REPORT

OF THE

FAO TECHNICAL CONSULTATION

ON

FOOD ALLERGIES

Rome, Italy, 13-14 November 1995

Food and Agriculture Organization of the United Nations

FAO TECHNICAL CONSULTATION ON FOOD ALLERGIES
Rome, Italy, 13-14 November 1995

CONTENTS

Page

Executive summary 1

Introduction 3

Background 4

Working Papers and Room Documents 5

Discussion of Areas to Consider 6

Criteria to determine which substances should always be declared on a label 6

Approach to class naming conventions for allergenic food products 7

Labelling requirements for allergenic components of composite ingredients 7

Recommendations 7

ANNEXES

1. List of Participants
2. Final Agenda
3. Food Allergy Paper
4. Consideration by Codex of Food Allergies and Hypersensitivity Paper
5. Areas to Consider

FAO TECHNICAL CONSULTATION ON FOOD ALLERGIES
Rome, Italy, 13-14 November 1995

EXECUTIVE SUMMARY

On 13 and 14 November 1995, a FAO Technical Consultation on Food Allergies was convened at an Italian Government Ministry of Health facility in Rome, Italy. The consultation comprised thirteen experts on food allergies and was international in scope as the participants came from nine different countries, both developed and developing.

The Consultation was asked to provide their scientific opinion and recommendations in three areas of concern to FAO:

1. Provide guidance on the development of science-based criteria to determine which foods or food products should be placed on a list of those foods or food products whose presence should always be declared in the list of ingredients on a food label, because of their allergenic properties.

2. Propose an approach to the problem of class naming conventions for those products of allergenic foods, which are themselves also allergenic and which may be used as food ingredients. (Current label names of some products of allergenic foods do not clearly indicate their food origin and in some cases only state their technological function - e.g. an emulsifier).

3. Provide guidance on scientific considerations to be made in striking a balance between health requirements and technological limitations when considering labelling requirements for components of composite ingredients, which are allergenic.

The Consultation considered and discussed each of these three areas individually and in detail, and arrived at recommendations for each, which were addressed to FAO. These recommendations are summarized below. The Consultation recommended:

- Specific modifications to the listing of foods and food ingredients known to cause hypersensitivity, which is presently being considered by the Codex Committee on Food Labelling for inclusion in the Codex General Standard for the Labelling of Prepackaged Food.

- That food ingredients or additives which are the products of allergenic foods, be included on the food label, unless they can be shown to be free of allergenic components. An ingredient or additive so named would include a parenthetical statement of the food source.

- That the 25% level for the required complete labelling of a composite ingredient (as now given in the Codex general standard for food labelling) be reduced as outlined in the proposal presently being considered by the CCFL.

The Consultation also made some general recommendations regarding food allergens including future research, testing methodology and stndardized substances for diagnostic purposes. A final report and recommendations were adopted at the conclusion of the Consultation.

INTRODUCTION

The Food and Agriculture Organization of the United Nations (FAO) convened a Technical Consultation on Food Allergies, which was held at the Italian Government Ministry of Health, Rome, Italy, from 13 to 14 November 1995. The list of Consultation participants is presented in Annex 1.

The Consultation was opened by Mr. Anthony Whitehead, a Senior Officer in the Food Quality and Standards Service, Food and Nutrition Division, FAO. He welcomed the participants on behalf of the Director-General of FAO and stressed the importance of the work to be done by the Consultation. He noted that allergic reactions to foods have no national boundaries and are international in scope. In part this has been due to the success of international trade in food, where new foods are now available to larger populations. Individuals who suffer allergic or hypersensitive reactions when consuming certain foods, can only control this problem by avoiding those foods. For processed and packaged foods this then becomes a labelling issue.

The Codex Alimentarius Commission (CAC) through its' Committee on Food Labelling (CCFL) is keenly aware of the problems which arise in considering the proper labelling of foods and ingredients which may be allergenic or which may cause hypersensitivity. The CCFL is considering major amendments to the Codex General Standard for the Labelling of Prepackaged Foods. These include an addition of a list of foods and ingredients which are known to cause hypersensitivity, and which would then always be declared in the label ingredients statement. The present General Standard also provides that if a composite ingredient comprises less than 25% of the food product total, then the individual components of that ingredient do not have to be declared on the label, unless they have some technical function (antioxidants, etc.). This provision can obviously result in a substantial amount of an allergenic substance being present in the finished food, but not being named on the label. The CCFL is now considering a reduction of the 25% provision to 5%.

Mr. Whitehead noted that any decisions taken by the Codex on recommended labelling practices, including the proposed amendments to the General Standard, shall be based on the principle of sound scientific analysis and evidence. He pointed out that this consultation can perform a valuable service to FAO by providing their scientific opinion and recommendations in three areas:

1. Provide guidance on the development of science-based criteria to determine which substances should be placed on a list of those substances whose presence must always be declared in the list of ingredients on a food label, because of their allergenic properties.

2. Propose an approach to the problem of class naming conventions for the products of allergenic foods, which are themselves also allergenic and which may be used as food ingredients. (Current label names of some products of allergenic foods, do not clearly indicate their food origin and in some cases only state their technological effect - e.g. emulsifier).

3. Provide guidance on scientific considerations to be made in striking a balance between health requirements and technological limitations when considering

labelling requirements for minor ingredients or for components of composite ingredients, which are allergenic.

Mr. Whitehead reminded the participants that they had been invited to the Consultation on the basis of their qualifications as independent experts and that their participation in the Consultation was to be in their individual capacity and not as a representative of any organization, affiliation or government.

Professor Vittorio Silano, Director General, Food Hygiene and Nutrition, Ministry of Health welcomed the participants on behalf of the Italian government and the Ministry of Health. He also pointed out the importance of food allergens and proper labelling for foods containing substances causing hypersensitivity.

The Consultation elected Professor Silano as the Chairman. Following his acceptance of the Chair, Professor Silano appointed Dr. Dean Metcalfe as Consultation Rapporteur. The provisional agenda was presented to the Consultation for consideration and adoption. The agenda was adopted following a few changes. The final adopted agenda (CONALLGY 1) is attached as Annex 2.

BACKGROUND

The CCFL will be considering a change in the General Standard for Labelling of Prepackaged Foods to include a mandatory listing of foods and ingredients which "are known to cause hypersensitivity" and which "shall always be declared as such". At the 1995 meeting of the CAC, the Commission reaffirmed the role of science in any Codex decision-making processes. This means that any modifications of the general labelling standard by the CCFL must be based on scientific criteria and assessments. The CCFL has asked the Codex Committee on Nutrition and Foods for Special Dietary Use (CCNFSDU) for assistance in establishing such criteria.

Food allergenicity and hypersensitivity in adults and children has been attributed to the intake of certain foods. Those most thoroughly investigated are natural foods including milk, egg, nuts, peanuts, crustacea, wheat, fruit and fish. Sensitivity to these foods can manifest itself in a range of symptoms affecting the respiratory tract, skin, gastrointestinal tract and anaphylaxis. The prevalence of food allergy using prospective, population-based studies has shown less than 2% of adults and 2-7% of infants and children, to be allergic. This does not include food intolerances such as enzyme deficiencies. However, these studies are not fully conclusive as the prevalence of food allergy is also influenced by genetic and geographic factors as well as regional diets.

Children generally display a higher incidence of food allergy, but as they grow older the symptoms tend to subside and certain food allergies may disappear completely. The intake of proteins is different for adults and children and it has been observed that cow's milk and egg allergy may subside while allergy to fish, crustacea, tree nuts and peanut often persist throughout adulthood.

In addition to the known natural allergens, modern day life is continually introducing new technologies as well as new uses of traditional foods and food ingredients. Thus, processed foods may be subjected to ultrafiltration, high temperatures, irradiation and may also contain food

substances not in their natural form but present as a functional ingredient (e.g. as a stabiliser, emulsifier, etc.). Further, genetic modification of foods may pose new hazards.

International trade and the introduction of new foods to individual countries as well as large population shifts, has resulted in an increase in certain types of food allergy. This adds importance to the need for international harmonisation and a uniform approach to the labelling of foods causing hypersensitivity. Similarly, the incidence of food allergencity due to cross-reactive allergens between food and inhalent allergens should also be considered in patients who are allergic to inhalent allergens and who may as a result often be severely allergic to some foods.

Previous attempts to reduce the incidence of hypersensitivity have included the removal of food allergens from food through enzymatic hydrolysis of proteins and heat treatment of foods. These processes do not always result in a "hypoallergenic" food and some studies have reported confirmed cases of allergenic reactions to treated foods.

Individuals who believe they suffer from food allergy require correct diagnosis to confirm the allergy and proper treatment when the allergy is known. Experience has shown that far more people believe they are allergic to certain foods, than is actually the case when they are clinically tested. A placebo controlled double-blind food challenge is an important diagnostic tool for supporting a diagnosis and determining which foods cause allergic reactions in patients, when this can be performed safely. Where a patient is allergic, elimination of the offending food from their diet is the treatment. The safety and effectiveness of this process requires that adequate information be provided to the consumer to allow them to avoid those foods to which they are allergic. When the foods are prepackaged, then the ingredients need to be listed on the food label in a form which will allow the consumer to make an informed decision as to the safety of that food for their individual protection. The use of a class name (e.g. "antioxidant") for an ingredient on a food label is therefore not adequate information in many cases. Accurate labelling of a packaged food plays a vital role in allergy risk management by informing consumers and medical professionals alike.

These are among the issues addressed and considered during this Technical Consultation in arriving at recommendations for future approaches to proper labelling of foods or ingredients which may cause allergic or hypersensitivity reactions when consumed.

WORKING PAPERS AND ROOM DOCUMENTS

The first working paper (CONALLGY 2) presented to the Consultation, which served as background document, was entitled "Food Allergy". It reviewed definitions of food allergy, food hypersensitivity and food intolerance; the prevalence of food hypersensitivity reactions; the distinct clinical pathologic entities due to immune responses to foods; the pathogenesis of these diseases; diagnostic approaches including laboratory tests and food challenges; and the approaches to treatment. This paper was well received by the Consultation and is attached as Annex 3. It was recognized that there is significant information available concerning food allergies, but that there are also significant gaps in that information particularly in regard to prevalence, and that much research remains to be done on a number of additional issues. These include such issues as characterization of allergens and variation of reactions from population to population.

The second paper presented to the Consultation was a Room Document entitled, "Hidden Allergens in Foods". This paper reviewed current problems in labelling foods which may contain ingredients or additives which were themselves produced from known allergenic foods. The fundamental problem being the variety of terms used to denote, for example, the presence of soya, milk or wheat protein. In the discussion of the paper, it was noted that some products of allergenic foods such as milk have been shown to be allergenic themselves, while for many other products the question of allergenicity of the derived substance has not been answered. In the US, for example, a consumer support group has produced cards that provide alternative names of food ingredients which an individual sensitive to a specific food (e.g. milk, soya) may use for their personal protection when selecting prepackaged foods.

The next paper presented was also a Room Document, entitled, "Comments - Food Allergy and Labelling", which was provided to the Consultation for information by one of the participants.

The final paper presented to the Consultation was the second working document (CONALLGY 3) and was entitled, "Consideration by Codex of Food Allergies and Hypersensitivity". It reviewed the history and actions taken within the Codex Alimentarius regarding the Codex General Standard for the Labelling of Prepackaged Foods. It also was well received by the Consultation and is appended as Annex 4.

DISCUSSION OF AREAS TO CONSIDER

The Chairman provided a document prepared by the Secretariat which outlined the three areas which FAO requested the Consultation to consider (see Annex 5). Each area was discussed separately, as follows, prior to adoption of recommendations by the Consultation:

1. Criteria to determine which substances should always be declared on a label

In the initial discussion of criteria which may be used, the Consultation considered a number of alternatives. One member suggested that any food be listed that was documented to have caused death due to, for example, anaphylaxis in more than one instance. It was then suggested that death should not be the only endpoint, but that severe systemic reactions short of death should be considered. It was recognized that listing all foods which have caused severe systemic reactions or death in at least one case would result in an extensive list which would be only confusing. It was therefore considered necessary to concentrate on the major foods which cause the majority of food-induced hypersensitivity reactions. Criteria suggested to select the foods causing the majority of reactions included:

- Severity of immediate and delayed reactions
- Prevalence in the population
- Level of the allergen in the food

Because the level of allergen in a food, required to cause a reaction, can be minimal and may vary from individual to individual, it was considered that severity and prevalence were the primary criteria. However, it was recognized that prevalence data was also problematic in that such data was often limited and suggested significant geographic variation.

The Consultation agreed that the practical approach should be to list those foods which are generally recognized by experts to be frequent causes of severe systemic reactions.

The Consultation then discussed the listing of foods and ingredients presented in Appendix II of Annex 4, which is part of the proposed draft amendments to the Codex General Standard for the Labelling of Prepackaged Foods. This listing represents those foods and ingredients which are known to cause hypersensitivity and are proposed to always be declared on a packaged food label. It should be noted that the only additive considered by the Consultation to cause frequent severe life-threatening reactions is sulphite and is thus listed. The point was made that other food additive labelling is mandatory. Following this discussion, the Consultation recommended modifications to the listing (see Recommendations below). It was recognized that the proposed listing would also require modification in the future as new allergenic problems are identified.

In certain geographic areas, rice, celery and certain seeds (e.g. cottonseed, poppy, sesame and sunflower) may be a problem. Adverse reactions to these foods should be followed for possible future inclusion as common allergens.

2. **Approach to class naming conventions for allergenic food products**

The Consultation was unanimous that food ingredients and additives derived from commonly allergenic foods (see Recommendation 1) should be listed on food labels with an indication of the original food source in addition to their regular name. This could be accomplished by addition of a parenthetical statement of the source food following the substance name. For example, "emulsifier (soya)". This would include materials derived from gluten-containing foods.

The Consultation further considered that if the ingredient derived from the allergenic food is shown to be free of the allergenic component(s), this labeling should not be required. The demonstration of the absence of allergenic component(s) can be accomplished by laboratory means. For example, RAST inhibition assays or ELISA tests may be used to show that there is no wheat protein (the allergen) in wheat starch.

3. **Labelling requirements for allergenic components of composite ingredients**

The Consultation was unable to assess the implications of the decrease of 25% to 5% as proposed in the new Codex General Standard for the Labelling of Prepackaged Food, since minimal amounts of allergens may produce reactions. However, members of the Consultation felt that a decrease of the level from 25% would be advantageous in that more less-commonly allergenic foods would be listed, but could not suggest what the new level should be, because no data were available. This being said, the Consultation felt that the real protection to the consumer is the required listing of commonly allergenic foods and their products.

RECOMMENDATIONS

The Consultation arrived at recommendations in each of the three areas it was asked to consider. These are presented below:

1. It was RECOMMENDED that the listing of foods and ingredients known to cause hypersensitivity (see Appendix II of Annex 4) be modified as follows:

a. Change "Barley, oats, wheat, triticale and products of these (gluten and starch included)" to "Cereals containing gluten, i.e. wheat, rye, barley, oats, spelt or their hybridized strains and products of these"

b. Change "Crustaceans, shellfish and products of these" to "Crustacea and products of these"

c. Change "Legumes, peas, peanuts, soybeans and products of these" to "Peanuts, soybeans and products of these".

d. Change "Tree nuts, poppy seeds, sesame seeds and products of these" to "Tree nuts and nut products".

e. Place "Sulphite in concentrations of 10 mg/kg or more" last in the listing.

2. It was RECOMMENDED that all food ingredients or additives which are products of allergenic foods, be included on the food label unless it can be shown that the ingredient or additive is free of allergenic components. It was further RECOMMENDED that when an ingredient or additive is to be so named, its name would be followed by a parenthetical statement of the food source. For example "emulsifier (soya)".

3. It was RECOMMENDED that the reduction of the 25% rule be carried forward as specified above under 3. of Discussion of Areas to Consider.

4. As this Consultation has been convened to deal primarily with food allergies, it was RECOMMENDED that the significance of other types of food intolerance of concern to consumers, be considered at a later date.

5. It was RECOMMENDED that:

a. Future research should investigate the prevalence of serious adverse reactions due to food allergy using appropriate experimental design.

b. In-vitro methodology for testing food allergens in processed foods be developed and validated.

c. Standardized allergenic extracts be developed and prepared for diagnostic purposes.

ANNEX 1

LIST OF PARTICIPANTS

EXPERTS

Professor Vittorio Silano
Director-General
Food Hygiene and Nutrition
Ministry of Health
Piazza Marconi 25
00144 Rome, Italy

Professor Jean Bousquet
Professor of Chest Medicine
Clinique des Maladies Respiratoires
University of Montpellier
34059 Montpellier Cedex, France

Dr. Dean Metcalfe
Head, Allergic Diseases Section
Laboratory of Clinical Investigation
National Institute of Allergy
and Infectious Diseases/NIH
Bethesda MD, USA

Dr. Steve Taylor
University of Nebraska
Dept. of Food Science and Technology
Lincoln, NE 68583-0919, USA

Dr. Palarp Sinhaseni
Director, Faculty of Medical Sciences
Naresuan University
Bangkok, Thailand

Dr. Carlos Baena-Cagnana
Head, Division of Allergy, Clinical
Immunology and Respiratory Medicine
Department of Pediatrics
Hospital Infantile Municipal de Cordoba
5000 Cordoba, Argentina

Dr. Yoseph Mekori
Department of Medicine B
Meir General Hospital
KFAR-SABA 44281, Israel

Professor Jean Rey
Dept de Pédiatric Générale
Groupe Hospitalier
Necker-Enfants Malades
149, rue de Sèvres
75743 Paris Cedex 15, France

Dr. Harris Steinman
Allergology Unit
Dept. of Clinical Science and Immunology
University of Cape Town Medical School
Capetown, South Africa

Dr. David Hill
Director, Department of Allergy
Royal Children's Hospital
151 Flemington Rd
North Melbourne V 3051, Australia

Dr. James Emerson
International Life Sciences Institute
1126 Sixteenth Street, NW
Washington, DC 20036-4804, USA

Dr. Riccardo Troncone
Ricercatore
Department of Pediatrics
University of Naples
Via S. Pansini 5
80131 Naples, Italy

Dr. Charlotte Madsen
Toxicology Department
National Food Agency
Mrokhoj Bygade 19
DK 2860 Soberg Copenhagen, Denmark

ADVISORS TO THE SECRETARIAT

Chairman of the Codex Committee on Nutrition and Foods for Special Dietary Use

Professor Arpad Somogyi
Director
Federal Institute for Health Protection of Consumers and Veterinary Medicine
Ministry of Health
Postfach 130033
D-14191 Berlin, Germany

Chairperson of the Codex Committee on Food Labelling

Dr. Anne MacKenzie
Director General
Food Inspectorate Directorate
Agriculture and Agri-Food Canada
Nepean, Ontario K1A OY9, Canada

SECRETARIAT

Mr. Anthony Whitehead
Senior Officer
Food Quality and Standards Service
Food and Agriculture Organization (FAO)
Via Terme di Caracalla
00100 Rome, Italy
(Consultation Secretary)

Mr. John Weatherwax
Consultant
Food Quality and Standards Service
FAO, Rome, Italy

Ms. Katharine Gourlie
Consultant
Food Quality and Standards Service
FAO, Rome, Italy

Ms. Mary Kenny
Associate Professional Officer
Food Quality and Standards Service
FAO, Rome, Italy

ANNEX 2 *CONALLGY 1*

FINAL AGENDA

1. Opening of the Consultation

   Welcome and opening remarks - FAO
   Welcome and remarks - Ministry of Health
   Introductions - FAO

2. Election of Chairman

   Appointment of Rapporteur

3. Adoption of the Agenda *CONALLGY 1*

4. Tabling of Background Document - Food Allergy *CONALLGY 2*

5. Distribution of Room Document - "Hidden" Allergens in Foods

6. Distribution of Room Document - Comments - Food Allergy and Labelling

7. Tabling of Background Document - Consideration by Codex of Food Allergies and Hypersensitivity *CONALLGY 3*

8. Expert Discussion and Development of Recommendations

9. Adoption of Report and Recommendations

10. Closure of Consultation

ANNEX 3 *CONALLGY 2*

FOOD ALLERGY[1]

INTRODUCTION

Food allergy has always posed a difficult problem. Food allergy exists and can be readily demonstrated but some investigators continue to deny its existence whereas others tend to overestimate it. Non-allergic food intolerance is far more common than food allergy but even the diagnosis of an allergic reaction to foods is often difficult. Life-threatening immediate reactions appear to be relatively rare but are increasing in prevalence. The pattern of reactions to different foods is changing with the change in diet. Food allergy is usually relatively easy diagnosed, but where reactions cannot be related to an immune response, diagnosis is more difficult despite the phenomenon being far more common.

It is not clear whether food allergy is increasing in prevalence as has been observed for inhalant allergy. The recent introduction of new allergens such as kiwi, papaya and mango has lead to the generation of new food sensitivities that were unknown a few years ago. The processing of food may enhance the allergenicity of a given food but little is known. New technologies (1) are allowing the food industry to develop products from standard foods which may not be recognized in their modified form by food allergic patients or may become allergenic in previously non-sensitized patients (2). Special attention should also be paid to novel foods or novel food ingredients *i.e.* foods which have not hitherto been used for human consumption to a significant extent and/or which have been produced by extensively modified or entirely new food production processes (3). Biotechnology makes it possible to prepare recombinant food proteins, the allergenicity of which is unknown and needs to be tested. Furthermore there should be continuing surveillance after release of these foods.

Adverse reactions to foods can be classified on the basis of the mechanism of the reaction (4, 5). Allergic or food hypersensitivity reactions are those that result from an immune event and represent in reality a group of distinct clinico-pathologic entities (6). The best known example of such reactions is IgE-mediated food anaphylaxis, but other types of hypersensitivity reactions have also been linked to food allergy. All other non-immunologic adverse reactions should be classified as food intolerance. This is the case of sulphite or aspirin-induced asthma.

DEFINITIONS

For the purpose or this report, following definitions apply:

Allergy: a hypersensitive state acquired through exposure to a particular allergen, re-exposure bringing to light an altered capacity to react by an immune response.

---

[1] Prepared by Jean Bousquet, Clinique des Maladies Respiratoires, Hopital Arnaud de Villeneuve, Montpellier, France; Dean D. Metcalfe, Chief, Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA; J.O. Warner, Prof. of Child Health, University of Southampton/Southampton General Hospital, Southampton, UK.

Hypersensitivity: an abnormal (exaggerated) reaction to a foreign agent affected by the immune response or chemical mediators.

- type I: immediate hypersensitivity reaction; the immune response is mediated predominantly by IgE antibodies.
- type II: injury is produced by an antibody against tissue antigen
- type III: injury is produced by antigen-antibody complexes
- type IV: delayed hypersensitivity reaction in which lymphocytes play a key role. Such reactions of delayed hypersensitivity also account for at least some of the intestinal problems which occur in coeliac disease (7).

Food allergy or food hypersensitivity: untoward reaction due to an immunological mechanism induced by a food.

Food intolerance: non-psychologically mediated untoward reaction induced by a food, including food allergy. Non-immunological reactions may be due to an enzyme deficiency, a pharmacological effect, or, as in the majority of instances, of unknown etiology (idiopathic).

Food aversion: Psychologically based food reactions with a conditioned response elicited by recognition of the appearance, smell or taste of a particular food. Aversion reactions do not occur reproducibly if the food is presented in a disguised form. However, many patients with food allergy develop aversion as a secondary psychological problem or because the food gives a bad taste (8).

Food induced symptom: symptom caused by an adverse reaction to a food whatever mechanism is involved (immunologic and non-immunologic).

Symptom with food allergy: patient presenting a given symptom and an allergy to a food, but the causal relationship between food allergy and the symptom is not confirmed.

Symptom due to food allergy: patient presenting a symptom induced by a demonstrated food allergy.

Incidence: the number of new cases diagnosed with the given disease in the population sampled during a given time period.

Prevalence at a given time: the number of subjects with the given disease in the population sampled without distinction between newly diagnosed and old cases.

Cumulative prevalence: Number of subjects with the disease at any time during their life, whatever their health status at the time of the study.

PATHOGENESIS

Both clinical and experimental observations support a role for mast cells, basophils, and IgE in immediate reactions to foods. IgE on mast cell surfaces that reacts with food extracts has been demonstrated by immediate wheal and erythema reactions in the dermis after local injection of these extracts (9). Such reactions have been passively transferred by intracutaneous injection of allergic sera into the skin of normal recipients followed by local injection 24 hours later of food antigen to which the donor was sensitive (Prausnitz-Küstner test) (10). Similar local reactions have been reported when the food antigen was administered orally 24 hours after injection of serum into the skin (11).

Food antigen-specific IgE has been demonstrated indirectly to lead to the degranulation of gastrointestinal mast cells. Mucosal reactions similar to those that follow mast cell degranulation in human skin have been reported in vivo after passive sensitization of human mucosa (12). Human mucosal mast cells have been reported to degranulate ex vivo in IgE-dependent reactions (13).

Mast cells exert effects on tissues during allergic reactions by the generation and release of chemical mediators (14, 15). Mediator release, or degranulation, is triggered by a variety of stimuli. While food antigen-specific IgE appears to be responsible for the induction of immediate food reactions, other stimuli including anaphylatoxins may play a role in delayed reactions. Intestinal mast cell activation thus increases mucosal permeability and the entry of a food antigen, allowing it to be distributed to other target organs, initiating degranulation of mast cells at those sites.

The production of IgE in response to dietary food antigens is usually detrimental. The basis of one individual's ability to limit or prevent the synthesis of food-specific IgE, while another cannot is unknown. There is some ingress of intact antigen in the normal physiologic state. Consequently, there is no requirement for an alteration in mucosal permeability as the underlying defect. This is consistent with clinical data that have failed to demonstrate defects in IgA synthesis, to find associated gastrointestinal diseases including achlorhydria, or to generate evidence of immune complex diseases in patients with immediate reactions to foods.

The most reliable clinical correlates of immediate reactions to foods are a family and personal history of atopy and the presence of positive skin tests to foods and inhalants. This indicates that the basis of the production of IgE in response to foods is related to inherited patterns of IgE synthesis and regulation. This is not necessarily associated with the over-production of IgE. Patients with food allergy mediated by IgE usually do not consistently give a family history of adverse reactions to specific foods. This suggests that multiple factors contribute to the development of IgE directed to food antigens. It has been suggested that some individuals inherit an isotope-specific defect, which leads to an inability to down-regulate an IgE-mediated response. Such observations could relate to an increased IL-4 production or a decreased IFN-g generation (16). Other factors including viral infections may influence the regulation of an IgE-antibody response.

SYPMTOMS OF FOOD ALLERGY

Food allergy can elicit almost any allergic symptom and sign but some are more common and more widely demonstrated (17). IgE-mediated reactions are often implicated in the etiology of immediate reactions to foods because of a clear relationship between eating and the induction of symptoms. However, a number of other possibilities must be considered (Table 1). Symptoms can occur immediately after the ingestion of the offending food (acute urticaria or anaphylaxis) but they may be delayed by several hours in the case of atopic dermatitis. Patients may present a single symptom but often there is a multi-organ involvement. In particular, most patients with asthma due to food allergy present with atopic dermatitis (18).

TABLE 1
Categorization of Adverse Reactions to Foods

DISEASE	PRIMARY TARGET ORGANS	EFFECTOR SYSTEM
Immediate Reactions		
Rhinoconjunctivitis	Eyes; upper respiratory tract	IgE: Basophils/mast cells
Oral allergy syndrome	Mouth	IgE: Mast cells
Urticaria/angioedema	Skin	IgE: Basophils/mast cells
Atopic dermatitis	Skin	IgE: Mast cells, eosinophils
Gastrointestinal reactions	GI mucosa	IgE: Mast cells
Asthma	Lower respiratory tract	IgE: Mast cells, eosinophils, lymphocytes
Systematic anaphylaxis	Skin; respiratory tract; GI tract; cardiovascular system	IgE: Basophils/mast cells
Delayed Reactions		
Allergic eosinophilic gastroenteritis enteritis	GI mucosa; submucosa	IgE: Mast cells, eosinophils, lymphocytes
Food-induced colitis/enterocolitis	GI mucosa	IgA: Lymphocytes, mast cells
Gluten-sensitive enteropathy	GI mucosa	IgA, IgG: Lymphocytes
Dermatitis herpetiformis	Skin	IgA: Lymphocytes, neutrophils

Symptoms with demonstrable food allergy

Generalized reactions

- Anaphylaxis (19, 20) eventually causing death (21).

- Exercise-induced anaphylaxis (22) associated with food allergy (23, 24)

Cutaneous reactions

- Skin reactions including acute urticaria and/or angioedema are common. Chronic urticaria is much less frequent (25).

- Atopic dermatitis (food allergy is a more common cause of atopic dermatitis in infants and children than in adults) (26, 27).

Respiratory reactions

- Asthma (28) and rhinitis, but both appear less frequently than gastrointestinal symptoms and rarely occur without other organ involvement. (29, 30). Patients who have asthma in association with an allergy to peanut are at higher risks of having severe and life-threatening reactions than those who do not have asthma.

- Laryngeal oedema

Gastrointestinal reactions (18, 31)

- Abdominal pain and nausea

- Vomiting and diarrhea

- Colic (more common in infants and children). In one study of 27 patients with irritable bowel syndrome who suspected foods as being the cause of their symptoms, only three patients had their complaints reproduced by food challenge (32).

- Allergic eosinophilic gastroenteritis is an uncommon chronic digestive disease that is characterized by peripheral eosinophilia and by edema and eosinophilic infiltration of the stomach, and to a lesser extent, the small intestine (33). It is seen more frequently during the third decade of life (34), although children also develop this disease.

- Food protein-induced enteropathy is a disease of infants and children. It is diagnosed by verifying changes in the tissues of the intestinal mucosa that occur following the ingestion of specific foods. These changes are transient and resolve with time, presumably because of maturation of the gastrointestinal and immune systems. Transient enteropathies have been associated with cow's milk, soy protein, fish, rice, chicken, and egg (35, 36).

- Food-induced colitis in infancy (37), best documented in relation to cow's milk, presents with all symptoms of ulcerative colitis. The colonic biopsy shows an eosinophil infiltrate and

dramatic improvement occurs on removal of the offending food. This appears to be a self-limiting phenomenon but it is commonly associated with the latter development of other atopic symptoms.

Ocular reactions

- Conjunctivitis

Others

- Oral allergy syndrome: tongue swelling and itching, palatal itching (38),

- Food aversion is often claimed by patients with food allergy but care should be taken to avoid a positive diagnosis of food allergy in many such patients in whom aversion is not due to allergy (39),

- Failure to thrive.

Unproven symptoms of food allergy

Food allergy can elicit almost any allergic symptom but some have been proposed more often even although food allergy has been rarely demonstrated:

- Migraine in which food allergy was supposed to be a major cause (40), but when the appropriate tests were performed it was observed that food allergy was rarely involved (41).

- "Hyper-reactivity" and tension-fatigue syndrome (42). Occasionally behaviour can be adversely affected by some foods but this is unlikely to be an allergic phenomenon and is never the primary cause of the behaviour problem (8).

- A series of poorly defined digestive symptoms including aphtosis, dyspepsia, irritable bowel disease, colitis in infancy and, occult gastrointestinal bleeding, protein-losing enteropathy and other GI syndromes (43).

- Dysuria.

- Arthritis (44).

FOOD ALLERGENS

A heterogeneous group of proteins is ingested in a normal diet. This varies, in part, according to age. Infants ingest proteins from fewer sources which include mother's milk and/or commercial formulas, often based on bovine milk or soybean proteins. The dietary proteins ingested by older children and adults are in descending order derived from meat, poultry, fish; dairy products; flour and cereal products; dry beans, peas, nuts, and soya products; vegetables; eggs; and fruits and miscellaneous sources (45).

Despite the wide variety of foods ingested, only a relatively few foods cause most allergic reactions. In infants less than 6 months, the majority of allergic reactions are due to milk or soy.

In adults, the most common food allergens causing severe reactions are peanuts, tree nuts, crustaceae, fish, and egg (46).

Cow's milk protein intolerance

Cow's milk protein intolerance is relatively common in infancy. It occurs in about 2 to 5% of infants but its prevalence decreases with age. Intolerance to cow's milk involves several mechanisms in which allergy is one of the best identified but not the most common. Allergy to cow's milk is mainly an IgE-mediated allergic reaction but other immune mechanisms have been identified (47). Although developing usually during early infancy, allergy to cow's milk may be acquired later in life. Allergic reactivity to cow's milk is lost during childhood in the vast majority of cases. IgE and challenge tests show that most cow's milk-allergic patients react to several protein fractions of cow's milk including casein, alpha-lactalbumin, and ß-lactoglobulin (48). However, casein was shown to produce the highest rate of skin test reactivity in children with milk allergy (49), ß-lactoglobulin produced the highest rate of positive oral challenges (50) and α-lactalbumin was occasionally positive in skin tests and oral challenge. Patients may react to one or more of several protein fractions of cow's milk and the range of reactions will differ from patient to patient. This will also account for the variation in sensitivity to different diary products, for which the method of preparation may reduce or enhance the allergenicity of raw cow's milk.

All major cow's milk proteins in native form are potential allergens in subjects with cow's milk allergy. The allergenicity of cow's milk can be reduced by different treatments (51). Enzymatic hydrolysis cleaves the polypeptide chain at specific sites, which leads to the breakdown of the antigenic architecture of the molecule and causes a progressive disappearance of its allergenic properties, including epitopes resulting from its amino acid sequence if the duration of hydrolysis is sufficient (52). The α- and ß-caseins, ß-lactoglobulin and α-lactalbumin are highly sensitive to enzymatic hydrolysis by endopeptidases, such as trypsin and chymotrypsin. On the other hand, k-caseins, bovine serum albumin and immunoglobulins are quite resistant to this process when directly applied to their native structure, and a combination of hydrolysis and thermic treatment may be necessary (53). Heat treatment destroys heat-labile milk proteins (bovine serum albumin and immunoglobulin) and changes the antigenicity of other whey proteins (ß-lactoglobulin) but it has virtually no effect on the antigenicity of casein (54, 55). However, even for whey proteins, the thermic shock necessary to reduce significantly protein allergenicity would induce a Maillard reaction and their nutrional value would be reduced to an unacceptable extent (56). Heat treatment alone is therefore unable to provide a good quality "hypoallergenic" formula, but the combination of selective hydrolysis and heat treatment has been used to prepare partly hydrolysed formulae without decreasing the nutritional value of whey proteins (53). Filtration can also be applied to remove remaining high molecular-weight peptides and residual proteins, and some ultrafiltrated whey hydrolysates have been developed (57).

The therapeutic efficacy of semi-elemental diets for treating proven enteropathies related to cow's milk proteins or anaphylactic reactions triggered by milk products or other dietary proteins is well established. Most studies were carried out with highly processed casein hydrolysates. The positive effect of these extensively hydrolysed preparations in children with cow's milk allergy was largely documented (52, 58). However, confirmed cases of allergenic reactions were reported, implying that a risk for general reactions always exists when providing any hydrolysed product to subjects highly reactive to cow's milk. Moreover, skin prick tests with

undiluted hydrolysate formulae are often positive in such patients, but positive skin tests with hypoallergenic formulae do not correlate necessarily with symptomatic reactivity, suggesting that skin prick tests alone are not indicative of hypersensitivity to extensively hydrolyzed formulae (59, 60). The efficacy of extensive whey-protein hydrolysates, or of a mixture of soya proteins and beef collagen has also been demonstrated in infants with cow's milk allergy (52, 58, 61), and anaphylactic reactions to these highly processed hydrolysates infrequently reported (62, 63). Using double-blind, placebo-controlled food challenges in documented cow's milk allergic subjects, three of these extensively hydrolysed preparations (two casein-based and one ultrafiltered whey-based formula) were proven "hypoallergenic" (57, 59) according to the guidelines of the Subcommittee of Nutrition and Allergic Diseases of the American Academy of Pediatrics (64).

Only extensively hydrolysed preparations can be recommended for the treatment of cow's milk allergy, owing to their overall proven safety and hypoallergenicity. The partly hydrolysed whey formulae, which contain a number of unresolved proteins on high density SDS-PAGE and non-degraded whey proteins in the molecular range of 1 to 20 kD (59) can cause allergic reactions (63, 65). Consequently, partly hydrolysed formulae should be avoided in allergic infants (52, 58, 66).

Allergens in Foods

Commercially processed proteins used as food ingredients include casein and whey from bovine milk; soy protein isolates from soybeans; and gluten from the flours of wheat, corn, and oats. Newer sources of proteins include yeasts and the oil seeds including soybean, peanut, rapeseed, cottonseed, sunflower, and safflower. Changes in the processing of foods also have impact. Chemical modification of foods during ultrafiltration, high-temperature processing, introduction of new proteins into a food by molecular biology, or preservation by irradiation have the potential to present or create new allergens or to impact digestibility (67). Finally, using antibodies raised against major food allergens it is possible to screen for plant strains containing low amounts of a major allergen as it is the case for the 16-kDa rice allergen (68) or the 27-kDa wheat albumin (69) making it possible to select "low-allergenic" strains.

Many investigators have sought to isolate and characterize components of food that are responsible for immunological reactions. Attempts to isolate relevant antigens have focused, almost without exception, on their ability to bind to antigen-specific IgE. In early studies, water-soluble food components were examined for antigenicity by their ability to induce immediate skin tests in subjects with immediate reactions to foods. Recent studies have tended to determine antigenicity using in vitro assay techniques that examine the ability of water-soluble food fractions to bind IgE in serum from patients with proven immediate reactions to foods.

Major food antigens are proteins or glycoproteins. Molecular weights of these substances tend to be between 10,000 and 40,000 daltons. These allergens tend to be relatively resistent to denaturation by heat or to degradation by proteases.

Allergen M (Gad c I) from codfish was the first extensively studied allergen. Codfish hypersensitivity is common in countries where consumption of this fish is high. Allergen M is a parvalbumin found in the muscle of fish and amphibians. It has a molecular weight of approximately 12,000 daltons, is heat stable, partially resistent to proteases, and exists as a single

polypeptide chain (70-72). Linear peptides corresponding to regions 13-32, 49-64, and 88 to 103 have been synthesized and bind IgE from cod-allergic subjects (73).

Many additional food antigens have now been purified. Antigens have been isolated from shrimp (74). The major allergen designated previously as Antigen II (75) or Sa II (76), and now referred to as Pen i I, has a molecular weight of 34,000 to 36,000 daltons. It is heat resistant. Amino acid sequence analysis of Pen i I indicates significant homology with the muscle protein tropomyosin from *Drosophila melanogaster* (77, 78). Isolated shrimp tropomyosin also binds Sa II-specific IgE. Limited proteolysis results in peptides, which retain IgE binding activity (77). Tropomyosin is also thought to be the common allergen responsible for cross-reactivity between members of the crustacea (shrimp, lobster, crab, and crawfish) (77, 78).

Peanut I, isolated from raw, defatted, peanut meal consists of two major bands of 20,000 and 30,000 daltons by SDS-Page (79). It does not however, account for all the allergenicity of peanuts since over 10 different allergens have been identified, many of which being low molecular weight allergens (80, 81). Two allergens of peanut have been identified; Ara hI (82) and Ara hII (83, 84). Soybeans are also a major crop of the legume family. In one instance, an allergic reaction to soybeans was traced to a reaction to Kunitz soybean trypsin inhibitor (85).

Rice major allergenic protein (RAP) has been isolated from a cDNA library of maturing rice seeds (86). The cDNA has an open reading frame of 486 nucleotides which codes for a 162 amino acid residue polypeptide. The deduced amino acid sequence of RAP is similar to barley trypsin inhibitor and wheat α-amylase inhibitor (87).

In addition to identifying and isolating specific proteins with allergenic activity such as the examples above, many studies have examined major proteins or protein fractions for allergenic activity. In eggs, the egg albumin is more allergenic than egg yolk. The major egg allergens appear to be ovalbumin (Gal dI), ovomucoid (Gal dII), and conalbumin (88-93). Ovomucoid is heat stable. In some individuals, IgE can be found directed to egg yolk proteins (94).

Common allergenic foods

Almost any food can induce an allergic reaction. However, some foods are more commonly allergenic although the prevalence of sensitization depends on regional diets and cross-reactivities with inhalant allergens. Among the major sensitizing foods are fruits, legumes (especially peanuts and soybean) (95), eggs and milk (particularly in young children), crustaceae (shrimps, crab, lobster and crayfish) (96), tree nuts (almonds, walnuts, hazelnuts, Brazil nuts, etc), fish (97), vegetables (celery and other foods of the Ombelliferae family), wheat and other cereals, sesame seed and other seeds (98-101).

The allergenic activity of some food allergens is destroyed by heating or during storage (e.g. in apples (102)) whereas others are resistant to denaturing including cooking and digestion (casein, egg and fish).

The problem of trace amounts of allergenic foods in processed foods is a matter of unresolved concern. This deserves further investigation since although very rare, trace amounts of allergenic proteins can be found as contaminants in foods such as oils (103). The method of

preparation of foods is directly involved in such contaminations. Considerable effort should be made to develop highly sensitive tests which will identify allergens in foods so that it may become possible in the future for manufacturers to safely label products as being devoid of, or at least sufficiently free of, allergenic products not to cause a significant problem for allergic individuals. However, until such testing is in place, food allergic individuals should be advised to be very circumspect about their use of processed foods.

A major problem of food allergy is the presence or absence of low amounts of a given food allergen in a processed food. Although it is relatively easy to include in the label the presence of a food allergen when it is one of the components of the food, it does not seem realistic and may even be dangerous to label a food as "devoid of..." because trace amounts of allergens can always be present, and their content may differ depending on the processing.

Cross reactive allergens between food and inhalant allergens

Patients with allergic rhinitis/conjunctivitis to birch and to a lesser extent to other Betulaceae (hazel, alner) pollen are frequentely hypersensitive to tree nuts, fruits and vegetables, including apple, carrots and potatoes (104). Most patients present mild symptoms but anaphylaxis may occur with these cross-reacting foods. Some birch or hazel pollen allergens cross-react with those of apple, other fruits (105) or various nuts (106). Most of the patients with food hypersensitivity are those with a severe allergy to pollens (104). Some Compositeae pollen allergens (mugwort) cross-react with foods of the Ombelliferae family (celery in particular) (107). Although IgE antibodies to food allergens are highly prevalent in patients allergic to Betulaceae and Compositeae pollens, only a proportion of patients present symptoms of food allergy (108). Ragweed (*Ambrosia* pollen) sensitive individuals may get symptoms when eating banana or melon.

Although it is common to find positive skin tests and IgE antibodies to a range of legumes in peanut allergic patients, only a small percentage of the individuals also have clinical responses which are almost always less severe than to the peanut itself.

Allergy to latex has been increasing recently because of the overwelming use of latex gloves by medical and paramedical professionals (109) and its extensive use in many devices such as catheters. Cross reactive antigens have been identified between latex and banana, chestnut or kiwi fruit (110).

DIAGNOSIS OF FOOD ALLERGY

Although most immune mechanisms may induce a food allergic reaction, besides coeliac disease, the IgE-mediated allergic reaction is more easily diagnosed than others. The diagnosis of food allergy is compounded, however, because allergen extracts currently available are not standardized, and their stability is poorly determined (111). For allergen extracts that are rapidly degraded like those of fruits and legumes, skin tests may be falsely negative in allergic individuals. Even more so than in inhalant allergy, the presence of food-IgE in serum or a positive skin test to a food does not always correlate with a food allergy since (i) many patients outgrow their allergy with age (112, 113) and (ii) not all patients with food-specific IgE have a clinical sensitivity. In many instances the diagnosis has to be confirmed by a double-blind food challenge that should be carried out under precisely specified conditions and by trained

investigators. As for other forms of food allergy, unproven and controversial techniques such as cytotoxic tests or sublingual provocation tests have no proven value.

Patients who develop acute urticaria or anaphylaxis often make the diagnosis of "food intolerance" by themselves; and the presence of positive skin tests and/or serum specific IgE correlating with the claims of the patient makes a diagnosis possible without performing a food challenge. This latter test may cause severe untoward reactions in patients with anaphylaxis and therefore should not be done. However, for many other symptoms including asthma, patients rarely incrimate a food as the cause of wheezing so (i) it is necessary to suspect a food allergy and (ii) to confirm the diagnosis by double-blind food challenges (114).

History

The diagnosis of food allergy should always begin with a detailed clinical history. However, a variety of toxins may produce symptoms that appear indistinguishable from immediate hypersensitivity reactions. These include scromboid, histamine and ciguatera poisoning (18).

Skin tests and serum specific antibodies

The performance of skin prick tests with food allergens is the second step of the diagnosis. If possible, positive skin tests should be confirmed by the titration of serum specific IgE. Some investigators prefer to use intradermal skin tests, but although they are slightly more sensitive than skin prick tests, they also cause more non-specific positive reactions and may also induce systemic reactions. Extracts made from fruits and vegetables are usually of poor quality since the allergens are rapidly destroyed and skin tests with fresh foods are more accurate (115). A positive skin prick test and/or serum specific IgE should not preclude the use of a food challenge since only one third of patients presenting with positive skin prick tests and/or serum specific IgE have asthma during food challenge (30, 114, 116), and many patients outgrow their clinical allergy but retain skin test reactivity. A diet should not therefore be started before food challenges have been performed. The titration of serum food specific IgG or IgG_4 is useless in the diagnosis of food allergy.

Food challenge

Food challenge is an important diagnostic tool not only for supporting a diagnosis , but, also to identify that a person is not allergic, thereby avoiding an unnecessary expensive intrusive diet which may have nutritional consequences. Food challenges should be performed in a manner similar to that reported by Bock (117) or Sampson *et al* (116). The food suspected as causing symptoms should be eliminated from the diet for a minimum of two weeks before testing. Although patients who have presented anaphylactic symptoms should not be tested, it is always advisable to start with a very small dose and increase them slowly and carefully. Some patients after a period of an exclusion diet may occasionally have an anaphylactic reaction when challenged with the offending food (118). Challenges should preferably be conducted in a double blind manner, but if several food stuffs are incriminated, screening with single blind challenges may be carried out first. In case of food-induced asthma, a series of pulmonary function tests should be conducted for up to 8 hours following challenge since late reactions can occur (114). It has also been observed that food challenges increase non-specific bronchial hyperreactivity to

histamine or methacholine without causing frank wheezing in some (119, 120) but not all studies (121). For eczema, some scoring systems have proven their value (SCORAD) in assessing the response. For overall symptoms, Young et al have developed a combined clinical score that may be used (122). During all challenges a physician should monitor the patient since an untoward systemic reaction might occur.

Food challenges may be improved by measuring the release of mediators in peripheral blood (123) or an increase in gut permeability (124); or by assessing the response by gut mucosal biopsies. The measurement of non-specific bronchial responsiveness before and after an oral challenge may enhance the interpretation of oral challenge. In asthmatic subjects, some patients only develop an increase of bronchial responsiveness to histamine or methacholine after a food challenge without any change in baseline peak flow or FEV_1.

A positive food challenge does not necessarily imply that the patient presents an IgE-mediated allergy, but only he or she is intolerant to foods. If specific IgE and/or prick tests to this food are positive, an IgE-mediated mechanism is likely to be involved. Only one quarter to one third of patients with positive skin tests and/or specific IgE have a positive oral challenge.

Elimination diets

Elimination diets tend to be nutritionally unsound and must be supervised very carefully by fully qualified dieticians. They are primarily used for the diagnosis of chronic diseases such as eczema, asthma and rhinitis. The results of elimination diets are difficult to interpret because many children with genuine food allergy, even if symptoms were severe, have only a transient problem. One study of 323 patients with chronic allergic rhinitis revealed 21 who had improvement on a cow's milk free diet and relapsed on open challenge. However, only two of the 21 reacted on subsequent double-blind challenge (125).

In the case of asthma, it is even more difficult to make the diagnosis of food allergy by elimination diets for many reasons: (i) food allergy is almost constantly associated with inhalant allergy and possibly with other triggers, and variations in the airways obstruction may be due to factors unrelated to foods, (ii) food allergens as well as inhalant allergens aggravate non-specific bronchial hyperreactivity and it may take days or even weeks to observe an improvement of asthma, and (iii) the great variability of the airways obstruction in patients with chronic disease may mask the benefits of dietary manipulations. However, when a patient is highly allergic to a given food, significant improvement or even complete remission can be observed.

NATURAL HISTORY OF FOOD ALLERGY

Most cases of food allergy are observed in early infancy and are often related to hypersensitivity to cow's milk. The prevalence of food allergy peaks in children and decreases with age. Differences in the disappearance rate depends on the allergen and on individual factors (47, 112, 113, 126-129). Most children with cow's milk allergy tolerate at least small amounts of cow's milk at 3 years of age. Egg allergy usually subsides before puberty but if it has started early or if atopic symptoms are severe, allergy tends to persist. On the other hand, allergy to fish, shelfish, nuts and peanut does not disappear in most patients, although it may be less severe.

Food allergy in infancy is very commonly the first manifestation of an allergy march that proceeds to asthma and rhinitis, often associated with inhalant allergy.

PREVALENCE OF FOOD ALLERGY

Although there is a better recognition of food allergy, its real prevalence has only been investigated in a few studies. Prospective, population-based studies are required to assess the true incidence of food-allergic diseases. The rate of food intolerance depends on the methods used. In response to a questionnaire, the number of people who think they have experienced adverse reactions to foods may be as high as 33% (130). However, when appropriate tests are used this percentage decreases sharply (131, 132). It has been reported that the prevalence of adverse reactions to foods in children less than 6 years of age is less than 8% (133).

The prevalence of cow's milk allergy and intolerance has been examined in a number of retrospective and prospective studies, and estimates of prevalence range from 0.1 to 7.5% (134). It seems however, that a more realistic rate is from 1 to 3% (133, 135-137). This variation reflects differences in criteria for diagnosis, differences in study design, and possibly differences in diets accounting for geographical differences. In particular, the prevalence and duration of breast feeding may be of importance. Moreover, in many studies, allergy and non-immunologic intolerance was not differentiated (138-140).

The prevalence of food allergy and intolerance (FA/FI) was studied in a random sample (n = 1483) of the Dutch adult population with subjects ranging in age from 18 to 70 years (131, 132). First, the self-reported FA/FI reactions were investigated by questionnaire. Subsequently, in a clinical follow-up study, it was determined in how many cases this self-reported FA/FI assessment could be objectively confirmed by double-blind placebo-controlled food challenge. 12.4% of the population reported FA/FI to specific food(s). Half of the 144 subjects potentially available for the clinical follow-up study completed the whole protocol. In 12 subjects, FA/FI could be confirmed by double-blind placebo-controlled food challenge. This indicates a prevalence of FA/FI in the Dutch adult population estimated to be 2.4%. The foods involved included pork, white wine and menthol. Two persons reacted to additives. In three subjects, glucose intolerance was observed. Thus, in this study, the prevalence of food allergy was below 1% in the population.

Bousquet *et al* (unpublished data) studied the prevalence of positive skin tests to the seven most common foods of the Montpellier area in a representative sample of 2500 men and 2500 women (20 to 44 years of age) selected according to the EC epidemiological study on Respiratory Health (141). The prevalence of positive skin tests to inhalant allergens was around 25%. Only 1.3% of the subjects had a positive skin test to one food type. Moreover, symptoms of food allergy were observed in only 50% of these subjects.

Young *et al* (122) did a population study to identify the prevalence of reactions to 8 foods commonly perceived to cause sensitivity in the United Kingdom. A cross-sectional survey of 7500 households was followed by questionnaire and those who agreed entered a double-blind, placebo-controlled food challenge. 19.9% of the group complained of food intolerance but the prevalence rate after challenge was estimated to be 1.4%. It is interesting to note from this study that the vast majority of individuals considering themselves to be food intolerant had not sought any medical attention to substantiate a diagnosis and had merely taken action themselves to

modify their diets. The nutritional, medical, psychological, social and financial consequences of such actions can only be surmised. However, clearly, this is an area that requires further investigation. The media have a great deal to answer for in relation to this false perception which exists in the community of some countries at present.

To determine the prevalence of food allergy as a cause of exacerbation of asthma, Onorato *et al* studied 300 consecutive patients with asthma (7 months to 80 years of age) who attended a respiratory clinic (114). Each patient was screened for possible food allergy by means of a questionnaire and by skin prick tests with the six food allergens most common in the area. Patients with either a suggestive history and/or a positive prick test and/or RAST underwent a double-blind food challenge with lyophilized food in capsules or food mixed up into a broth to disguise its taste. Pulmonary function tests and symptoms were followed for 8 hours after each challenge. Of the 300 patients screened, only 25 had either a history or skin prick tests or RAST responses suggestive of food allergy. Twenty patients had interpretable food challenges. In these 20 patients, food challenge caused asthma in six and caused other symptoms (atopic dermatitis and gastrointestinal symptoms) in five. The prevalence of asthma due to food allergy was below 1% in adults.

These studies combine to indicate that using double-blind food challenge, the prevalence of food allergy is below 1% of the population in adults and may be slightly greater in children (142). However, this may be a somewhat low estimate since food challenge may not identify the entire population of food allergic individuals and there are some genetic and environmental factors that can increase the prevalence of food allergy.

In non-Caucasian populations the prevalence of food allergy may be greater and these figures may also be increased. Indian children in Great Britain appear to develop food-induced asthma more frequently than non-Indians.

The prevalence of food allergy is highly dependent on geographical area. In areas where birch and mugwort pollen are prevalent, 30 to 50% of patients sensitive to these pollens report symptoms when ingesting fruits and vegetables. Thus, in these areas, the prevalence of food allergy in adults may be as high as 5 to 6%. The diet of a given country is also of importance. For example, peanut allergy was very common in the US, and since this food has been widely marketed throughout Europe it is now a major allergen in Europe. Shrimp allergy is common in Southern USA, fish allergy is common in the Nordic countries and in Japan because in these countries these foods are commonly ingested. It has been found that fish allergy may be as high as 3% in 3-year old Finnish children (143).

MANAGEMENT OF FOOD ALLERGY

The presence of a positive skin prick test or serum specific IgE to a given food should not lead to an elimination diet because only 30 to 40% of patients have a chronic symptom like asthma or rhinitis when they are challenged orally with the offending food. A positive food challenge favours dietary avoidance but the nutritive value of a diet must always be maintained, especially calcium intake for cow's milk avoidance (144). Also, the reintroduction of a food, accidental or intentional, may cause anaphylaxis or severe respiratory obstruction since individual patients tend to continue to react with the same symptoms as they had before. In case of cow's milk allergy, contrary to popular belief, sheep and goat's milk are not suitable

alternatives as they are likely to produce allergic reactions due to cross reactivity (145). Finally, it has been proposed to reduce allergenicity of foods by removing potent allergens (146) or by hydrolyzing the foodstufs (61, 65, 147).

The efficacy of oral sodium cromoglycate has not been completely established. However, in some studies this drug was found to prevent asthma due to food allergy (148). It is clear that only a fraction of patients benefit from this treatment but, when available and effective, it may be used (i) to decrease the reactivity of the gastro-intestinal tract to dietary allergens and (ii) to permit a less restrictive diet. Ketotifen was also studied and seemed to have a greater value in the treatment of skin symptoms. Neither drug will prevent systemic reactions or prevent anaphylaxis and both must be used with great caution.

There is no evidence at present to support specific immunotherapy by either the oral or the parenteral route except for research purposes and it must be pointed out that this form of treatment may lead to severe untoward reactions (149, 150).

In any case, the treatment of symptom(s) is of importance. Due to the severity of the reaction anaphylaxis should be treated immediately using adrenalin (epinephrin) and emergency measures instituted if required. Asthma is a disease of the airways and patients should always have a treatment for bronchial inflammation and obstruction besides the treatment of food allergy. Skin symptoms also require specific treatment.

Prevention of food allergy is a difficult matter. Although a large number of studies have been carried out, there is no convincing data demonstrating the efficacy of interventions. There is much evidence that the development of allergic disorders may be related to early exposure of allergens, including those in breastmilk of maternal dietary origin. Breast feeding is strongly advocated by paediatricians but it is not yet known whether it can prevent the onset of allergy to cow's milk or if it only delays the onset of allergic symptoms. Moreover, although breast feeding has been observed to delay the onset or reduce the severity of atopic dermatitis, no evidence of any effect was found on asthma or later allergic disorders in most studies (151-153). However, in a recent study examining the occurrence of atopic symtpoms over a 17-yr follow-up, asthma appeared to be prevented by breast feeding (154). Mothers reducing ingestion of highly allergenic foods during breast feeding may improve the preventive efficacy of breast feeding but data are conflicting (155-157). Hypoallergenic infant formula may also be preventive but more data are needed to better evaluate their real value (61, 65). Finally, it seems appropriate to delay for a period of four to six months the introduction of solid foods which may sensitize newborns and young infants (158, 159). However, the cost-benefit and quality-of-life effects of such interventions have not hiterto been subjected to any prospective study.

GLUTEN-SENSITIVE ENTEROPATHY

Gluten-sensitive enteropathy or celiac disease is a mucosal disease of the small intestine precipitated by the alcohol-soluble portion of gluten, gliadin, in susceptible individuals (160). It is thought that individuals who develop celiac disease have a genetic predisposition to acquiring the disease. HLA studies have revealed that patients with celiac disease are often positive for HLA-B8 and that many patients are positive for HLA-Dw3. Several lines of evidence obtained during the last years strongly suggest that a particular HLA-DQ heterodimer, encoded by the DQA1*0501 and DQB1*0201 genes in cis or trans configuration, confers the primary disease

susceptibility (161). A human adenovirus that has been found to contain a protein that has an almost identical amino acid sequence to that of the gliadin molecule has been suggested as a possible sensitizing agent (162).

The acute reaction of the intestinal mucosa in patients with celiac disease to gliadin exposure consists of an infiltration of the mucosa with eosinophils and neutrophils along with edema and an increase in vascular permeability. With time, the infiltration evolves into predominantly mononuclear cells, plasma cells, and lymphocytes (163). Blunting of the muscosal surface, villous atrophy, and a dense infiltration of the lamina propria with plasma cells, B cells, and T cells is observed in chronic disease.

Gliadin is the 70% alcohol-soluble fraction of gluten. Gliadin has been spearated by gel electrophoresis into four proline and glutamine-rich fractions designated as alpha, beta, gamma, and omega. All fractions precipitate small bowel injury in vitro (164). The expression of celiac disease appears to involve products of both HLA genes and none-HLA genes that facilitate a hyperresponsiveness and specificity to gliadin.

A role for immunoglobulin in the pathogenesis of gluten-sensitive enteropathy is suggested by an increase in local mucosal IgA and IgM after challenge. Quantitative serum IgA and IgM abnormalities in patients with celiac disease have been observed to return to normal with remission of disease (165).

Mature lesions contain T cells that bear the aß T cell receptor. They are either $CD4^+$ or $CD8^+$. The T cells tend to bear markers (CD45RO) of memory cells, and bear markers of cell activation. These T cells may make large amounts IFN-γ. Other findings include infiltration with (γ/δ) T cells (166).

The onset of symptoms typically occurs 6 to 12 months after introduction of gluten into the diet, with the average age of diagnosis thus at 18 months. The symptoms may consist initially of an intermittent diarrhea with abdominal pain and irritability. With extensive mucosal injury, steatorrhea, peripheral edema from gastrointestinal protein loss, pallor from anemia, bleeding diathesis from vitamin K deficiency, and tetany from calcium and magnesium deficiency may be observed. Malabsorption may result in growth failure. A subsequent increase in the incidence of gastrointestinal lymphoma has been observed in some but not all studies (167, 168).

The diagnosis is dependent on demonstrating biopsy evidence of small intestinal mucosa injury on challenge with gluten. Patients show histologic improvement of their small intestinal mucosa after exclusion of gluten from their diet for 2 to 3 months. The differential diagnosis of celiac disease includes tropical sprue, lymphoma, hypogammaglobulinemia with malabsorption, IgA deficiency, α-chain disease, and food-mediated gastroenteropathies.

Treatment is directed at eliminating gluten from the diet. Wheat, barley, rye, and oats all contain gluten. Improvement in symptoms is seen as soon as 2 weeks after the institution of a gluten-free diet. In the child who is manifesting failure to thrive because of malabsorption, growth should return to normal once the small intestinal mucosa has healed. Strict gastrointestinal rest and in some instances the use of steroids is necessary to suppress the diarrhea when inflammation is severe.

DERMATITIS HERPETIFORMIS

Dermatitis herpetiformis is a chronic papulovesicular skin disorder frequently associated with asymptomatic gluten-sensitive enteropathy. It is similar to gluten-sensitive enteropathy in its increased association with specific cell surface antigens, The HLA antigens B8 and Drw3 are frequently found in these patients. The histologic appearence of skin lesions is one of a granulocytic infiltration located between the epidermis and dermis, associated with edema and blister formation. Granular IgA deposits with associated J chains can be found in the papillary dermis. Complement-mediated injury is implicated. Histologic evaluation of the small intestine in patients with granular deposits of IgA typically reveals mucosal injury as in gluten-sensitive enteropathy but to a lesser degree. Patients with the linear deposits of IgA show no histologic abnormalities of the small intestinal mucosa. The linear form may thus represent another disease.

Skin lesions are distributed symmetrically on the extensor surfaces including the elbows, knees, and buttocks. Most patients have little or no history of gastrointestinal complaints. The diagnosis rests on the typical appearance and distribution of the skin lesions and histologic findings of IgA deposits in the perilesional or uninvolved skin. Fifteen percent of patients will have a normal small intestinal mucosa on histologic evaluation. Treatment centers on removal of gluten from the diet and the use of dapsone or sulfapyridine.

Acknowledgments: The authors thank Professor Jean Rey for helpful comments

REFERENCES

1. Hardy RW. Uses of biotechnology and technology transfer to keep food safe. J Dairy Sci 1990;73:1665-9.

2. Sampson HA, Cooke S. The antigenicity and allergenicity of microparticulated proteins: Simplesse. Clin Exp Allergy 1992;22:963-9.

3. Advisory Commitee on Novel Foods and Processes. Guidelines on the assessment of novel foods and processes. Report on Health and Social Subjects. In: HMSO, London, 1991:

4. Bindslev-Jensen C, Skov PS, Madsen F, Poulsen LK. Food allergy and food intolerance--what is the difference? Ann Allergy 1994;72:317-20.

5. Ferguson A. Definitions and diagnosis of food intolerance and food allergy: consensus and controversy. J Pediatr 1992;121:S7-11.

6. Anderson J, Sogn D. Adverse reactions to foods.Bethesda MD: NIH Publication 84-2442, 1984 NIAID ACoartfa, ed.

7. Lessof M. Food allergy and other adverse reactions to food. Brussels: 1993 ILSI Europe

8. Warner JO. Food and behaviour. Allergy, intolerance or aversion. Pediatr Allergy Immunol 1993;4:112-6.

9. Bock SA, Lee WY, Remigio LK, May CD. Studies of hypersensitivity reactions to foods in infants and children. J Allergy Clin Immunol 1978;62:327-34.

10. Prausnitz C, Küstner H. Studien über die Ueberempfindlichkeit. Zentralbl Bakteriol 1921;62:160-4.

11. Ratner B, Gruel H. Passage of native proteins through the normal gastrointestinal wall. J Clin Invest 1934;13:517-21.

12. Gray I, Harten M, Walzer M. Studies in mucous membrane hypersensitiveness. IV. The allergic reaction in the passively sensitized mucous membranes of the ileum and colon in humans. Am J Intern Med 1940;13:2050-4.

13. Selbekk BH, Aas K, Myren J. In vitro sensitization and mast cell degranulation in human jejunal mucosa. Scand J Gastroenterol 1978;13:87-92.

14. Barrett K. Mast cells, basophils and immunoglobulin E. In: Metcalfe D, Sampson H, Simon R, ed. Food allergy: adverse reactions to foods and food additives. Oxford: Blackwell Scientific Publications, 1991: 13-35.

15. Sampson S. Mast cell involvement in food allergy. In: Kaliner M, Metcalfe D, ed. The mast cell in health and disease. New York: Marcel Dekker Inc, 1993: 609-26.

16. Warner J, Miles E, Jones A, Quint D, Colwell B, Warner J. Is deficiency of interferon gamma production by allergen triggered cord blood cells as a predictor of atopic eczema? Clin Exp Allergy 1994;24:523-30.

17. Bruinzeel-Koomen C, Ortolani C. Adverse reactions to foods. Position Paper of the European Academy of Allergy and Clinical Immunology. Allergy 1995;50:623-35.

18. Sampson H, Metcalfe D. Immediate reactions to foods. In: Metcalfe D, Sampson H, Simon R, ed. Food allergy. Adverse reactions to foods and additives. Boston: Blackwell Scientific Publications, 1991: 99-113.

19. Settipane R, Settipane G. Anaphylaxis and food allergy. In: Metcalfe D, Sampson H, Simon R, ed. Food allergy. Adverse reactions to foods and additives. Boston: Blackwell Scientific Publisher, 1991: 150-63.

20. Yocum MW, Khan DA. Assessment of patients who have experienced anaphylaxis: a 3-year survey. Mayo Clin Proc 1994;69:16-23.

21. Yunginger JW, Sweeney KG, Sturner WQ, et al. Fatal food-induced anaphylaxis. Jama 1988;260:1450-2.

22. Sheffer AL, Austen KF. Exercise-induced anaphylaxis. J Allergy Clin Immunol 1980;66:106-11.

23. Kidd J, Cohen SH, Sosman AJ, Fink JN. Food-dependent exercise-induced anaphylaxis. J Allergy Clin Immunol 1983;71:407-11.

24. Maulitz RM, Pratt DS, Schocket AL. Exercise-induced anaphylactic reaction to shellfish. J Allergy Clin Immunol 1979;63:433-4.

25. Atkins F. Food-induced urticaria. In: Metcalfe D, Sampson H, Simon R, ed. Food allergy. Adverse reactions to foods and additive. Boston: Blackwell Scientific Publisher, 1991: 129-38.

26. Sampson H. Eczema and food hypersensitivity. In: Metcalfe D, Sampson H, Simon R, ed. Food allergy. Adverse reactions to foods and additives. Boston: Blackwell Scientific Publications, 1991: 113-28.

27. Sampson HA. Mechanisms in adverse reactions to food. The skin. Allergy 1995;50:46-51.

28. Bousquet J, Chanez P, Michel F. The respiratory tract and food hypersensitivity. In: Metcalfe D, Sampson H, Simon R, ed. Food allergy. Adverse reactions to foods and additives. Boston: Blackwell Scientific Publications, 1991: 139-50.

29. Atkins FM, Steinberg SS, Metcalfe DD. Evaluation of immediate adverse reactions to foods in adult patients. II. A detailed analysis of reaction patterns during oral food challenge. J Allergy Clin Immunol 1985;75:356-63.

30. Atkins FM, Steinberg SS, Metcalfe DD. Evaluation of immediate adverse reactions to foods in adult patients. I. Correlation of demographic, laboratory, and prick skin test data with response to controlled oral food challenge. J Allergy Clin Immunol 1985;75:348-55.

31. Crowe SE, Perdue MH. Gastrointestinal food hypersensitivity: basic mechanisms of pathophysiology. Gastroenterology 1992;103:1075-95.

32. Bentley SJ, Pearson DJ, Rix KJ. Food hypersensitivity in irritable bowel syndrome. Lancet 1983;2:295-7.

33. Min K, Metcalfe D. Eosinophilic gastroenteritis. In: Anderson J, ed. Food allergy and intolerance. Immunol Allergy Clin North Am 1991: 799-813.

34. Johnstone JM, Morson BC. Eosinophilic gastroenteritis. Histopathology 1978;2:335-48.

35. Iyngkaran N, Abidin Z, Meng LL, Yadav M. Egg-protein-induced villous atrophy. J Pediatr Gastroenterol Nutr 1982;1:29-33.

36. Vitoria JC, Camarero C, Sojo A, Ruiz A, Rodriguez-Soriano J. Enteropathy related to fish, rice, and chicken. Arch Dis Child 1982;57:44-8.

37. Jenkins I, Pincott J, Soothill J, Milla P. Food allergy as a cause of infatile colitis. Arch Dis Child 1994;59:326-9.

38. Ortolani C, Ispano M, Pastorello EA, Ansaloni R, Magri GC. Comparison of results of skin prick tests (with fresh foods and commercial food extracts) and RAST in 100 patients with oral allergy syndrome. J Allergy Clin Immunol 1989;83:683-90.

39. Mattes RD. Learned food aversions: a family study. Physiol Behav 1991;50:499-504.

40. Monro J, Brostoff J, Carini C, Zilkha K. Food allergy in migraine. Study of dietary exclusion and RAST. Lancet 1980;2:1-4.

41. Vaughan T, Mansfield L. Neurologic reactions to foods and food additives. In: Metcalfe D, Sampson H, Simon R, ed. Food allergy. Adverse reactions to foods and food additives. Boston: Blackwell Scientific Publications, 1991: 355-69.

42. Matthews DA, Manu P, Lane TJ. Evaluation and management of patients with chronic fatigue. Am J Med Sci 1991;302:269-77.

43. Mullin GE. Food allergy and irritable bowel syndrome. Jama 1991;265:1736.

44. Golding DN. Is there an allergic synovitis? J R Soc Med 1990;83:312-4.

45. Allison R. An evaluation of the potential for dietary proteins to contribute to systemic diseases. In: Life Science Research Office, Federation of American Societies for Experimental Biology, p 2, 1982:

46. Sampson HA, Metcalfe DD. Food allergies. Jama 1992;268:2840-4.

47. Hill DJ, Firer MA, Ball G, Hosking CS. Natural history of cows' milk allergy in children: immunological outcome over 2 years. Clin Exp Allergy 1993;23:124-31.

48. Savilahti E, Kuitunen M. Allergenicity of cow milk proteins. J Pediatr 1992;121:S12-20.

49. Goldman A, Anderson D, Sellars W, et al. Milk allergy. II. Skin testing of allergic and normal children with purified milk proteins.Pediatrics 1963;32:573-7

50. Goldman A, Anderson D, Selles W, et al. Milk allergy I. Oral challenge with milk and isolated milk proteins in allergic children. Pediatrics 1963;20:400-7.

51. Lee YH. Food-processing approaches to altering allergenic potential of milk-based formula. J Pediatr 1992;121:S47-50.

52. Businco L, Dreborg S, Einarsson R, et al. Hydrolysed cow's milk formulae. Allergenicity and use in treatment and prevention. An ESPACI position paper. European Society of Pediatric Allergy and Clinical Immunology. Pediatr Allergy Immunol 1993;4:101-11.

53. Jost R, Monti J, Pahud J. Whey protein allergenicity and its reduction by technological means. Food Technol 1987;41:118-21.

54. Kilshaw PJ, Heppell LM, Ford JE. Effects of heat treatment of cow's milk and whey on the nutritional quality and antigenic properties. Arch Dis Child 1982;57:842-7.

55. Heat-treated cow's milk remains allergenic. Nutr Rev 1983;41:96-7.

56. Rudloff S, Lonnerdal B. Solubility and digestibility of milk proteins in infant formulas exposed to different heat treatments. J Pediatr Gastroenterol Nutr 1992;15:25-33.

57. Halken S, Host A, Hansen LG, Osterballe O. Safety of a new, ultrafiltrated whey hydrolysate formula in children with cow milk allergy: a clinical investigation. Pediatr Allergy Immunol 1993;4:53-9.

58. ESPGAN Committee on nutrition: Antigen-reduced infant formulae. Acta Paediatr 1993;82:1087-8.

59. Oldaeus G, Bjorskten B, Einarsson R, Kjellman N. Antigenicity and allergenicity of cow milk hydrolysates intended for infant feeding. Pediatr Allergy Immunol 1991;4:156-64.

60. Sampson HA, Bernhisel-Broadbent J, Yang E, Scanlon SM. Safety of casein hydrolysate formula in children with cow milk allergy. J Pediatr 1991;118:520-5.

61. Rapports du comité scientifique de l'alimentation humaine (vingt-huitième série). Rapport relatif aux préparations pour nourrissons présentées comme "hypoallergéniques" ou "hypoantigéniques". In: Commission des Communautés Européennes, DG XII, 1993:

62. Businco L, Cantani A, Longhi MA, Giampietro PG. Anaphylactic reactions to a cow's milk whey protein hydrolysate (Alfa-Re, Nestle) in infants with cow's milk allergy. Ann Allergy 1989;62:333-5.

63. Ragno V, Giampietro PG, Bruno G, Businco L. Allergenicity of milk protein hydrolysate formulae in children with cow's milk allergy. Eur J Pediatr 1993;152:760-2.

64. Kleinman R, Bahna S, Powell G, Sampson H. Use of infant formulas in infants with cow milk allergy. A review and recommendations. Pediatr Allergy Immunol 1991;2:146-55.

65. Ruge E, Wahl R, Wahn U. How allergenic are hypoallergenic infant formulae. Clin Exp Allergy 1992;22:635-9.

66. Aggett PJ, Haschke F, Heine W, et al. Comment on antigen-reduced infant formulae. ESPGAN Committee on Nutrition. Acta Paediatr 1993;82:314-9.

67. Satterlee L. Proteins for use in foods. Food Technology 1981;35:53.

68. Adashi T, Alvarez A, Aoki N, Nakamura R, Garcia V, Matsuda T. Screening of rice strains deficient in 16-kDa allergenic protein. Biosci Biotechnol Biochem 1995;59:1377-8.

69. Weiss W, Vogelmeier C, Görg A. Electrophoretic characterization of wheat grain allergens from different cultivars involved in baker's asthma. Electrophoresis 1993;14:805-16.

70. Aas K, Jebsen J. Studies of hypersensitivities to fish. Partial purification and crystallization of a major allergenic component of cod. Int Arch Allergy 1967;32:1.

71. Elsayed S, Aas K. Isolation of purified allergen (cod) by isoelectric focusing. Int Arch Allergy 1971;40:428.

72. Elsayed S, Bennich H. The primary structure of allergen M from cod. Scand J Immunol 1975;4:203-8.

73. Elsayed S, Apold J. Immunochemical analysis of cod fish allergen M: locations of the immunoglobulin binding sites as demonstrated by the native and synthetic peptides. Allergy 1983;38:449-59.

74. Nagpal S, Metcalfe DD, Rao PV. Identification of a shrimp-derived allergen as tRNA. J Immunol 1987;138:4169-74.

75. Hoffman DR, Day E Jr., Miller JS. The major heat stable allergen of shrimp. Ann Allergy 1981;47:17-22.

76. Nagpal S, Rajappa L, Metcalfe DD, Rao PV. Isolation and characterization of heat-stable allergens from shrimp (Penaeus indicus). J Allergy Clin Immunol 1989;83:26-36.

77. Shanti KN, Martin BM, Nagpal S, Metcalfe DD, Rao PV. Identification of tropomyosin as the major shrimp allergen and characterization of its IgE-binding epitopes. J Immunol 1993;151:5354-63.

78. Daul CB, Slattery M, Reese G, Lehrer SB. Identification of the major brown shrimp (Penaeus aztecus) allergen as the muscle protein tropomyosin. Int Arch Allergy Immunol 1994;105:49-55.

79. Sachs MI, Jones RT, Yunginger JW. Isolation and partial characterization of a major peanut allergen. J Allergy Clin Immunol 1981;67:27-34.

80. Barnett D, Baldo BA, Howden ME. Multiplicity of allergens in peanuts. J Allergy Clin Immunol 1983;72:61-8.

81. Loza A, Brostoff J. Peanut allergy. Clin Exp Allergy 1995;25:493-500.

82. Burks AW, Williams LW, Helm RM, Connaughton C, Cockrell G, O'Brien T. Identification of a major peanut allergen, Ara h I, in patients with atopic dermatitis and positive peanut challenges. J Allergy Clin Immunol 1991;88:172-9

83. Burks AW, Cockrell G, Stanley JS, Helm RM, Bannon GA. Isolation, identification, and characterization of clones encoding antigens responsible for peanut hypersensitivity. Int Arch Allergy Immunol 1995;107:248-50.

84. Burks AW, Williams LW, Connaughton C, Cockrell G, O'Brien TJ, Helm RM. Identification and characterization of a second major peanut allergen, Ara h II, with use of the sera of patients with atopic dermatitis and positive peanut challenge. J Allergy Clin Immunol 1992;90:962-9.

85. Moroz LA, Yang WH. Kunitz soybean trypsin inhibitor: a specific allergen in food anaphylaxis. N Engl J Med 1980;302:1126-8.

86. Izumi H, Adachi T, Fujii N, et al. Nucleotide sequence of a cDNA clone encoding a major allergenic protein in rice seeds. Homology of the deduced amino acid sequence with members of alpha-amylase/trypsin inhibitor family. Febs Lett 1992;302:213-6.

87. Adachi T, Izumi H, Yamada T, et al. Gene structure and expression of rice seed allergenic proteins belonging to the alpha-amylase/trypsin inhibitor family. Plant Mol Biol 1993;21:239-48.

88. Bleumink E, Young E. Studies of the atopic allergen in hen's egg. I. Identification of the skin-reactive fraction in egg white. Int Arch Allergy 1969;35:1-19.

89. Bleumink E, Young E. Studies of the atopic allergen in hen's egg. II. Further characterization of the white and yolk of hen's egg. A study of the IgE binding by egg proteins. Int Arch Allergy 1971;42:72-88.

90. Hoffman DR. Immunochemical identification of the allergens in egg white. J Allergy Clin Immunol 1983;71:481-6.

91. Anet J, Back JF, Baker RS, Barnett D, Burley RW, Howden ME. Allergens in the white and yolk of hen's egg. A study of IgE binding by egg proteins. Int Arch Allergy Appl Immunol 1985;77:364-71.

92. Langeland T. A clinical and immunological study of allergy to hen's egg white. III. Allergens in hen's egg white studied by crossed radio-immunoelectrophoresis (CRIE). Allergy 1982;37:521-30.

93. Bernhisel-Broadbent J, Dintzis HM, Dintzis RZ, Sampson HA. Allergenicity and antigenicity of chicken egg ovomucoid (Gal d III) compared with ovalbumin (Gal d I) in children with egg allergy and in mice. J Allergy Clin Immunol 1994;93:1047-59.

94. Langeland T. A clinical and immunological study of allergy to hen's egg white. VI. Occurrence of proteins cross-reacting with allergens in hen's egg white as studied in egg white from turkey, duck, goose, seagull, and in hen egg yolk, and hen and chicken sera and flesh. Allergy 1983;38:399-412.

95. Keating MU, Jones RT, Worley NJ, Shively CA, Yunginger JW. Immunoassay of peanut allergens in food-processing materials and finished foods. J Allergy Clin Immunol 1990;86:41-4.

96. Daul CB, Morgan JE, Lehrer SB. Hypersensitivity reactions to crustacea and mollusks. Clin Rev Allergy 1993;11:201-22.

97. de-Martino M, Novembre E, Galli L, et al. Allergy to different fish species in cod-allergic children: in vivo and in vitro studies. J Allergy Clin Immunol 1990;86:909-14.

98. Malet A, Valero A, Lluch M, Bescos M, Amat P, Serra E. Hypersensitivity to mustard seed. Allergy 1993;48:62-3.

99. Atkins FM, Wilson M, Bock SA. Cottonseed hypersensitivity: new concerns over an old problem. J Allergy Clin Immunol 1988;82:242-50.

100. Axelsson IG, Ihre E, Zetterstrom O. Anaphylactic reactions to sunflower seed. Allergy 1994;49:517-20.

101. Vocks E, Borga A, Szliska C, et al. Common allergenic structures in hazelnut, rye grain, sesame seeds, kiwi, and poppy seeds. Allergy 1993;48:168-72.

102. Bjorksten F, Halmepuro L, Hannuksela M, Lahti A. Extraction and properties of apple allergens. Allergy 1980;35:671-7.

103. Kanny G, Fremont S, Nicolas J, Monneret-Vautrin D. Food allergy to sunflower oil in a patient sensitized to mugwort pollen. Allergy 1994;49:561-4.

104. Eriksson NE, Formgren H, Svenonius E. Food hypersensitivity in patients with pollen allergy. Allergy 1982;37:437-43.

105. Ebner C, Birkner T, Valenta R, et al. Common epitopes of birch pollen and apples--studies by western and northern blot. J Allergy Clin Immunol 1991;88:588-94.

106. Hirschwehr R, Valenta R, Ebner C, et al. Identification of common allergenic structures in hazel pollen and hazelnuts: a possible explanation for sensitivity to hazelnuts in patients allergic to tree pollen. J Allergy Clin Immunol 1992;90:927-36.

107. Pauli G, Bessot JC, Dietemann-Molard A, Braun PA, Thierry R. Celery sensitivity: clinical and immunological correlations with pollen allergy. Clin Allergy 1985;15:273-9.

108. Bircher AJ, Van-Melle G, Haller E, Curty B, Frei PC. IgE to food allergens are highly prevalent in patients allergic to pollens, with and without symptoms of food allergy. Clin Exp Allergy 1994;24:367-74.

109. Levy DA, Charpin D, Pecquet C, Leynadier F, Vervloet D. Allergy to latex. Allergy 1992;47:579-87.

110. Fernandez-de-Corres L, Moneo I, Munoz D, et al. Sensitization from chestnuts and bananas in patients with urticaria and anaphylaxis from contact with latex . Ann Allergy 1993;70:35-9.

111. Yunginger J. Food antigens. In: Metcalfe D, Sampson H, Simon R, ed. Food allergy. Adverse reactions to foods and food additives. Boston: Blackwell Scientific Publications, 1991: 36-51.

112. Dannaeus A, Inganas M. A follow-up study of children with food allergy. Clinical course in relation to serum IgE- and IgG-antibody levels to milk, egg and fish. Clin Allergy 1981;11:533-9.

113. Bock SA. The natural history of adverse reactions to foods. N Engl Reg Allergy Proc 1986;7:504-10.

114. Onorato J, Merland N, Terral C, Michel FB, Bousquet J. Placebo-controlled double-blind food challenge in asthma. J Allergy Clin Immunol 1986;78:1139-46

115. Dreborg S. Skin test in diagnosis of food allergy. Allergy Proc 1991;12:251-4.

116. Sampson HA, Albergo R. Comparison of results of skin tests, RAST, and double-blind, placebo-controlled food challenges in children with atopic dermatitis. J Allergy Clin Immunol 1984;74:26-33.

117. Bock SA. A critical evaluation of clinical trials in adverse reactions to foods in children. J Allergy Clin Immunol 1986;78:165-74.

118. David TJ. Anaphylactic shock during elimination diets for severe atopic eczema. Arch Dis Child 1984;59:983-6.

119. Wilson NM, Dixon C, Silverman M. Increased bronchial responsiveness caused by ingestion of ice. Eur J Respir Dis 1985;66:25-30.

120. James J, Eigenmann P, Eggleston P, Sapson H. Airway reactivity changes in food-allergic, asthmatic children undergoing double-blind placebo-controlled food challenges. Am J Respir Crit Care Med 1995;in press.

121. Zwetchkenbaum JF, Skufca R, Nelson HS. An examination of food hypersensitivity as a cause of increased bronchial responsiveness to inhaled methacholine. J Allergy Clin Immunol 1991;88:360-4.

122. Young E, Stoneham M, Petruckevitch A, Barton J, Rona R. A population study of food intolerance. Lancet 1994;343:1127-30.

123. Sampson HA, Jolie PL. Increased plasma histamine concentrations after food challenges in children with atopic dermatitis. N Engl J Med 1984;311:372-6.

124. Andre F, Andre C, Feknous M, Colin L, Cavagna S. Digestive permeability to different-sized molecules and to sodium cromoglycate in food allergy. Allergy Proc 1991;12:293-8.

125. Simpson SI, Somerfield SD, Wilson JD, Hillas JL. A double-blind study for the diagnosis of cows' milk allergy. N Z Med J 1980;92:458-9.

126. Daul CB, Morgan JE, Lehrer SB. The natural history of shrimp hypersensitivity. J Allergy Clin Immunol 1990;86:88-93.

127. Bishop JM, Hill DJ, Hosking CS. Natural history of cow milk allergy: clinical outcome. J Pediatr 1990;116:862-7.

128. Guillet G, Guillet MH. Natural history of sensitizations in atopic dermatitis. A 3-year follow-up in 250 children: food allergy and high risk of respiratory symptoms. Arch Dermatol 1992;128:187-92.

129. Kjellman N. Natural course of asthma and allergy in childhood. Pediatr Allergy Immunol 1994;5 (suppl 1):13-8.

130. Bender AE, Matthews DR. Adverse reactions to foods. Br J Nutr 1981;46:403-7.

131. Jansen JJ, Kardinaal AF, Huijbers G, Vlieg-Boerstra BJ, Martens BP, Ockhuizen T. Prevalence of food allergy and intolerance in the adult Dutch population. J Allergy Clin Immunol 1994;93:446-56.

132. Burr ML, Merrett TG. Food intolerance: a community survey. Br J Nutr 1983;49:217-9.

133. Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. Pediatrics 1987;79:683-8.

134. Høst A. Cow's milk protein allergy and intolerance in infancy. Pediatr Allergy Immunol 1994;5, suppl 5:1-36.

135. Host A, Husby S, Osterballe O. A prospective study of cow's milk allergy in exclusively breast-fed infants. Incidence, pathogenetic role of early inadvertent exposure to cow's milk formula, and characterization of bovine milk protein in human milk. Acta Paediatr Scand 1988;77:663-70.

136. Schrander JJ, van-den-Bogart JP, Forget PP, Schrander-Stumpel CT, Kuijten RH, Kester AD. Cow's milk protein intolerance in infants under 1 year of age: a prospective epidemiological study. Eur J Pediatr 1993;152:640-4.

137. Hide DW, Guyer BM. Cows milk intolerance in Isle of Wight infants. Br J Clin Pract 1983;37:285-7.

138. Collins-Williams C. The incidence of milk allergy in pediatric practice. J Pediatr 1956;48:39-47.

139. Bachman K, Dees S. Milk allergy. I. Observations on incidence and symptoms in "well" babies. Pediatrics 1957;20:393-9.

140. Johnstone D, Dutton A. Dietary prophylaxis of allergic disease in children. N Engl J Med 1966;274:715-9.

141. Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. Eur Respir J 1994;7:954-60.

142. Anderson JA. The clinical spectrum of food allergy in adults. Clin Exp Allergy 1991;1:304-15.

143. Saarinen UM, Kajosaari M. Does dietary elimination in infancy prevent or only postpone a food allergy? A study of fish and citrus allergy in 375 children. Lancet 1980;1:166-7.

144. McGowan M, Gibney MJ. Calcium intakes in individuals on diets for the management of cows' milk allergy: a case control study. Eur J Clin Nutr 1993;47:609-16.

145. Dean TP, Adler BR, Ruge F, Warner JO. In vitro allergenicity of cows' milk substitutes. Clin Exp Allergy 1993;23:205-10.

146. Samoto M, Akasaka T, Mori H, Manabe M, Ookura T, Kawamura Y. Simple and efficient procedure for removing the 34 kDa allergenic soybean protein, Gly mI, from defatted soy milk. Biosci Biotechnol Biochem 1994;58:2123-5.

147. Watanabe M, Ikezawa Z, Arai S. Fabrication and quality evaluation of hypoallergenic wheat products. Biosci Biotechnol Biochem 1994;58:2061-5.

148. Dannaeus A, Foucard T, Johansson S. The effect of orally administered sodium cromoglycate on symptoms of allergy. Clin Allergy 1977;7:109-15.

149. Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DY. Treatment of peanut allergy with rush immunotherapy. J Allergy Clin Immunol 1992;90:256-62.

150. Sampson HA. Food allergy and the role of immunotherapy. J Allergy Clin Immunol 1992;90:151-2.

151. Arshad SH, Matthews S, Gant C, Hide DW. Effect of allergen avoidance on development of allergic disorders in infancy. Lancet 1992;339:1493-7.

152. Hide DW, Matthews S, Matthews L, et al. Effect of allergen avoidance in infancy on allergic manifestations at age two years. J Allergy Clin Immunol 1994;93:842-6.

153. Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. J Allergy Clin Immunol 1995;95:1179-90.

154. Saarinen U, Kajosaari M. Breast-feeding as prophylaxis against atopic disease: Prospective follow-up until 17 years. Lancet 1995;346:1065-9.

155. Sigurs N, Hattevig G, Kjellman B. Maternal avoidance of eggs, cow's milk, and fish during lactation: effect on allergic manifestations, skin-prick tests, and specific IgE antibodies in children at age 4 years. Pediatrics 1992;89:735-9.

156. Falth-Magnusson K, Kjellman NI. Allergy prevention by maternal elimination diet during late pregnancy--a 5-year follow-up of a randomized study. J Allergy Clin Immunol 1992;89:709-13.

157. Halken S, Host A, Hansen LG, Osterballe O. Preventive effect of feeding high-risk infants a casein hydrolysate formula or an ultrafiltrated whey hydrolysate formula. A prospective, randomized, comparative clinical study. Pediatr Allergy Immunol 1993;4:173-81.

158. Fergusson DM, Horwood LJ, Shannon FT. Risk factors in childhood eczema. J Epidemiol Community Health 1982;36:118-22.

159. Kajosaari M, Saarinen UM. Prophylaxis of atopic disease by six months' total solid food elimination. Evaluation of 135 exclusively breast-fed infants of atopic families. Acta Paediatr Scand 1983;72:411-4.

160. Schmitz J. Coeliac disease in childhood. In: Marsh M, ed. Coeliac disease. London: Blackwell Scientific Publications, 1992: 17-48.

161. Sollid LM, Thorsby E. HLA susceptibility genes in celiac disease: genetic mapping and role in pathogenesis. Gastroenterology 1993;105:910-22.

162. Kagnoff MF, Austin RK, Hubert JJ, Bernardin JE, Kasarda DD. Possible role for a human adenovirus in the pathogenesis of celiac disease. J Exp Med 1984;160:1544-57.

163. Strober W. Gluten-sensitive enteropathy-an abnormal immunologic response of the gastrointestinal tract to a dietary protein. In: Shorter R, Kirsner J, ed. Gastrointestinal immunity for the clinician. Orlando, Fl: Grune & Stratton, 1985: 75-84.

164. Howdle PD, Ciclitira PJ, Simpson FG, Losowsky MS. Are all gliadins toxic in coeliac disease? An in vitro study of alpha, beta, gamma, and w gliadins. Scand J Gastroenterol 1984;19:41-7.

165. Businco L, Benincori N, Cantani A, Tacconi L, Picarazzi A. Chronic diarrhea due to cow's milk allergy. A 4- to 10-year follow-up study. Ann Allergy 1985;55:844-7.

166. Strober W, Neurath M. Immunologic diseases of the gastrointestinal tract. In: Rich R, Fleisher T, Schwartz B, Shearer W, Strober W, ed. Clinical Immunology, Principles and Practice. St Louis: Mosby Year Book,1995:1401-28

167. Collin P, Reunala T, Pukkala E, Laippala P, Keyrilainen O, Pasternack A. Coeliac disease--associated disorders and survival. Gut 1994;35:1215-8.

168. Holmes GK, Prior P, Lane MR, Pope D, Allan RN. Malignancy in coeliac disease--effect of a gluten free diet. Gut 1989;30:333-8.

ANNEX 4 *CONALLGY 3*

CONSIDERATION BY CODEX OF FOOD ALLERGIES AND HYPERSENSITIVITY[1]

INTRODUCTION

This paper reviews the deliberations of the Codex Alimentarius Commission and two of its general subject committees, the Codex Committee on Food Labelling and the Codex Committee on Nutrition and Foods for Special Dietary Use, on the appropriate treatment of foods and ingredients that can cause allergic or hypersensitivity reactions in the Codex General Standard for the Labelling of Prepackaged Foods (CODEX STAN 1- 1985). The labelling of ingredients which are themselves composites of other ingredients in relation to the "25% rule" in Section 4.2.1.3 of the above referenced General Standard and the development of a list of potential food allergens and ingredients giving rise to hypersensitivity or intolerance reactions have been the focus of recent discussions.

BACKGROUND

At its inception in 1965 the Codex Committee on Food Labelling (CCFL) established the principle that the labelling of prepackaged foods should give the consumer full information about the food product and ensure that there was no deception. The interest of the consumer was to be paramount, although proper labelling also was seen as protecting honest traders. Full ingredient listing, including the listing of components of an ingredient, was accepted as a basic requirement for label declarations. However, exemptions were foreseen in relation to practicality, standardized products, and class names for food additives (1).

The first reference to food allergies appears in the report of the third session of the CCFL in 1967. Those deliberations were accompanied by what today might be termed a *risk assessment* initiative in that WHO was asked "...to seek expert advice on the potential health hazards that might be involved in the omission of listing of ingredients on prepackaged foods, especially in relation to allergic reactions..." (2). Further, in seeking information from governments, the Committee drew their attention "...to the public health risks, such as allergies, involved in exempting foods from the list of ingredients..." and sought comment on this aspect as well (3).

The first General Standard for the Labelling of Prepackaged Foods was finalized by the CCFL at its fourth session in 1969 (4). The problems of listing ingredients and additives, once again, gave rise to the issue of allergies. The Committee found the requested WHO paper on Intolerance to Foods useful for these deliberations. In what today might be termed *risk management* the CCFL "...recognized that allergies to food were a serious problem which it should bear in mind. However,...in practice the problem could not be solved by requirements for food labelling..." (5). Considerable time in the same discussion was also spent on the problem of listing of ingredients in a composite food ingredient and several draft proposals were reviewed before the Committee settled on wording for inclusion in the above noted General

---

[1] This paper was prepared by Ms. Katharine E. Gourlie, FAO Consultant and former Chairperson of the Codex Committee on Food Labelling

Standard. When the Codex Alimentarius Commission (CAC) at its sixth session in 1969 reviewed and adopted the proposed General Standard as CAC/RS 1-69, Section 3.2. (ii) was approved as follows:

> "When an ingredient of a food has more than one component, the names of the components shall be included in the list of ingredients, except where such an ingredient is a food for which a Codex standard has been established and such standard does not require a complete list of ingredients" (6).

Eleven years later, the fifteenth session of the CCFL in November 1980 began the process of revising CAC/RS 1-1969 with discussion centred around a report prepared by a consultant. It is important to situate this process of revision in the context of issues of importance to consumers at that time and thus for national governments as they considered the food label. Food additives had been cited as responsible for many food hypersensitivity or allergenic reactions. The widely publicized theories of B. F. Feingold, which laid the blame for childhood hyperactivity at the feet of food additives, led many parents to try to eliminate food additives from their family diet. The popular press found a receptive audience for alarming reports about adverse reactions to food additives, whatever the source or scientific credentials of the author. The proponents of "organic" foodstuffs also were claiming "superiority" in terms of nutritional quality and purity because they were "free from food additives or pesticide residues". Given this consumer unease over food additives, it is not surprising that the "Carry-Over Principle" for food additives, elaborated by the Codex Committee on Food Additives, (7) also had been scrutinized by the CCFL for food labelling purposes. At its twelfth session in 1977 this Committee had agreed that any additive present in the final product as a result of carry-over in accordance with the circumstances described in Section 4 of the Carry-Over Principle must be declared (8). The CCFL subsequently took the position that carried-over food additives not having functional or technological properties in the final product (Section 3 of the Carry-Over Principle) as well as processing aids meeting the same test, need not be declared in the list of ingredients (9).

In this same period, consumers in a number of countries were expressing strong opposition to any government approval for the sale of foods treated with ionizing radiation. No matter how strong the supporting scientific evidence of safety, for some consumer activists, it was all suspect because it had been generated with the involvement of the nuclear industry. Given this climate, it is interesting to note that the CCFL at its fourteenth session in 1979 took the position that no mention of irradiation treatment was needed in the list of ingredients for products containing irradiated ingredients (second generation) (10). Yet one year later at the fifteenth session, when the proposed draft revised text for CAC/RS 1-1969 was reviewed, there was what appears to be a 180 degree shift with the addition of a new Section 5.5.2 "...when an irradiated product is used as an ingredient in another food, this shall be declared in the list of ingredients by use of the term "irradiated" in conjunction with the name of the product so treated..." (11). Insofar as multi-component ingredients in foods were concerned, the recommended revision to Section 3.2.(ii) proposed a bracketed disclosure of the constituent ingredients immediately following the declaration of the ingredient itself (12). If accepted, there appeared now to be a consistency between the sections on Irradiated Foods and List of Ingredients, in terms of second generation ingredient declarations.

LABELLING MINOR INGREDIENTS: The Impact of the 25% Rule

When one considers the direction in which the requirements for ingredient listing in the labelling of prepackaged food were evolving, it is clear that consumers at national levels were demanding more information on food labels and were less prepared to accept government evaluations and assurances of safety. They wished, rather, sufficient transparency to make an informed choice among competing products on the basis of a number of characteristics, including ingredients, additives and treatment or processing methods. The practicality of providing long lists of minor ingredients, many with complex chemical names of questionable utility or interest for the consumer, was a concern for both governments and food manufacturers as they attempted to respond to this demand.

The sixteenth session of the CCFL in 1982 saw the introduction of the proposed "25% rule" in the List of Ingredients Section (13). The concept was based upon fixing a cut-off point, in terms of the amount of the end food product that was represented by an ingredient itself made up of two or more ingredients, and requiring full ingredient listing for such a composite ingredient if it represented more than 25% (m/m) of the end product, but only the name of the composite ingredient itself if it represented less than 25% of the end product. The selection of 25% as the cut-off point was arbitrary, but was felt to be reasonably responsive to consumers and practicable for the food industry. Also proposed were amendments to the Irradiated Foods Section, the latter taking into account referrals from CAC, the Codex Committee on Food Additives and the Joint FAO/IAEA/WHO Expert Committee on Food Irradiation (14). There were lengthy discussions around the new proposal for the subsidiary listing of ingredients comprising two or more ingredients and as the Committee could not reach a consensus, it kept the statement referring to the 25% level below which the subsidiary ingredients of food ingredients, excluding food additives, need not be declared in the list of ingredients in square brackets, which indicated a lack of agreement (15).

Two more sessions of the CCFL were required for finalization of the revised Draft General Standard and advancement to CAC in 1985 for final adoption. The recorded discussions at the seventeenth and eighteenth CCFL sessions indicate that a "25% rule" in what was now Section 4.2.1.3 was still controversial, as was the declaration of the presence of food additives, because of food allergy concerns. Some delegations felt "...all food additives should be declared whatever the reason for their presence since, in some cases, food additives could cause allergic reactions..." (16) and again later, some delegations thought that "...the consumer should be informed as completely as possible of the ingredients in the food since, in many cases, these were of vital importance for health reasons..." (17). In respect of the 25% figure itself, some delegates wanted to lower it to 10-15% , but in the end it was held at 25% to allow for fluctuations in supply and seasonal variations.

Equally contentious were the proposed Sections 5.2.2 and 5.2.3 under Irradiated Foods. The IAEA Observer brought to the attention of the Committee the earlier stated view of the Joint FAO/IAEA/WHO Expert Committee on the Wholesomeness of Irradiated Foods that the labelling of irradiated foods was not necessary for scientific reasons. As well a recently established FAO/IAEA Advisory Group had taken the view that labelling of irradiated foods in response to consumer demands should be left to national governments and also that labelling provisions related to irradiated ingredients would be of little value (18). In the end the Committee decided to include these sections with a footnote to indicate they remained under review. It was not until

the twenty-first session of the CCFL in 1991 that the Irradiated Foods Section was settled (19). The relationship between the 25% rule in Section 4.2.1.3 and the requirement for listing of irradiated ingredients in Section 5.2.2 played a large role in these later discussions when it became clear that in most cases, the former would negate the intent of the latter to inform consumers of the presence of any irradiated constituent in a food since, for many such products, irradiated components and second generation irradiated ingredients would constitute less than 25% of the final product. Nonetheless, both Sections were retained. Worth noting is that during this period there were a series of initiatives sponsored by FAO, WHO, the IAEA and other UN agencies whose purpose was to advance the use of food irradiation as a means of safe and effective food preservation. By 1988 the advice being given to, and accepted by, these bodies was that irradiated foods should carry clear and unambiguous labelling and that such labelling should state the fact, in close proximity to the name of the food, that the food had been treated with ionizing radiation/energy. One might observe that it had taken international bodies responsible for the *risk assessment* of food irradiation eight more years to reach the *risk management* and *risk communication* conclusions which the consumer responsive government delegations to the CCFL in 1980 had recognized as necessary in order to allow consumers to make an informed choice between irradiated and non-irradiated foods (20).

The Draft General Standard for the Labelling of Prepackaged Foods which was adopted by the sixteenth session of the Codex Alimentarius Commission in 1985 became CODEX STAN 1-1985. The sections which have been discussed above are those which are most relevant in the current debate on the disclosure of ingredients in foods which are recognized as having the potential to cause allergic or intolerance reactions in hypersensitive individuals. An understanding of the manner in which *risk management* decisions were arrived at in the CCFL, and the importance of consumer demands for transparency on food labels in shaping government positions, is key to addressing the food allergens issue. Today, for many consumers, the food label is an important *risk communication* vehicle and the one that is in closest proximity to the food itself, when they choose among competing products.

For reference purposes the key sections of CODEX STAN 1-1985 as amended in 1991 are presented in Appendix I.

REVISIONS TO THE GENERAL STANDARD: Addressing the Food Allergies Problem through Food Labelling

The current deliberations of the CCFL in respect of the problem of food allergens dates from the nineteenth session in 1987 when the Committee took note of the availability of a reliable method for the determination of gliadin, which had been identified as the causative agent of gluten intolerance in coeliac disease, and agreed that this and similar problems of food allergy and intolerance and their relationship to the adequacy of the ingredient listing requirements in the General Standard should be considered at a future meeting (21). Norway, at the twenty-first session in 1991, proposed that a working paper be prepared for the next session of the CCFL to examine the labelling of potential allergens which were included as components of composite ingredients in foods and thus not listed as ingredients on the label. The Committee agreed, recognizing that such a discussion would re-open the debate over Section 4.2.1.3 and the "25% rule" (22). The Codex Executive Committee in June 1991 expressed concern as to the practicality of such a discussion and recommended that the CCFL proceed cautiously when examining the subject since almost all foods contain potential allergens (23).

When the twenty-second session of the CCFL first reviewed the paper prepared under the direction of Norway, there was considerable support for revision to the "25% rule" in Section 4.2.1.3 . The expanding use of glutens in a variety of foods and unlisted composite ingredients was pointed out as being of particular concern for individuals requiring a gluten-free diet. Other comments from delegates noted that "...food hypersensitivity was both a public health and a labelling issue and that hypersensitive consumers relied on labelling to avoid certain foods...the principle of complete and accurate ingredient declarations was generally accepted by government and industry alike, but additional industry co-operation was required where second and third generation ingredients were concerned...actions required should be relative to the amount of risk...attempts should be made to define the ingredients and additives involved, as a balance was required to provide adequate, as opposed to burdensome, labelling information...the importance of justifying any changes to composite label requirements with appropriate criteria resting on a scientific basis.....care should be taken not to create a false security by action on labelling..." (24).

In the continuing discussion at the twenty-third session of the CCFL in 1994, the Committee had the benefit of comments from a number of governments and observers, almost all of whom supported a revision of the "25% rule", at least to the proposed 5% level, coupled with the development of a positive declaration list of substances known to give rise to allergenic or hypersensitivity reactions in susceptible individuals. The United States, based on its experience with regulations requiring virtually full ingredient declaration on the food label, pointed out that changing to a "5% rule" might not eliminate the concerns of sensitive individuals, and that complete elimination of the percent exemption rule for composite ingredients would negate any need for a special provision in 4.2.1.3 that required the declaration of specific ingredients (25). Delegates cited the need to have supporting scientific evidence on the effect of reducing the "25% rule" to 5% in terms of reducing hypersensitivity reactions, and the need for scientific based criteria for inclusions in the proposed list of substances which could cause severe reactions in sensitive individuals. For the latter, the advice of the Codex Committee on Nutrition and Foods for Special Dietary Use (CCNFSDU) was sought on the establishment of the list and the criteria to be applied in the process. There was discussion also on the related matter of Section 4.2.2.1 in respect of the use of "class names" and the identification of substances present in small amounts as carriers,e.g. flavour carriers, which could cause hypersensitivity reactions. The question of the Carry-Over Principle as applied to food additives and processing aids which might elicit a hypersensitivity reaction was referred to the Codex Committee on Food Additives and Contaminants (CCFAC) (25). Both the CCNFSDU and the CCFAC have addressed the requests from the CCFL for assistance. The CCNFSDU expects to discuss a paper prepared by France (Professor Bousquet's paper) at its next session (27). The CCFAC was of the view that no specific action on its part was necessary in relation to the Carry-Over Principle, since the Joint Expert Committee on Food Additives (JECFA) took account of hypersensitive reactions when evaluating food additives (28).

The changes proposed for Sections 4.2.1.3 , 4.2.2.1 and 4.2.3.2 of the General Standard are found in underline at Appendix II. Government comment is being sought, particularly in respect of the substances to be included in a list of potential allergens and substances responsible for severe hypersensitivity reactions and the labelling to be required. As well, scientific information on the national occurrence and severity of food allergies and the national approaches used in dealing with this issue have been requested.

The challenge for the CCFL in developing an acceptable labelling approach to the question of food allergies and hypersensitivity, and for CCNFSDU in advising on criteria for a list and the substances to be included, is to respect the 1995 decision of the twenty-first session of the Commission (29) that Codex Standards and other texts should be based on the following four statements of principle which confirm the pre-eminent role of science in Codex decision-making processes while allowing for other factors to be taken into account:

1. *The food standards, guidelines and other recommendations of Codex Alimentarius shall be based on the principle of sound scientific analysis and evidence, involving a thorough review of all relevant information , in order that the standards assure the quality and safety of the food supply.*

2. *When elaborating and deciding upon food standards Codex Alimentarius will have regard, where appropriate, to other legitimate factors relevant for the health protection of consumers and for the promotion of fair practices in food trade.*

3. *In this regard it is noted that food labelling plays an important role in furthering both of these objectives.*

4. *When the situation arises that members of Codex agree on the necessary level of protection of public health but hold differing views about other considerations, members may abstain from acceptance of the relevant standard without necessarily preventing the decision by Codex.*

The Executive Committee and the Commission have recognized that Risk Analysis with its three inter-related components, *risk assessment, risk management,* and *risk communication,* provides a harmonized and transparent framework for the application of sound scientific analysis and evaluation, as well as other legitimate factors relevant for the health protection of consumers, in the setting of food standards. The recommendations of the Joint FAO/WHO Expert Consultation on the Application of Risk Analysis to Food Standards Issues (30) have been accepted in principle. Risk Analysis has been defined as:

> "A process to scientifically evaluate the probability of occurrence of known or potential adverse health effects, resulting from human exposure to foodborne hazards (*risk assessment*), to weigh policy alternatives in light of the results of risk assessment and, if required, to select appropriate control options (*risk management*) and to exchange information and opinion interactively among risk assessors, risk managers, consumers and other interested parties."

The Commission recognized that further work is needed on the uncertainty in Risk Analysis in relation to standard setting and food regulation, and on the elaboration of consistent *risk management* and *risk communication* principles and procedures, and that *risk assessment* carries with it a degree of uncertainty when estimating human risk in qualitative terms. Nonetheless, an attempt to apply them to the proposals for labelling of food allergens and substances causing hypersensitivity reactions may be helpful for this technical consultation in developing possible approaches. In particular, it is worth noting that the Commission directed that the definition for *risk communication* include explicit reference to consumers, recognizing

that transparency in communicating with consumers, as part of the process of Risk Analysis, is necessary (31).

The above noted Expert Consultation elaborated four steps for *risk assessment:* (i) hazard identification, (ii) hazard characterisation, (iii) exposure assessment and (iv) risk characterisation. If one applies this generic framework to the problem of potential food allergenicity and hypersensitivity, one can see that uncertainty plays a significant role in the interactivity that must take place between *risk assessment* and *risk management*. While there is a considerable body of scientific evidence to draw upon for the hazard identification and hazard characterisation steps, there is considerably less certainty in the scientific evidence available for use in the exposure assessment and risk characterisation steps.

The foods and ingredients associated with allergy, hypersensitivity and intolerance reactions which were considered by the CCFL for inclusion in a positive declaration list (cereals, eggs, fish, legumes, milk, tree nuts, shellfish/crustacea, certain fruits and vegetables, and food additives and processing aids such as azo-colours and sulphites) are well documented in the scientific literature. However, there still appear to be uncertainties in respect of the qualitative and/or quantitative evaluation of the nature of the adverse effects (hazard characterisation). One only has to look at the emerging suggestion that coeliac disease may be more widespread than previously assumed (32), the regional variability in lactose intolerance (33) and the recent interest in delayed onset food allergy (34) to realize the task faced by the CCFL and CCNFSDU in developing criteria for inclusion in the list.

The "25% rule" , the use of "class names" for food additives and processing aids, the Carry-Over Principle and the "technological effect" definition, when they result in the absence of any indication on the food label of the presence of a hypersensitivity or intolerance causing substance, make it extremely difficult to generate accurate exposure data for evaluation. This is exacerbated by the increasing globalization of the food trade and the presence of new and unfamiliar imported foodstuffs for which exposure data will be extremely difficult to capture by national governments. Allergy specialists and dieticians, if they are not able to consult the food label to determine what ingredients are present in food products available in local markets, cannot give timely advice to patients. Further, since estimates as to the frequency of food hypersensitivity and intolerance vary widely and are complicated by known regional differences, the estimation of severity and occurrence required for the risk characterisation step is extremely difficult. The paper under consideration by the CCFL suggested that 2% would be a conservative estimate and that 10% might be a reasonable estimate for the overall incidence of food hypersensitivity, including allergenicity and intolerance, in the general population (35).

From the foregoing it is evident that there are considerable gaps in the *risk assessment* evaluation available to the CCFL and the CCNFSDU as they attempt to weigh the policy alternatives and select and implement appropriate control options in the *risk management* phase of the Risk Analysis process. It is, however, fairly evident that the current construct of the General Standard, in respect of the sections in question, does not meet the intent of the above noted statements of principle adopted by the Commission.

When one considers the labelling requirements for compound ingredients and the exemption allowed by the "25% rule" the paradoxical situation which has been created cannot be justified on the basis of sound science. As was pointed out in the aforementioned CCFL

discussion paper, if a substance known to cause hypersensitivity is a single ingredient, it must be declared in the list of ingredients, no matter how small the amount. However, if it is a component of a compound ingredient, theoretically it could constitute more than 24% but less than 25% of the finished product, yet not be declared in the list of ingredients on the food label and thus be unrevealed to the consumer. The proposal now before the CCFL, in calling for a reduction to 5% , is recognized as going only part way in resolving the problem, since even small amounts of certain substances can cause a hypersensitivity or allergic reaction in susceptible individuals. The complementary proposal for the addition to Section 4.2.1.3 of a list of substances which are known to give rise to such reactions and the requirement that these substances must always be declared on the food label when present in the product, no matter at what level, would address the gap. This list would also be referred to in the sections dealing with "class names", "carried-over" and "technological functions", with the result that the presence of any amount of one of these listed substances could not be masked by a generic name. A revision to the General Standard along these lines would more closely parallel the full ingredient listing requirements now in force in the United States (except for the 5% exemption). However, it would move the General Standard away from current EU legislation and that of other countries who have adopted this standard. Another option (which has not been proposed) would be to follow the United States and require the full declaration of all ingredients present in a food product including ingredients of compound ingredients and food additives and processing aids).

A change of this nature to the General Standard will engender significant costs for food manufacturers, which cost must be assumed to be met in the long run by the consumer. On the other hand, if the alternative is that increasing numbers of consumers avoid prepackaged foods in order to eliminate any uncertainty as to what ingredients are actually present in the food, the cost of not changing may be even higher.

Alternatives to the food label as a source of ingredient information do exist, but they tend to be fragmented, not always up to date and often difficult for consumers to access when they are considering the purchase of a particular product. They include specialized composition foods, government or special interest group data banks with detailed product information usually supplied by food manufacturers, direct manufacturer contact, product catalogues, and informational materials put out by special interest groups or specialists. All are useful to the individual with special needs, however, they are likely only to deal with nationally produced foods and certainty about currency in terms of recent formulation changes is always a concern.

In weighing policy alternatives, the Codex Committees must consider the complexity of the problem of food allergies and hypersensitivity inducing substances in foods, the uncertainties present in the *risk assessment* information currently available, the certainty sought by affected consumers when consulting the food label, the utility of the possible control options suggested in terms of their costs for consumers and food manufacturers, and the ability of governments to implement them, as well as the obligation to protect the health of vulnerable consumers.

CONCLUSION

The most logical *risk management* option for the CCFL, at this time would appear to be the proposed revisions to Sections 4.2.1.3, 4.2.2.1, and 4.2.2.2 of the General Standard for the Labelling of Prepackaged Foods (CODEX STAN 1-1985). However, the Committee would benefit from expert advice and scientific evidence for the substances to be included in the list for

mandatory declaration. As a starting point, recommendations from this technical consultation as to the criteria which might be applied for inclusion in terms of the generic *risk assessment* framework outlined above would be very helpful:

- Are there other options available in respect of food labelling or consumer information which have not been considered?

- Should there be a hierarchy of reactions and responses in terms of the criteria for inclusion in the list of substances?

- Should there be a minimum incidence or prevalence level before a substance merits consideration?

The Committee would also benefit from advice from the food industry as to what is practicable while meeting the intent of the principles for elaborating food standards as set out by the Commission. Industry's experience in meeting the full ingredient declaration requirements of the United States of America should provide useful insights on this issue.

The food label is the vehicle used by the consumer, and the retailer, for that matter, to obtain information about a product at the point of purchase. If the label is deficient or not transparent as to contents, the health of the consumer may be at risk. The label is the vehicle for *risk communication* with consumers, probably the most effective vehicle available. It is doubtful that experts involved with the treatment of individuals suffering from a food allergy, hypersensitivity or intolerance can do other than advise their patients to avoid certain specific foods or ingredients. They may have limited information on specialized products or refer patients for diet counselling and design to eliminate problem foods or substances. Consumers, for their part, must educate themselves about their particular needs. They must be prepared to exercise extreme caution when approaching a new food product and deny themselves any questionable choice. Ultimately, however, governments have the responsibility, as they approve an ever increasing number of technological innovations, ingredient modifications and the manipulation of familiar foodstuffs, to meet the information needs of consumers and ensure even more transparency about the food products they allow into national markets. The proposed revisions to the General Standard for the Labelling of Prepackaged Foods would appear to go further than any other option considered thus far to meet these objectives.

REFERENCES

1. Alinorm 65/22, para. 4 and paras. 10-12
2. Alinorm 66/22, para. 15
3. Alinorm 68/22, paras. 11-13
4. Alinorm 69/22, Appendix II
5. Alinorm 69/22, para. 18
6. Alinorm 69/67, para. 128
7. Alinorm 76/12, Appendix IV
8. Alinorm 78/12, paras. 12-14
9. Alinorm 81/22, para. 22
10. Alinorm 81/22A, paras. 15-16
11. Alinorm 81/22, Appendix VII, Section 5.5.2
12. Alinorm 81/22, Appendix VII, Section 4.2.2
13. Alinorm 83/22, Appendix V, para. 17 and Annex 1, Section 4.2.2
14. Alinorm 83/22, Appendix V, para. 19 and paras. 22-4
15. Alinorm 83/22, Appendix VI, Section 4.2.1.3
16. Alinorm 85/22, para. 190
17. Alinorm 85/22A, para. 58
18. Alinorm 85/22A, paras. 103-4
19. Alinorm 91/22, Appendix III
20. Alinorm 91/22, paras. 16-19
21. Alinorm 87/22, paras. 53-4
22. Alinorm 91/22, paras. 146-7
23. Alinorm 91/4, paras. 49-50
24. Alinorm 93/22, paras. 50-6
25. Alinorm 94/7, ADD. 1
26. Alinorm 95/22, paras. 98-112 and Appendix V
27. Alinorm 95/2, para. 21
28. Alinorm 95/12A, para. 15
29 Alinorm 95/37, paras. 23-5
30. WHO/FNU/FOS/95.3 Geneva
31. Alinorm 95/37, paras. 27-30
32. Catassi C. Et al.: Celiac disease in the year 2000: exploring the iceberg. Lancet 1994; 343: 200-3.
33. Lessof M.H. Food allergy and other adverse reactions to food. Brussels: 1993 ILSI Europe: 10.
34. Cow's milk allergy said to influence onset of diabetes. Food Labelling News 1995; 36:11-13
35. Alinorm 93/22, Appendix IV: 42-43

APPENDIX I

General Standard for the Labelling of Prepackaged Foods (CODEX STAN 1-1985) in its current form

(extracted Sections)

4.1 The Name of the Food

4.1.1 The name shall indicate the true nature of the food and normally be specific and not generic:

4.2 List of Ingredients

4.2.1 Except for single ingredient foods, a list of ingredients shall be declared on the label.

4.2.1.3 Where an ingredient is itself the product of two or more ingredients, such a compound ingredient may be declared as such, in the list of ingredients provided that it is immediately accompanied by a list in brackets of its ingredients in descending order of proportion (m/m). Where a compound ingredient for which a name has been established in the a Codex Standard or in national legislation constitutes less than 25% of the food, the ingredients other than food additives which serve a technological function in the finished product need not be declared.

4.2.2.1 The following class names may be used for the ingredients falling in these classes[1]:

Name of Classes	Class Names
Refined fats	"Fat" together with either, the term "vegetable" or "animal" as appropriate
All spices and spice extracts	"Spice", "spices" or "mixed spices", as appropriate.
Starches, other than chemically modified starches	"Starch"

4.2.2.2 Notwithstanding the provision set out in Section 4.2.2.1 , pork fat, lard and beef fat shall always be declared by their specific names.

4.2.2.3 For food additives falling in the respective classes and appearing in lists of food additives permitted for use in foods generally, the following class titles shall be used together with the specific numerical identification as required by national legislation:

---

1 Examples only of those listed in the General Standard

Anti-caking Agent; Antioxidant; Colour; Preservative; Enzyme; Preservative; Thickener

4.2.2.4 The following class titles may be used for food additives falling in the respective classes and appearing in lists of food additives permitted generally for use in foods:

Flavour(s) and Flavouring(s); Modified Starch(es)

4.2.3 Processing Aids and Carry-Over of Food Additives

4.2.3.1 A food additive carried over into a food in a significant quantity or in an amount sufficient to perform a technical function in that food as a result of the use of raw materials or other ingredients in which the additive was used shall be included in the list of ingredients.

4.2.3.2 A food additive carried over into foods at a level less than that required to achieve a technological function, and processing aids, are exempted from declaration in the list of ingredients.

APPENDIX II

Proposed Draft Amendments to the General Standard for the Labelling of Prepackaged Foods as currently being considered by CCFL[1]

4.2.1.3 Where an ingredient is itself the product of two or more ingredients, such a compound ingredient may be declared, as such, in the list of ingredients, provided that it is immediately accompanied by a list, in brackets, of its ingredients in descending order of proportion (m/m). Where a compound ingredient (for which a name has been established in a Codex standard or in national legislation) constitutes less than [25% / 5%] of the food, the ingredients, other than food additives which serve a technological function in the finished product and ingredients known to cause allergic or intolerance reactions need not be declared.

The following foods and ingredients are known to cause hypersensitivity and shall always be declared as such:

[Barley, oats, wheat, triticale and products of these (gluten and starch included);

Crustaceans, shellfish, and products of these;

Egg and egg products;

Fish and fish products;

Legumes, peas, peanuts, soybeans and products of these;

Milk and milk products (lactose included);

Sulphite in concentrations of 10 mg/kg or more; and

Tree nuts, poppy seeds, sesame seeds and products of these.]

4.2.2.1 Except for those ingredients listed in section 4.2.1.3 and unless a general class name would be more informative, the following class names may be used..... (remainder of section as is)

4.2.3.2 A food additive carried over into foods at a level less than that required to achieve a technological function, and processing aids, are exempted from a declaration in the list of ingredients. The exemption does not apply to food additives and processing aids listed in section 4.2.1.3 .

---

1 Proposed amendments are underlined. The presence of square brackets indicates material still not finalized and which will be reviewed at the next Session

ANNEX 5

FAO CONSULTATION ON FOOD ALLERGIES
AREAS TO CONSIDER

As noted during the opening remarks, FAO would like to have recommendations from the consultation in three major areas. These are:

1. **Criteria to determine which substances should always be declared on a label**

   As noted in the Codex paper, the Codex Committee on Food Labeling (CCFL) will be considering a change in the General Standard for Labelling of Prepackaged Foods to include a mandatory listing of foods and ingredients which "are known to cause hypersensitivity" and which "shall always be declared as such". At the 1995 meeting of the Codex Alimentarius Commission (CAC), the Commission reaffirmed the role of science in any Codex decision-making processes. This means that any modifications of the general labelling standard by the CCFL must be based on scientific criteria and assessments. The CCFL has asked the Codex Committee on Nutrition and Foods for Special Dietary Use (CCNFSDU) for assistance in establishing such criteria.

   That listing of allergenic foods and ingredients should be dynamic in that substances can be added (or deleted if sufficient reason is found). Therefore, the criteria used to establish the original listing, should also be usable when it is deemed necessary to modify the listing in the future. This consultation could contribute some valuable insights into this area by recommending what scientific criteria should be used.

2. **Approach to class naming conventions for allergenic food products**

   On the surface this appears to be a relatively simple matter, but in reality is a very complex issue. In the proposed change to the general labelling standard, the CCFL proposes to list allergenic foods and their products. In Appendix II of the Codex paper, the proposed draft amendment lists, for example, "..soybeans and products of these..". For labelling purposes the question then becomes, what is a "soybean product"? Many food products may be made into additives or ingredients which are most often listed by their technological use rather than by the food they are derived from. In the case of soya, for example, Dr. Steinman's paper indicates that soya products are often declared as "vegetable protein", "hydrolyzed protein", "lecithin" or simply "emulsifier". None of these product names even hint at the original food source, namely soybeans.

   The problem then is, what approach(es) may be used to identify, for labelling purposes, those food ingredients or additives which are derived from allergenic foods and which are themselves allergenic?

3. Labelling requirements for allergenic components of composite ingredients

One other major change in the general labelling standard being considered by the CCFL is a reduction of the so-called "25% rule" to 5%. This refers to composite ingredients of a food which may be comprised of one or more allergenic components. The present general labelling standard states that if a composite ingredient is less than 25% of the food total, then individual components of that ingredient do not have to be listed on the label. This can obviously result in a significant amount of an allergenic component being present in the finished food, but not declared on the label. The proposed reduction of the 25% level to 5% accompanied by the mandatory listing noted in 1 above, is an attempt to address this problem.

On the face of it, a reduction of the 25% level to a lower level such as 5%, would seem to be both necessary and reasonable. The difficulty, however, is in the determination of what specific scientific considerations should be made to arrive at what the new lower level should be. These considerations must balance the obvious health requirement (the prescence of an allergenic substance) with the current technological limitations of the food industry as they relate to labelling. Health requirements would of course include such defining parameters as nature of the allergen, prevalence in the population, levels in the diet which trigger symptoms, and the severity of those symptoms.

D/W 0724