as a clarifying agent minimises the potential level of residual isinglass in the final product.

Information provided by the Applicant indicates that low but variable levels of parvalbumin may be present in commercial isinglass. Reducing the level of parvalbumin in isinglass is technically achievable by incorporating steps, including further washing, into the GMP for isinglass manufacturing. The Applicant states that the revised GMP is now widely adopted by the isinglass manufacturers which supply the Australia and New Zealand markets.

Together, the GMP for the production of isinglass and the GMP for the use of isinglass in the fining of beer and wine provide a high level of safety that counteracts uncertainties identified in this paper. The uncertainties relate to the newly developed analytical methodologies used in generating the data provided by the Applicant, the lack of information on the prevalence of fish allergy among the adult population in Australia and New Zealand, and the lack of an agreed threshold for parvalbumin.

Therefore, FSANZ considers that isinglass fined beer and wine, are not likely to present a risk of allergic reactions in fish allergic consumers.

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Attachment 3

Food Technology Report

Summary

Isinglass is derived from fish swim bladders and is used as a clarifying agent in the brewing and wine industry. The rod-like helical structure and amphoteric nature (able to be both an acid and base) of the isinglass collagen are responsible for isinglass's clarification properties. The yeast cells, polyphenolic and protein substances form complexes with the isinglass and settle to the bottom of the fermentation vessels, thereby assisting in clarifying the liquid.

Residual isinglass is filtered and in packaged beer and wine has been shown to be removed by the filtration process, whereas cask conditioned beer (which is unfiltered) would require sufficient sedimentation time to ensure all the isinglass has time to settle and form a stable mass at the bottom of the cask. Good Manufacturing Practice (GMP) needs to be followed when isinglass is utilised as a clarifying agent to ensure the minimum possible residue of isinglass in the finished product.

The isinglass may potentially contain the protein parvalbumin, a known fish allergen. The level of parvalbumin in the isinglass can be minimised by establishing and adopting a manufacturing Code of Practice which is intended to reduce the level of parvalbumin.

1. Introduction

Isinglass is used extensively as a processing aid in the brewing and wine industry to improve the efficiency of the fining process (also called clarification) of beer and wine. Isinglass has been used for several centuries for this purpose. An estimated 200 tonnes of isinglass is used annually to clarify an estimated 150 million hectolitres of beer worldwide.

2. Production process of isinglass

Isinglass is a collagen derived from dried swim bladders of specific tropical and subtropical fish. The traditional basic production process may vary between manufacturers, which can also depend on the source and species of the fish and does not seem to have a high level of standardisation (EFSA, 2007). The main steps involve blending swim bladders of specified fish to meet quality, functionality, cost and supply; granulation to reduce the size; washing in chilled water, sterilizing in dilute hydrogen peroxide solution and final rinsing with water. The sterilised granulated swim bladder is then further processed to different product forms such as powder, paste, ready-to-use paste and dry parchment or matted form. The three main forms of commercial isinglass are summarised below.

2.1 Isinglass powder

The sterilised hydrated isinglass is extruded using narrow apertures, which disrupts the collagen fibres. It is then dried and milled into a powder of less than 1000 microns.

2.2 Isinglass paste

The sterilised hydrated isinglass is macerated to less than 1000 microns paste by high shear mixing with the addition of sodium or potassium metabisulphite (as preservative). The paste is standardised to about 10% solids.

2.3 Ready-to-use paste

The isinglass paste can be further diluted then acidified with food grade acids to a pH of 2.0-3.0. The solids level is typically 0.3-1.5%. Sulphur dioxide is often used as a preservative.

2.4 The new manufacturing protocol for isinglass production

An industry-agreed GMP for isinglass has been adopted by the major suppliers of isinglass to ensure the presence of parvalbumin can be minimised. This GMP includes an additional washing stage using a phosphate buffer and successive washing steps with fresh water, the introduction of a sieving step in the granulation stage to ensure that swim bladder wall size does not exceed 25 mm and the exclusion of certain fish species. Some fish species appear to have low levels of parvalbumin and therefore have been specifically included in the new GMP (EFSA, 2007).

3. Physico-chemical characteristics and technological function of isinglass

3.1 Functions and characteristics

A fining agent such as isinglass is added to beer and wine to reduce or remove the presence of one or more undesirable components in order to achieve clarity and potentially improve organoleptic appeal, flavour and physical stability in the final product (Morris and Main, 1995).

The major component of isinglass is type 1 collagen (95%) along with small amounts of gelatine, its denaturation product (Hickman *et al*., 2000; EFSA, 2007). The isinglass collagen exists as a rod-like triple helical molecule, amphoteric in nature (able to be both an acid and base) and is thermally labile, denaturing at about 29^{o}C to form the random coils of gelatine (Hickman *et al*., 2000). However, the major fish allergen, parvalbumins, present mainly in fish muscles and at low levels in fish bladders, seems to be heat stable after heating for three hours at 90^{o}C (Arif *et al*., 2007). The parvalbumin has a pI (isoelectric point) of around 3.9-5.5 (Bugajska-Schretter *et al*., 2000).

Isinglass collagen has a molecular weigh of 800-1300 kDa and contains hydroxyproline in its structure, important to its functionality (EFSA, 2007). The rod-like structural integrity of the collagen triple helix was hypothesised to be crucial for efficient clarification (Hickman *et al*., 2000). However, a more popular hypothesis of the fining activity is based upon charge interactions. The isinglass is assumed to electronically attract yeast cells with negatively charged cell wall and other suspended charged polyphenolic and protein components. These aggregated complexes would then settle to the bottom of the container. In the sediment, further interactions may take place resulting in firm sediment that is resistant to disturbance when the clear beverage is drawn off.

3.2 Clarifying process procedure in the brewing industry

In the brewing process, after fermentation, the beer is cooled to around freezing, which encourages settling of the yeast and causes proteins to coagulate and settle out with the yeast. Similar to the wine production process, it is at this stage that isinglass powder dissolved in dilute solutions of food grade acids is added to the fermented beer to aid in the clarifying process. The pH of beer is typically between 3.9 and 4.6 (Siebert and Lynn, 2005). At this pH, isinglass is positively charged (iso-electric point of isinglass is around 5.5) and thus attracting and aggregating negatively charged particles. However, if the pH of the beer is below 3.5, the fining activity is severely inhibited (Ward, 2008).

For optimum fining performance, beer must be fined at the coldest point in the process. The reason is that if the chill haze (from protein precipitation) is present prior to isinglass addition, it is then readily removed by fining. This is especially important for cask beer, since there are no effective alternatives to the use of isinglass in producing bright unfiltered beer (Ward 2008).

Information provided by the applicant suggests that the brewing industry typically uses isinglass at a low level of between 10-15 mg/L but this level can potentially go as high as 60 mg/L in some brews. The sediment formed by the collagen and yeast complex is removed by filtration and/or the centrifugation processes, resulting in very low residual levels of isinglass in the final product. Cask conditioned beer does not undergo filtration or centrifugation and relies on gravity settling.

3.3 Clarification function of isinglass in wine production process

The flowchart in Figure 1 below shows generalised processing steps of white wine. The red wine process is expected to be similar. The fining step, where isinglass is usually added, occurs after alcohol fermentation has been completed and before filtration. The main purpose is to aggregate polymeric carbohydrates, proteins and polyphenols to form larger aggregates that sink to the bottom. Such aggregation improves the filtering efficiency as a consequence by initially clarifying the wine (Wucherpfenning, 2003).

Three different types of filters are commonly used in wine filtration; precoat filter, sheet filter and membrane filter, which are membranes of different pore size that can be used to remove particles down to the molecular level from the wine.

After the fining and filtration process, the wine is normally sufficiently clear and has a pH value ranged from 2.8-4.0, depending on the types of wine (Ribéreau-Gayon *et al*., 2000). Some wines are subjected to further cold stabilisation before they are ready for development to maturity and bottled.

Isinglass is claimed to be a preferred clarification agent compared to egg or casein, because of its mild effect on flavour. Different batches of wine require different amounts of isinglass, as determined by laboratory tests. In Australia isinglass is typically added at between approximately 20-50 mg/L in the production of wine (Wine Australia, 2008), in New Zealand, use in wine is typically about 6-10 mg/L (New Zealand Winegrowers, 2008) and use in white wine in France is typically between 10-25 mg/L (Ribéreau-Gayon *et al*., 2000). In both Australia and New Zealand isinglass is considered as the best and most expensive clarifying agent and is not likely to be used in excess if usage is not warranted.

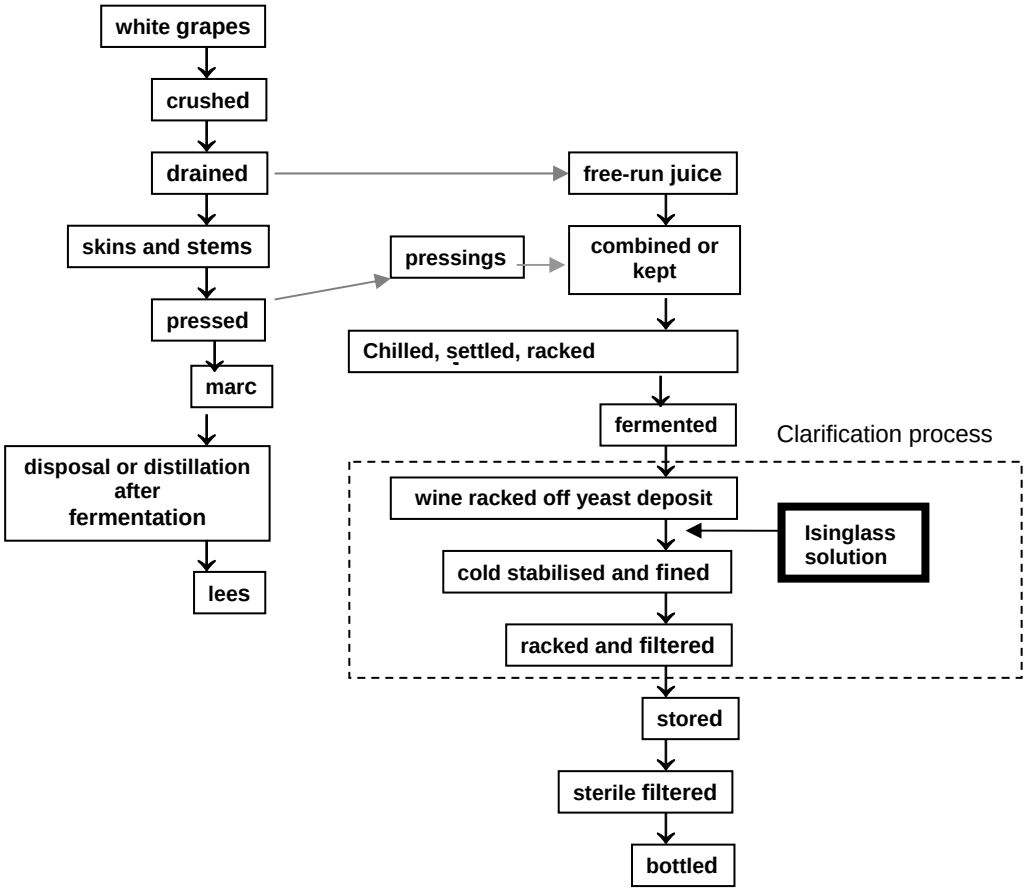

Figure 1: Flow chart of white winemaking stages with the clarification steps indicated in the dotted box (Amended from diagram provided by Winemakers' Federation of Australia, 2005).

3.3 Good Manufacturing practice for usage of Isinglass

Good Management Practice (GMP) is a requirement in regulating the maximum amount of the isinglass which may be present in a food. The relevant GMP criteria for isinglass are:

(a) the quantity added to food shall be limited to the lowest possible level necessary to accomplish its desired effect;

(b) the quantity that becomes a component of food as a result of its use in the manufacture, processing or packaging of a food and which is not intended to accomplish any physical, or other technical effect in the finished food itself, is reduced to the extent reasonably possible; and

(c) the material is prepared and handled in the same way as a food ingredient.

4. Allergenic residue issues

4.1 Parvalbumin as the allergen

Parvalbumin has been identified as a fish allergen, based mainly on studies of three species of fish: Atlantic salmon, carp and Japanese horse mackerel.

Further immuno-blotting analyses led to the conclusion that parvalbumin is the major fish albumin independent of fish species (Hamada *et al*., 2001). Parvalbumin is generally associated with skeletal muscle tissue, even though the presence of parvalbumin has previously been detected in swim bladders of fish not used for isinglass manufacture (Feher *et al*., 1998; Parmentier *et al*., 2003).

4.2 Reported studies on residues of isinglass in beer and wine

It was reported that the filtration process removed all isinglass residues in filtered beer during the process, tested using a HPLC method that can detect amino acids concentration as low as 3.9×10^{-13} mg/L. However, the study showed that in order for the cask beer to be free of isinglass, sufficient time is required for the sediment to settle properly before dispensing (Chlup *et al*., 2006).

A recent study investigated the manufacturing processes on the removal of a range of fining agents in four German wines. The wines were dosed with isinglass at 10-50 mg/L and other fining agents at five times their normal dosage levels. ELISA assays were used as the analytical method and detected no isinglass or fish gelatine in wine, except lysozyme and dried egg white, which are soluble in wine. It demonstrated that fining agents used for wine are removed during the manufacturing process or those that are insoluble are removed by filtration (Weber *et al*., 2007).

5. Conclusion

Isinglass derived from fish swim bladders used as a clarifying agent in the brewing and wine industry may contain parvalbumin. The level of parvalbumin in the isinglass can be minimised by following a GMP that is specifically designed for this purpose.

Residual isinglass has been shown to be removed by the filtration/settling process in wine, in beer that is filtered; and in cask conditioned beer (that is unfiltered) if sufficient sedimentation time is received. It is very likely that parvalbumin with its pI at around 3.9-5.5, could precipitate out in wine and beer, which also has pH around 4 and lower. The precipitated parvalbumin would then settle with the sediment with isinglass-protein complexes or be filtered out by the filtration processes.

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Attachment 4

Initial Assessment Report – Summary of Submissions

Submitter	Comments
AB Vickers	• Fully supports the Application to exempt isinglass from the allergen labelling legislation and considers that the exemption will benefit the consumer, industry and the environment. • Supports any legislation concerning foods and beverages that is designed to provide consumers with factually correct information to allow them to make informed choices, particular with respect to food safety. This information should be presented in a clear and unambiguous manner. • States that the current allergen labelling legislation requiring the labelling of isinglass when used as a processing aid is based purely on the assumption that isinglass is allergenic due to its association with 'fish'. There is no evidence to demonstrate that isinglass, when used as a processing aid in beer and wine, is capable of causing an allergic reaction. • Notes that the current legislation does not take into account specific instances whereby substances may be non-allergenic even though they may fall into one of the major allergen categories. • Notes the situation in Europe where a temporary labelling exemption has been granted as there is sufficient doubt as to the allergenicity of isinglass when used to clarify beer and wine. A similar approach exists in Canada and the United States is currently reviewing the issue. • States that prior to the implementation of the allergen labelling legislation, Australia and New Zealand represented one of the major export markets for AB Vickers isinglass. The introduction of allergen labelling and the associated removal of isinglass as a processing aid in brewing, has had a significant and damaging impact on AB Vickers' business. Also states that the legislation has had a significant secondary effect in other markets where confidence in isinglass has been undermined and has also caused problems for beer producers exporting to Australia or New Zealand. • States that incorrect labelling due to incorrect assumptions may lead to restriction of consumer choice. • Also considers that the ability of beverage companies to sell their products in different geographic markets is potentially damaged if a level playing field is not adopted with respect to labelling issues. • States that the removal of highly effective processing aids will lead to potentially higher prices, as production efficiency is reduced and manufacturers attempt to maintain profits through increased consumer prices. • Believes that granting an exemption for isinglass will have the following benefits: - it will allow winemakers to remove a potentially misleading statement from the label, thus increasing consumer choice and confidence in label information; - it will enable brewers to resume the use of isinglass and subsequently benefit from improved operational efficiency, improved operating profitability and reduction in the quantity of filter powder being disposed to landfill; - it will allow isinglass producers to resume sales in the region resulting in a requirement to employ locally based technical sales staff; and

Submitter	Comments
	- it will underpin confidence in the isinglass industry as a whole, resulting in increased usage worldwide and thus extending the environmental and cost benefits resulting from the use of isinglass in beer and wine production.
Australian Food and Grocery Council	• Supports Option 2 in-principle on the grounds that there is no substantial evidence that isinglass induces an allergic reaction at the concentrations normally present in beer or wine. • However, is concerned that in agreeing to this exemption, FSANZ is moving away from the objective of establishing outcome-based standards and instead is addressing a defective standard in a selective and piecemeal approach. • Notes that the principle that all substances that require a mandatory declaration under Standard 1.2.3 be reviewed, where there is little clinical evidence of allergic reaction and there is a low risk that the substances are capable of inducing an allergic response at the concentrations present in the final product. • Considers that it is appropriate to review the allergen labelling provisions of Standard 1.2.3 to remove the requirement to declare products of allergens where it can be demonstrated that they do not contain the allergenic protein. • Supports the requirement for allergen labelling but notes the growing body of evidence demonstrating that threshold doses for food allergens are finite, measurable and detectable. The requirement that the presence of allergens be declared even when undetectable leads to consumer confusion and an unnecessarily restrictive diet for allergic consumers. • Notes the information provided by FSANZ in the Initial Assessment Report on historical evidence of safe use and the allergenicity assessment and considers it unlikely that isinglass would induce an allergic reaction in a fish sensitive individual at the concentrations typically present in beer or wine. • Suggests that if the presumption of allergenicity to fish products is based on the presence of parvalbumins, then the absence of parvalbumins in other fish products should also be grounds to consider an exemption from allergen labelling requirements. • Notes that there is no international consistency in relation to the declaration of allergens and that there is some international precedent for not declaring all products of allergens. • Notes that a less restrictive standard than Codex is acceptable under WTO rules.
Australian Wine Research Institute	• Supports the Application. • Emphasises the stance proposed by the EC and the EFSA in Directive 200/13/EC, where a temporary labelling exemption has been granted for a list of potentially allergenic material, pending research being undertaken as to their allergenicity. A permanent exemption will be granted if non-allergenicity can be satisfactorily demonstrated. • States that the AWRI, in conjunction with the Department of Allergy, Immunology and Respiratory Medicine at The Alfred and Monash University, is currently undertaking research into the allergenicity of wine produced with potential allergens from specific processing aids. The objectives of the project are: - to establish sensitive and reliable assays to detect and measure allergenic proteins from the processing aids casein, egg white, isinglass and milk in the final bottled wine; - to determine if there are any detectable residual allergenic proteins from the processing aids casein, egg white, lysozyme, milk and potassium caseinate in the final bottled wine.

Submitter	Comments
	This has comprised an initial survey of 102 commercially available Australian wines produced with the above processing aids and a further analysis to wines to which residual processing aids have been added; and - to determine whether 26 individuals with a known allergy to eggs, fish, milk or nuts and 11 non-allergic individuals exhibit an allergic reaction on blinded consumption of wine that was fined with a known food allergen source to which they have a confirmed food allergy and a comparable wine that was not fined with a potential food allergen. • The detection of residual allergenic proteins in the wines is being determined through the development of sensitive ELISAs and from basophil activation tests (BAT) using flow cytometry. • Envisages that the results of the research project will form the basis of a subsequent application from the Australian wine industry to FSANZ to exempt other food protein processing aids (casein, egg white, lysozyme, milk and potassium caseinate) from the mandatory declaration requirements when present in wine. <u>Allergenicity Assessment</u> • Provides a summary of allergenicity assessment and associated references. • Notes that fish allergy is important in both children and adults, and once present, tends to persist throughout life. • Parvalbumins have a molecular weight of between 10.5-14 kD (including Gad c 1, molecular weight 12.3 kD) have been identified as a major muscle allergen in fish, although collagen may be commonly allergenic irrespective of species. The carbohydrate moiety has no demonstrable allergenicity. There may be cross-reactivity with most, and occasionally all other fish. • Isinglass is a form of fish-derived collagen having the following properties: - a mixture of predominantly type I and type IV collagen derived from fish maws, the latter having a globular structure containing a high concentration of hydroxyproline and the repeated sequence of glycine-proline-hydroxyproline; and - a molecular weight of 800-1300 kD, considerably greater than that of the allergenic parvalbumins. <u>History of Safe Use</u> • Provides a summary relating to history of safe use and associated references. • States that from the 13 year-old database of consumer/general public enquiries to the AWRI, there appears to be no verifiable incidence of obvious or recognisable allergic reactions to the use of isinglass in winemaking. • Appears to be only one recorded incident of an Australian winery over-fining with isinglass in the past 10 years at the AWRI. • Appears to be no recorded measurement of the concentration of isinglass in wine, following a comprehensive literature review. • Identifies only a few case reports of severe adverse reactions to wine ingestion, largely anecdotally attributed to biogenic amines, salicylates or sulphites, however the question of a reaction to fining agents is not specifically considered. • Refers to two recent food challenge studies of fish gelatine – one sourced from a codfish species known to elicit allergic reactions in sensitive individuals and the other sourced from tuna fish skin.

Submitter	Comments
	• Fish gelatine is made by denaturing collagen and hence has a similar amino acid composition to collagen. None of the individuals in either study (n=13 and n=3) experienced an adverse reaction following ingestion. • Accumulated data involving DBPC challenges of fish indicates that the lowest provoking dose was 5 mg of cod or herring in 32 fish allergic individuals and was 10-100 times higher in challenges using different species of fish. In winemaking, generally only 10-25 mg isinglass/L wine is used, and if the wine was not subsequently filtered, a 100 mL glass of wine would contain a maximum of 1-2.5 mg of isinglass. However, in this circumstance, the isinglass-phenolic compound complex formed upon addition of the isinglass, would settle to the bottom of the fining tank and following racking, it would be left behind leaving a brilliantly clear wine. <u>Residues of Isinglass in Beer and Wine</u> • Isinglass is used to remove phenolic and tannin compounds from white wine. When used in winemaking, isinglass is not intended to be present in the final product, and if used and removed in accordance with GMP, any residue is likely to be negligible. • States that there is no published literature available on the concentration of isinglass in the finished wine, nor are there published assays for measurement of its concentration in wine. There is only one commercially available ELISA specific for egg, peanut and milk allergens (assays are currently being developed for tree nut allergens), however, the lower level of sensitivity of these assays is at the mg/L level, which is approximately 100-1000-fold higher than the likely level of processing aid residue in wine under GMP. • Refers to analysis of two white wine samples fined with 0.42 and 4.4 mg isinglass/L wine, respectively, which was conducted by NZ Institute for Crop and Food Research in 2002. The samples were analysed for collagen residues using a method adapted from that developed for beer, where concentrations of collagen as low as 0.02 mg/L had been detected. No collagen bands were detected in the wine samples. Further analyses found that collagen residues could be detected at a 'spiked' concentration of 1 mg/L, which is an indicative minimum detection limit for the wine samples analysed. <u>Costs and Benefits – Option 1</u> • Considers that there is no benefit to wine producers if the status quo is maintained. • The cost to wine producers relates to the: - additional analyses required for each wine product; - costs associated with the development of these analyses; and - costs associated with the development of other processing aids that are not potentially allergenic and hence do not require declaration on the label. • In terms of isinglass manufacturers, states that the costs could be significant, as wine producers will seek to source other processing aids that are not potentially allergenic, and hence do not require declaration on the label. • The cost to consumers is a restriction of choice, as fish-allergic consumers will not purchase these beverages in case an allergic reaction is elicited on consumption. Conversely, advice from Anaphylaxis Australia is that, with the increasing number of disclaimers on food packages, food allergic consumers are questioning the validity of disclaimers, potentially leading to increased risk taking.

Submitter	Comments
	Costs and Benefits – Option 2 • Considers that the benefit to wine producers is that they do not necessarily have to produce different labels for different vintages and also different labels for domestic and export markets which do not require the declaration of isinglass. • Considers that the benefit to consumers is that their choice of beverage is not restricted and they can consume the beverage confident that it is unlikely to elicit an adverse reaction.
Margaret Aylward	• Does not agree that there should be an exemption from the requirement to label beer and wine for the presence of isinglass under clause 4, Standard 1.2.3.
BFBi Isinglass Committee	• Strongly supports the Application. • Agrees with the aim of providing consumers with sufficient labelling information on foods and beverages to allow informed choice to be made with respect to the safety of particular foods. The information presented should be factually correct and presented in a clear and unambiguous manner to make these informed choices. • States that the current allergen labelling legislation in Australia and New Zealand requires beverage producers to label beer and wines in which isinglass is used as a processing aid as 'may contain fish products'. Isinglass is captured by the legislation only because it is derived from fish. No evidence or data is presented to prove that isinglass will produce an allergenic response when used as a processing aid in beer or wine production. • Proposes that isinglass is not allergenic even though it is derived from fish, and notes that the current legislation does not take into account specific instances whereby substances may be non-allergenic even though they may fall into one of the major allergen categories. • Notes that the EU has granted a temporary exemption for isinglass from European allergen labelling legislation based on the assessment that isinglass is 'not very likely to cause severe allergenic reaction when used as a process aid in beer, wine and cider'. Canada has agreed that labelling is not required unless a substance is proven to be allergenic and the US is currently discussing the best way forward. Likely Allergenicity of Isinglass • Comments that isinglass has been used as a processing aid in beer and wine production for at least 100 (and possibly up to 250) years, with the UK remaining a major market for isinglass. • States that cask beers typically use high isinglass rates directly into the cask from which the beer is dispensed. This theoretically exposes consumers to residual isinglass levels that would be significantly higher than for filtered lagers or ales. • Notes that throughout the long history of use there has not been a single documented allergic reaction from the use of isinglass as a processing aid, including from the ingestion of isinglass in its raw 'fish maw' form in Asian communities. • States that allergen experts have documented their opinion that the risk of isinglass being allergenic appears to be very small, given the known molecular properties of common fish allergens, the long history of safe use and the absence of evidence that fish allergic subjects react to beer or wine any differently to the rest of the population (opinion provided by J. Hourihane, School of Medicine, University of Southampton).

Submitter	Comments
	Residual Levels of Isinglass in Beers and Wines • Notes that the development of methods for assessing residual levels of isinglass in beer is ongoing., however, results so far demonstrate that residual levels would typically be significantly less than 1 ppm in beers. • States that residual levels in wine have not been documented but are believed to be similar to those found in beer, given that application rates and subsequent filtration regimes are similar in both industries. On-Going Studies • States that a programme designed to scientifically determine the allergenic status of isinglass is being managed by FARRP on behalf of the BFBi Isinglass Committee (as described in Section 5.5 of the A490 IAR). Impact of Granting Exemption • Notes the primary effect of isinglass is to efficiently sediment yeast and proteinaceous material to the bottom of the fermentation or storage tank. This ensures greatly improved filtration efficiency and significantly reduces the overall requirement for filter powders and cold beer storage capacity. • States that the decision by the Australian and New Zealand brewers to remove isinglass from the process has had significant impact on their operations. • Based on a production volume of approximately 4 million hectolitres in New Zealand and 20 million hectolitres in Australia, considers that the elimination of isinglass as a processing aid will result in a potential increase in filter powder of 360,000 kg per annum for disposal to landfill. This results in a direct cost increase to the brewer, while the environmental impact of increased landfill requirement is substantial. • While filtration capacity can be increased by increasing cold storage capacity, this results in increased capital expenditure on non-renewable resources and increased refrigerant usage, with associated cost and environmental implications. In a typical million hectolitre brewery, additional costs (representing increased storage capacity, centrifuges and ongoing operational costs) have been estimated as several million dollars. • Believes that the requirement for wine products to state that they may contain an allergenic 'fish product' is potentially misleading and restricting consumer choice, given that isinglass has not been proven to be allergenic. • Believes that granting an exemption for isinglass will have the following benefits: - it will allow winemakers to remove a potentially misleading statement from the label, thus increasing consumer choice; - it will enable brewers to resume the use of isinglass and subsequently benefit from improved operational efficiency, improved operating profitability and reduction in the quantity of filter powder being disposed to landfill; - it will allow isinglass producers to recover sales in the region, resulting in a requirement to employ locally based technical sales staff to support the business; and - it will underpin confidence in the isinglass industry as a whole, resulting in increased usage worldwide and thus extending the environmental and cost benefits resulting from the use of isinglass in beer and wine production.

Submitter	Comments
Brewers of Europe	• Fully supports the request for exemption of allergen declaration as requested by the Beer, Wine and Spirits Council of New Zealand. • Notes current FSANZ legislation requires brewers using isinglass as a clarifying agent to label beer with the following: 'This product contains fish products or essence of fish'. Such information is ill-founded and misleading, as isinglass is not allergenic and is only present in the finished product in residual trace quantities. • Considers that isinglass is not allergenic for the following reasons: - there have been no recorded cases of allergic reaction to isinglass treated beer, either from within the general population or among people with a known allergy to fish; - the protein molecules in isinglass are much larger than the size of known allergens; - the residual amounts of isinglass are so low that even if it were allergenic, it would be unlikely to provoke a reaction; and - the product is eaten undiluted in Chinese cuisine without ever eliciting an allergic reaction. • Notes that The Brewers of Europe and the BFBi sought and obtained temporary exemption from the EU allergen labelling requirements on the grounds of: - long history of safe use; - absence of published reports of allergenicity; - defined product which is distinct from recognised allergens; and - low dietary exposure. • States that scientific studies are underway to support the case for non-allergenicity and to allow permanent exemption in the EU. The results of these studies can be shared with FSANZ when available.
Department of Human Services, Victoria	• Supports Option 2, to exempt isinglass from the mandatory allergen declaration.
Devro Pty Ltd	• States that an amendment to Standard 4.1.1-Wine Production Requirements (Australia only), provided winemakers in Australia with the ability to use collagen, of any food-approved origin, to be used in the clarification of wine. • Notes the definition of isinglass by the applicant, as the usual term for piscine collagen. • Advises that collagen is commonly isolated from bovine and porcine sources and extensively used in a range of established food applications and do not require mandatory allergen labelling. Additionally, non-isinglass collagen can be sourced from local, traceable origin without reverting to material which is sourced, processed and imported from overseas. • Advises that a bovine fining agent has been used extensively in the processing of beer in Australia and New Zealand since 2002 and has been shown to provide equivalent functionality to isinglass when used at comparable concentrations. Porcine, ovine, avian and wild game sources of collagen could also be potentially utilised as effective alternatives to isinglass.

Submitter	Comments
Dietitians Association of Australia	• Believes that the introduction of clause 4, Standard 1.2.3 has been well received by both dietitians and patients, despite the controversy over 'may contain' statements. • Currently opposes any exemptions from this clause because it is still not possible to determine a safe level of exposure for every individual with food allergies. • Does not oppose this Application proceeding to Draft Assessment, given that studies into the safety of isinglass in food allergic individuals are either planned or underway. • Supports Option 1, to maintain the current provisions in clause 4, Standard 1.2.3, until such time as controlled, peer reviewed trials have shown that the residual level of isinglass in beer and wine poses no threat to the most severe fish allergic individuals.
Food Technology Association of Australia	Accepts Option 2 with the following comments: • that only isinglass specifically derived from the swim bladders of tropical and subtropical fish be permitted to be exempt; and • that the Draft Assessment Report include the results of the research currently being undertaken in Europe and USA as reported in Section 5.5 of the Initial Assessment Report, particularly the results of isinglass ingested by people with an established allergy to fish.
Foster's Australia	• Believes that the Application has merit for the following reasons, as stated by the Applicant: - Foster's is unaware of any evidence in the published medical and scientific literature to suggest that isinglass provokes allergic reactions in fish sensitive individuals; - an extensive review of isinglass and allergenicity to which FSANZ has access does not indicate that isinglass is an allergen; - the actual concentration in beers is low and this needs to be considered in addition to the absence of any evidence of allergenicity; and - the EC has granted an exemption from labelling until 25 Nov 2007, and USA and Canada are considering such exemptions. • States that while there is no current use of isinglass in the Australian brewing industry, and the materials in use function effectively, their availability or acceptability could change at short notice and production needs may also change. • Considers that in the absence of a fallback such as isinglass, major production changes would be required and significant costs imposed. Such costs would need to be passed on to consumers, where there may be no real safety concern. • Therefore supports Option 2 as it would ensure supply continuity of products to consumers without additional cost and delay. • Also suggests the following: - that FSANZ undertakes further investigations of residual allergenic material to ensure the exception can be applied across all standardised alcoholic drinks; and - a defined timeframe for the exemption, aligned with the European Commission exemptions.

Submitter	Comments
Inter-Industry Coalition	• Provides the following information regarding isinglass: - it is used during beer and wine production as a gentle method of clarifying these products prior to their final preparation for bottling. - it has a long history of use as a safe and natural processing aid. - the rationale for its use as fining agent is that it attaches to substances in the beer or wine and precipitates or is subsequently filtered from the beer or wine. • States that it is unaware of any scientific evidence that supports mandatory labelling for isinglass or of any demonstrated cases of allergic reactions to wines or beers fined with isinglass. • Notes that the Food Allergy and Anaphylaxis Network (FAAN) has stressed that any labelling for food allergens must take into account whether or not that food will produce an allergic reaction and that labelling for all allergens may lead to further restricted diets, increased frustration and risk taking, and undermining the integrity of labelling statements. Consumers need to trust that labelling information is reliable and not be subjected to misleading, precautionary statements that may be ignored based upon prior experience of consuming the food and not suffering an adverse reaction. • Supports the exemption of an allergen declaration for isinglass. • Notes that requiring compliance with measures that do not increase consumer safety, does not serve the interests of government, the industry or the consumer. Such measures place unnecessary burden upon breweries and wineries, and unnecessarily restrict consumer choices, without commensurate benefits. • States that determinations made by respective government bodies about allergen labelling should not impede trade without serving a public interest.
Ivan Jeray	• Does not support the Application. • Believes that every consumer has a right to know what they consume. • Notes the Applicant's comments that some people may suffer from an adverse reaction from the product. • Considers the possibility that the ingredient at a future date may be replaced with a GM ingredient that could escape current GM labelling laws that are inferior and deceptive if approval is finally granted.
Bill Leonard	• Considers that there should be no exemption given to manufacturers of beer, wine or any other product for labelling of the presence of isinglass. • States that, health concerns aside, there is a moral aspect as vegetarians are not expecting fish material in alcoholic drinks and allowing an exemption for labelling could conceal the non-vegetarian nature of the product.
New Zealand Food Safety Authority	• Supports the Application proceeding to Draft Assessment. • Agrees in principle that exemptions be granted from the requirements in clause 4 of Standard 1.2.3, if there is conclusive evidence that a substance within the scope of this clause is unlikely to cause and allergic reaction. • States that NZFSA will review the evidence presented in the Draft Assessment Report.
New Zealand Winegrowers	• Supports the Application. <u>Toxicological and Allergenicity Assessment</u> • Does not have additional information on the toxicology or allergenicity of isinglass at the present time.

Submitter	Comments
	• Is aware of research being conducted by the AWRI and Alfred/Monash University into the possible allergenic effects of isinglass and other processing aids in wine. The research will cover the development of effective assays, the detection of allergenic protein residues (if any) and the assessment of the allergenicity of any such residues in wine. • Considers that the evidence contained in the Application regarding the toxicology and allergenicity of isinglass, together with the longstanding history of safe use throughout the world, should provide a sufficient basis for acceptance of the Application. • If FSANZ requires further evidence for the safety assessment of wine, requests that a final decision on the Application be deferred until the results of the Australian study are known. <u>History of Safe Use</u> • States that neither NZW nor the Wine Institute of New Zealand are aware of any incident of a consumer having suffered an allergic reaction due to the use of isinglass in wine, nor has any such incident been relayed to either organisation from the relevant health authorities in New Zealand. <u>Residues of Isinglass in Wine</u> • States that isinglass is used in wine as a clarifying and filtration agent. It is a permitted processing aid that must be used in accordance with GMP. As a processing aid, isinglass is not intended to remain in the final product. • Notes that in terms of wine quality, isinglass is considered to be the best clarifying agent to use. It is one of the most expensive fining agents available and is used sparingly. In New Zealand, isinglass is usually added at approximately 0.05-0.25 g/L, however, this does not reflect the level of isinglass in the finished product as the isinglass and other particulate matter are removed during subsequent processing. • States that isinglass and the phenolic compounds with which it forms a complex, is allowed to settle before the wine is racked off the sediment to produce a brilliantly clear product. In the majority of cases, the wine will also undergo subsequent filtration to further remove residual traces of such matter. These processes mean that any isinglass present in a finished wine is likely to be at a very low concentration. Other than the current AWRI study, NZW is unaware of any studies that determine the amount of residue present in a wine clarifies with isinglass. <u>Costs and Benefits – Option 1</u> • Considers that there are no benefits to wine producers if the *status quo* is maintained. <u>Costs and Benefits – Option 2</u> • Considers that consumers and wine producers will have more precise and accurate information on a wine label under Option 2. • The experience of New Zealand wine producers is that consumers are confused and often react negatively when they read information on a wine label regarding the presence of fish products. • States that consumers suffering from fish allergies are unlikely to purchase a wine with such labelling, therefore restricting their choice of beverages unnecessarily. Moreover, the presence of allergen declarations on products such as wine, undermines the significance and confidence of allergy sufferers in such declarations.

Submitter	Comments
	• Considers that some consumers may choose another product in preference to a wine that has a declaration of fish products on the label, as they are unlikely to be aware that isinglass is a traditional fining agent and does not remain in the final product in significant concentrations. • Notes that many imported wines do not bear any form of allergen declaration and it is very likely that a proportion of these will have been made using isinglass. This disadvantages compliant wine producers. • There is little opportunity to enforce the Standard, given the lack of reliable tests for isinglass residues in wine and the lack of significant food safety risk related to this issue. • A significant benefit under Option 2 is that wine producers will be able to choose the best quality clarification option without losing consumer confidence associated with the declaration of fish products. • A further benefit of Option 2 is that it will reduce the number of labelling changes required for wines that are sold in both the domestic and export markets. This will reduce costs to exporters and enhance the design options available to them. • Notes that currently New Zealand and Australia are the only major wine producing countries in the world that require an allergen declaration if isinglass is used in the production of wine. Consequently, wine exporters are required to remove the allergen declaration from the label before exporting. <u>Labelling issues</u> • Is not aware of any specific labelling issues associated with the Application in New Zealand. However, notes that Canada and the EU have granted exemptions to wine manufacturers while the allergenicity of isinglass is assessed. This is in distinct contrast to the approach adopted in the Food Standards Code which imposes regulation on wine producers before any evidence of allergenicity has been established.
NSW Food Authority	• Supports the overriding principle that ingredients, additives and processing aids not containing material that could provoke an allergenic response, should not be declared. Also noted that the declaration of ingredients as allergens when no allergenic material is present denies affected consumers a wider range of food choices. • Considers that this Application represents a piecemeal approach to the issue of providing exemptions from allergen labelling and suggests that a broader approach to the issue should be considered. For example, FSANZ should consider the merits of widening the ambit of the Application to all foods where isinglass is used as a clarifying agent. • States that the paper identifies a number of issues requiring further evaluation in terms of allergenicity and that it is expected that these will be addressed in the DAR. • Believes that the onus on ensuring that any ingredient will not provoke a reaction should rest with the manufacturer. The exemption from labelling should therefore be limited to batches of isinglass which have been certified by the supplier to be free of potentially hazardous allergenic proteins.

Submitter	Comments
NSW Health Department	• Understands that the Standard regarding allergen declaration was put in place so that consumers would be aware of all possible sources of allergens in foods, and that this is important because it is not possible to know how much protein is needed to cause an allergic reaction. • Given that this situation has not changed, believes that there should be no exceptions to this Standard in the interests of public health, and particularly not for trade reasons. • Considers that the Application should not be assessed until the results of studies to determine whether people with fish allergy react to products containing isinglass, are known. Therefore, manufacturers should still be required to declare the presence of isinglass on the labels of wine and beer. • Believes that possible departures from the allergen declaration should be dealt with in a systematic way and not through individual applications.
Queensland Health	• Notes that there is still significant missing information, which is the subject of current research. • Also notes that there is currently no data on the prevalence of fish allergy in the Australian and New Zealand populations. • Supports the retention of the current labelling requirements in clause 4, Standard 1.2.3 (Option 1) unless the missing information becomes available and provides a very good basis that allergy is not likely, or a problem. • Provides advice from A/Professor Pete Smith, Gold Coast allergist stating that the threshold dose or allergen for fish allergic patients is unknown. Dr Smith also states that the sensitivity of food allergic patients is being investigated and it would be premature to exempt isinglass prior to this study being done. • Provides a reference to a study designed to identify whether wines which are produced using the common potential food allergens such as proteins derived from fish, milk or egg are likely to contain sufficient food allergens to cause reactions in susceptible individuals http://www.clinicaltrials.gov/ct/gui/show/NCT00163735
SA Department of Health	• Gives cautious support to the Application but will await the results of the safety assessment before giving full support.