Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the evaluation of lupin for labelling purposes

(Request N° EFSA-Q-2005-086)

(adopted on 6 December 2005)

SUMMARY

Lupin (genus *Lupinus*, subfamily *Papilionaceae*, family *Leguminosae*) is a legume which includes over 450 species. *Lupinus albus* (*white lupin*, Mediterranean countries), *Lupinus luteus* (yellow lupin, Central Europe), *Lupinus angustifolius* (*blue lupin*, Australia) are used for human and animal consumption. Lupin seeds have been part of normal food intake since ancient times and are consumed as snacks in several European countries. Since the introduction of lupin flour as an ingredient in wheat flour in the 1990s for its nutritional and food processing qualities, lupin consumption became more widespread in Europe.

Allergic reactions to lupin have been documented. IgE-binding proteins of lupin flour extracts have been identified and show *in vitro* cross-reactivities with peanut and other legumes, although the most clinically relevant cross-reactions are with peanut proteins. There is no definite indication that technological treatments alter the allergenic potential of lupin, although reduction in allergenicity has been reported after autoclaving lupin seeds at 138°C for 30 minutes.

The frequency of allergic reactions to lupin in the general population is unknown. Most, though not all, allergic reactions have been reported in peanut allergic individuals. The possibility of under-reporting of allergy cases cannot be excluded, as until recently lupin was a hidden ingredient in various bakery and meat products. One controlled study in peanut allergic patients suggests a clinically relevant cross-reactivity rate of about 30%, but higher (68%) rates have been reported. Clinical reactions range from mild local reactions to systemic anaphylaxis. Ingested doses of lupin flour reported to have triggered clinical reactions range from 265 to 1000 mg, but the lowest dose triggering reactions has not been established.

KEY WORDS

Lupin, peanut, legumes, cross-reactivity, food allergy.

BACKGROUND

Annex IIIa of Directive 2000/13/EC, as amended by Directive 2003/89/EC, establishes a list of ingredients that are known to trigger allergies or intolerances. The aforementioned Directive states that whenever the listed ingredients are used in the production of foodstuffs they must be labelled.

Article 6, paragraph 11 of the same Directive requests that the list in Annex IIIa shall be systematically re-examined and, where necessary, updated on the basis of the most recent scientific knowledge.

Furthermore, paragraph 11 states that Annex IIIa may be amended, in compliance with the procedure referred to in Article 20 (2), on the basis of a scientific opinion of the European Food Safety Authority.

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 provide a scientific opinion on the appropriateness for inclusion of lupin, and its eventual derived products in the list of food allergens set up in Annex IIIa of Directive 2000/13/EC, in the light of the most recent scientific evidence.

ASSESSMENT

The Panel decided to focus on the evidence basis upon which a decision on the appropriateness of inclusion under the Terms of Reference could be based. The Panel considers the decision whether or not to include lupin a risk management task which is outside the remit of the Panel.

1. INTRODUCTION

Lupin (genus *Lupinus*, subfamily *Papilionaceae*, family *Leguminosae*) is a legume which includes over 450 species. It has been used for human food and animal feed since ancient times in Europe and lupin seeds are a common snack in several European countries. It is widely grown as a flowering plant for animal feed and farm land management. The usual garden species are poisonous. Some species *Lupinus luteus* (yellow lupin, Central Europe), *Lupinus albus* (white lupin, Mediterranean countries), *Lupinus angustifolius* (blue lupin, Australia) are low alkaloid varieties and are used as whole seed flour, or as lupin derived drinks ("milks") for human and animal consumption. The yellow lupin variety, because of its colour, is preferably used as egg substitute. The above varieties are known as sweet lupines.

The nutritional value of lupin and its potential as a human food has been under consideration for about 30 years (Gross *et al*., 1976; Yáñez *et al*., 1979 and 1983). One of the major points for consideration was the low costs, high protein quality, and the associated increased protein-efficiency ratio compared to other members of the legume family (Yáñez *et al.*, 1979). Lupin flour is an excellent source of protein (39%-45%, depending on the lupin species) (Yáñez *et al*., 1983; Zacarias *et al*., 1989; Vásquez *et al*., 1989; Marss, 1996). Lupin protein contains essential amino acids (lysine, leucine and threonine) (Kanny *et al*., 2000). It is low in methionine and addition of methionine improves the protein efficiency ratio (Yáñez *et al*., 1983; Catricheo *et al*., 1989). Lupin does not contain gluten and can be used in gluten-free foods (Marss, 1996; Kanny *et al*., 2000). Supplementation rates studied range from 5%-15% of wheat flour (Yáñez *et al*., 1979; Taha *et al*., 1982). Since its introduction as an ingredient

in wheat flour, lupin flour became a more widely consumed food ingredient (inclusion of lupin in wheat flour at a 10% level was authorised in France in 1997) (Moneret-Vautrin *et al*., 1999; Smith *et al*., 2004). Lupin flour was introduced in 1996 in the UK and in 2001 in Australia. Lupin flour is used in biscuits, pasta, sauces, dietetic products sold as milk and soy substitutes (Wittig de Penna *et al*., 1987; Petterson *et al*., 1994; Moneret-Vautrin *et al*., 1999). Due to its emulsifying properties, the use of lupin concentrates in meat and cold-cut industry is also being studied (Kanny *et al*., 2000).

2. FREQUENCY

2.1 Population at risk

The prevalence of primary allergy to lupin in the general population is unknown and currently seems to be low (see case reports below). It is likely to be dependent on local eating habits and other routes of exposure. Lupin consumption appears to be increasing in several European countries. To date, the main population at risk is peanut allergic individuals, which represent about 0.7-1.5% of the European population (NDA, 2004), due to the potential cross-reactivities. Allergic reactions to lupin have emerged as an issue following its introduction in processed foods in the late 1990s in Europe. The possibility of under-reporting of allergic reactions to lupin cannot be excluded, as until recently[1], it was a hidden (undeclared) ingredient in various bakery and other food products. Further studies are needed to establish the prevalence of allergic reactions to lupin in peanut allergic individuals as well as in the population of allergic individuals.

2.2. Reported incidents

There have been a number of reports of allergic reactions to lupin (see Table 1), mostly referring to patients with a known allergy to peanuts attending specialist medical services (Hefle *et al*., 1994; Moneret-Vautrin *et al*., 1999; Faeste *et al*., 2004).

One case of anaphylaxis (with open oral challenge negative for peanut and green bean but positive for pea) was reported by Matheu *et al*. (1999). Recently, three cases of allergic reactions after ingesting lupin as a bread ingredient or in the form of snack food were reported in subjects with no prior allergy to peanut and negative skin prick test (SPT) for this food (Smith *et al*., 2004). Sensitization to lupin via inhalation has also been reported in a child with no immunologic reactivity to other legumes (Novembre *et al*., 1999) and for three occupationally exposed adults with no allergy to peanut (Crespo *et al*., 2001; Parisot *et al*., 2001).

3. CLINICAL FEATURES

3.1 Different patterns of allergy

Three clinical patterns of allergy to lupin emerge from the literature:

[1] Labelling Directive 2000/13/EC, as amended by Directive 2003/89/EC, that entered into force on 25 November 2005, which applies only to pre-packaged foodstuffs.

a) Triggering a reaction via ingestion among individuals allergic to peanuts (Hefle *et al*., 1994; Moneret-Vautrin *et al*. 1999; Kanny *et al*., 2000; Faeste *et al*., 2004). Peanut allergic patients are likely to represent the major risk group.

b) Sensitisation via ingestion among individuals with no known allergy to peanuts (Matheu *et al*., 1999; Smith *et al*., 2004).

c) Sensitisation and triggering via inhalation (Novembre *et al*., 1999; Moreno-Ancillo *et al*., 2005) and occupational exposures among individuals with no known allergy to peanuts (Crespo *et al*., 2001; Parisot *et al*., 2001).

Table 1. Allergic reactions to lupin-containing products

Author	Age (years), gender, country	Known allergy	Oral food trigger	Amount ingested	Symptoms
Hefle *et al*., 1994	5, F USA	peanut	noodles	NK	urticaria, angioedema
Matheu *et al*., 1999	38, F Spain	peas	lupin seeds	3 lupin seeds	anaphylaxis (urticaria, angioedema, SOB)
Faeste *et al*., 2004	24, F Norway	peanut	bread	NK	urticaria, lip oedema
Smith *et al*., 2004	42, 42, 26, F Austria	hay fever (pollen)	bread with lupin grain	NK	urticaria, angioedema, SOB, abdominal pain
Wüthrich *et al*., 2004	24, 27, F Switzerland	peanut, hay fever (pollen)	pizza gingerbread	NK	severe asthma, oedema, abdominal pain
Radcliffe *et al*., 2005	25, F Great Britain	peanut	lupin flour in dough	NK	oral allergy syndrome, anaphylaxis
Romano *et al*., 1997	n = 3 Italy	NK	lupin seeds	NK	oral allergy syndrome
Leduc *et al*., 2002	Child France	NK	pizza with lupin flour	NK	anaphylaxis
Wassenberg and Hofer, 2004	8, F Switzerland	NK	waffle with lupin flour	NK	SOB, facial oedema, rhinitis
Crespo and Rodríguez, 2003	28, 27, 39, F Spain	atopy rhinitis & asthma	lupin flour inhalation	NK	SOB, asthma, rhinitis
Moreno-Ancillo *et al*, 2005	8, M, Spain	peanut allergy, asthma	lupin seed handling / inhalation	NK	SOB, asthma

SOB: Shortness of breath; NK: Not known.

3.2 Clinical symptoms reported

Clinical symptoms reported after lupin inhalation or ingestion are similar to those reported for other inhalant or food allergens (NDA, 2004). Individuals with inhalant allergies suffer from asthma, rhino-conjunctivitis and dermatitis and their symptoms include throat tingling, cough, wheeze dyspnoea, cyanosis and reduction of FEV_1 (Moneret-Vautrin *et al*., 1999 and 2001; Novembre *et al*., 1999; Crespo *et al*., 2001; Parisot *et al*., 2001). Individuals reacting after ingestion show symptoms of mucosal erythema, facial oedema, angioedema, rhino-conjunctivitis, throat tingling, cough, asthma, urticaria, atopic dermatitis and abdominal symptoms (Hefle *et al*., 1994; Gutiérrez *et al*., 1997; Moneret-Vautrin *et al*., 1999; Smith *et al*., 2004). Oral allergy-like symptoms confined to the oral cavity have also been reported (Romano *et al*., 1997). Cases of lupin anaphylaxis have been reported by Matheu *et al*. (1999), Smith (2004), and Radcliffe *et al*. (2005) (see Table 1).

4. IDENTIFIED ALLERGENS

The proteins of *L. albus* are mainly comprised by four fractions called α, β, γ and δ-conglutin which are all glycosylated storage proteins (Table 2).

It appears that the major IgE-binding protein of lupin is located in the 43-45 kDa immunoblot band (Novembre *et al*., 1999; Moneret-Vautrin *et al*., 1999; Parisot *et al*., 2001). Moneret-Vautrin and colleagues (1999) reported that the most distinctly reactive band had a molecular mass of 43 kDa, and interpreted the total inhibition of immunoblot lupin flour by peanut as a confirmation of the cross-reactivity of the 43-kDa allergen. Lupin proteins, which react with sera from peanut allergic patients, do not correspond to the native forms of the major peanut allergens Ara h 1, Ara h 2 and Ara h 3. In a mouse model, Foss and Frøkiær (2005) suggested that a major cross-reactivity against peanuts is found in the γ-conglutin section of lupin.

Other possible major allergens of lupin flour have not been characterised in detail. In 2005, Magni and colleagues, using two-dimensional electrophoresis, reported that two lupin proteins, conglutin gamma (2S albumin) and 11S globulin, strongly reacted with the sera of their lupin-sensitised patients and that cross-reactivities with the homologous polypeptides of other legume species were observed (Magni *et al*., 2005). Guarneri and colleagues reported significant sequence and molecular homology between Ara h 8 of peanut and the pathogenesis related protein PR-10 of white lupin and suggests that these proteins could in part be responsible for some of the reported cross-reactivities in peanut allergic individuals (Guarneri *et al*., 2005).

Table 2. Proteins of *L. albus*

	α-Conglutin	**β-Conglutin**	**γ-Conglutin**	**δ-Conglutin**
Size (kDa)	69 to 89	19 to 60	17 and 29	9.4 and 4.6
% of protein	33	45	5	12
Type	7S – 12S	7S	7S	2S

Foss and Frökiær, 2005

5. METHODS OF ANALYSIS

Capillary zone electrophoresis (CZE) and HPLC have been employed for the detection of lupin in meat products (Mellenthin and Galensa, 1999). Polyphenols like isoflavones that are characteristic of certain legumes were the analytes detected by these methods. Lupin protein contains only small amounts of isoflavones and the detection limit for CZE was reported to be around 5% lupin protein in sausages. HPLC was reported to be superior, but no limit of detection has been given for this method. The fact that the major (detectable) polyphenols are not specific to lupin but also occur in, for instance, soy is a major disadvantage of the above mentioned techniques.

Immunological approaches to detect lupin protein in food consist of Western blotting, radio-allergosorbent tests (RAST) and enzyme-linked immunosorbent assays (ELISA). The use of serum from allergic patients in such methods hampers standardisation, and the limited availability of such serum prevents methods depending on this from becoming routine analyses. A quantitative sandwich ELISA that utilizes polyclonal rabbit anti-lupin antibodies can however be used as a routine method to detect lupin in food products with a detection limit of 1 mg lupin protein per 1 kg of food (Holden *et al.*, 2005). Generally, the extensive immunological cross-reactivities between legumes will represent a problem in the development of lupin-specific immunological assays (Magni *et al.*, 2005; Ibáñez *et al.*, 2003; Bernhisel-Broadbent and Sampson, 1989; Bernhisel-Broadbent *et al.*, 1989). Solubility issues of lupin specific proteins may also affect the sensitivity of ELISA assays (Duranti *et al.*, 2005). Currently there are no molecular biological techniques reported on the detection of lupin in food products. However, the availability of a sizeable amount of sequence information for lupin (there are more than 2500 expressed sequence tags publicly available) provides a good basis for the future development of PCR-based methods for lupin detection.

6. CROSS-REACTIVITIES

There are extensive *in vitro* cross-reactivities between members of the legume family, which are of clinical relevance in about 5% of legume allergic individuals (Bernhisel-Broadbent and Sampson, 1989; Bernhisel-Broadbent *et al.*, 1989; Sicherer, 2001; Mills and Shewry, 2004). Of clinical importance with respect to lupin is the cross-reactivity to peanut (Hefle *et al.*, 1994; Moneret-Vautrin *et al.*, 1999; Kanny *et al.*, 2000; Faeste *et al.*, 2004). A study by Moneret-Vautrin (1999) suggests a cross-reactivity rate to lupin flour in peanut allergic individuals of around 30% (7/24 peanut allergic patients, 6 of which were challenged with a DBPCFC). The youngest child (1.5 years) did not have a positive skin test but responded with deterioration of her atopic dermatitis. In this study, the male:female ratio was 1:8 and the allergen doses eliciting a positive response were similar for peanut and lupin (peanut 5-965 mg, lupin 265-1000 mg).

Leduc and colleagues have reported that in a double-blind challenge study, 68% (15/23) of patients allergic to peanuts have shown positive reactions to lupin flour (Leduc *et al.*, 2002). Positive skin prick tests for grass pollen have been reported in two cases of inhalation-induced lupin allergy (Novembre *et al.*, 1999; Parisot *et al.*, 2001). Both patients had negative skin prick tests for peanut. It should be stressed that a positive SPT does not necessarily correlate with clinical reactivity. Although a major lupin allergen, belonging to the PR10 is homologous to the birch pollen allergen Bet v 1 family (17-22 kDa) with common secondary structures, there is no information as to the likelihood of clinical reactions to lupin in these

individuals. The scarcity of clinical reports from countries with a high birch pollen sensitisation rate (for example Sweden) may suggest that this structural cross-reactivity is currently not of clinical relevance in these populations. The Panel is not aware of systematic studies which address the relationship of lupin pollen allergies to reactions to lupin flour after ingestion. Individuals sensitised via inhalation to lupin flour may react to lupin flour after ingestion (Crespo *et al*., 2001 and 2002).

7. POSSIBLE EFFECTS OF PROCESSING ON ALLERGENICITY

A common feature of most legume allergens is their relative resistance to thermal, chemical, and proteolytic degradation (Lalles and Peltre, 1996; Mills *et al.*, 2004). The allergenicity of lupin after thermal processing was studied by Álvarez-Álvarez and colleagues (2005). They studied the allergenic characteristics of lupin seeds after boiling (up to 60 minutes), autoclaving (121°C, 1.18 atmospheres, up to 20 minutes and 138°C, 2.56 atmospheres, up to 30 minutes), microwave heating (30 minutes), and extrusion cooking. They reported an important reduction in allergenicity only after autoclaving at 138°C for 20 minutes and absence of an IgE binding after autoclaving for 30 minutes.

8. DOSES TRIGGERING CLINICAL REACTIONS

There is little information in the literature on the lowest doses of lupin that could cause a clinical allergic reaction (see also Table 1). There is no explanation of the amount of lupin ingested in the case reports (Table 1). Existing data refer to peanut allergic individuals. Moneret-Vautrin and colleagues (1999) challenged orally with lupin flour six children allergic to peanut, in a double-blind placebo-controlled trial, and reported allergic reactions in five of them at doses of lupin flour ranging from 265 to 1000 mg (two children with grade 2 response to the labial challenge were not submitted to the oral challenge). Kanny and colleagues (2000) reported a case of anaphylaxis and deteriorating lung function in a highly peanut allergic 13 year old girl, after oral challenge with a cumulative dose of 965 mg of a crude lupin flour extract, and consider that this quantity could be present in 100 g of bread if the wheat flour contains 10% lupin. Further studies on the triggering dose levels of allergic reactions are needed.

CONCLUSIONS AND RECOMMENDATIONS

Lupin (genus *Lupinus*, subfamily *Papilionaceae*, family *Leguminosae*) is a legume which includes over 450 species. *Lupinus albus* (*white lupin*, Mediterranean countries), *Lupinus luteus* (yellow lupin, Central Europe), *Lupinus angustifolius* (*blue lupin*, Australia) are used for human and animal consumption. Lupin seeds have been part of normal food intake since ancient times and are consumed as snacks in several European countries. Since the introduction of lupin flour as an ingredient in wheat flour in the 1990s for its nutritional and food processing qualities, lupin consumption became more widespread in Europe.

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