AGENCE FRANÇAISE
DE SÉCURITÉ SANITAIRE
DES ALIMENTS

# *Food allergies and advisory labelling*

*- November 2008 -*

**Scientific and editorial coordination:**
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# List of abbreviations

| | |
|---|---|
| ANIA | French Food Industries' Association |
| ASPCC | 'Sugar and sweet products association, communication, consumption' survey |
| CCA | Codex Alimentarius Commission |
| CICBAA (F) | Circle of Clinical and Biological Investigations in Food Allergy |
| CREDOC | Research Centre for the Study and Observation of Living Conditions (F) |
| EAST | Enzyme Allergo- Sorbent Test |
| EC | European Community |
| EFSA | European Food Safety Authority |
| ELISA | Enzyme-Linked Immunosorbent Assay |
| EU | European Union |
| FAO | Food and Agriculture Organization |
| FARRP | Food Allergy Research and Resource Program (US) |
| FDA | Food and Drug Administration (US) |
| FPI | Food (processing) industry |
| FSA | Food Standards Agency (UK) |
| Ig | Immunoglobulins |
| ILSI | International Life Science Institute (Int) |
| INCA | Individual and national survey on food consumption (F) |
| INSEE | French National Institute for Statistics and Economic Studies (F) |
| kDa | kiloDalton |
| LTP | Lipid Transfer Protein |
| NOAEL | No Observable Adverse Effect Level |
| PCR | Polymerase Chain Reaction |
| PIR | Protein Information Resource (US) |
| RAST | Radioallergosorbent Test |
| RT-PCR | Reverse Transcriptase Polymerase Chain Reaction |
| TPODA | Double blind placebo controlled food challenge (DBPCFC) |
| UH | University Hospital (F) |
| WG | Afssa working group |
| WHO | World Health Organization |

# Working group members and operating method

## Working group members

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## Organisation of the group's work

| | | |
|---|---|---|
| **Chap. 1** | Definitions and terminology | **C. Le Stunff**<br>**S. La Vieille** |
| | *Response to Q1 of the request* | |
| **Chap. 2** | Amounts of allergens and how often they are unintentionally present in food | **S. La Vieille from interviews with food industries** |
| | *Response to Q2 of the request* | |
| **Chap. 3** | Proportion of food allergy sufferers for whom the accidental presence of allergens poses a reaction risk | **G. Kanny**<br>**DA. Moneret-Vautrin**<br>**JL. Volatier** |
| **Chap. 4** | dose/response relationships | **F. Rancé**<br>**DA. Moneret-Vautrin** |
| **Chap. 5** | Methods for detecting and quantifying allergens in foods | **H. Bernard**<br>**C. Demeulemester** |
| | *Responses to Q3, Q4 and Q5 of the request* | |
| **Chap. 6** | Growing complexity of formulations.<br>Increase in allergies and complexity of the formulation of food products | **JL. Volatier**<br>**G. Kanny** |
| | *Response to Q7 of the request* | |
| **Chap. 7** | Knowledge to be acquired | **All group members** |
| | *Response to Q6 of the request* | |
| **Chap. 8** | **WG conclusions and recommendations** | **All group members** |

***This report was validated by Afssa's "Human Nutrition" Scientific Panel during its meeting of 18 September 2008.***

# Contents

# Tables and figures

## Tables



## Figures

# Introduction

## Context and justification of the request

In April 2005, Afssa received a request from the consumers' association "Consommation, Logement et Cadre de Vie (Consumers, Housing and Living Environment/CLCV) to give its opinion on the accidental presence of allergens in foodstuffs. To respond to this request, Afssa created an *ad hoc* working group in June 2005.

Fully applicable since November 2005, European Directive 2003/89/EC makes the labelling of all ingredients used in the recipes of pre-packaged foods compulsory, with a few exceptions. Allergic patients' associations and doctors believe that this Directive has made it possible not only to improve the quality of life of food allergy sufferers but also to progress in terms of preventing allergic reactions.

However, while this Directive has been in force, preventive labelling, drawing the consumer's attention to the risk of allergens being accidentally present in foodstuffs, has flourished. This accidental presence of allergens is mainly due to the use of increasingly complex manufacturing processes. This type of labelling, generally called "advisory labelling", uses a wide array of expressions such as "product may contain a given allergen" or "product made in a factory using a specific allergen". It has been set up following the initiative of businesses in the food processing sector, but is not based on any regulatory text. Although this type of labelling enables manufacturers to limit legal disputes, it also risks presenting some allergic consumers with a difficult choice: either buy products that are guaranteed to be allergen-free but necessarily more expensive as they require the manufacturer to practise complex and costly allergen risk control, or consume everyday products bearing this advisory labelling without being able to accurately assess the risk of an allergic reaction occurring from this accidental presence. Some food allergy sufferers justify this type of labelling, however, in the belief that it is still preferable to no precautions at all.

Despite these divergences, everyone agrees that advisory labelling is currently used by most agro-food businesses, even though the precautions taken regarding the risk of allergens being present accidentally are not harmonised. Moreover, there are no standards for the tools used to screen for allergens in food matrices either. Although no standard is available to date in this field, a large number of screening tests are available on the market. Overall, the growing use of this labelling automatically limits the access of food allergy sufferers to a certain number of foods, as they are unable to interpret the meaning of the multiple expressions used.

In this context, manufacturers and allergic patients' associations would like practices and assistance tools for interpreting allergen screening tests to be standardised. To try and harmonise the use of this preventive labelling, the CLCV asked Afssa to respond to the following questions:

"① Part of the problem observed arises from the confusion between the notion of "trace" and that of "accidental presence". The former, which appears to relate to the analytical field, seems to refer to ever smaller amounts given the ongoing improvement of detection methods. The latter, however, seems to refer to hugely varying amounts depending on the manufacturing processes and products. In this context, can Afssa specify what should be understood by "trace" and "accidental presence" in the field of food allergens?

② In what amounts and how often are the major allergens (milk, egg, wheat, etc.) currently present in foods accidentally?

③ What proportion of food allergy sufferers is exposed to a risk if they eat foodstuffs presenting the current levels of contamination? To what type of risk and how often are they exposed at the scale of individual consumption?

④ Can a relationship be established, for each major allergen, between the amount of allergen and the proportion of food allergy sufferers exposed to a risk in the event of consumption?

⑤ Can a critical limit be defined for each major allergen from which a much larger proportion of food allergy sufferers would be exposed to a risk, above which the presence of cross contact should be indicated and below which advisory labelling may be removed?

⑥ If what we know to date does not allow responses to be formulated to the questions raised for certain allergens, can we at least define the method for the scientific community to follow and draw up research recommendations for the allergens concerned?

⑦ How has the complexity of processed food product formulation changed over recent years? What impact is this complexity likely to have on the frequency of allergic reactions?”

# 1 Definitions and terminology

**• Allergen**

An allergen is an antigen capable of sensitizing the organism of certain individuals and of determining allergic manifestations when it is reintroduced (*Vervloet D, 2003; Godeau P, 2004*).

**• Notifiable allergen**

In this document, a notifiable allergen means any allergen that is indicated in **Annex IIIb of European Directive 2000/13/EC**, mentioned in French law in **Annex IV** inserted at the end of Chapter II, Title I or Book I of the **French Consumer Code** following articles R. 112-1 and following.

This Annex was then included in **European Directive 2003/89/EC** on food labelling and then amended by **Directive 2007/68/EC** which includes "lupin and products thereof" and "molluscs and products thereof" in the list of ingredients that must be indicated under all circumstances on food labelling. Directive 2007/68/EC also includes the list of exemptions of substances that come from a notifiable allergen but which are excluded from Annex IIIb of Directive 2000/13/EC (see below). Directive 2007/68/EC was transposed into French law by Decree 2008-1153 of 7/11/2008, published in the Journal Officiel (Official Journal) on 9/11/2008.

| |
|---|
| ***Cereals containing gluten*** *(i.e. wheat, rye, barley, oats, spelt, kamut or their hybridised strains) and products thereof,* |
| ***Crustaceans*** *and products thereof,* |
| ***Eggs*** *and products thereof,* |
| ***Fish*** *and products thereof,* |
| ***Peanuts*** *and products thereof,* |
| ***Soybeans*** *and products thereof,* |
| ***Milk*** *and products thereof (including lactose),* |
| ***Nuts****, i.e. almonds (Amygdalus communis L.), hazelnuts (Corylus avellana), walnuts (Juglans regia), cashews (Anacardium occidentale), pecan nuts (Carya illinoiesis), Brazil nuts (Bertholletia excelsa), pistachio nuts (Pistacia vera), macadamia nuts and Queensland nuts (Macadamia ternifolia) and products thereof,* |
| ***Celery*** *and products thereof,* |
| ***Mustard*** *and products thereof,* |
| ***Sesame seeds*** *and products thereof,* |
| ***Sulphur dioxide and sulphites*** *at concentrations of more than 10 mg/kg or 10 mg/litre (expressed as $SO_2$).* |
| ***Lupin*** *and products thereof,* |
| ***Molluscs*** *and products thereof.* |

***Table 1:*** *Notifiable allergens (European Directive 2007/68/EC and French Decree 2008-1153 of 7/11/2008)*

**• Major allergen**

A major allergen is an allergen that is recognised by the specific IgEs of more than 50% of patients sensitized to the food (*Moneret-Vautrin D, A, Kanny G, Morisset M. Les allergies alimentaires de l'enfant et de l'adulte Paris: Masson; 2006).*

## • Cross contact

Contact occurring between two products, A and B. If A contains allergens and comes into contact with B, these allergens can then be found in B, which did not contain any before.

## • Component

A component is a substance found in the finished product, whether it was incorporated intentionally or is present accidentally. Components therefore include:

1) ***Ingredients***, as defined by Directive 2000/13/EC, art. 6 point 4:

*Article 6 point 4 (Directive 2000/13/EC):*

*a) 'Ingredient' shall mean any substance, including additives, used in the manufacture or preparation of a foodstuff and still present in the finished product, even if in altered form.*

*b) Where an ingredient of the foodstuff is itself the product of several ingredients, the latter shall be regarded as ingredients of the foodstuff in question.*

*c) The following shall not be regarded as ingredients:*

*i. the constituents of an ingredient which have been temporarily separated during the manufacturing process and later reintroduced but not in excess of their original proportions;*

*ii. additives:*

- *whose presence in a given foodstuff is solely due to the fact that they were contained in one or more ingredients of that foodstuff, provided that they serve no technological function in the finished product,*
- *which are used as processing aids;*

*iii. substances used in the quantities strictly necessary as solvents or media for additives or flavouring;*

*iv. substances which are not additives but are used in the same way and with the same purpose as processing aids and are still present in the finished product, even if in altered form.*

2) ***Substances*** which acquire the status of ingredients in the meaning of Directive 2000/13/EC art. 6 point 10, as they come from or contain notifiable allergens:

*Art.6 point 10 (Directive 2000/13/EC):*

*"Notwithstanding paragraph 4(c)(ii), (iii) and (iv), any substance used in production of a foodstuff and still present in the finished product, even if in altered form, and originating from ingredients listed in Annex IIIa shall be considered as an ingredient and shall be indicated on the label with a clear reference to the name of the ingredient from which it originates"*

Certain substances, listed in Directive 2007/68/EC, come from a notifiable allergen but are **excluded** from Annex IIIb of Directive 2000/13/EC (*Afssa opinion 2008-SA-0031 and Decree 2008-1153 of 7/11/2008 published in the Journal Officiel on 9/11/2008*):

| Ingredients | Products thereof, temporarily excluded |
|---|---|
| **Cereals containing gluten** | Wheat-based glucose syrups, including dextrose*;<br>Wheat-based maltodextrins*;<br>Glucose syrups based on barley;<br>Cereals used for making distillates or ethyl alcohol of agricultural origin for spirit drinks and other alcoholic beverages. |
| **Fish** | Fish gelatine used as a carrier for vitamin or carotenoid preparations;<br>Fish gelatine or Isinglass used as fining agent in beer and wine. |
| **Soybean** | Fully refined soybean oil and fat*;<br>Natural mixed tocopherols (E306), natural D-alpha tocopherol, natural D-alpha tocopheryl acetate, natural D-alpha tocopheryl succinate from soybean sources;<br>Vegetable oils derived from phytosterols and phytosterol esters from soybean sources;<br>Plant stanol ester produced from vegetable oil sterols from soybean sources. |
| **Milk** | Whey used from making distillates or ethyl alcohol of agricultural origin for spirit drinks and other alcohol beverages;<br>Lactitol. |
| **Nuts** | Nuts used for making distillates or ethyl alcohol of agricultural origin for spirit drinks and other alcohol beverages. |

* And products thereof, insofar as the process that they have undergone is not likely to increase the level of allergenicity assessed by the European Food Safety Authority for the relevant product from which they originated.

European Directive 2003/89/EC had indeed provided that, according to the opinion of the European Food Safety Authority, the European Commission would temporarily exempt derived products, whose safety has been proven by the submission of an EFSA-approved scientific dossier, from open labelling. Certain dossiers have therefore been approved by the European Commission as, given the manufacturing process and low level of allergens in derived products, the experts did not consider it very likely that the derived product would trigger an allergic reaction.

### • Accidental presence

A notifiable allergen is accidentally present when it is found in a finished product but is not an intentionally incorporated component (*ANIA, 2005*). The notion of *accidental presence* is the same as the notion of *contamination*, which is also used in everyday language.
The systematic unintentional presence of a notifiable allergen should not be considered an accidental presence.

### • Primary accidental presence

Primary accidental presence occurs when:

- a component used intentionally by the manufacturer and a source of notifiable allergen is found in a finished product that does not normally contain it.

e.g.: cheese crackers are made after fish crackers on the same production line. Fish may be found in the cheese crackers, even though they do not normally contain this component. This is a case of primary accidental presence.

- the notifiable allergen is found in a component that does not normally contain it during harvesting, processing, transport or storage. This component, intentionally used in the finished product, introduces the major allergen.

e.g.: cocoa is used to make a chocolate biscuit. This cocoa has been in contact with hazelnuts during transport and storage. By using the cocoa as an ingredient, the hazelnut – which is not an intentionally used component in the biscuit recipe – risks being introduced.

*(ANIA, 2005).*

• **Secondary accidental presence**

A notifiable allergen is accidentally present in a component that is itself unintentionally incorporated into the recipe.

e.g.: dark chocolate is made after chocolate containing hazelnuts in a factory. Peanuts may be found in the hazelnuts used to make the chocolate containing hazelnuts:

- the presence of hazelnuts in the dark chocolate is a primary accidental presence,
- the presence of peanuts in the chocolate containing hazelnuts is also a primary accidental presence,
- the presence of peanuts in the dark chocolate is a secondary accidental presence.

*(ANIA, 2005)*

• **Uniform or disparate accidental presence of a notifiable allergen**

The accidental presence of a notifiable allergen may be a one-off.

e.g.: a sesame seed transported by a member of personnel on clothing because of its electrostatic properties may fall into the food during manufacture.

This is a disparate accidental presence. In this case, the presence of the allergen can only concern one package.

However, the allergen may be "diluted" throughout a product.

e.g.: dark chocolate made in a mixer that was used to make milk chocolate.

This is a uniform accidental presence.

*(ANIA, 2005).*

• **Masked allergen(s)**

Allergen consumed unknowingly by the allergy sufferer (only the most common situations are listed below: product without labelling, labelling error, allergen labelled but unexpected in the food consumed and not spotted by the consumer, allergen present accidentally in the food consumed or contamination).

*(Moneret-Vautrin DA. Masked food allergens. In: De Weck A, Sampson H, editors. Intestinal immunology and food allergy. New York: Raven Press; 1995. p. 249-257).*

• **Traces**

The term "traces" in analytical language refers to amounts that can be detected but not quantified by the method used (Figure 1).

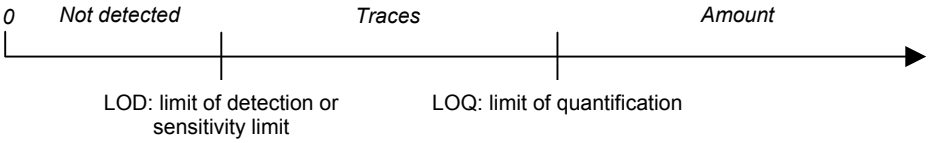


***Figure 1: limit of detection and limit of quantification***

The term "traces" is indicated on prepackaged product labelling. Consumers do not know whether this indication refers to an accidental presence of a notifiable allergen:

- corresponding to a detection of traces in the analytical sense of the term (detected but unquantifiable by the method used),
- or corresponding to the probable presence of a small amount of allergens that has not been analytically tested for by the manufacturer.

The working group recommends that the term "trace" be used in its analytical definition on prepackaged product labelling. This means that, if the term is used, detection methods have

been applied by manufacturers to test for the presence of a notifiable allergen; this allergen has been detected but could not be quantified by the method used.

### • HACCP method

HACCP is the abbreviation for “Hazard Analysis – Critical Control Point”, corresponding to a method and principles for managing food safety. It is a system allowing for the identification, assessment and control of significant food safety hazards. These hazards are usually biological (viruses, bacteria, etc.), chemical (pesticides, additives, etc.) or physical (wood, glass, etc.).

The term “allergen HACCP”, used in this document, means that this method is applied to the hazard posed by allergens for food allergy sufferers.

**Answer to Q1 of the request:**
**Can Afssa specify what should be understood by “trace” and “accidental presence” in the field of food allergens? (Chapter 1 of this document)**

A notifiable allergen is **accidentally present** when it is found in a finished product but is not an intentionally incorporated component (*ANIA, 2005*). The notion of ‘accidental presence’ is the same as the notion of ‘contamination’, which is also used in everyday language.

The term **traces** in analytical language refers to amounts that can be detected but not quantified by the method used (Figure 1). This term is used on prepackaged product labelling and may confuse consumers who do not know if it refers to:
- an accidental presence of a notifiable allergen corresponding to the detection of traces in the analytical sense of the term (i.e. detected but unquantifiable by the method used)
- or to the probable presence of a small amount of allergens that has not been analytically tested for by the manufacturer.

The working group recommends that the term “trace” be used in its analytical definition on prepackaged product labelling.

## References


ANIA (2005). *Guide des bonnes pratiques pour la réduction des présences fortuites d'allergènes majeurs*. Février 2005.

Godeau P, Herson S, Piette J (2004). *Traité de médecine.* Flammarion Médecine-Sciences (Paris). 2004 (4ème édition).

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Vervloet D, Magnan A (2003). *Traité d'allergologie*. Flammarion Médecine – Sciences (Paris). 2003.

Moneret-Vautrin DA, Kanny G, Morisset M. Les allergies alimentaires de l'enfant et de l'adulte. Paris : Masson, 2006.

# 2 Amounts of allergens and how often they are unintentionally present in food

There is no public data in France enabling the allergen contamination amounts and frequencies of food, depending on preparation, to be estimated.

To obtain such information, the working group consulted professionals in the food industry sector: large companies, SMEs (Small and Medium-sized Enterprises) and ANIA (French Food Industries' Association). In June 2006, ANIA sent a letter addressed to the chairperson of Afssa's working group containing its thoughts on the issue of allergen limits of detection in foodstuffs.

## *2.1 Summary of interviews with food processing manufacturers*

### *2.1.1 Knowledge of the risks of notifiable allergens being accidentally present and manufacturer obligations*

According to SMEs, some 75% of their suppliers take the allergen risk into account. For the remaining 25%, consideration of this risk is not systematic, particularly among certain wholesalers from whom it is difficult to obtain information. It is common for companies to demand specifications on the allergen risk from their suppliers. In some cases, a charter is drawn up with suppliers, enabling the company to obtain a fairly high level of requirement, higher than merely having specifications.
The major difficulty lies in the fact that most suppliers do not have the means to commit to this issue, and state that contamination is always possible. However, for a few years now it has seemed easier to obtain products free from certain allergens.

Large food industry are well aware of the allergen risk and highly demanding of their subcontractors.

### *2.1.2 Knowledge of the risks of allergens being accidentally present in factories*

The manufacturers consulted are aware of the risks associated with allergens being accidentally present in finished products. In professional practice, they therefore deliberately limit the use of certain ingredients in their recipes and try to control the essential ingredients as much as possible.
For SMEs, it is difficult to know exactly what the risks are of allergens being accidentally present on their production chains, mainly because of the small-scale organisation of certain sectors and requirements that continue to be insufficient as regards suppliers.
Large food industry could not provide exact figures on how often contamination occurred. The reason put forward is the "*random character of contaminations*". Although information on the ingredient contamination risk of these manufacturers' suppliers is usually available, it is not entirely relevant for them as it corresponds to "*the contamination level revealed at a given moment at a supplier's rather than to the contamination level that may be found in the finished product*".
A single response was given by a major firm "in the event that the production chains of dark chocolate and milk chocolate are not entirely separate, milk contamination levels on the dark chocolate production chains could be found at approximately 800 ppm of milk". Note, however, that this figure concerned a manufacturing incident that occurred during the 1980s, before any allergen HACCP method had been put in place.

### *2.1.3 Managing the cross contact risk*

The smallest companies do not really take account of accidental presence in factory allergen risk control. Instead, there are requirements upstream to 1) limit the use of multiple ingredients in recipes as far as possible, and 2) obtain precise information from their suppliers.

The largest food industry intentionally apply “allergen HACCP” methods to limit the risk of cross contact. However, it is not possible to assess whether the establishment of such methods has achieved higher safety levels.
Professionals point out that, through the validation of HACCP methods, they do not have any references to determine whether or not the contamination level detected justifies an eviction of foodstuffs. In other words, they do not have any reference threshold values, which vary depending on allergen. This lack of information is a real problem for the risk management of professionals and has been highlighted across the food industry sector.
The detection tests used by manufacturers are the methods currently available on the market (Elisa and PCR techniques). They are not available for all 14 notifiable allergens, however.
In practice, the largest businesses generally adopt the threshold of 10 ppm (1mg/100g) when there is no threshold value available. If the threshold exceeds 50 ppm, the labels may be modified.
Detection tests are sometimes used directly on food matrices, but for the most part they are used as markers in food chain cleaning operations. They are not applied for each batch leaving production plants, but a “*quality method [has been set up] to meet the concerns of food allergies*”.

Note that only one of the companies interviewed does not use advisory labelling. By encouraging a responsible attitude among suppliers (around 400) and forging a contractual relationship with them on the problem of allergic risks (raw material datasheet), this company only had one problem of cross contact to report in 2003.

*2.1.4 Communication on the risk of cross contact*

During the interviews conducted by the working group, the food industry specified that the words “may contain" or equivalent (advisory labelling) are not used when they are not justified. This advisory labelling means “*that there is no possibility of guaranteeing the absence of an undesired ingredient in the recipes*. *It is technically impossible*”. Moreover, “*due to the number of products and raw materials managed by manufacturers, it is not possible to have separate lines for all products to prevent cross contact”.*
There are no overall statistics on the percentage of labelling indicating “may contain…”. That said, for some product groups such as chocolate or dried products, advisory labelling is used more often than for other products. In the biscuit sector, this type of labelling is often used on 100% of products.

***Overall,***

1) All manufacturers, irrespective of the size of their company, are aware of the allergen cross contact risk.
2) Although the “allergen HACCP” method is not applied systematically at all levels of the food chain, efforts are made to limit the use of multiple ingredients in recipes as far as possible and to try to obtain precise information from suppliers.
3) In the vast majority of cases, the detection tests are only used to validate HACCP methods.
4) The professionals stress that, with no defined limits of detection, there are uncertainties over the raw materials bought from different suppliers.
5) It is currently not possible to obtain exact information on contamination frequency.

**2.2 Survey published by the review “Que Choisir”, no. 230, October 2005.**

A survey conducted by UFC – Que Choisir, published in October 2005 and funded by the European Commission aimed to measure the presence of allergens in various products and to compare them with labelling by selecting products bearing the words: “may contain…”, “traces of …” and so on.

The labelling of 27 (73%) of the 37 products analysed in this survey turned out to be true. This was not the case for 10 products. However, the article made no mention of the proportion of products containing traces of allergens, nor of the proportion of foodstuffs that did not contain the allergen, when advisory labelling was present. Furthermore, the survey method and detection kits applied, beyond the fact that they used PCR and EliSA techniques, were not specified.

**Response to Q2 of the request:**

**In what amounts and how often are the major allergens (milk, egg, wheat, etc.) currently present in foods accidentally?**

The manufacturers consulted are aware of the risks associated with allergens being accidentally present in finished products. Because of the small-scale organisation of certain sectors and partial guarantees obtained from suppliers, it is not possible for SMEs to know exactly what the risks are of allergens being accidentally present on their production chains. Our interviews also highlighted the difficulty of assessing how often contamination occurs in large food industry, and exact figures could not be obtained on this question. The working group does not therefore consider it possible to estimate the accidental occurrences and amounts of the main notifiable allergens in food.

Quantifying the exposure of food allergy sufferers to allergens that are accidentally present in complex products is instrumental to being able to assess the reaction risk in such people (see Chapter 3). This information may be obtained from an analysis programme conducted nationwide. It seems important to set up this programme in collaboration with the risk managers and manufacturers of the food industry.

# 3 Quantitative risk assessment associated with the accidental presence of allergens in foodstuffs and proportion of food allergy sufferers for whom this presence poses a reaction risk

**Quantitative risk assessment on food allergies associated with the accidental presence of allergens in foods, methodological limits and recommended further study and research**

Quantitative risk assessment models are increasingly used to assess chronic (contaminants, additives) or acute (microbiology) food risks.
They assess the risk by indicating the probability of an adverse effect occurring in a given population, with an estimation of the variability of this risk and the associated uncertainty.
The purpose of a quantitative risk assessment is not only to quantify the risk of an accident occurring, but also to assess the impact of various risk factors of this type of accident occurring so as to objectively define the management options. Several quantitative risk assessments by modelling have been conducted by Afssa in recent years, but they have concerned other areas of food risk: microbiology and physical-chemistry.
The aim here is to study the feasibility of a quantitative risk assessment of an allergic reaction associated with the accidental presence of allergen(s) in food, regardless of whether or not this presence is labelled. This quantitative risk assessment may be extended to the accidental consumption of allergens intentionally used as ingredients in food.

### *3.1 Method*

The general method for quantitative risk assessment involves combining different types of probabilistic information on the risk components so as to estimate a law of probability of the events being studied, in this case allergic reactions. The event to be modelled needs to be precisely defined beforehand. What do we mean by an allergic reaction? Different allergic manifestations can occur of variable severity.
One allergen must also be chosen as it seems theoretically impossible to quantitatively assess the risk of total food allergy, since the risk determinants and level differ widely depending on allergen. Moreover, the information available for conducting this quantitative risk assessment also varies considerably depending on allergen; some have been studied much more than others. For example, the peanut is an allergen with a large bibliography available for a quantitative risk assessment.

***3.1.1*** The following information must be obtained for a quantitative risk assessment:

- Identification of foods that may contain allergen,
- Consumer exposure to one allergen,
- Occurrences of this allergen being present in the food(s) that may contain it,
- Quantitative levels of the presence of allergens corresponding to these occurrences,
- How often the foods that may contain the allergen in question are consumed,
- Portion size of foods that may contain the allergen in question,
- Dose-response of the allergic event depending on exposure to the allergen, with account taken of the inter-individual variability of the allergic reaction to the same dose.

The risk is then expressed as follows:

P=f(o, a, c) where o is the occurrence or frequency of accidental allergen presence in foods, a is the amount of allergen in the event of accidental presence and c is the consumption of

foods containing the allergen(s). The function f corresponds to the modelling of the allergic reaction probability depending on the different parameters qualifying exposure.

***3.1.2*** In the specific case of food allergies, several parameters complicate the risk assessment:

- *the number of food allergy sufferers,*

These make up some 3% of the French population (Kanny et al, 2001), or around 2 million people. According to data from the Allergy Vigilance Network, the prevalence of peanut allergy reportedly accounts for 0.3 to 0.75% of the French population, or 200,000 to 500,000 people (Morisset et al, 2005). Note, however, that the population allergic to a specific allergen is heterogeneous, particularly as regards the minimum exposure doses that may trigger an allergic reaction.

- *the avoidance of foods by allergy sufferers,*

This parameter must be considered when studying the consumption of foods that may contribute to exposure to the allergen in question because of its accidental presence in food, because the systematic avoidance of certain foods with labelling that they may accidentally contain allergens reduces the exposure risk. This is the purpose of advisory labelling indicating “may contain…”. Likewise, the labelling of allergens present in the form of ingredients may also help to reduce the risk. However, a recent study conducted in the US (Hefle et al, 2007) shows that, between 2003 and 2006, there was an increasing trend among peanut allergy sufferers not to pay attention to labelling on the accidental presence of peanuts. Between 14 and 42% of peanut allergy sufferers still consume products bearing advisory labelling. The authors of this study therefore anticipate a potential increase in the risk of allergic reactions, insofar as a small but not insignificant proportion of foods bearing advisory labelling (7.3%) actually contain detectable amounts of peanut (at least 2.5mg/kg).

- *Other sources of allergen exposure than accidental presence*

If we want to study how well the risk modelling results correlate with epidemiological data, we need to take account of the fact that allergen exposure does not amount solely to exposure to accidental presence, whether this is labelled or not. For example, accidental exposure may occur to allergens via non pre-packaged products (and which are therefore not labelled) intentionally using an allergen as an ingredient (e.g. restaurant meals).

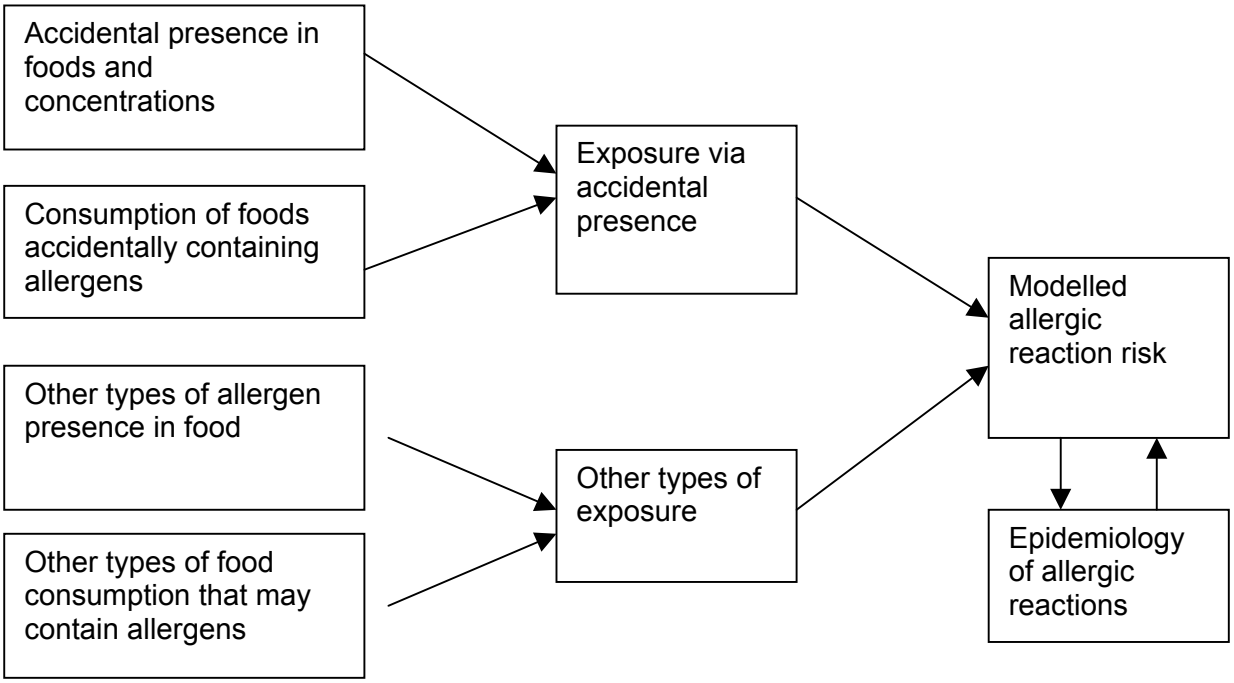
***3.1.3*** At least two statistical approaches are possible from all of the available data to quantify the risk:

- *conventional Monte-Carlo type probabilistic modelling*

This approach involves combining the different variables making up the risk by successive convolutions. It can be fine-tuned to separate the variability measurement from the uncertainty one (2D Monte-Carlo approach).

- *Bayesian network type probabilistic modelling*

This approach uses the MCMC (Monte Carlo Markov Chain) methods to describe the links between the different variables enabling the risk to be calculated, including epidemiological data.




***3.2 Application to the question of an acceptable threshold of allergens in food***

Once the risk has been modelled for a given allergen, a "retro-calculation" based on the acceptable risk makes it possible to define an acceptable level of allergen presence in the main foods concerned:

1) Different levels of acceptable risk of an allergic reaction occurring (risk managers)
⇓
2) Analysis and summary of dose-responses
⇓
3) Acceptable level of exposure
⇓
4) Acceptable level of presence in the foods

Accordingly, based on Afssa's quantitative risk analysis, the risk manager would choose the acceptable risk level hypotheses determining the levels of acceptable presence in the foods (stage 1).

Some authors already advocate this approach but by sticking to the successive stages 1), 2) and 3) (Crevel et al, 2007). This saves on the amount of data to be gathered on the exposure of food allergy sufferers, since this approach only uses dose-responses and acceptable risk levels. However, this simplified approach does not take account of the fact that, for allergens that are accidentally present in foods, there is already a labelling system in place that prompts allergy sufferers to avoid those foods bearing advisory labelling. In this case, an acceptable level of presence in the food cannot be deduced from the acceptable exposure level by simply dividing the acceptable dose by the food portion size (stage 4).

A conventional quantitative risk assessment approach could be considered to begin with, based on consumer exposure, quantifying the risk according to different dose-response scenarios. The retro-calculation described above could then be made. This approach may provide risk managers with more information when they are deciding what the acceptable risk is.

### *3.3 Experiments of applying quantitative risk analysis to the question of allergens in food*

Mainly because of the absence of reliable exposure data, we have not identified any international publications on quantitative risk assessment models. Most quantitative studies on the risks associated with allergens being present in food focus solely on hazard characterisation, i.e. testing for the NOAEL or dose-response models (Taylor et al., 2004).
The FDA lists four types of different approaches in its report dated June 2005 on approaches to establish thresholds for major food allergens and for gluten in food (FDA, 2005):

- The methods based on analytical capacities,
- The approach based on hazard characterisation only (establishing NOAELs),
- The quantitative risk assessment methods as presented in this chapter,
- The approaches using extrapolations from similar situations.

The FDA states that, of the four approaches described, the quantitative risk assessment-based method provides “the strongest, most transparent scientific analyses to establish thresholds for the major food allergens”.
Based on several recent scientific articles (Bindslev-Jensen et al, 2002), (Moneret-Vautrin D A, Kanny G, 2004), (Wensing et al, 2002a), the FDA concludes “However, this approach has only recently been applied to food allergens, and the currently available data are not sufficient to meet the requirements of this approach concerning allergen thresholds and gluten thresholds”.

In the French case, it must be ensured that the modelling techniques and data are available and the key information to be obtained for conducting such a quantitative risk assessment on allergens, particularly their accidental presence in food, must be known.

### *3.4 Methods for obtaining the necessary data for a quantitative risk assessment*

As stated in Chapter 2, two types of data are essential for a quantitative risk assessment on allergens: data on exposure to allergens and data describing the quantitative links between exposure to allergens and allergic reactions.

#### *3.4.1 Exposure to allergens*

To estimate the dietary exposure of food allergy sufferers to allergens, two types of data are required: the frequency and concentration of allergens in food and the consumption of different types of food likely to contain allergens.

- How often and to what extent allergens are present in food consumed by food allergy sufferers.

This point has already been examined in detail in this report, in the chapter on question no.2. We define the necessary information for a quantitative risk assessment.

For the different foods consumed, even rarely, by food allergy sufferers, whether these foods contain the allergen as an ingredient or accidentally, how often the allergens are present at detectable levels and the concentrations reached need to be found out. The international bibliography provides occurrence and level data for some major allergens such as peanuts (Pomes A et al, 2003), (Vadas et al, 2003), (Hefle et al, 2007). However, this data can be difficult to extrapolate directly to the French situation. In 2003, an American study noted the wide differences in frequency of accidental peanut presence in chocolate bars between the United States, Western Europe and Eastern Europe (Vadas et al, 2003). These differences may have changed since, depending on how much European manufacturers take account of the allergic risk.
During an interview with the working group, ANIA suggested working on ranges of maximum allergen limits (the bounds being possible thresholds) considered to be manageable by manufacturers. However, no data was provided on how often allergens are accidentally present in foods (see Afssa's interviews with manufacturers, Chapter 2). The study by Hefle et al, 2007 nevertheless shows that, given how often allergens are present at levels above the analytical limits of detection, it is possible to estimate such parameters through several hundred analyses (200 analyses were conducted in this study). State monitoring plans or specific surveillance studies conducted by Afssa, such as the Total Diet Study, generally concern the same size or larger samples. This type of study may therefore be reasonably considered at national level in collaboration with the risk managers and manufacturers (see response to Q2 of the request on page 19).

- How often and how much foods likely to contain allergens are consumed by food allergy sufferers.

Nutritional or food consumption surveys generally focus on generic foods and the ingredient lists are not known on the whole, which makes it difficult to estimate the consumption of allergens (see chapter on the response to question 7: change in the complexity of formulations).
Moreover, these consumption surveys do not specifically deal with food allergy sufferers. As a result, little is known about the specific dietary practices of such consumers, particularly the avoidance of certain foods likely to expose them to an allergen, and whether or not they take account of the information available on labelling. These behaviours certainly differ depending on the allergy in question. A peanut allergy sufferer does not consume the same foods as a fish allergy sufferer.
It again appears difficult to use solely national data, and some ranges of uncertainty should be taken into account from the study of the international bibliography or from non-representative food surveys conducted locally among food allergy sufferers. A preliminary study listing these local food surveys among food allergy sufferers should be carried out to begin with, and food questionnaires could be filled in at the same time by such patients, recruited via the Allergy vigilance network for example.
The Food Quality Observatory project plans to systematically collect nutritional information indicated on food packaging for the main groups of the most consumed foods. It would be worthwhile using this information to see how often allergens are labelled, both as ingredients and in accidental presence.

#### *3.4.2 Dose-response equations*

Bibliographical references exist for the most studied allergens, including peanuts. In order to construct dose-response curves, we first need experimental measurements through

controlled oral challenge tests. It is not possible to define the thresholds below which no allergic reaction occurs in the population studied from these tests. Rather, they determine "eliciting doses", i.e. the minimum doses of allergen that produce responses in a proportion p% of the population studied.
The smaller this reaction proportion (or probability) to be studied in a population, the larger the sample size must be to quantify this dose. For example, in a recent study (Crevel et al, 2007), the minimum size of study population required to estimate that less than 1% of food allergy sufferers react is between 299 and 473. It is therefore evident that most tests on several dozen or hundred subjects will not enable the empirical estimation of the doses corresponding to low risks (less than 1%). The population size of 29 is often recommended for oral challenge tests, as it can ensure that 90% of patients will not react to a dose to which none of the 29 patients reacted (Taylor et al, 2004). These tests often begin with a 10 µg dose.

A second stage in the construction of a dose-response curve involves adjusting a parametric function to the data gathered. The relationships between allergen doses and frequency of allergies triggered are clearly not linear in appearance. There is generally a zone of doses for which the frequence of allergic response increases sharply, and the curves are sigmoid, which can be modelled via Weibull or logistics functions for example.
One of the difficult questions then lies in the extrapolation of these functions to low doses that can correspond to accidental presence (around 10 mg or less, according to the article by Hefle et al, 2007), whereas these functions have been estimated from doses that are often higher (from 10 to 30,000 mg). A sensitivity study to quantify uncertainty is essential here.
Other difficulties are listed in detail by Crevel et al, 2007: managing the heterogeneity of dose-response functions depending on study, the differences in defining threshold doses, the consideration of differences in allergic reaction frequency depending on the food containing the allergen and its transformation mode (cooking).

All of these factors influencing the results of the quantitative risk assessment must be simulated during a sensitivity study analysing the uncertainties and variability of results obtained according to the hypotheses. A variety of more or less optimistic or realistic hypotheses must be tested. As in the case of "benchmark doses" used in toxicology to characterise a hazard, the lower bound of the dose confidence interval range resulting in a given incidence level must be preferred, as a precaution.

#### *3.4.3 Available epidemiological data*

Accidents caused by masked allergens account for 8.6% of serious allergic reactions reported in the Allergy vigilance network since its creation in 2001. Peanut is the most commonly implicated allergen (Codreanu et al, 2007). These reactions are usually caused by 1) no labelling on products when they are sold or 2) a change in packaging and/or recipe with a subsequent labelling error. The allergy sufferer may also read the label incorrectly after a change in recipe. Only 2 out of 485 observations (0.4%) have been caused by contamination during manufacture: one concerns the contamination of saucission by nuts and the other the small-scale contamination of traditional bread by buckwheat flour.
Note that since the European directive on the compulsory labelling of 12 (and then 14) allergenic ingredients came into force in November 2005 (see list on page 11), no case of anaphylaxis caused by an accidental presence of allergens has been recorded by the Allergy Vigilance network (Codreanu et al, 2007).

***Conclusion***
There is still much to do with regard to quantitative risk assessment in the field of food allergies.

The most gaps in knowledge currently concern exposure:

- Occurrence of the presence of allergens in food, whether or not this bears advisory labelling,
- Food consumption of food allergy sufferers.

But in view of the most recent bibliographic data, there does not seem to be any insurmountable obstacle to acquiring such knowledge, especially for certain notifiable allergens such as peanuts, for which the dose-response relationships have been documented. Indeed, the ranges of variables to be measured are sufficient for reasonably sized tools (a few hundred to around a thousand pieces of data) to provide useable information.

An initial feasibility study should therefore be completed by:

- A study on how often the allergen in question (e.g. peanuts) is accidentally present in the food that may contain them (biscuits, bars, sweets, etc.).
- A bibliographic and possibly field study on the food consumption and avoidance practices of peanut allergy sufferers.
- An initial attempt to model dose-response curves to estimate the variability and uncertainty for the different segments of exposure doses considered (less than 10 mg, between 10 and 100 mg, between 100 and 1,000 mg, over 1,000 mg).

Beyond discussions on the allergen thresholds in food, it should be pointed out that such a quantitative risk assessment would particularly provide information for consumers on the objective risks they take in consuming foods bearing advisory labelling, based on what they may know of the doses at which they react.

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# 4 Study of reactivity thresholds and dose/response relationships

The term “reactivity threshold” corresponds to the minimum dose of food that can trigger a reaction in an allergy sufferer. To be able to carry out a risk analysis, the number (prevalence would be ideal) of individuals reacting to this smallest dose of food needs to be identified. What little literature data there is on this subject, particularly reactivity thresholds, mainly focuses on three food allergens: cow’s milk, hen’s egg and peanuts. There is not much data published on the other notifiable allergens listed in Annex IIIb of Directive 2003/89/EC of 10 November 2003[1].

There are three approaches to determining reactivity thresholds (Moneret-Vautrin DA, 2004): the values obtained during observations of reactions with accidentally added allergens, the theoretical determination of thresholds using a statistical method (Bindslev-Jensen C, 2002) and lastly, the analysis of published results of oral challenge tests defining the reactogenic dose.

### *4.1 Observations of reactions with small amounts of allergens*

In this case, the reactivity threshold is defined using published data on allergic reactions to accidentally added allergens, which the food allergy sufferer could have encountered in a finished product. In fact, the literature mentions severe reactions in patients who have developed allergic reactions for tiny amounts of food (around a microgram), or even when ingesting a foodstuff that, according to its composition, should not have contained the food to which the patient is allergic. These observations of accidental allergic reactions, caused by allergens that should not be present in the finished product, provide information on the minimum amounts of allergen that can trigger an allergic reaction.

McKenna et al. reported the observation of a systemic reaction in a peanut allergy sufferer after ingesting an undeclared product (McKenna C, 1997). Kemp et al. described an observation of an anaphylactic shock upon ingesting a product whose ingredients contained no peanuts but which had become cross contaminated by them (Kemp SF, 1996). Gern et al. reported allergic reactions from products whose ingredients contained no milk but which had become contaminated by cow’s milk proteins (Gern JE, 1991).

An anaphylactic shock was reported following the ingestion of less than 50mg of casein in salmon (Koppelman S, 1999), 180µg of lactoserum proteins in a sorbet (Laoprasert N, 1998) and 100µg of cow’s milk proteins in a cereal-based product for infants that was guaranteed to be free from cow’s milk (Frémont S, 1996).

Reactions have also been described upon ingesting hazelnut proteins (Wensing M, 2001), fish (Sackesen C, 2003) or seafood (Faeste CK, 2003) in foods that should not have contained them.

Allergic reactions have also been described after skin contact (kissing a person who has consumed the food) (Eriksson NE, 2003; Wuthrich B, 2001), direct skin contact with the food (Liccardi G, 2004) or inhalation of food vapours (opening a tin, during cooking). It is not possible to know the amount of proteins that triggered the allergic reaction from these observations.

Allergic reactions have been reported in 10 children, including one anaphylactic shock after ingesting probiotics contaminated with cow’s milk proteins. The presence of cow’s milk proteins was confirmed by Western Blot. One in 10 children presented an anaphylactic shock. (Lee, 2007).

[1] This directive has been transposed into French law by Decree 2005-944 of 2 August 2005.

*The "anecdotal" observations published show the possibility of severe allergic reactions being triggered by very small amounts of food. However, from them it is not possible to determine the percentage of patients that react to such amounts.*

### *4.2 Theoretical determination of a threshold*

This involves calculating a theoretical dose threshold by conducting a statistical analysis of the data published, using the oral challenge test as the reference examination. The statistical model must estimate the threshold dose that triggers a reaction in the allergy sufferer by using data from the literature. The threshold dose is defined as the smallest dose that triggers a reaction in the allergy sufferer. This approach puts forward a threshold that would trigger a reaction in one in every one million allergy sufferers.

Bindslev-Jensen has listed 414 publications referring to the oral challenge test by an open, single or double blind technique (Bindslev-Jensen C, 2002). The validity of a dose-response in the publication led to 25 articles being selected. These concern adults and children who presented an immediate allergic reaction. The data was compiled and used for a statistical analysis (Bindslev-Jensen C, 2002). In order to compare the studies published, the amounts of food used during the oral challenge test were gathered in amounts of protein. For example, the amount of protein in cow's milk corresponds to 3.6% of the total when the milk is liquid and 37.5% in its powdered form. Regarding hen's egg, the amount of protein in its raw form corresponds to 26% of the total amount, 84% in powdered form and the egg white corresponds to 10%. The protein levels in the peanut were estimated to be 25%. The foods used in the studies were thus converted into protein amounts.
Cow's milk, hen's egg, peanut and soybean were analysed. A dose-response curve was calculated for each food, as well as for 4 foods tested in a single curve compiling the four curves. The x axis represented the logarithmic amount of food and the y axis corresponded to the total proportion of respondents. The curve compiled with the four foods established a threshold dose of 0.005 mg for cow's milk, 0.002 mg for egg, 0.0007 mg for peanuts and 0.0013 mg for soybean (expressed in amount of food consumed). The threshold dose, obtaining a reaction in one in every 100 patients observed, would be 0.28 mg of cow's milk protein, 0.024 mg of hen's egg white protein, 0.19 mg of peanut proteins and 12.9 mg for soybean.
The approach put forward in this study allows an estimation of the thresholds triggering an allergic reaction. However, the results are limited by several biases:

- The amount of foods able to trigger an allergic reaction, defined by this type of study, is definitely overestimated. This is because very sensitive patients, reacting severely to very low amounts, are excluded from this type of study which comprises an oral challenge test;
- Secondly, for patients reacting to the first dose of allergen, it is possible that their own reactogenic dose is lower than this initial dose administered;
- Lastly, the studies published are not comparable in general: children cannot be compared with adults as the two populations do not react in the same way or to the same doses.

To compile the studies, Bindslev-Jensen had to consider them comparable and that there was no difference in the inclusion criteria, food source, symptoms, initial dose administered during the oral challenge test, increase of doses and interval adopted between the administration of doses in each protocol, the maximum dose, the interpretation of a positive challenge test and a reaction to a placebo.

Moreover, without specifying the amount of foods determining an allergic reaction, a hypothetical dose/response curve model has been put forward (Hourihane JO, $2005_a$). The curve correlates the dose of allergenic proteins with the severity of the reaction. It is modified depending on the different parameters inherent to the patients and the food.

### *4.3 Determining a threshold by the oral challenge test*

The reference for determining the minimum dose or reactivity threshold of a food allergy is still the double blind oral challenge test. This can determine the smallest dose to trigger a

reaction. It also shows the smallest dose not to trigger a reaction. The latter definition is important for food industries, as this knowledge may make it possible to define a labelling threshold.

The limits of this type of study nevertheless stem from the fact that the patients who presented an anaphylactic shock are excluded from the oral challenge test. It is therefore not possible to know their reactivity threshold. But here again, differences in the protocols currently used for oral challenge tests between the studies published make comparison impossible. The starting dose, interpretation of positive reactions, interval between doses and type of food administered vary from author to author. Lastly, the oral challenge test does not take account of other major factors in the triggering of an allergic reaction: effort, alcohol, associated asthma and balance, concomitant treatments, natural everyday situations, anxiety, fat contents of the food, season and cross pollen/food reactions. Accordingly, Grimshaw *et al*. (2007) have, for example, showed that fat content has an influence on the intensity of allergic response (a low level of fat tends to decrease the reactivity threshold of peanuts). They stress the importance of the food matrix in the intensity of the allergic response.

Not all foods are comparable. By analysing the responses to the oral challenge test, Sicherer et al show that 25% of allergy sufferers react to the 100mg dose of cow's milk protein whereas 11% of allergy sufferers react to 100mg of egg protein (Sicherer SH, 2000). In children, 5% of peanut allergy sufferers react from the first 1mg dose administered (Rancé F, 2002). According to Hourihane et al., 3 out of 40 allergy sufferers reacted to the first administered dose of 1mg of peanut proteins, without being to know the actual dose that would trigger their symptoms (Hourihan JO, $2005_b$). The data available for hazelnuts demonstrates a reaction from the 1mg dose of hazelnut protein in 2 out of 26 patients subjected to the double-blind oral challenge test, or an equivalent of 6.4mg of actual hazelnut (Wensing M, $2002_b$).

Three studies are instructive for determining the threshold values and percentage of patients who react to this dose for cow's milk, hen's egg and peanuts (Taylor SL, 2004; Morisset M, $2003_b$; Wensing M, $2002_a$):

- The publication by Taylor et al. analyses the oral challenge tests conducted in different countries (United States, Australia, England, France, Canada, Denmark and Sweden). After adjusting the protein contents of the foods used during the oral challenge test, it is possible to say that 0.33% of allergy sufferers react to 600µg of cow's milk protein, 0.35% to 130µg of hen's egg protein and 0.32% to 250µg of peanut protein.

- According to Morisset et al., 1.6% of allergy sufferers react to 3.2mg of cow's milk protein, 0.8% to 200µg of hen's egg protein and 0.97% to 1.25mg of peanut protein.

- Wensing et al. carried out a study on 26 adult peanut allergy sufferers and defined that 3 of them reacted to the 100µg dose of peanut proteins. The selection criteria were a history of immediate allergy to peanut ingestion, a positive skin test to peanuts and/or a concentration of specific IgEs directed against peanuts more than or equal to 0.7 kU/L. Half of the patients reacted to 3mg of peanut proteins and none reacted to the initial 30µg dose of peanut proteins. Moreover, Wensing et al. established a correlation between the severity of symptoms and reactogenic doses: the patients with the most severe symptoms react to the lowest doses.

Other studies using the double blind oral challenge test are also available:

- Nordlee et al (2007) determines a NOAEL dose for objective symptoms of 1mg of peanut flour (354µg proteins or 11 ppm) in 29 peanut allergy sufferers, which leads the authors to suggest the absence of reaction in 90% of peanut allergy sufferers.

- In a double blind oral challenge test on 27 children of an average age of 7.2 years, allergic to peanuts, Flinterman et al (2006) determined that the smallest dose not to trigger reactions is 1mg of peanut flour (or 2mg of whole peanut). The smallest dose to trigger subjective symptoms (oral syndrome, nausea, abdominal pain) was 10mg of peanut flour (20mg of whole peanut). It was 100mg of peanut protein for objective symptoms. Children who had never presented allergic reactions had a higher reactogenic dose than children with a history of allergic reactions ((≥ 1000 mg *versus* ≥ 10 mg). 4 children described previous reactions to products labelled “may contain peanut”.

- Regarding wheat, we have data obtained from double blind oral challenge tests on 27 patients aged 14 to 60 years old and suspected of being allergic to wheat (Scibilia et al., 2006). 48% of patients reacted to raw wheat (13 out of 27). Of the patients who reacted to raw wheat, 10 also reacted to cooked wheat. The symptoms are varied: 62% presented manifestations affected 2 organs during the challenge test. The dose that triggers symptoms varies from 100mg to 25g of wheat flour (Figure 2).


***Figure 2: Cumulative frequency of raw wheat allergy sufferers according to the reactive dose (13 positive double blind oral challenge tests) (Scibilia et al 2006)***

The reactivity threshold varies in children and adults as shown by the the CICBAA data, collected for food allergy to wheat flour (Figure 3).

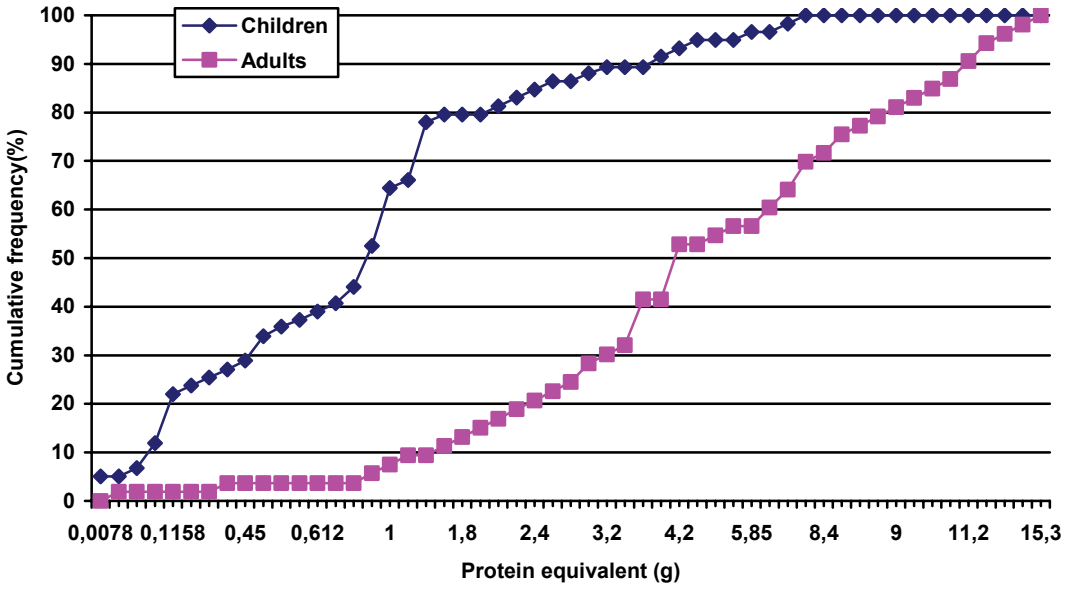


***Figure 3: Non-published CICBAA data: reactogenic thresholds to wheat flour in 59 children and 53 adults allergic to wheat***

### *Conclusion*

It is necessary to continue studies to define the smallest dose that can trigger an allergic reaction. The studies currently published cannot be compared because the oral challenge test is not standard. The number of patients included in the studies is often insufficient to draw conclusions. Lastly, we lack data on foods other than milk, egg, peanuts and wheat.

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# 5 Methods for detecting and quantifying allergens in foods

To detect allergens at doses that are likely to trigger an allergic reaction in a food, sensitive and specific methods are required to guarantee the absence of allergenic risk. At present, the sensitivities achieved by all methods are around one ppm (part per million), which corresponds to the presence of at least 100µg of the ingredient responsible for the food allergy (milk, soybean, egg, etc.) being detected in 100g of food.

## *5.1 Detection and quantification methods*

Detection and quantification methods mainly use two approaches. The first applies immunochemical techniques using the allergen's specific antibodies. The most commonly used method is ELISA. The second involves molecular biology tools using DNA probes characteristic of the targeted allergen (PCR methods). Enzyme and colorimetric determinations as well as histology can be used for certain ingredients. Lastly, the presence of a food allergen can be determined by complex systems (proteome- or chromatography-based method combined with mass spectrometry) using "marker" protein fragments (Chefcheck and Musser 2004, Chassaigne et col. 2007).

ELISA and PCR are quantitative methods. That said, when applied to detect food allergen sources, they usually become qualitative. This is because these sources can have different origins and therefore variable DNA or protein levels. They undergo different technological treatments as ingredients (caseinates are rich in caseins whereas whey is low in casein; the DNA and protein levels are not the same in flours or concentrates; and proteins and DNA are greatly denatured in texturats). The technological treatments implemented after incorporating the ingredients are variable. In any case, the limits of detection are indicative, set from controls. Depending on the ingredients and finished products, they are not completely fixed. They are generally around 1 to 10 ppm.

"Shareable" methods, for which the reagents are accessible on the market and public protocols, should be distinguished from "non-shareable" methods which are internal methods and only applicable in the laboratories possessing the reagents and protocols (Demeulemester, 2006). Note that service providers can use both types of methods to determine the different allergens of a food on request.

### *5.1.1 Immunochemical techniques*

The immunochemical techniques used to detect allergens are represented by all sorts of methods, including RAST (Radioallergosorbent Test) or EAST (Enzyme Allergo Sorbent Test) inhibition, ELISA (Enzyme Linked ImmunoSorbet Test), RIE (Rocket Immuno-Electrophoresis) or even biosensor methods which use antigen/antibody interactions. Allergen quantification is not possible with all of these methods. The characteristics and performances of immunological methods depend on the allergen studied. The heterogeneity of the food and diversity of constituent proteins direct the analysis to a relevant protein target, indicating an allergenic risk. This marker may be an individualised entity such as β-Lactoglobulin in milk (Negroni L, 1998), or more heterogenous, such as the 7S globulin fraction of peanuts or whole casein from milk (Mills ENC, 1997; Plebani A, 1997). In addition, the selectivity of the method must be considered: testing for the casein fraction of milk, for example, will not be suitable for foods that are potentially contaminated by the whey fraction of milk only. Lastly, some methods target proteins or protein groups, the allergenic potential of which has not been clearly defined.

### *5.1.2 Molecular biology techniques*

Molecular biology techniques are developed around PCR (Polymerase Chain Reaction) type methods. From specific probes and primers, the sequence of a coding gene for a protein of interest is amplified millions of times and then characterised. Detection of DNA in the food depends on the quality of extraction. Moreover, the existence of coding

DNA for an allergen, or its relative quantification to be more exact, is not necessarily correlated with the presence of protein in the food. Lastly, the method may prove difficult to implement in inexperienced or inadequately equipped laboratories.

*5.1.3 Influence of technological processes and extraction of allergens*

The technological process that the food undergoes and possible subsequent modifications of the allergen should be taken into account for tracing and detecting the protein. Although the methods applied are specific, they must be able to analyse a variety of foods with compositions that are different and/or modified by the technological treatments and maintain an allergenic potential. The influence of heat treatment on allergen detection has particularly been demonstrated for β-lactoglobulin in milk (Negroni L, 1998). The food matrix may also influence detection by masking the allergen, which means that prior procedures of allergen extraction must be combined with the immunological methods. For peanuts, the detection sensitivity depends on the extraction method and food matrix (Poms RE, 2004; Westphal CD, 2004). The importance of effective extraction on the detection and quantification of an allergen has also been highlighted in the case of egg (Watanabe Y, 2005).

*5.1.4 Limits of analytical methods*

All of the studies described thus offer a wide range of effective immunological systems with lower limits of detection for milk and peanuts than the ppm (Yeung JM, 1996; Newsome WH, 1999; Hefle SL, 2004). However, the systems developed may require considerable apparatus and expertise, making technology transfer difficult (Shriver-Lake LC, 2004; Haasnoot W, 2004). The specific nature of some reagents used in the methods (human serum antibodies for example) can prevent their widespread use from an ethical or technical point of view. Likewise, the complexity and duration of methods can prove incompatible with industrial constraints. Ease of use and analysis duration are therefore characteristics that have been highlighted in recent studies (Wen HW, 2005; Kiening M, 2005).

*5.1.5 Evaluation and standardisation of methods*

Because of these multiple different parameters and the diversity of techniques and reagents employed, the methods need to be validated. With such an approach, the ability of techniques to provide a reliable response at a determined confidence level could be assessed. The validation is based above all on criteria of sensitivity, yield, repeatability and reproducibility and compares these values between the different methods and food matrices. However, numerous studies highlight the difficulty of comparing and validating detection methods in the absence of certified reference equipment, reagents and standardised procedures. Although there is little reference equipment available at present, some standardised food matrices of peanut, milk and gliadin exist or are currently being developed (NIST, Joint Research Centre of the European Commission  Sharpless et coll. 2007).

### *5.2 Analysis and production stage*

Most of the studies mentioned reported analyses on finished products. But detection methods can be applied at different stages of production. Use of the test depends on the different stages linked to the production of the food and its possible contamination by an allergen. While analysis of the finished product is sufficiently significant in some cases, in others, an assessment during manufacture is more appropriate. Analysing a liquid sample before cooking can limit the extraction stages. Moreover, in the event of disparate contamination, the allergen risks being distributed irregularly in different food batches or even in different products within the same batch. Sampling is therefore decisive.
The allergen must therefore be tested for in the closest stages to the possible contamination. Lastly, analyses may be carried out during the cleaning of a production chain making different foods that may or may not contain allergens one after the other.

### *5.3 Commercial methods for detecting food allergens that must be labelled*

The methods available are presented in Table 5. This list is not exhaustive as new methods are published or developed in commercial applications on a regular basis.

**Peanuts**

The difficulties encountered during peanut detection have been identified above. This is because peanuts are a complex protein source with a wide allergenic diversity. Its allergenic potential varies depending on the variety of peanut used and above all on the industrial processes applied.

Peanut detection and allergen assessment in different foods therefore involve the combination of parameters such as the protein target chosen, the industrial process, the food matrix and the protein extraction conditions. Peanuts are still commonly found in food. A "consensus" extraction method needs to be defined to isolate this target, despite the variability of the food matrix. Certain tests focus on detecting a specific allergen, Ara h 1 or Ara h 2 for example. Other tests detect "soluble" proteins containing a diversity of allergens. There are therefore many methods for detecting peanuts on the market.

Sue Hefle (2006) believes these methods to be suitable for detecting peanuts with regard to food allergy risks. At present, commercial kits for detecting peanuts are some of the rare methods to have been assessed in detail. Three collaborative studies comparing two to five immunoenzymatic methods have recently been published. The first compared two ELISA kits (Peanut Protein Elisa Kit and Faskit Peanut Elisa kit) tested in 10 laboratories on 4 food matrices (Akiyama et al., 2004). For one of the tests, the repeatability and reproducibility variation coefficients are less than 30%. The limit of detection is in this case 2-2.5 ng/ml of solution.

A second study organised by the FDA and Association of Analytical Communities (AOAC) assessed 3 commercial kits (Noegen's Veratox for peanut Allergen, R-biopharm's Ridascreen Fast peanut and Tepnel's Biokits Peanut testing kit) on 4 food matrices: cake, ice cream, milk chocolate and cereal (Park et al., 2005). The assessment was based on the analysis of 60 samples, either free from peanut or contaminated by up to 5µg of peanut per gram of food. The results show the ability of all 3 tests to identify the samples containing 5µg/g (ppm) of peanut and the uncontaminated ones. However, based on the statistical analyses and estimated risks of error, the study authors recommend the combined use of 2 out of the 3 tests assessed.

A third test was coordinated by the Joint Research Centre of the European Commission (Poms et al., 2005). 30 laboratories from 16 European countries were involved in comparing 5 commercial kits (Neogen's Veratox for peanut Allergen, R-biopharm's Ridascreen Fast peanut, Pro-Lab diagnostics' Prolisa Peanut Pak, Elisa Systems' Peanut Residue Elisa Kit and Tepnel's Biokits Peanut testing kit) detecting either an allergen (Ara h 1 or Ara h 2) or "soluble" proteins of the peanut. 2 different matrices containing 4 different concentrations of peanut were analysed. All 5 tests are able to detect peanut at a contamination level of 5-10mg/kg. 2 of the tests are functional at concentrations below 5mg/kg with reproducibility variation coefficients of 27-36% for biscuits and 45-57% for chocolate.

Another commercial method (Lateral flow assay or Dipstick test) was assessed as part of a collaborative analysis between 18 laboratories (Van Hegel et al., 2006). This test may seem easier and quicker to implement. The results obtained from 1,260 analyses showed that the sensitivities of the Dipstick test are similar to those of the ELISA tests. However, the existence of false positives and false negatives observed in some cases means that this type of method should not be used as it is.

**Milk and egg**

There are ELISA and PCR methods available to test for these ingredients (Demeulemester et al., 2006). The PCR methods are not suitable as they cannot differentiate between egg and chicken on the one hand or milk and beef on the other. The performances of commercial tests have not been completely assessed. The Allergen Methods Committee, set up by Health Canada and the AMC, tested a commercial kit for detecting egg (*http://www.hc-sc.gc.ca/fn-an/res-rech/analy-meth/allergen/neogen_egg_overview-neogen_oeuf_apercu_f.html).* Various methods have been officially adopted in Japan for detecting milk or egg allergen in 5 types of food matrix. In-depth studies to validate commercial egg detection kits are currently under way.

**Soybean**
The first ELISA test to be marketed, and the only one for over 10 years, had a limit of detection of 5,000 ppm, which is not enough to prevent allergic risks. Limits of detection between 20 and 100 ppm have been achieved, but only a few specialist laboratories could use this method.
Other ELISA tests have now been marketed with declared limits of detection of 1 ppm. There is little information on the performances of these commercial kits on products that have undergone technological treatments (hydrolysis, fermentation or heat treatment), however. PCR methods, which have progressed in line with the need to detect GMOs, are nonetheless sensitive and effective, including on products that have undergone considerable technological treatment.

**Cereals containing gluten**
These are included in the list of ingredients that must be labelled for two reasons. Firstly, gluten, the main protein in wheat, is the trigger factor in celiac disease, and secondly, it is responsible for an increasing number of food allergies (Janssen, 2006). Numerous methods are available on the market, with limits of detection usually ranging between 2.5 and 10 ppm. Some of these commercial methods have been assessed in two collaborative studies (Mendez et al., 2005, Gabrovska et coll. 2006). The methods determining gluten by gliadin present sensitivities of up to 1.5 ppm. Tested in 20 laboratories and on 12 food samples, they have acceptable repeatability and reproducibility variation coefficients and, for one of them, these are less than 25 to 35% respectively.

**Nuts**
These sources are varied: almond, hazelnut, walnut, Brazil nut, cashew, etc. The effects of nut heat treatments on the allergenicity of their proteins are still not clear (Koppelman, 2006).
Because of the diversity of nuts, only a few ELISA kits are available on the market (almond, hazelnut). Furthermore, a wide range of internal ELISA methods, the performances of which little is known and which can present cross reactions, are reportedly used.
There are also numerous internal PCR-based methods (PCR-ELISA, real-time PCR) that are more specific. It is also possible to detect all types of nuts with some methods, whose limits of detection are from 1 to 10 ppm. These methods are due to be marketed as kits.

**Fish**
There are several internal methods for detecting fish by PCR. It is possible to identify numerous fish species, differentiate between fish with cartilage or bony skeletons or detect fish, all species included. Commercial kits for such purposes are also due to be marketed.

**Crustaceans**
Because there is such a wide variety of crustaceans, they are difficult to detect. There is currently an ELISA commercial kit available to detect them, but little is known of its performances (what are the limits of detection? Do technological treatments have an impact?).
There are internal PCR methods for identifying crustacean species, but these cannot be used at present to detect all species.

**Sulphites**
Sulphites must be labelled for concentrations of 10mg/kg (10 ppm) and over. There are two standardised methods for sulphite assay (NF EN 1988-1 and NF EN 1988-2), with different fields of application. Applied to food, these methods can present different results and therefore need comparing on a wide range of matrices.

***Conclusions and future prospects***
Over the last decade, numerous techniques have been developed to detect the different sources of food allergens. Some of them have led to the marketing of systems that are able to detect up to 2 ppm of an allergenic component. Although these analyses and commercial

kits are still expensive, their costs are tending to stabilise or go down. However, the performances of these tests seem to be very variable and depend on the method used, extraction conditions, specific nature of the system and food matrix analysed. Such a diversity of method and performance requires a comparative and exhaustive analysis of the methods available for routine distribution. Inter-laboratory validation, initiated for some techniques (ELISA, dipstick test) and some allergens (peanut, egg, gluten) should become widespread to enable the assessment and comparison of the capacities of the tests available for determining allergenic presence in the different food matrices.

The versatility and homogenisation of detection methods could be future challenges, for the differences in industrial processes and food matrices change the state and presentation of allergens. Detection of an accidentally present allergen could be guaranteed by optimum denaturing protein extraction, independent from the food matrix, and by applying a suitable test for determining the allergen thus modified. This approach is used in the detection kits provided by the Moriganate Institute of Biological Science (Japan). Its functionality could be observed during a comparative egg detection study (Faeste et al., 2007).

Without being universal, this strategy may be applied to different allergens that are accidentally present in a food matrix. It would constitute a stage for the multiple detection of allergens, which is another challenge for the future. Indeed, for the time being no single system can simultaneously detect most food allergens in a food. Only some models enable a simultaneous analysis of several allergens (Ben Rejeb S, 2005). Specific multi-detection methods such as multiplex technology have currently been developed for environmental allergens, and biosensor type technologies are also available (Yman et al., 2006). The relevant techniques for analysing food matrices are still expensive and complex to implement, however. Miniaturising systems and using bio-chips would resolve these disadvantages and provide swift, automated application. Other techniques such as the dipstick test (Baumgartner S, 2002; Stephan O, 2002; Wen HW, 2005) could combine simplicity with multiple detection. They would be useful for a swift analysis of complex foods when they are being made, subject to reliability being correctly established.

| Source of food allergen | ELISA<br><br>Commercial kits | (LODs)<br><br>Internal methods | PCR<br><br>Commercial kits | (LODs)<br><br>Internal methods | Histology (LODs) | Colorimetry (LODs) | Enzyme assays (LODs) | Suppliers |
|---|---|---|---|---|---|---|---|---|
| Milk | x (0.5 – 10 | x | x | x | | | | A,B,C,E,F, G,H,J |
| Egg | x (5 ppm) | x | | x | | | | A,B,E,F,G, H,I,J |
| Soybean | x (1-5 ppm) | x | x (10 ppm) | x | NF V04-417* (20-100 ppm) | | | A,B,F,H,J |
| Peanut | x (0.5 – 5 | x | x | x | | | | A,B,C,E,F, G,I,J |
| Wheat | x (2.5 – 10 | x | | x | | | | A,B,D,E,F, G,J |
| Fish | | | | x | | | | J |
| Crustaceans | X | x | | | | | | A,C,J |
| Nuts<br>Almond<br>Cashew<br>Hazelnut<br>Walnut<br>Macadamia | <br>x (1-5 ppm)<br><br>x (0.1 – 10 | x<br><br>x (1 ppm)<br>x (1 ppm) | <br>x<br><br>x | x<br>x<br>x<br>x<br>x<br>x | | | | A,B,C,E,J |

| | | | | | | |
|---|---|---|---|---|---|---|
| nut<br>Pecan<br>Brazil nut<br>Pistachio | <br><br>x (1 ppm) | <br>x<br>x<br>x | | | | |
| Celery | | | | | | |
| Mustard | x x | | | | | A,C,J |
| Sesame seed | x | | | | | A,C,J |
| Sulphites | | | NF EN 1988-1** (10 ppm) | NF EN 1988-2*** (10 ppm) | | |

* NF V04-417 (September 1999) – Meat and products thereof - Preparation of a histological section – Paraffin technique
** NF EN 1988-1 (April 1998) - Food products - Sulphite assays - Part 1: optimised method by Monier-Williams
*** NF EN 1988-2 (April 1998) – Food products – Sulphite assays – Part 2: enzyme method

A: ELISA Systems (www.elisas.com.au)
B: Neogen (www.neogen.com)
C: Abkem (www.abkemiberia.com)
D: ELISA-TEK (www.elisa-tek.com)
E: R-Biopharm (www.r-biopharm.com)
F: Tepnel (www.tepnel.com)
G: Morinaga Institut / Crystal chem. Inc (www.crystalchem.com)
H: SafePath (www.safepath.com)
I: Tecra (www.biotrace.co.uk)
J: Congen (www.congen.de)

**Table 5: Limits of detection of the ELISA and PCR methods per category of food allergen**

**Response to Q3 of the request:**
**What proportion of food allergy sufferers is exposed to a risk if they eat foodstuffs presenting the current levels of contamination? To what type of risk and how often are they exposed at the scale of individual consumption?**

To estimate the dietary exposure of food allergy sufferers to allergens, two types of data are required: (i) the frequency and concentration of allergens in food and (ii) the consumption of different types of food that may potentially contain allergens.
- Regarding the frequency and concentration of allergens in food (i), the current levels of food contamination by notifiable allergens are unknown (see above, response to question 2 of the request). The international bibliography supplies data on the occurrence and level of some major allergens such as peanut, but this is difficult to extrapolate directly to the French situation.
- Regarding the consumption frequency by food allergy sufferers of food likely to contain allergens (ii), it can be observed that food consumption surveys generally focus on generic foods and the ingredient lists are not known in most cases, which makes it difficult to estimate the consumption of foods likely to contain allergens. Moreover, these surveys do not specifically deal with food allergy sufferers.
Based on the data available, in view of the fact that the type of risk is specific to each allergy sufferer, it is not possible to determine how often the French population is exposed to notifiable allergens.

**Responses to Q4 and Q5 of the request:**
**- Can a relationship be established, for each major allergen, between the amount of allergen and the proportion of food allergy sufferers exposed to a risk in the event of consumption?**

**- Can a critical limit be defined for each major allergen from which a much larger proportion of food allergy sufferers would be exposed to a risk, above which the presence of cross contact should be indicated and below which advisory labelling may be removed?**

Questions 4 and 5 of the request can be grouped together as they concern the notion of reactivity threshold and associated dose/response relationships.

The reactivity threshold corresponds to the minimum dose of food (or reactogenic dose) that can trigger a reaction in an allergy sufferer.
It is possible to theoretically determine these thresholds using a statistical method that involves calculating a theoretical threshold dose by analysing the data published from oral challenge tests. The statistical model must estimate the threshold dose that triggers a reaction in the allergy sufferer by using data from the literature. This approach puts forward a threshold that would correspond to a reaction being observed for one in every million allergy sufferers.
Although the threshold dose is different when the amount of foods is expressed in amount of food consumed or in protein content, some publications are available and supply results (see Chapter 4).
The reference for determining the minimum dose or reactivity threshold of a food allergy is still the oral challenge test, conducted as a double blind study. This test can determine the smallest dose to trigger a reaction as well as the smallest dose that did not trigger a reaction. Some studies help to determine threshold values and the percentage of patients reacting to this dose, but there is a certain number of limits to them. This is because those patients who have presented an anaphylactic shock are excluded from the oral challenge test. It is therefore not possible to know their reactivity threshold. Moreover, differences in the protocols currently used for oral challenge tests between the studies published make comparison impossible. The starting dose, interpretation of positive reactions, interval between doses and type of food administered vary from author to author. Lastly, the studies

published, beyond the comparison problems associated with the units used (concerning the threshold dose and response levels), cannot generally be compared in terms of study populations (the results are to be distinguished in particular between adult and child populations).

**Overall**,
For the main allergens studied (egg, milk and peanut), the studies published at present cannot be compared because of the different protocols used and populations studied. The number of patients included in the studies is usually not enough to draw definitive conclusions either.

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# 6 Growing complexity of food product formulations

Today it is only possible to give a partial answer to the question of consumer exposure trends to allergens present in food and food ingredients. This is because a full answer assumes knowledge not only of the changes in food consumption but also in the composition of foods containing ingredients that are allergenic sources.

The increasing consumption of processed products to the detriment of homemade dishes is well documented.
The less frequent preparation of homemade products and dishes is well illustrated by socioeconomic studies. For example, CREDOC[2] studies on the dietary habits of French people show that the time devoted to meal preparation has been decreasing steadily over recent years. The average time spent making dinner during the week, when guests are not expected, has fallen markedly from 42 minutes in 1988 to 36 minutes in 1997, and for weekend meals from 60 to 44 minutes (Volatier JL, 1999). This trend can only be partly explained by the availability of ready meals and easy-to-use composite ingredients (culinary preparations).
We do not have a summary index of the consumption trends of processed products. However, we know that consumption of many categories of processed foods is increasing (see below).
Lastly, eating out accounted for 25% of lunches and 12% of dinners in 1999 (source: INCA study). Eating out more often can be problematic for food allergy sufferers as the ingredients of meals in these cases are not generally indicated on the menu.

### *6.1 Definitions*

What is a food product with a formulation? The simplest definition may use the notion of ingredient. An ingredient is “an element included in the composition of any type of mixture or preparation”. A foodstuff with a formulation is made up of at least two ingredients. “Formulation” here therefore means the list of ingredients of a complex foodstuff and their respective amounts. A “complex foodstuff” means one that is made up of at least two ingredients.

### *6.2 Increasing consumption of complex foods*

Two data sources are currently available for assessing the trends in complex food consumption: data on “apparent consumption”, from national accounting, and data from individual and national surveys on food consumption.

Most food groups that are increasingly available on the food markets are complex processed groups: yoghurts (including fruit yoghurts), pâtés, sausages and other prepared meat products, preserved meat, all types of dairy desserts (crème caramel, chocolate mousse, etc.), fizzy drinks, fruit juices and nectars, sweets and chocolate. Although the consumption of sweet biscuits has been relatively stable over the last decade, that of savoury biscuits is rising steadily (INSEE[3], 2006).

We do not have much apparent consumption data from national accounting for the time being, i.e. in kg/year or g/d, for all marketed foods. In 2005, INSEE set up a major programme with the aim of better covering most food markets.
Nutritional or individual food consumption surveys are another key source of food consumption data. These sources are more suited to use in the field of biological sciences, as they concern actual consumption, i.e. ingestion and not consumption in the economic sense of the term (Figure 4).

[2] Research Centre for the Study and Observation of Living Conditions
[3] French National Institute for Statistics and Economic Studies

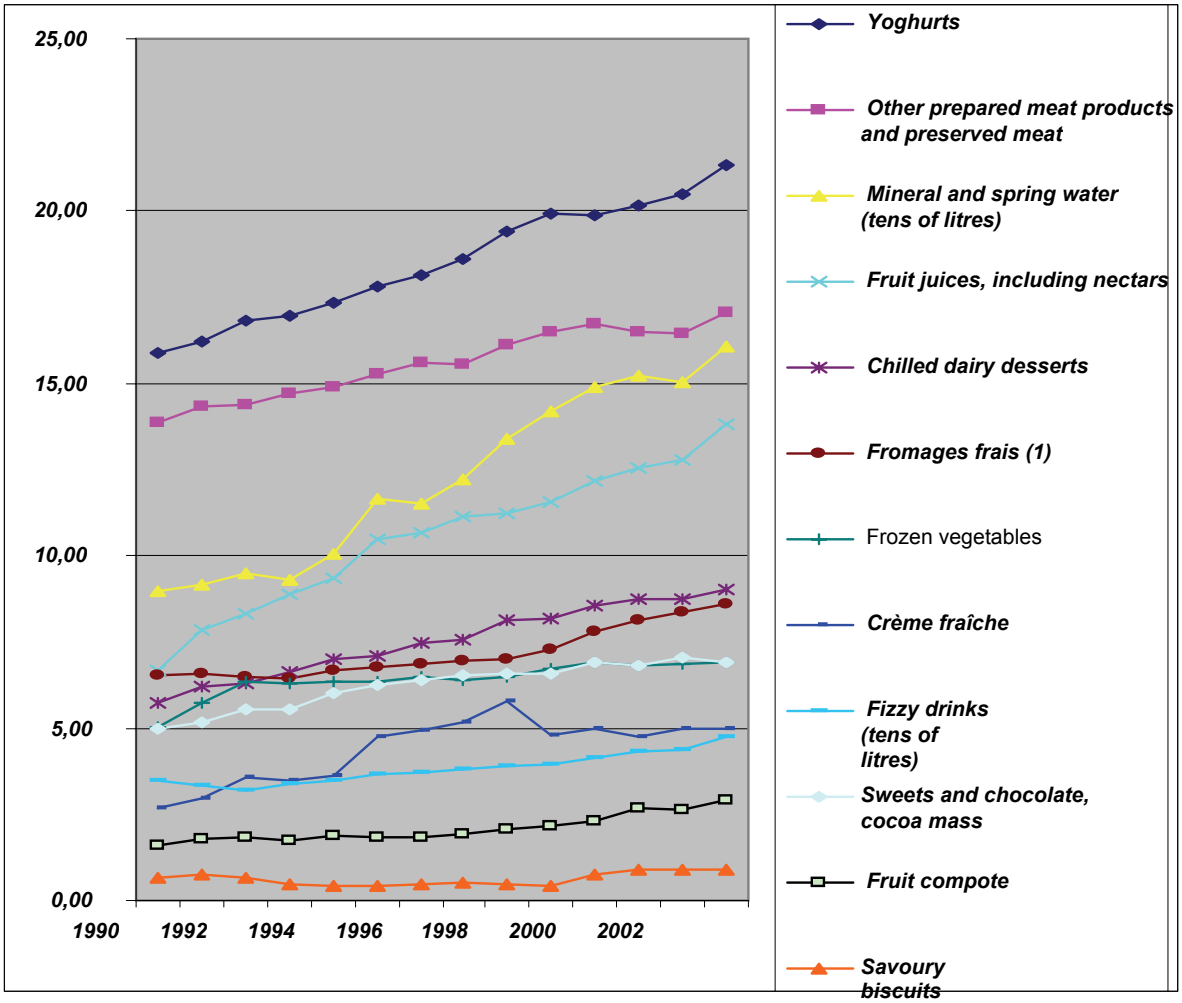


***Figure 4: food groups with the highest increases in consumption (in kg/year) over the last 15 years (data not published by INSEE). Source: INSEE ASF, 2006.***

| | 1994 | 1999 | 2003 |
|---|---|---|---|
| Ready meals | - | 80 | 120 |
| Pizzas-quiches and savoury tarts | 23 | 37 | 45 |
| Fruit juices and fizzy drinks | - | 100 | 123 |
| Yoghurts and dairy desserts | 92 | 105 | 108 |

***Table 6: food groups with the highest increases in consumption (in g/d) over the last decade according to individual food consumption surveys. Source: ASPCC 1994, INCA 1999 and CCAF 2003 studies. Base: adults aged 15 years and over.***

In individual nutritional studies, measurement of ready meal consumption depends on how this food category is defined. Two contrasting coding strategies may be applied for a food made up of several ingredients, such as paella. The paella is either considered to be a food as such, placed in the “ready meals” category, or the paella ingredients declared by the consumer (rice, mussels, crayfish, squid, cod, chorizo and so on) are described and split into the different food categories to which these ingredients belong (cereal products, crustaceans and molluscs, seafood, etc.). This is why it is difficult to compare different studies as the studies for breaking down the complex foods may differ and are not always specified. That said, the results of three studies (ECCA 2004 [Lehuédé F, 2004], INCA 1999 and ASPCC 1994 [Volatier JL, 2000]) confirm that consumption of complex foods is increasing. This increased consumption of different complex food groups, observed by different sources of food consumption data, does not, however, allow conclusions to be drawn on trends in allergen exposure. For this, we need to look into the growing complexity of formulations.

### *6.3 Presence of allergens in formulations and growing complexity of recipe foods*

The complexity of recipe foods can be addressed by looking at the number of ingredients included.
This information is not available at present as considerable maintenance would be required to collect it constantly and create a recipe database. Afssa has just compiled the first database of 420 average recipes for the purposes of monitoring nutritional intake (Calamassi G, 2004). These average recipes do not attest to the diversity of formulations for each food considered as a result, and particularly to the differences in recipe depending on product range and brand. The objective is strictly nutritional and does not involve the monitoring of ingredients and allergens.
There are two types of sources that can be used to monitor how this complexity is evolving:

- labelling, including the list of ingredients (public information),
- the recipes used by industries or independent food makers (private and often confidential information).

#### *6.3.1 Using the ingredient list on the label to assess the degree of food complexity*

The ingredient list and composition of complex food products on labelling is now better known thanks to the appeal by Directive 2003/89/EC of the so-called “25%" rule that meant that those ingredients contributing to less than 25% of the total quantity of food labelled did not have to be indicated in the list of ingredients. The notification of allergens mentioned in Annex IIIb of this Directive also sheds light on the use of allergenic foods.

However, since food products are sometimes sold without packaging, it is not possible to gather this list of ingredients from labels (bread and pastries bought in bakeries, delicatessen dishes, etc.).

#### *6.3.2 Access to recipes used by industries or independent food makers*

The recipes used by such professionals are generally considered confidential and are not published. However, it is possible for the risk manager or assessor (Directorate General for Competition, Consumer Affairs and Fraud Control/DGCCRF) to access this information if there is a proven need to protect consumers.

For example, Directive 95/2/EC on food additives requires each Member State to monitor the consumption of additives. In France, sulphites belong to the types of additive whose consumption must be monitored in realistic conditions (List of 14 monitored additives at Stage 3). Accordingly, an assessment of French population exposure to sulphites was conducted by Afssa (Afssa, 2005) through a collection by the DGCCRF of 1,288 pieces of data of sulphite use in food, 1,213 of which concern wine and 75, other products (dried fruit, fruit juice, pealed or processed potatoes). Sulphites were almost always present in wine (particularly white wine) and peeled potatoes. They were more rarely found in dried fruit and processed potatoes, at the regulatory but often high doses (1g/kg on average in dried fruit using sulphites).

The method of this type of study requires preliminary information on foods that are likely to contain the allergen in question. Indeed, the survey plan is based on the maximum additive limits provided for by the European directive to rank the foods potentially containing sulphites. The method may be adapted for monitoring notifiable allergens in food.

#### *6.3.3 Study among manufacturers or middlemen involved in the marketing of allergenic ingredients*

Another method for identifying the allergens present in complex foods may, unlike the approaches previously described, which look at marketed foods to quantify the ingredients used, involves obtaining information from ingredient manufacturers or middlemen (for example dried fruit importers) about their outlets in food industries.

This type of approach is already used by the State departments responsible for national food accounting (SCEES[4] of the Ministry of Agriculture, INSEE) to measure intermediate consumption, which includes the purchasing of food ingredients by food industries. It would need reliable data on the imports and exports of food ingredients as well as of the complex foods using these ingredients.

### 6.4 Increase in allergies and complexity of the formulation of food products

The complexity of a food is correlated with a larger number of ingredients included in its composition and therefore with an increase in the number of people likely to react to one or other of the proteins it contains. Technological food treatments (cooking, texturising, etc.) can modify the allergenicity of food. These treatments can either induce a decrease in allergenicity (the allergenicity of apples and red fruits disappears after cooking for example) or a new allergenicity (wheat isolates, for example).
A current concern is to assess the allergenic risk of new foods or foods resulting from new manufacturing processes. Two recent examples incurring new allergic risks highlight this need.

1. Lupin, a legume introduced into human food in 1997 in France, presents an allergenic risk with cross reactivity with peanuts, which was not foreseen before it was marketed. Severe reactions have been reported and account for 5% of serious allergic reactions reported on the Allergy vigilance network. The recent survey carried out by this network shows that latent sensitization to lupin flour reaches 2.5% in children and 3.7% in adults, presenting a progressive atopical disease. The most recent European law to come into force on the subject, in 2006, now makes its labelling compulsory.

2. Another risk of the influence of manufacturing processes on food allergenicity is illustrated by wheat isolates. Several observations of serious allergic reactions have just been reported in connection with this allergen in people who tolerate wheat flour. This accounts for 2% of the allergic reactions reported on the Allergy Vigilance network and the frequency has increased over the last two years as consumption has increased.

Most serious allergic reactions occur after the consumption of prepared foods, and not with the food in its native form. Assessment of the allergic risk of a food must be weighted by the analysis of the matrix effect of the recipe in which it is incorporated.

***Conclusion***

There is currently no public database in France on the recipes of complex food products, and it is therefore not possible to track trends in the use of an ingredient, which is the source of a given allergen. It is nevertheless established that most allergic reactions occur after consumption of complex prepared foods, although the ingredients making up a food and the matrix effect that can significantly modify the allergenicity of the finished product must be taken into account when assessing the allergic risk of a food.

Consumer and dietary habit trends point to an increase in the consumption of complex mass- or locally produced food products, with an ingredient list of variable length.

Three types of approaches may be used to specifically track the trends in food formulation complexity. The first approach would involve a study of the ingredients listed on food product packaging. The second would involve a direct survey among manufacturers, and the third would involve a study of the use of a given food raw material as ingredients, based at least partially on the national accounting system in the food field.

[4] Central Department of Statistical Studies and Surveys

Whatever the chosen approach, the eating-out sector must also be considered in this type of study.

The current lack of suitable database for answering this question means that a prospective rather than retrospective approach should be taken.

**Response to Q7 of the request:**
**How has the complexity of processed food product formulation changed over recent years? What impact is this complexity likely to have on the frequency of allergic reactions?**

The consumption of processed products has been increasing for several years now, to the detriment of homemade foods. Consumer and dietary habit trends point to an increase in the consumption of complex mass- or locally produced food products, with an ingredient list of variable length.
Accordingly, the "apparent consumption " data obtained from national accounting shows that most food groups whose availability on the food markets is increasing are complex processed food groups: yoghurts, pâtés, sausages and other prepared meat products and preserved meat, all types of dairy desserts, fizzy drinks, sweets and chocolate (INSEE, 2006).
Data from individual and national studies on food consumption also show that the food groups with the highest increases in consumption over the last decade are ready meals, pizzas, quiches and savoury tarts, fruit juices and fizzy drinks, yoghurts and dairy desserts (ASPCC, 1994; INCA, 1999 and CCAF, 2003 studies).
Regarding changes in formulation complexity, there is currently no public database in France on the recipes of complex food products. It is therefore not possible to track trends in the use of an ingredient, which is the source of a given allergen.

The complexity of a food is correlated with a larger number of ingredients included in its composition and therefore with an increase in the number of people likely to react to one or other of the proteins it contains. Recent studies stress the importance of the food matrix in the intensity of the allergic response. Assessment of the allergic risk of a food must be weighted by the analysis of the matrix effect of the recipe in which it is incorporated.
The recent occurrence of allergic reactions in some people after consuming lupin or wheat isolates highlights the need for a precise assessment of the allergenic risk of new foods or foods obtained from new manufacturing processes.

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# 7 Knowledge to be acquired

**Response to Q6 of the request:**
If what we know to date does not allow responses to be formulated to the questions raised for certain allergens, can we at least define the method for the scientific community to follow and draw up research recommendations for the allergens concerned?

***Epidemiological data***

It appears important to conduct prevalence surveys, obtain data on dietary habits and behaviour, quantify exposure to notifiable allergens and analyse their influences.
Developing the Allergy vigilance network is one way to acquire this knowledge. It may be completed by prevalence surveys. The only national survey to be conducted on this theme dates back to 2001.

***Develop the means for validating the quality of the HACCP allergenic risk management method***

- Advisory labelling may not be necessary if the companies applying the HACCP method could guarantee the quality of the allergenic risk prevention measures set up through validated and accredited detection tests. This proposal implies that the allergenic detection tests have been subject to multicentric validation. Developing trials for the inter-laboratory validation of detection tests is a priority.
- It is important to foster applied research for developing detection/quantification methods for all notifiable food allergens. Their performances will be assessed and validated on different matrices.
- A current concern is the assessment of the allergenic risk of new foods or foods obtained from new manufacturing processes, and this justifies a research investment to define and set up the practical arrangements for conducting it.
- It should be possible to swiftly set up a scientific food analysis programme for obtaining information on the frequency of food contamination by notifiable allergens. Such a programme, conducted nationwide, will only be possible with the input of risk managers and food manufacturers (see Chapter 2).

***Development of risk prevention and diagnostic tools***

Allergic reactions can occur when a food allergy sufferer ingests an unidentified allergen. The detection and labelling of the allergens we have studied in this report aim to control this risk and are part of secondary prevention. They do not prevent the initial risk. It is important to foster studies seeking to develop particularly biological diagnostic tools that can identify at-risk subjects and assess the size of risk (predictive severity tests).

# 8 Conclusions and recommendations

Current provisions on regulatory labelling result from the transposition of Directive 2003/89/EC amending Directive 2000/13/EC (framework directive on the labelling of prepackaged foodstuffs) as regards the indication of ingredients present in foodstuffs. Indication on the ingredient list of all Notifiable Allergens has been fully applicable since 25 November 2005, with a few labelling exemptions provided for by Directive 2007/68/EC (Decree 2008-1153 of 7/11/2008 published in the Journal Officiel of 9/11/2008).
It is important to remember that there are no regulatory provisions on advisory labelling, i.e. the indication that allergens may be accidentally present because of the manufacturing process of a foodstuff. This is an initiative taken by the largest food industry and which is gradually being adopted across the board.

The working group's conclusions and recommendations concern:

1) Labelling of allergens present accidentally: the working group does not cast doubt over the use of advisory labelling, but considers that its use must enable the food allergy sufferer to assess the risk s/he takes in consuming the product, from the information provided. The working group puts forward a certain number of recommendations with the intention of clarifying the use of this labelling.

2) Use of the indication "guaranteed free from allergens": recommendations are also formulated by the working group as the accidental presence of allergens in these products is not always guaranteed for now.

3) Regulatory labelling of certain ingredients: the working group would like the labelling of certain allergens, added intentionally, to be more precise. The labelling of accidentally present allergens should also use precise terms.

Moreover, the working group recalls that all published clinical observations show that severe allergic reactions can be triggered for very small amounts of allergen ingested.

**1) Concerning the labelling of allergens present accidentally**

a) The Allergy vigilance network shows that, since 2001 in France, 8.6% of serious allergic reactions reported to this network concern masked allergens. These reactions are usually caused either by no labelling on products when they are sold or by a change in packaging and/or recipe with a subsequent labelling error. The allergy sufferer may also read the label incorrectly after a change in recipe. Less than 1% (0.4%) of these serious reactions concern contamination occurring during manufacture of the product.
This result should nevertheless be weighted by the fact that these observations are limited to serious cases and do not concern less severe cases.
Note that since the European directive on the compulsory labelling of 14 allergenic ingredients came into force in November 2005, no case of anaphylaxis caused by an accidental presence of allergens has been recorded by the Allergy vigilance network[5].

b) The working group notes that the indications used by companies are not harmonised. Each company uses its own indications on advisory labelling. These indications are fairly imprecise (of the type "May contain…") and are followed by a list of notifiable allergens. Precise indications such as "Product made in a factory containing a given allergen" suggest that allergen HACCP-type quality assurance methods have been set up by the professional,

[5] The allergy monitoring network is coordinated by the Department for Internal Medicine, Clinical Immunology and Allergology – Central Hospital - Avenue du Maréchal de Lattre de Tassigny - 54035 Nancy (France).

but do not state the product safety level. In the context of advisory labelling becoming more widespread, consumers take the lack of indication either to mean that the professional is less concerned about the possible accidental presence of notifiable allergens in his products or, quite the reverse, that there is no risk of allergens being accidentally present in the product.
The working group highlights the need to harmonise this labelling and quantify the associated risk.

*Recommendation: Based on this observation, it is recommended to limit the number of indications given on advisory labelling by using precise expressions appropriate for the actual contamination of a foodstuff by a notifiable allergen that could have occurred during the manufacturing process. The working group considers that proposals could be drawn up by professionals together with risk managers and allergy sufferers' associations for a restrictive list of indications to be used in the future and so that these indications are precise enough to inform allergy sufferers.*

c) To avoid the systematic nature of advisory labelling, the working group thinks it is important that food processing professionals can set up an HACCP method concerning the allergenic risk within each company, according to the criteria laid out below.

Highly sensitive allergen detection kits are currently available on the market, some of which are capable of detecting up to 2 ppm of allergenic compound. However, the performances of these tests appear variable as they depend on:
- the method proposed,
- extraction conditions and the system's specific nature,
- the food matrix analysed.

Such a diversity of methods and performances requires a comparative and exhaustive analysis of the methods available for routine distribution. This type of analysis is not available to date. It therefore seems premature, based on currently available scientific knowledge, to recommend detection strategies.
Likewise, the multiple allergen detection methods are still not developed enough to identify all allergens present accidentally in foodstuffs. Indeed, no single system can simultaneously detect most food allergens in a food.
As a result, it does not appear possible to rely solely on detection tests for guaranteeing a satisfactory safety level for allergy sufferers.

*Recommendation: The working group therefore recommends all companies to set up an allergen HACCP method. This would imply that precautions in terms of sector organisation have been taken and can be justified. This clarification of sectors should improve control of the risk of allergic reactions occurring as a result of cross contact. This type of approach has already been successfully set up in some companies (interviews with manufacturers by the working group). Detection tests may be used to assist with the establishment of the HACCP method.*

*The working group considers that the use of advisory labelling should be justified by the establishment of an allergen HACCP method as described above. The indications given will be appropriate for the type of contamination that may actually occur despite the existence of quality assurance, such as the HACCP method. If no HACCP method has been put in place, the working group recommends that preventive labelling also be provided, explicitly informing consumers that no precautions have been taken regarding the allergenic risk by the product manufacturer.*
*Advisory labelling must be sufficiently informative for food allergy sufferers to be able to consume the product in full awareness, i.e. with the possibility of assessing the risk they are taking by consuming the product from the information provided.*

**2) Concerning the labelling of certain foods "free from…"**
There is currently some confusion over the absence of allergenic ingredient in the recipe and absence of contamination. Some companies applying such labelling guarantee the absence of use of certain ingredients in their recipes, but cannot guarantee that no allergens are accidentally present.

*Recommendation: In this context, it appears essential to clarify the meaning of the claim "guaranteed free from…" for highly allergic consumers who intentionally purchase this type of product. It would, in all cases, be preferable that the ingredients used in products bearing this claim can be guaranteed "free from accidental presence" and not just "free from allergens". It is also of the utmost importance that the use of "guaranteed free from…" claims is validated by HACCP methods and quality controls confirming the absence of allergens, which is not always the case at present.*

**3) Concerning allergens introduced intentionally**
The provisions make a distinction, when describing the indication procedure, between allergens that are used directly as ingredients and those used indirectly, by a substance such as a processing aid, transfer additive, additive or flavour carrier.
In accordance with article R. 112-16-1, paragraph 1, the following must systematically be labelled with account taken of the remaining labelling exemptions:
- any allergen substances or ingredients used in the manufacture of a foodstuff and still present in the finished product, even if in altered form,
- any ingredients coming from "allergen ingredients" (products thereof), used in the manufacture of a foodstuff and still present in the finished product, even if in altered form.
The name of the allergen must be indicated as soon as the ingredient in question is not clearly identified by the consumer as coming from an allergen.

*Recommendations:*

*a) For intentionally used and accidentally present allergens, the working group considers that, when using an explicit indication of the allergen, identifiable by the consumer, it is important that the indication is not too imprecise. For example, the term "lactose" should not be replaced by "milk", or "peanut oil" by "peanut". These clarifications are important in terms of prevention for food allergy sufferers.*

*b) It is possible for the labelling of dairy products sold as "cheese", "butter" or "yoghurt" not to list ingredients insofar as it is considered that reference to the allergen "milk" is clear. However, because the list of notifiable allergens does not specify the type of milk that must be notified and due to the occurrence of certain serious reactions observed in France to ewe's and/or goat's milk sometimes used as a substitute for cow's milk, the working group considers it important to mention the origin of the milk used: cow's milk, ewe's milk or goat's milk.*

# Annex 1: Afssa request from the Association "Consumers, Housing and Living Environment" (CLCV)

Paris, 1 April 2005

Ms. Muriel Eliaszewicz
Director for the Evaluation of Nutritional and Health Risks
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BP 19
94701 MAISONS-ALFORT
FRANCE

**RE: Afssa request from the CLCV on the accidental presence of allergens in foodstuffs.**

Madam Director,

Please find attached a request for Afssa from the CLCV on the accidental presence of allergens in food products and its indication on packaging.

The presence of intentionally added allergenic ingredients considerably reduces the choice of food allergy sufferers. This choice is reduced even further by the recent development of preventive labelling, drawing attention to the risk of allergens being accidentally present because of uncontrolled manufacturing processes. This labelling, also known as "advisory labelling" unnecessarily worries a large proportion of food allergy sufferers and presents them with an unacceptable choice: buy allergen-free products at an expensive cost or consume everyday products without being able to assess the risks to which manufacturers are subjecting them. This is why we are asking you to respond to the questions raised in this request.

Yours faithfully.

Reine-Claude Mader
President

# Afssa request


**Consommation, Logement et Cadre de Vie**

## *Grounds:*

Preventive labelling is becoming increasingly widespread on the labels of prepackaged food products, of the type “possible traces”, “may contain” and so on, warning food allergy sufferers of possible contamination by compounds that have been accidentally added to the foodstuffs.
This labelling places food allergy sufferers in a difficult situation, as it does not give them any information on the level of possible product contamination or allow them to make an informed choice during purchase.
Indeed, while allergy sufferers must all follow strict and rigorous avoidance diets, they do not all present the same reactivity thresholds and only a minority is sensitive to the smallest doses. Such people, suffering from severe allergies, have no choice but to opt for specific product ranges.
Most allergy sufferers present a much lower sensitivity however, suffering from allergies that would seem to be compatible with the level of cross contact of everyday food. This is particularly the case if the manufacturer has taken precautions to reduce the risks of these contaminations.
Some manufacturers have certainly set up such procedures already, or are working on them. But unable to guarantee zero risk, they continue to use preventive labelling under the same conditions, which does not inform food allergy sufferers that the accidental presence has been reduced to an acceptable level with regard to their diet. Preventive labelling therefore acts as a precaution that unnecessarily and falsely worries these food allergy sufferers, who can probably consume these products safely.
Some food allergy sufferers choose to ignore this labelling, banking on a very low level of contamination, below their reaction threshold, but without being able to guarantee this. Out of uncertainty and precaution, other food allergy sufferers opt for specific dietary products that are guaranteed to be free from the allergen in question but which are much more expensive, without the need for this extra expense being justified every time.
With no assessment of the sensitivity thresholds of most food allergy sufferers, it is not possible to determine the amounts of allergen contamination below which it is no longer relevant to use preventive labelling on everyday food products.
Moreover, Afssa (1), along with the French High Council for Public Hygiene (CSHPF) (2), have stressed the importance of restricting the conditions for using these preventive indications at the same time as reducing the risks of cross contact in manufacturing processes.
People who are intolerant to gluten, although different in terms of mechanism and symptom, must also avoid the compound affecting the integrity of their intestinal wall. Their needs may cover some needs of food allergy sufferers. The fact that there is a regulatory threshold below which “gluten-free” labelling is authorised (200ppm) and that the scientific community is currently seeking to bring this threshold in line with the reality of the disease, may guide experts in their definition of thresholds for allergy sufferers, with the necessary precautions.
The analysis presented in these grounds is shared by the following associations representing food allergy or intolerance sufferers: Association Française des Polyallergiques, Association Française de la Prévention des Allergies (AFPRAL) and Association Française Des Intolérants Au Gluten (AFDIAG).

References:

(1) *« Ainsi, les principales modifications à effectuer sur la réglementation actuelle en matière d'étiquetage sont (...) des restrictions sur les conditions d'emploi des mentions préventives du type « peut contenir… » devraient être mises en place. Il est en effet préférable de privilégier les bonnes pratiques de fabrication et de demander des justifications techniques à ces mentions, plutôt que de laisser se développer une pratique qui, à terme, pourrait bien réduire injustement les produits accessibles aux individus allergiques*. »
AFSSA (Carine Dubuisson, Sébastien La Vieille, Ambroise Martin) : Allergies Alimentaires - Etat des lieux et propositions d'orientations. (January 2002. p.93).

(2) « *Il est ainsi proposé (dès lors qu'il s'agit d'un ajout volontaire de l'ingrédient dans un produit de la part de l'industriel) (.....) de ne pas accepter un étiquetage inquiétant ou non documenté tel que le recours par l'industrie à la mention «peut contenir...» : le CSHPF estime qu'il faut développer un étiquetage informatif et loyal, se référant à la liste proposée, et déconnecter la responsabilité juridique de l'industrie de l'information loyale du consommateur*. »
Opinion of 9 March 1999 of the C.S.H.P. (SP 4 437 / 3515 - NOR : MESP9930625V)

We ask that Afssa would develop or coordinate research with a view to answering the following questions:

- Part of the problem observed arises from the confusion between the notion of "trace" and that of "accidental presence". The former, which appears to relate to the analytical field, seems to refer to ever smaller amounts given the ongoing improvement of detection methods. The latter, however, seems to refer to hugely varying amounts depending on the manufacturing processes and products. In this context, can Afssa specify what should be understood by "trace" and "accidental presence" in the field of food allergens?

- In what amounts and how often are the major allergens (milk, egg, wheat, etc.) currently present in foods accidentally?

- What proportion of food allergy sufferers is exposed to a risk if they eat foodstuffs presenting the current levels of contamination? To what type of risk and how often are they exposed at the scale of individual consumption?

- Can a relationship be established, for each major allergen, between the amount of allergen and the proportion of food allergy sufferers exposed to a risk in the event of consumption?

- Can a critical limit be defined for each major allergen from which a much larger proportion of food allergy sufferers would be exposed to a risk, above which the presence of cross contact should be indicated and below which advisory labelling may be removed?

- If what we know to date does not allow responses to be formulated to the questions raised for certain allergens, can we at least define the method for the scientific community to follow and draw up research recommendations for the allergens concerned?

- How has the complexity of processed food product formulation changed over recent years? What impact is this complexity likely to have on the frequency of allergic reactions?

# Annex 2: decision to create the working group

## FRENCH FOOD SAFETY AGENCY

**Decision no. 2005/09/379 on the working group**
**"Accidental presence of allergens in foodstuffs and advisory labelling"**

The Director General of the French Food Safety Agency,

Having regard to the Public Health Code and its articles L.1323-4 and R.1323-22;

Having regard to the Order of 23 August 2000 concerning the scientific panels within the French Food Safety Agency;

Having regard to the Decision of 17 July 2003 laying down a list of experts within the French Food Safety Agency;

Having regard to the Order of 3 September 2003 concerning appointments to the scientific panels of the French Food Safety Agency;

Having regard to the Order of 15 October 2003 amending the Order of 3 September 2003 concerning appointments to the scientific panels of the French Food Safety Agency;

Having regard to the Order of 18 August 2004 concerning appointments to the scientific panels of the French Food Safety Agency;

Having regard to the rules of procedure of the French Food Safety Agency;

**HEREBY DECIDES:**

**Article 1.** A working group entitled "Accidental presence of allergens in foodstuffs and advisory labelling" is created, tasked with specifying the use of this type of labelling and discussing the possibility of setting thresholds by which it can be determined whether or not the presence of a food ingredient or compound requires the use of said advisory labelling.

**Article 2.** The working group mentioned in Article 1 is made up of the following members:

- Members of the "Human Nutrition" scientific panel:
  Ms Denise-Anne Moneret-Vautrin

- Members of the "Additives, Flavourings and Processing Aids" scientific panel:
  Ms Gisèle Kanny

- Members of the "Biotechnology" scientific panel:
  Mr Gabriel Peltre

- Other experts:
  Ms Fabienne Rance (Toulouse University Hospital)
  Ms Caroline Morice (French Association for Multi-Allergies)
  Mr Hervé Bernard (French National Institute for Agricultural Research/INRA)
  Mr Claude Demeulemester (French Technical Centre for Salted Meats, Pork Products and Tinned Meat/CTSCCV)

…/…

**Article 3.** Ms Dominique Baelde (Directorate General for Competition, Consumer Affairs and Fraud Control/DGCCRF) may participate in the group's work depending on the items on the meeting agendas.

**Article 4.** Ms Gisèle Kanny is appointed Chairman of the working group mentioned in Article 1.

**Article 5.** The working group's conclusions shall be presented to the "Human Nutrition" scientific panel within *one year*.

**Article 6.** The secretariat for the working group mentioned in Article 1 shall be provided by the Department for the Evaluation of Nutritional and Health Risks.

Given in Maisons-Alfort, on 23 September 2005.

The Director General of the French Food Safety Agency

**Pascale Briand**

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- Allergies alimentaires : les plantes génétiquement modifiées ont elles un impact ? (June 2006).

- Allergies alimentaires : Enquête auprès des industries agroalimentaires françaises (September 2005).

- Allergies alimentaires – État des lieux et propositions d'orientations (January 2002).

*These 3 reports are available on Afssa's website:*
*http://www.afssa.fr* Publications section.

- Allergies alimentaires – Connaissances, clinique et prévention (January 2004).

*This summary is available on the French Ministry of Health's website:*
*http://www.sante.gouv.fr Nutrition topic.*