submissions

From: standards.management@foodstandards.gov.au
Sent: Monday, 21 September 2015 6:19 PM
To: standards management
Subject: FSANZ: Applications and Submissions - Submission [SEC=INCONFIDENCE]
Attachments: FSANZ Submisssion.zip

FSANZ: Applications and Submissions - Submission

Monday, 21 September, 2015

1. Assessment Report Number: Proposal P1031

2. Assessment Report Title: Allergen Labelling Exemptions

3. Organisation Name: Tata Global Beverages Ltd

4. Organisation Type: Individual

5. Representing: Tata Global Beverages Ltd

6. Street Address: Kirloskar Business Park, Block C , 4th Floor, Hebbal Bengaluru - 560024

7. Postal Address: Kirloskar Business Park, Block C , 4th Floor, Hebbal Bengaluru - 560024

8. Contact Person: [redacted]

9. Phone: [redacted]

10. Fax: [redacted]

11. Email Address: [redacted]

12. Submission Text: Tata Global Beverages would like to support the allergen labelling exemptions proposed by FSANZ. Two EFSA documents (Opinion of scientific panel) to substantiate this exemption have been enclosed along with the submission form

Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to a notification from AAC on wheat-based glucose syrups including dextrose pursuant to Article 6 paragraph 11 of Directive 2000/13/EC

(Request N° EFSA-Q-2004-091)

(adopted on 19 October 2004)

SUMMARY

Information is provided by the applicant on wheat starch hydrolysates, particularly on glucose syrups and dextrose concerning their preparation, analysis and potential effects in coeliac disease and cereal allergy. It is stated that wheat-based glucose syrups (including dextrose) are not likely to trigger adverse reactions. This statement is based on the description of the manufacturing process which includes protein removal by active carbon treatment. The evidence of non-allergenicity of wheat starch glucose syrups and dextrose provided includes information on the safe use of wheat starch-based gluten-free diet in coeliac disease which is indirectly relevant to the topic. Similar information on wheat allergy is missing. Trace amounts (1-15 mg/kg) of residual intact gliadin as well as peptides arising from degradation of gluten were found by mass spectrometry in wheat starch glucose syrups and dextrose. Additional information is given on preliminary results of specfic T cell function testing in coeliac disease and on immunoblotting based on sera from patients with bakers' allergy. Finally, two studies planned into coeliac disease and into wheat allergy are outlined from which relevant information can be expected by the end of 2006.

Wheat-based glucose syrups including dextrose may contain low levels of proteins, peptides or fragments thereof. It is not known at which levels of intake wheat-based glucose syrups including dextrose would cause allergic reactions in cereal allergic individuals. Based on the data provided by the applicant the Panel is unable to predict the likelihood of adverse reactions in cereal allergic individuals. Nevertheless, taking into account the levels of wheat proteins reported to cause allergic reactions in severe allergic individuals, the Panel considers that it is not very likely that this product will cause a severe allergic reaction in the majority of cereal allergic individuals. More clinical information is needed with regard to the effects of wheat-based glucose syrups including dextrose in cereal allergy. Appropriate clinical studies applying best clinical and laboratory practice should be carried out.

For coeliac disease, assessment of the evidence provided indicates that wheat-based glucose syrups including dextrose are unlikely to cause an adverse reaction in individuals with coeliac disease provided that the provisional value of gluten considered by Codex Alimentarius for foods rendered gluten-free (currently 200 mg/kg) is not exceeded.

KEY WORDS

Wheat starch hydrolysates, glucose syrups, dextrose, coeliac disease, food allergy.

BACKGROUND

In November 2003, the European Parliament and the Council adopted Directive 2003/89/EC[1] amending Directive 2000/13/EC, as regards indication of the ingredients present in foodstuffs.

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

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

TERMS OF REFERENCE

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

ASSESSMENT

Since wheat is relevant both as a source of epitopes known to elicit coeliac disease and as a source of allergens eliciting wheat allergy (NDA, 2004), it is fully justified to investigate wheat products, namely wheat starch hydrolysates (WSH) for their potential to induce coeliac disease or wheat allergy.

The applicant comes to the conclusion that based on wheat-based glucose syrups' history of safe use and based on the available analytical data, these substances are not likely to trigger adverse reactions. Furthermore, the applicant lists completed and ongoing experimental and clinical studies.

The following evidence is presented by the applicant in support of the statement given above.

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

1. Manufacturing process

The data provided shows that in the preparation process of wheat starch hydrolysates (isolation, conversion, purification, preservation, blending) the code of good practice is observed including HACCP principles. The applicant plans to reach a voluntary maximum protein content of glucose syrups and dextrose expressed as nitrogen of 100 mg/kg by the end of the year 2006. Purification includes filtration and refining, removing residual non-carbohydrate components, specifically proteins. Analytical data submitted shows that all samples tested contained trace amounts of proteins and peptides (1-15 mg/kg). This included native gliadin (see below for analytical data).

2. Characterisation of the product

Wheat-based glucose syrups and dextrose are used for confectionery, jams and fruit preparations, dairy ice-cream, beverages and fruit syrups, dairy desserts and biscuits, infant foods, bakery products, and also for dietetic and medicinal products for oral use. They are a major ingredient in the production of food additives such as sorbitol, xylitol, mannitol, maltitol, caramel colour, ascorbic acid and lactic acid among others after fermentation.

A study analysing dietary exposure to gluten from wheat starch hydrolysates is currently being conducted by TNO Nutrition and Food Research (The Netherlands). This study is designed to collect data from The Netherlands, Italy and Ireland and it is expected to be completed by December 2004. It is unclear how much the study will be able to answer the central question, namely the potential effect of wheat hydrolysates in coeliac disease and in wheat allergy.

3. Evidence of non-allergenicity

3.1 History of non-allergenicity of the product

A large literature review gives partly redundant information on wheat protein analysis and effects in coeliac disease and wheat allergy. Wheat starch hydrolysates are not dealt with in this literature review directly.

In a study on coeliac disease, wheat starch-based gluten-free diet was compared to naturally gluten-free diet in 76 adult coeliac patients (Collin *et al.*, 2004). The authors showed gluten contamination up to the level of 200 mg/kg of diet in both dietary groups. The long-term mucosal recovery of the patients was good in both groups. By this and other studies it has been shown that wheat starch derived gluten-free products still containing trace amounts of gluten are safe for children and adults with coeliac disease. The authors come to the conclusion that a gluten threshold of 100 mg/kg of food “can safely be set”. Although the paper is not directly devoted to the use of wheat-based glucose syrups and dextrose in coeliac disease, the evidence given is relevant to the application.

Another study submitted concerns wheat allergy in children and adults (Moneret-Vautrin *et al.*, 2003). Most of the paper is not directly relevant to the use of wheat starch hydrolysates in wheat allergy. However, provocation tests using 1 mg-19.99 g of wheat protein have been used as part of the diagnostic procedure. It is not made clear how the figures reported for wheat proteins relate to the quantities of wheat flour used for provocation tests. The results given cannot be used as dose-response information with general validity. The authors’ conclusion that “threshold doses of wheat flour in wheat flour allergics were globally higher than those

considered risk levels for coeliac disease, seeming to indicate that a wheat starch-based diet could be safe for allergic patients" is not sufficiently based on the evidence presented.

Based on the literature review submitted no adverse reactions have been reported on wheat starch hydrolysates in coeliac disease and wheat allergy. However, most of the evidence provided is indirect and inconclusive and potentially misleading.

3.2 Laboratory-based tests

Using nitrogen analysis (Kjeldahl) residual nitrogen compounds were analysed in wheat starch and wheat starch hydrolysates. A wide range of calculated protein content based on Kjeldahl nitrogen x 6.25 is shown for different samples (0.15-0.38%) of the commercial product taking dry substance into account as well as the fact that phospholipids are the main source of wheat starch nitrogen. The true protein content is much lower than the figures given above. Protein nitrogen represents only 30% of total nitrogen in wheat starch. HPLC amino acid determination showed that the true protein content of wheat starch hydrolysates was less than 100 mg/kg (detection level of HPLC).

Further evidence is provided using R5 ELISA and Western blot analysis. While in wheat starch up to 243 mg/kg gluten were found, there was no detected gluten level higher than 3.1 mg/kg (detection limit) in glucose and dextrose samples. Therefore the conclusion is justified that the gluten/gliadin epitope QQPFP was absent in most wheat starch hydrolysates.

A large and exhaustive body of evidence on quantitative and qualitative protein and peptide content of wheat starch hydrolysates was provided. Twenty-one samples (14 wheat glucose syrups, 3 crystalline dextrose) were studied by a highly refined methodology based on a detailed purification scheme and different applications of mass spectrometry. The limit of detection for gliadin was 1 mg/kg. The recovery of gliadin by the method was 86%. It was found that all samples contained some level of residual intact gliadin as well as peptides arising from degradation of gluten in the range of 1-15 mg/kg. Protein composition was slightly variable. It was observed that specific peptides from well-defined regions of gliadins and glutenins were shown relatively resistant to hydrolysis, as indicated by a summary table on 21 single samples.

The data submitted contain preliminary data and an outline for studies on specific T cell reactivity. Specific monoclonal ELISA has not been published yet and is not standardized. Therefore all results should be evaluated with caution. This is particularly true for the T cell assay which did not give any indication of T cell reactive peptides in four wheat starch hydrolysate samples. It also applies to the monoclonal ELISA indicating a very low protein level for a mixed sample. A clear significance of the findings submitted with regard to coeliac disease cannot be stated. There seems to be no relevance with regard to wheat allergy.

Immunoblotting data based on sera from five patients with bakers' asthma were included. Three wheat starch samples were investigated. In a preliminary study there was no reactivity observed of sera with one commercial sample of glucose syrup and two subfractions. It cannot be concluded that these negative reactions are representative.

3.3 Proposed clinical studies

3.3.1 Coeliac disease

This is the outline of a well-designed clinical study on the effects of wheat starch hydrolysates in coeliac disease. Study duration is August 2004 to December 2006. The protocol is based on a double-blind placebo control design on 90 coeliac patients. It randomizes into a glucose syrup/maltodextrin/placebo group for a duration of 24 weeks. The decisive information is expected from small intestinal biopsy with histological examination. Relevant information can be expected from the design given, provided the study can be realized as indicated.

3.3.2 Wheat allergy

A study protocol is given for the study of wheat starch hydrolysates in wheat allergy. However, at present diagnosis of patients included is not based on double-blind placebo-controlled food challenge (DBPCFC). This is a deficiency of the protocol. The study is based on investigation of prick test, serology and DBPCFC based on different doses of wheat starch hydrolysates (0.9/7/20 g) of glucose syrup, maltodextrin and placebo. Clinical evaluation is appropriate. However, the study protocol seems preliminary. It is not stated how many children and adults shall be included. Twenty sera from wheat allergic patients and ten sera from pollen allergic and ten sera from non-atopic controls are proposed to enter the serological part of the study. Provided diagnosis at study entry is based on DBPCFC and provided that the decisive DBPCFC part of the study can be carried out appropriately (Taylor *et al.*, 2004), conclusive information can be expected from the study outline given.

CONCLUSIONS AND RECOMMENDATIONS

1. Wheat-based glucose syrups including dextrose may contain low levels of proteins, peptides or fragments thereof. It is not known at which levels of intake wheat-based glucose syrups including dextrose would cause allergic reactions in cereal allergic individuals. Based on the data provided by the applicant the Panel is unable to predict the likelihood of adverse reactions in cereal allergic individuals. Nevertheless, taking into account the levels of wheat proteins reported to cause allergic reactions in severe allergic individuals, the Panel considers that it is not very likely that this product will cause a severe allergic reaction in the majority of cereal allergic individuals. More clinical information is needed with regard to the effects of wheat-based glucose syrups including dextrose in cereal allergy. Appropriate clinical studies applying best clinical and laboratory practice should be carried out.

2. For coeliac disease, assessment of the evidence produced indicates that wheat-based glucose syrups including dextrose are unlikely to cause an adverse reaction in individuals with coeliac disease provided that the provisional value of gluten considered by Codex Alimentarius for foods rendered gluten-free (currently 200 mg/kg) is not exceeded.

DOCUMENTATION PROVIDED TO EFSA

Dossier submitted by Association des Amidonneries de Céréales de l'Union européenne (AAC) to the European Commission pursuant to Article 6 paragraph 11 of Directive 2000/13/EC as amended by Directive 2003/89/EC, 14 June 2004.

Collin P, Thorell L, Kaukinen K, Mäki M (2004). The safe threshold for gluten contamination in gluten-free products. Can trace amounts be accepted in the treatment of coeliac disease? Aliment Pharmacol Ther 19: 1277-1283.

Moneret-Vautrin DA, Kanny G, Perrier P, Denery-Papini S, Morisset M, Leduc V, Parisot L, Beaudouin E, Croizier A, Guenard L, Sergeant P, Guérin L, Frémont S, Commun N, Battaus F (2003). 1999-2002 prospective study of wheat flour allergy in children and adults, with reference to celiac disease. Relationship of DR1 allele to allergy in children. Alim Inter 8: 2-8 (in French, publication by the Cercle d'Investigations cliniques et Biologiques en Allergie Alimentaire [CICBAA], not peer-reviewed).

REFERENCES

NDA (Scientific Panel on Dietetic Products, Nutrition and Allergies) (2004). Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission relating to the evaluation of allergenic foods for labelling purposes. The EFSA Journal 32, 1-197. http://www.efsa.eu.int/science/nda/nda_opinions/catindex_en.html

Taylor SL, Hefle SL, Bindslev-Jensen C, Atkins FM, Andre C, Bruijnzeel-Koomen C, Burks AW, Bush RK, Ebisawa M, Eigenmann PA, Host A, Hourihane JO, Isolauri E, Hill DJ, Knulst A, Lack G, Sampson HA, Moneret-Vautrin DA, Rance F, Vadas PA, Yunginger JW, Zeiger RS, Salminen JW, Madsen C, Abbott P (2004). A consensus protocol for the determination of the threshold doses for allergenic foods: how much is too much? Clin Exp Allergy 34: 689-695.

PANEL MEMBERS

Wulf Becker, Francesco Branca, Daniel Brasseur, Jean-Louis Bresson, Albert Flynn, Alan A. Jackson, Pagona Lagiou, Martinus Løvik, Geltrude Mingrone, Bevan Moseley, Andreu Palou, Hildegard Przyrembel, Seppo Salminen, Stephan Strobel, Henk van den Berg, and Hendrik van Loveren.

ACKNOWLEDGEMENT

The Scientific Panel on Dietetic Products, Nutrition and Allergies wishes to thank Elide Pastorello, Martin Stern, and Jean-Michel Wal for their contributions to the draft opinion.

European Food Safety Authority

The EFSA Journal (2007) 488, 1-8

Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to a notification from AAC on wheat-based glucose syrups including dextrose pursuant to Article 6, paragraph 11 of Directive 2000/13/EC

(Request Nº EFSA-Q-2006-164)

(adopted on 3 May 2007)

SUMMARY

Since wheat is relevant both as a source of epitopes known to induce coeliac disease and as a source of allergens triggering wheat allergy, it is appropriate to investigate wheat products, namely wheat starch hydrolysates, for their potential to induce coeliac disease or trigger wheat allergy.

The applicant provides information on wheat starch hydrolysates, particularly concerning the potential effects of wheat-based glucose syrups including dextrose in coeliac disease and wheat allergy. The history of safe use of wheat-based glucose syrups including dextrose is claimed based on the safe use of wheat starch-based gluten-free diet in coeliac disease. Similar data do not exist on wheat-allergic individuals. Low amounts of residual gluten and peptides were found by mass spectrometry and high-pressure liquid chromatography analysis in wheat starch glucose syrups including dextrose (0.3-1.4 mg/kg).

A biopsy-controlled clinical study in 27 adult patients with coeliac disease shows no deterioration of coeliac disease after a wheat starch-based glucose syrup challenge over 24 weeks. Two challenge studies in 32 wheat allergic individuals examining clinical allergic reactions to wheat starch-based glucose syrups are considered by the Panel to be inconclusive regarding the likelihood that the product may trigger an allergic reaction in susceptible individuals.

Wheat-based glucose syrups including dextrose may contain low levels of proteins and peptides. It is not known at which levels of intake glucose syrups including dextrose would cause allergic reactions in wheat-allergic individuals. Nevertheless, taking into account all the scientific information provided and in particular the levels of wheat proteins reported in glucose syrups including dextrose, the Panel considers that it is not very likely that this product will trigger a severe allergic reaction in susceptible individuals.

For coeliac disease, assessment of the evidence provided including a new clinical study indicates that wheat-based glucose syrup is unlikely to cause an adverse reaction in individuals with coeliac disease provided that the (provisional) value of gluten considered by Codex Alimentarius for foods rendered gluten-free is not exceeded.

KEY WORDS

Wheat starch hydrolysates, glucose syrups, dextrose, coeliac disease, food allergy.

BACKGROUND

In November 2003, the European Parliament and the Council adopted Directive 2003/89/EC[1] amending Directive 2000/13/EC, as regards indication of the ingredients present in foodstuffs.

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

Article 1, paragraph 11, subparagraph 2 of the Directive establishes a procedure allowing for temporary labelling exemption of derivatives from ingredients listed in Annex IIIa for which it has been scientifically established that it is not possible for them to cause adverse reactions. In accordance with this provision, submissions of requests for temporary labelling exemption were notified to the Commission before 25 August 2004. The Commission, after consultation with the European Food Safety Authority, adopted a list (Directive 2005/26/EC[2]) of those ingredients which are temporarily excluded from Annex IIIa until 25 November 2007, pending the final results of the notified studies.

Consequently, applicants who submitted a dossier in 2004 on the basis of subparagraph 2, resulting in the inclusion of a product in the list of Directive 2005/26/EC, and who are seeking exclusion of that product from Annex IIIa beyond 25 November 2007 will have to submit a request enclosing the final results of the notified scientific studies. Therefore in the context of the permanent labelling exemption procedure, the European Food Safety Authority is asked to provide scientific opinions on the submissions in accordance with the present terms of reference.

TERMS OF REFERENCE

In accordance with Article 29 (1) (a) of Regulation (EC) N° 178/2002, the European Commission requests the European Food Safety Authority to evaluate the scientific data submitted by AAC in the framework of the procedure laid down in Article 6, paragraph 11 of Directive 2000/13/EC. On the basis of that evaluation, EFSA is requested to issue an opinion

[1] Directive 2003/89/EC of the European Parliament and of the Council amending Directive 2000/13/EC as regards indication of the ingredients present in foodstuffs. OJ L 308. 25.11.2003, p. 15.
[2] Commission Directive 2005/26/EC of 21 March 2005 establishing a list of food ingredients or substances provisionally excluded from Annex IIIa of Directive 2000/13/EC of the European Parliament and of the Council. OJ L 75, 22.03.2005, p. 33-34.

on the information provided, and particularly to consider the likelihood of adverse reactions triggered in susceptible individuals by the consumption of the following ingredients/substances used under the conditions specified by the applicant: wheat-based glucose syrups including dextrose.

ASSESSMENT

Since wheat is relevant both as a source of epitopes known to elicit coeliac disease and as a source of allergens eliciting wheat allergy (NDA, 2004a), it is appropriate to investigate wheat products, namely wheat starch hydrolysates for their potential to induce coeliac disease or wheat allergy.

In 2004, the panel issued an Opinion on a notification submitted by AAC to the European Commission pursuant to article 6, paragraph 11 of Directive 2000/131/EC as amended by the Directive 2003/89/EC, for temporary exemption from labelling (NDA, 2004b).

Under the framework of permanent exemption from labelling, the present Opinion is based on assessment of an updated dossier from AAC which contains additional information on dietary exposure to gluten from wheat starch hydrolysates, on immunochemical and HPLC analysis of products and new clinical studies into coeliac disease and into wheat allergy.

1. Manufacturing process

Different purification steps, in particular the active carbon treatment, removes proteins and other nitrogen-containing compounds. The data provided show that the preparation process of wheat starch hydrolysates includes isolation, conversion, purification, preservation and blending. The applicant also states that GMP protocols are followed and that particular attention should be given to avoid gluten contamination during the manufacturing process.

2. Characterisation of the product

Wheat-based glucose syrups are a purified and concentrated aqueous solution of saccharides obtained from starch. Dextrose is purified and is crystallized as α-D-glucose. Wheat-based glucose syrups and dextrose are used for confectionery, jams and fruit preparations, dairy ice-cream, beverages and fruit syrups, dairy desserts and biscuits, infant foods, bakery products, and also for dietetic and medicinal products for oral use. They are ingredients in the production of food additives such as sorbitol, xylitol, mannitol, maltitol, caramel colour, ascorbic acid and lactic acid among others.

2.1 Exposure estimation

A new study analysing dietary exposure to gluten from wheat starch hydrolysates has been conducted by TNO Nutrition and Food Research and provided by the applicant. Main sources of exposure were soft drinks, dairy desserts, yoghurt drinks, candy and canned food, soups and savoury sauces. This study was designed to collect data from The Netherlands, Italy and Ireland (representative sample of Dutch population including children, Italian students living in the district of Rome, Irish adults aged 18-64 years) based on food consumption data from these countries and on gluten content in glucose syrups and dextrose from wheat starch hydrolysates of 10-20 mg/kg (mass spectrometry). According to the applicant, exposure to gluten from

glucose syrups and dextrose was less than 3.5 mg per day for 95% of the adult Dutch men. All other population subgroups had lower exposure.

3. Evidence of non-allergenicity

3.1 History of non-allergenicity of the product

An extensive literature review has provided information on wheat protein analysis and effects of wheat on coeliac disease and wheat allergy. This review has not identified papers on wheat starch hydrolysates.

In a study on coeliac disease, wheat starch-based gluten-free diet was compared to naturally gluten-free diet in 76 adult patients with coeliac disease (Collin *et al.*, 2004). The authors showed gluten contamination up to the level of 200 mg/kg of diet in both dietary groups. The long-term mucosal recovery of the patients was good in both groups. By this and other studies it has been shown that wheat starch-derived gluten-free products still containing trace amounts of gluten are safe for children and adults with coeliac disease. The authors came to the conclusion that a gluten threshold of 100 mg/kg of food "can safely be set". Although the paper is not directly devoted to the use of glucose syrups including dextrose in coeliac disease, the evidence given is relevant to the application.

Another study submitted concerns wheat allergy in children and adults (Moneret-Vautrin *et al.*, 2003). Most of the paper is not directly relevant to the use of wheat starch hydrolysates in wheat allergy. However, provocation tests using 1 mg-19.99 g of wheat protein have been used as part of the diagnostic procedure. 80% of allergic children reacted to less than 2 g, 40% to less than 1 g of wheat protein. However, 6% (two out of 32) of the children reacted to less than 10 mg of protein. It is not made clear how the figures reported for wheat proteins relate to the quantities of wheat flour used for provocation tests, even if the authors consider protein content of wheat flour to be 12% by weight (as cited by the applicant). The results given cannot be used as dose-response information with general validity. The authors' conclusion that "threshold doses of wheat flour in wheat flour allergic individuals were globally higher than those considered risk levels for coeliac disease, seeming to indicate that a wheat starch-based diet could be safe for allergic patients" is not sufficiently based on the evidence presented. A further study has been carried out recently in 37 adult patients with wheat allergy by Scibilia *et al*. (2006). By double-blind placebo-controlled food challenge (DBPCFC), the lowest provocation dose was 0.1 g of raw and cooked wheat flour. 27% of the subjects had a provocation dose ≤ 1.6 g. The papers by Moneret-Vautrin *et al.* (2003) and Scibilia *et al.* (2006) have only indirect relevance to the application, since the protein content of the eliciting dose of wheat flour was not determined.

By history, non-allergenicity of wheat starch hydrolysates is assumed by the applicant. Based on the literature review submitted no adverse reactions have been reported to wheat starch hydrolysates in coeliac disease or wheat allergy. However, the evidence provided is indirect and under-reporting of allergic reactions may have occurred.

3.2 Laboratory-based tests

Further evidence was provided using R5 enzyme-linked immunosorbent assay (ELISA) specific for the gluten/gliadin epitope QQPFP. While in starches up to 279.3 mg/kg of gluten were found, there was no detected gluten level higher than 25.3 mg/kg (limit of detection 3.1

mg/kg, LOD) in glucose syrups and dextrose samples in the years 2005-2006 (3-43 samples per year). One dextrose sample (AAC 29) showed a gluten content of 39.6 mg/kg by R5 ELISA due to assumed contamination. Therefore the conclusion that the gluten/gliadin epitope QQPFP was absent or present only in low amounts of glucose syrups and dextrose samples is justified.

A large and exhaustive body of previous evidence on quantitative and qualitative protein and peptide content of wheat starch hydrolysates was provided. Twenty-one samples (14 wheat glucose syrups, 3 crystalline dextrose, 4 glucose syrups) were studied by a highly refined methodology based on a detailed purification scheme and different applications of mass spectrometry. The limit of detection for gliadin was 1 mg/kg. The recovery of gliadin by the method was 86%. It was found that all samples contained some level of residual intact gliadin as well as peptides arising from degradation of gluten in the range of 1-40 mg/kg. Protein composition was slightly variable. It was observed that specific peptides from well-defined regions of gliadins and glutenins were relatively resistant to hydrolysis as indicated by a summary table on 21 single samples. By high-pressure liquid chromatography (HPLC) the applicant showed that protein concentrations ranged from 0.3 to 1.4 mg/kg.

IgE-binding was found by ELISA in 7 out of 32 sera from wheat-allergic patients with 1-3 out of 4 preparations of glucose syrups and dextrose (antigen-coated plates (ACP) ELISA). These seven sera also showed strong IgE-binding to different native wheat protein fractions (gluten, gliadin, albumins and globulins, lipid transfer protein). The authors assume that this reactivity does not reflect the *in vivo* potential of glucose syrups including dextrose products to induce an allergic reaction in these patients.

3.3 Clinical studies

3.3.1 Coeliac disease

A new DBPCFC was provided by the applicant involving 90 adult patients with a biopsy-based diagnosis of coeliac disease. Patients were challenged with either wheat starch-based maltodextrin (n = 30), glucose syrup (n = 30) or placebo (n= 30) daily for 24 weeks. Patients with refractory coeliac disease or with dietary transgressions had been excluded. Assessment was accomplished by clinical evaluation, dietary and laboratory analyses, telephone assessment and initially and ultimately a small intestinal biopsy. Differences between baseline and end of study were indicated by delta values. Daily ingestion of wheat starch-based glucose syrups and dextrose did not have any deleterious effect on the small bowel mucosa. Differences in small intestinal villous height by crypt depth ratio and density of intraepithelial lymphocytes were not statistically significant. The same was observed for gastrointestinal symptoms, quality of life and laboratory parameters.

There were eight drop-outs, seven due to abdominal symptoms, one to non-compliance. None of those patients developed villous atrophy. Three of those drop-outs belonged to the maltodextrin group, three to the placebo group, and two to the glucose syrup group.

Minor dietary lapses were observed in six out of 90 patients. Four of those patients belonged to the glucose syrups group, one to the placebo group. 86 out of 90 patients (including drop-outs) consented to a final biopsy and full evaluation. It is concluded by the applicant that there was no adverse effect of the glucose syrup preparation used over a 24-week challenge in 30 fully evaluated adult Finnish coeliac patients.

3.3.2 Wheat allergy

A new clinical study was provided by the applicant. Thirty-six patients were enrolled, and 32 completed the study. This included 22 children aged 2-12 years old and ten female adults aged 22-54 years. Diagnosis of wheat allergy was based on DBPCFC using raw wheat flour in 23 patients, in three highly allergic patients diagnosis was based on application on the lips and in six patients diagnosis was based "on the fact that the patients did not pass the trial of reintroduction". Symptoms were atopic dermatitis, angioedema, urticaria, growth failure, diarrhoea and abdominal pain. For the clinical study, a powdered orange-flavoured soft drink containing glucose syrup was used containing 0.1 mg wheat protein in 34.6 g powdered soft drink. Sucrose was used for placebo.

Differences in skin prick test results were difficult to evaluate due to a positive reaction in a negative control and due to the small numerical differences in diameters compared with reactions in positive controls.

Two challenge studies were provided by the applicant. A DBPCFC was conducted in 15 patients with three doses at 30-minute intervals. The total dose of challenge was 150ml of a solution containing 13.85 g of dried glucose syrup (0.3 mg of cereal proteins) for children and 300 ml of the same solution containing 27.7 g of dried glucose syrup (0.6 mg of cereal proteins) for adults. One patient had symptoms (pruritus, headache) after glucose syrup and two (urticaria, diarrhoea, abdominal pain, asthenia) after placebo. A second challenge was done at home over a 20-day period. In a blind manner the glucose product and placebo were consumed consecutively for 10 days by 15 patients. Five patients showed symptoms (atopic dermatitis, diarrhoea, asthma, asthenia, urticaria, pollakisuria) after glucose syrup and three (diarrhoea, nausea, asthma, abdominal pain, urticaria, atopic dermatitis) after placebo administration. With the limitation that only one glucose syrup product was tested and only children over two years of age were included in the study for ethical reasons, there was no statistically significant clinical reactivity to glucose syrups including dextrose over placebo shown in the study presented.

The Panel considers that these challenge studies are inconclusive regarding the likelihood that the product may trigger an allergic reaction in susceptible individuals.

CONCLUSIONS

1. Wheat-based glucose syrups including dextrose may contain low levels of proteins and peptides. It is not known at which levels of intake glucose syrups including dextrose would cause allergic reactions in wheat-allergic individuals. Nevertheless, taking into account all the scientific information provided and in particular the levels of wheat proteins reported in glucose syrups including dextrose, the Panel considers that it is not very likely that this product will trigger a severe allergic reaction in susceptible individuals.

2. For coeliac disease, assessment of the evidence produced including a new clinical study indicates that wheat-based glucose syrup is unlikely to cause an adverse reaction in individuals with coeliac disease provided that the (provisional) value of gluten considered by Codex Alimentarius for foods rendered gluten-free is not exceeded.

DOCUMENTATION PROVIDED TO EFSA

Dossier submitted by the "Association des Amidonneries de Céréales de l'Union Européenne" (AAC) to the European Commission pursuant to Article 6 paragraph 11 of Directive 2000/13/EC as amended by Directive 2003/89/EC on 31 August 2006.

REFERENCES

Codex standard for sugars. Codex Standard 212-1999 (Amd. 1-2001), p.1-5.

Collin P, Thorell L, Kaukinen K, Mäki M (2004). The safe threshold for gluten contamination in gluten-free products. Can trace amounts be accepted in the treatment of coeliac disease? Aliment Pharmacol Ther 19: 1277-1283.

NDA (Scientific Panel on Dietetic Products, Nutrition and Allergies) (2004a). Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission relating to the evaluation of allergenic foods for labelling purposes. The EFSA Journal 32, 1-197.
http://www.efsa.europa.eu/en/science/nda/nda_opinions/food_allergy/341.html

NDA (Scientific Panel on Dietetic Products, Nutrition and Allergies) (2004b). Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to a notification from AAC on wheat-based glucose syrups including dextrose pursuant to Article 6 paragraph 11 of Directive 2000/13/EC. The EFSA Journal 126, 1-6. http://www.efsa.europa.eu/en/science/nda/nda_opinions/food_allergy/681.html

Moneret-Vautrin DA, Kanny G, Perrier P, Denery-Papini S, Morisset M, Leduc V, Parisot L, Beaudouin E, Croizier A, Guenard L, Sergeant P, Guérin L, Frémont S, Commun N, Battaus F (2003). 1999-2002 prospective study of wheat flour allergy in children and adults, with reference to celiac disease. Relationship of DR1 allele to allergy in children [in French]. Alim Inter 8: 2-8.

Scibilia J, Pastorello EA, Zisa G, Ottolenghi A, Bindslev-Jensen C, Pravettoni V, Scovena A, Robino (2006). Wheat allergy: A double-blind, placebo-controlled study in adults. J Allergy Clin Immunol 117: 433-439.

PANEL MEMBERS

Jean-Louis Bresson, Albert Flynn, Marina Heinonen, Karin Hulshof, Hannu Korhonen, Pagona Lagiou, Martinus Løvik, Rosangela Marchelli, Ambroise Martin, Bevan Moseley, Andreu Palou, Hildegard Przyrembel, Seppo Salminen, John (Sean) J Strain, Stephan Strobel, Inge Tetens, Henk van den Berg, Hendrik van Loveren and Hans Verhagen.

ACKNOWLEDGEMENT

The Scientific Panel on Dietetic Products, Nutrition and Allergies wishes to thank Taraneh Dean, Martin Stern and Jean-Michel Wal for their contributions to the draft opinion.