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(37th series)

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food science and techniques

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(37th series)

Report of the Scientific Committee for Food on:
Adverse reactions to food and food ingredients

Opinion of the Scientific Committee for Food on:
Mineral and synthetic hydrocarbons

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EFTA/EEA Observer

J. ALEXANDER

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J. BOUSQUET

W. GRUNOW

T. HALLAS-MØLLER

E. HELLER

E. NAUGHTEN

S. O'HAGAN

E. POULSEN

J. WARNER

REPORT ON ADVERSE REACTIONS TO FOODS AND FOOD INGREDIENTS

EXPRESSED ON 22 SEPTEMBER 1995

Summary

1. The Scientific Committee for Food was asked to prepare a report on Adverse Reactions to Foods and Food ingredients taking into account the identity of those foods, food components and food ingredients which are associated with adverse reactions to food. This report does so and also attempts to characterise the adverse reactions frequently observed allowing considerable latitude in the meaning of the term 'adverse reactions'. The report also attempts to examine the frequency of such adverse reactions and to comment on their geographic distribution and public health significance.

2. The report presents a series of definitions which apply to the many allied and sometimes overlapping terms used in this topic. The broadest term 'Food Intolerance' excludes psychologically-mediated reactions and includes those of both an immunological and non-immunological nature. The latter may be related to an enzyme deficiency, to a pharmacological reaction or, as in the majority of cases to unknown causes. The term 'Food Allergy' always implies an immunological basis to the adverse reaction. The term 'Food Aversion' implies a psychological dimension which may overlap with an existing or former immunologically-based adverse reaction.

3. Food allergy, that is an adverse reaction involving the immune system, is often difficult to diagnose. The adverse reactions range from relatively rare life-threatening allergic reactions to far more commonplace adverse reactions which, while not being life threatening, lead to illness and reduced quality of life. While allergic reactions can occur with any food or food ingredient some are more common than others. This, however, requires qualification since focal, geographically isolated clusters of an allergy to a specific food can occur.

4. Common food allergens include cow's milk, fruits, legumes (especially peanuts and soybean), eggs, crustaceae (shrimps, crab, lobster and cray-fish), tree nuts (almonds, walnuts, hazelnuts, Brazil nuts etc.), fish, vegetables (celery and other food of the Ombelliferae family), wheat and other cereals. Some food allergens can be destroyed by cooking or storage while others are resistant to such. Food processing and the introduction of new food technologies may help create allergens.

5. The dose of food allergen required to induce an immunological reaction varies but in many instances is extremely low, particularly so for the life-threatening allergies. Accordingly, process contamination can introduce very low levels of an allergen to a food which in the case of certain allergies can be life threatening. This poses one of several problems for consumers who must read food labels because of their life-threatening allergic disorders. Such individuals are advised to be very circumspect about their use of processed foods. Problems also arise because of cross-reactivity of allergens. For example, patients with allergic reactions to inhalant allergens such as pollens may also become allergic to foods from plants other than those from which the inhalant pollen allergen originates. Allergies to latex are on the increase among health professionals because of increased haematological safeguards and contact allergy to latex may subsequently lead to allergic reactions to kiwi fruit, chestnut or banana.

6. The diagnosis of food allergy is difficult and may involve skin tests, food challenge, elimination diets and serum tests or combinations of all four and other possible approaches. In general, the diagnosis of food allergy involves extensive clinical consultation. Whereas widely publicised and simple procedures are available, treatment should only follow detailed clinical, immunological and dietetic investigations.

7. Food additives have only seldom been found to cause food allergy, that is adverse reactions involving an immunological aspect. Non-immunological based food intolerance is more common place with food additives. Sulphite-induced asthma is well documented but eczematous and urticarial reactions to sulphite are also well documented although the exact mechanisms remain unclear. Adverse reactions have also been recorded with tartrazine and with non-azo colours, with aspartame, monosodium glutamate, benzoates and several other additives. However, the prevalence is quite low.

8. Coeliac disease is an enteropathy due to an abnormal immune reaction to the wheat protein gluten. It may be considered as a form of food allergy but it is not IgE-mediated. The gluten-free diet remains the basis of the treatment, restoring health totally.

9. Inherited metabolic disorders arise from a single gene defect which leads to a deficiency of an enzyme and in so doing creates a metabolic imbalance. For example, phenylketonuria (PKU) results from a mutation of the gene responsible for coding for phenylalanine hydroxylase leading to variable levels of phenylalanine in the blood. Dietary management to reduce phenylalanine intake is the only recourse for the management of the disease.

10. The prevalence of food allergy and or food intolerance has been studied in only a few prospective studies in which the presence of food allergy is confirmed in double-blind, placebo controlled exposure studies. Studies of cow's milk allergy put the prevalence at 1 - 3%. A large Dutch study of 1483 adults found a prevalence of food intolerance of 2.4%. Two persons reacted to food additives giving a prevalence of 1.3 per 1000. Among 5000 adults studied in France only 1.3% had a positive skin test to one food type and of these only half suffered symptoms. A UK study of 7000 households found that about 1 in 5 adults reported a food intolerance but with double-blind, placebo controlled challenge, the prevalence fell to 14 per 1000. Some 7.4% of the overall sample reported an adverse reaction to food additives but the level confirmed by double-blind, placebo-controlled challenge was as low as 13 per 10,000. In a Danish study, 335 atopic children aged 4 - 15 years were questioned about hypersensitivity and 22.7% implicated food additives. An open challenge with food additives reduced this figure to 6.9% and a double-blind challenge reduced this further to 1.8%. A second and similar study investigated 173 children reporting hypersensitivity. In an open challenge with food additives 9.8% revealed a positive reaction while a double blind challenge of twelve of these positive children reduced the prevalence to 3.5%. The combined results revealed a prevalence of 2% with open challenge and the double blind challenges would indicate the true prevalence of intolerance to food additives to be 1%.

11. The prevalence of food allergy is highly dependent on geographical area. In areas where sensitivity to birch and mugwort pollen are prevalent, 30 to 50% of these patients present 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 but since this food has been widely marketed throughout Europe it is now a major allergen both in the US and Europe. Shrimp allergy is common in Southern USA, fish allergy is common in the Nordic countries and 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.

12. In conclusion, the true incidence of food allergy, while low and usually being under 1% of the population, is still such as to affect the lives of many people with conditions ranging from very mild to potentially fatal.

Terms of reference

Against the background of discussions in Codex Alimentarius and consultations between the Commission and Member States of the European Union on the question of labelling food ingredients to which some individuals may exhibit adverse reactions, the Working Group on Nutrition of the Scientific Committee for Food was asked to report on the subject paying particular attention to the following factors:

- the identity of those foods, food components and food ingredients which are associated with adverse reactions in consumers together with a characterisation of the adverse reactions concerned (adverse reactions in this context should include allergic reactions, reactions resulting from genetic and/or metabolic disorders and reactions of the type generally referred to as "intolerance").

- the geographic distribution and frequency of adverse reactions within different sub-groups of the population of the European Union.

- the severity and significance for public health of the adverse reactions identified

Background

Individuals exhibit enormous variation in food preferences with factors such as taste, age, ethnic and cultural background, health beliefs and food availability all playing a role. In human nutrition, it is now widely held that a less-than-optimal balance of nutrients may contribute to an increased prevalence of risk factors for chronic disease. To that end, many efforts are being made to increase "health beliefs" as a significant factor in determining food preference. However, for very many individuals, the expression of a preference for a given food or of an aversion to another food on the basis of health beliefs is more likely to be associated with putative or true adverse reactions to specific foods or specific food ingredients than with risk factors for chronic disease. In public health terms, at the level of the population, a less-than-optimal balance of nutrients is a far more significant issue than that of putative or true adverse reactions to foods. In health terms, at the level of the individual however, adverse reactions to specific foods can be of considerable importance ranging from chronic suffering of non-life threatening conditions to the risk of sudden death. In this latter spectrum of conditions the adverse effects range from subjective psychological effects (depression, lethargy, anxiety) and subjective physical effects (nausea, headache, dizziness) to objective psychological effects (depression, hyperactivity) and to objective physical effects (urticaria, asthma, eczema etc.). The underlying cause(s) of these conditions with their origins in food or food ingredients also cover(s) a wide spectrum from unknown cause to causes arising from psychological, pharmacological, metabolic and immunological factors.

Against this background, the committee was concerned to consider the issue in the context of its significance in regulatory decisions relating to food labelling. Moreover, the committee did not confine itself largely to food additives as was the case in an earlier report of the Scientific Committee for Food (Twelfth Series). Thus, within the wide spectrum of adverse reactions to food real or imagined, the Committee, given its terms of reference, confined itself largely to the following health issues:

Food allergy

Adverse reactions to food additives

Coeliac disease

Inherited metabolic disorders

However, other conditions were considered where, in the opinion of the Committee, they were of significant public health concern and at the same time were related to the issue of food labelling. In each section of this report consideration is given, where possible, to definitions, symptoms, diagnosis, foods and food ingredients implicated, prevalence and management. Prevalence of adverse reactions to food and food ingredients is considered as a separate section.

In the case of defining prevalence, however, there are particular problems which merit consideration in this introduction. Because adverse reactions to foods can be clustered in distinct groups determined by occupation, geography, leisure activity, age, genotype and underlying health characteristics, average population prevalence rates may say little of the rate prevailing in the cluster of the population particularly susceptible to an adverse reaction to a food or food ingredient. Thus for example, it is not possible to say on a European Union basis, the likely average prevalence of an adverse reaction to a food where the food in question is consumed in a specific geographic region. Equally, to consider the overall population prevalence of, for example food, allergy may fail to take account of a much higher prevalence rate among atopic individuals, who, because of their disorder of the immunological system, suffer reactions to many environmental factors, from pollen to pets. Inherited metabolic disorders can be very rare in the European Union as a whole or in specified member states, but particularly high in nation sub-groups. For example, galactosaemia occurs with a frequency of 1 per 20,000 in Ireland but has a frequency of 1 in 700 of Irish Travellers.

Case histories, while informative, do not assist in defining prevalence rates. Epidemiological surveys by questionnaire of representative samples regarding adverse reactions to food are also of limited value since they can only report perceived or putative adverse reactions to foods. Subsequent double-blind placebo-controlled challenges may be the only way of verifying true adverse reactions to food at the level of the individual but are limited in estimating the prevalence of true adverse reactions to foods because not all individuals reporting in large surveys to be sensitive to a food agree to participate in a double blind challenge. This can be illustrated by a UK study which will be alluded to later in this report. Of 18,582 subjects who answered a postal questionnaire on perceived reactions to food and drink, 1372 (7.4%) reported problems with food additives. Of these 1,233 were invited to attend for a further oral questionnaire of which 649 agreed. However, only 81 of these were subject to a double-blind challenge of which three were positive, suggesting a true prevalence of 3 per 10,000.

In reviewing this issue in the context of food labelling, the Committee was not asked to make specific recommendations but rather to prepare a document which might subsequently assist in regulatory decisions on food labelling.

Definitions

For the purpose of this report, the following definitions apply:

Adverse reactions:

Represent a very wide spectrum of reactions to foods.

Food intolerance:

Non-psychologically mediated untoward reaction induced by a foodstuff, 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).

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.

Atopy:

The propensity, usually genetic, for developing IgE-mediated responses to common environmental allergens.

Food allergy or food hypersensitivity:

Untoward reaction due to an immunological mechanism induced by a foodstuff.

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[1].

Food induced symptom:

Symptom caused by an adverse reaction to a foodstuff whatever mechanism is involved (immunologic and non-immunologic).

Symptom with food allergy:

Patient presenting a given symptom and an allergy to a foodstuff, 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:

The number of subjects with the disease at any time during their life, whatever their health status at the time of the study.

Food allergy

Introduction

Allergic or food hypersensitivity reactions are those that result from an immune event and represent in reality a group of distinct clinico-pathologic entities[2]. The best known example of such reactions is IgE-mediated food anaphylaxis but other types of hypersensitivity reactions have been linked to food allergy. As an example, reactions of delayed hypersensitivity also account for at least some of the intestinal problems which occur in coeliac disease[3].

Food allergy has always posed a difficult problem, especially in adults. That food allergy exists 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[2] but the diagnosis of an allergic reaction to foods is often difficult. Life-threatening immediate reactions appear to be rare but are apparently increasing in prevalence and are usually easily diagnosed, whereas reactions which cannot be related to an obvious immune response are 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[4] 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[5]. 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[6].

Symptoms of food allergy

Food allergy can elicit almost any allergic symptom and sign but some are more common and more widely demonstrated[7]. Symptoms can occur immediately after the ingestion of the offending food (acute urticaria or anaphylaxis) but they may be delayed several hours in the case of atopic dermatitis. Patients may present a single symptom but often there is a multi-organ involvement, including cutaneous, respiratory, gastrointestinal and ocular reactions. In particular, most patients with asthma due to food allergy present an atopic dermatitis[8].

The link between food allergy and the occurrence of adverse reactions is well established for a number of these symptoms. This is the case with urticaria / angioedema and (more rarely) chronic urticaria[9], atopic eczema (atopic dermatitis is more often caused by food allergy in children than in adults[10], conjunctivitis, laryngeal oedema, Lessof's syndrome[11], acute gastrointestinal reactions following the ingestion of specific food[8,12] and of course asthma[13]. Anaphylactic reactions, eventually causing death, and exercise-induced anaphylaxis[14-16] are also as a general rule easily attributed to food allergy.

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[17]. On the other hand, food allergy has been rarely demonstrated in "hyper-reactivity" and tension-fatigue syndrome[18], in dysuria, arthritis[19] and in a series of poorly defined digestive symptoms including protein-losing enteropathy. Food allergy was also supposed to be a major cause of migraine[20] but, when the appropriate tests were performed it was observed that food allergy was rarely involved[21].

Food allergens

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.

Cow's milk

Cow's milk protein allergy is relatively common in infancy. It occurs in up to 2% of infants but its prevalence decreases with age. Allergy to cow's milk is mainly an IgE-mediated allergic reaction but other immune mechanisms have been identified[22]. 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[23]. 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[24]. 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[25]. 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, κ-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[26]. 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[27,28]. However, even for whey proteins, the thermic shock necessary to reduce significantly protein allergenicity would induce a Maillard reaction and their nutritional value would be reduced to an unacceptable extent[29]. 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[26]. Filtration can also be applied to remove remaining high molecular-weight peptides and residual proteins, and some ultrafiltrated whey hydrolysates have been developed[30].

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[25,29]. 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 test with hypoallergenic formulae do not correlate necessarily with symptomatic reactivity, suggesting that skin prick tests alone are not indicative of hypersensitivity to extensively hydrolysed formulae[31,32]. 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[25,33], and anaphylactic reactions to these highly processed hydrolysates infrequently reported[34,35]. 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 ultra filtered whey-based formula) were proven "hypoallergenic"[29,31] according to the guidelines of the Subcommittee of Nutrition and Allergic Diseases of the American Academy of Pediatrics[36].

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[31] can cause allergic reactions[35,37]. Consequently, partly hydrolysed formulae should be avoided in allergic infants[25,38].

Other common food allergens

Among the major sensitising foods are fruits, legumes (especially peanuts and soybean), eggs, crustaceae (shrimps, crab, lobster and crayfish), tree nuts (almonds, walnuts, hazelnuts, Brazil nuts etc.), fish, vegetables (celery and other foods of the Ombelliferae family), wheat and other cereals[39-41].

The allergenic activity of some food allergens is destroyed by heating or during storage (e.g. in apples[42]) whereas others are resistant to denaturing including cooking and digestion (casein, egg and fish antigens).

The problem of trace amounts of allergenic foods in processed foods is a matter of unresolved concern. This deserves further investigations since although very rare, trace amounts of allergenic proteins can be found as contaminants in foods such as oils[43]. 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, 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.

Food allergens which cross-react with inhalant allergen

Patients with allergic rhinitis/conjunctivitis to birch and to a lesser extent to other Betulaceae (hazel, alder) pollen are frequently hypersensitive to nuts, fruits including apple, carrots and potatoes[44,45]. 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 [46] or various nuts[47]. Most of the patients with food hypersensitivity are those with a severe allergy to pollens[44]. Some Compositeae pollen allergens (mugwort) cross-react with foods of the Ombelliferae family (celery in particular)[48]. Although IgE fractions to food allergens are highly prevalent in patients allergic to Betulaceae and Compositeae pollens, only a proportion of these present symptoms of food allergy[49]. Ragweed (*Ambrosia* pollen) sensitive individuals may get symptoms when eating banana or melon.

Allergy to latex has been booming recently because of the overwhelming use of latex gloves by medical and paramedical professionals[50] and its extensive use in many appliances such as catheters. Cross reactive antigens have been identified between latex and banana, chestnut or kiwi fruit[51].

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 difficult because allergen extracts currently available are not standardized, and their stability is poorly determined[52]. For allergen extracts that are rapidly degraded like those of fruits and legumes, skin tests may be falsely negative in food allergic individuals. Even more so than in inhalant allergy, the presence of food-IgE in serum or a positive skin test to a foodstuff does not always correlate with a food allergy since (i) many patients outgrow their allergy with age[53,54] 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 absolutely no 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 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 incriminate 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[55].

Anamnesis

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 ciguaterra poisoning[8].

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 were shown to be slightly more sensitive than skin prick tests, they also cause more non-specific positive reactions and may 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[56]. 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[55,57,58], 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 of its subclass 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[59], or Sampson *et al* [57]. The food suspected as causing symptoms should be eliminated from the diet for a minimum of 2 weeks before testing. Although patients who had presented anaphylactic symptoms should not be tested, it is advised to start with a very small dose and increase them slowly and carefully. 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 hr following challenge since late reactions can occur[55]. Bronchial hyperresponsiveness to methacholine or histamine may be measured before and after challenge. 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[60]. During all challenges a physician should monitor the patient since some untoward systemic reaction might occur.

Food challenges may be improved by measuring the release of mediators in peripheral blood[61] or the increased gut permeability[62] or 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 in that some patients only develop an increase of bronchial responsiveness to histamine after a food challenge without any change in baseline peak flow.

A positive food challenge, indicative of food intolerance, does not necessarily imply that the patient presents an IgE-mediated allergy. 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 relapse on open challenge. However, only two of the 21 reacted on subsequent double-blind challenge[63].

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 the 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 asthma 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 disappearance rate depends on the allergen and on individual factors[22,53,54,64-67]. 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, shellfish, nuts and peanut does not disappear in most patients although it may be less severe.

Clinical 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[68]. 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 milk are not suitable alternatives as they are equally likely to produce allergic reactions due to cross reactivity[69]. Finally, it has been proposed to reduce allergenicity of foods by removing potent allergens[70] or by hydrolysing the foodstuffs[33,37,71]. The efficacy of medications has been demonstrated in some but not all trials.

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[72].

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

Prevention of food allergy is a difficult matter and although a large number of studies have been carried out, there are no convincing data demonstrating the efficacy of interventions. There is much evidence that the development of allergic disorders may be related to early exposure to allergens, including those in breast milk 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 it only delays the onset of allergic symptoms. Moreover, although the effect of breast feeding has been observed in delaying the onset or reducing the severity of atopic dermatitis, no evidence of any effect was found on asthma or later allergic disorders[73,74]. Allergenic foods including cow's milk can be found in breast milk and these foods can induce an IgE-mediated senstization of the new-born[75]. Mothers reducing ingestion of highly allergenic foods during breast feeding may improve the preventive efficacy of breast feeding but data are conflicting[76,77]. "Hypoallergenic" infant formulae may also be preventive but more data are needed to better evaluate their real value[33,37]. Finally, it seems appropriate to delay for a period of four to six months the introduction of solid foods which may sensitise new-borns and young infants[78,79]. However, the cost-benefit and quality-of-life effects of such interventions have not hitherto been subjected to any prospective study.

Adverse reactions to food additives

Introduction

There are many agents that are intentionally added to the food that we consume. These include preservatives, stabilisers, conditioners, thickeners, colourings, flavourings, sweeteners, antioxidants, etc. Yet, only a surprisingly small number have been associated with hypersensitivity reactions but there is ample evidence that food additives of several sorts may precipitate adverse reactions[80]. Only seldom have food additives been shown to cause true allergic (immunological) reactions. Adverse effects due to various pharmacological or other mechanisms are much more common[81]. Many patients suffering from food additive reactions have atopic constitutions and such clinical symptoms as atopic dermatitis, rhinitis and asthma[82,83]. Some of the adverse reactions may be fatal such as sulfite sensitivity in asthmatic patients but reactions to other food additives are unusual and less severe. The most important skin symptoms caused by food additives are urticaria, angioedema, and contact urticaria. Hypersensitivity reactions in organs other than the skin and respiratory tract are rare or poorly documented. While popular belief has it that additives may have harmful behavioural effects, and despite a large number of studies which have evaluated the role of food additives in hyperkinesis, results are not uniform. Some studies have suggested that there was some link between food additives and hyperkinesis[84,85] but when the studies have been more carefully carried out the demonstration of such interaction was not confirmed[86]. Evidence does suggest that there is a very small subset of primarily younger children in whom additives will impact on behaviour[87,88]. Psychological factors play an essential role in both food and food additive reactions[1].

Suspected food additive sensitivities are best documented by oral challenges, preferably in a double-blind placebo-controlled manner since many patients react under placebo[89]. Challenges in asthmatic patients need to be done with patients continuing on their routine medications to avoid false positives. All care should be taken to titrate the doses and schedule the doses appropriately, since several of these agents could provoke large reductions in pulmonary function. With urticaria patients, an adequate baseline of urticaria activity needs to be established before the challenges so that fluctuations in normal activity are not construed as a positive result. As with asthma, the problem appears to be much smaller than originally postulated[90].

Restricted diets are of no general benefit in asthmatic patients: In contrast to asthma, in urticaria or other cutaneous reactions to food additives, a restricted diet for a few months' duration may be beneficial, although the mechanism through which this is achieved is unclear[90]. However, food additive avoidance is often difficult to be carried out since not all additives may be labelled and when intolerant patients are eating in a restaurant it is impossible to determine which additive is in the food ingested.

Intolerance to sulfites

The term sulfiting agents is used to describe sulfur dioxide (SO_2) and several inorganic sulfites (sodium sulfite, potassium bisulfite and metabisulfite) that may be added to foods, beverages and pharmaceuticals. Sulfiting agents are used to control microbial growth in fermented beverages and have been widely used in the food and beverage industry for over 2,000 years. They have been shown to frequently trigger attacks of asthma[80] and more rarely other symptoms. Sulfites are also used in drugs and those administered by inhaled route have caused several asthmatic reactions[91]. Moreover, it seems that dental local anaesthetics preserved with sulfites have induced asthma in some patients[92].

Despite the increasing amount of data that has accumulated on sulfites as the intensity of medical interest has expanded in recent years, there are lingering, difficult, and, in most cases, as yet unresolved questions about sulfite sensitivity. These include questions about mechanism of action, prevalence and the most effective methods for protecting sulfite-sensitive patients from exposure to sulfites[93].

Mechanisms of sulfite intolerance

The exact mechanism of sulfite sensitive asthma is unknown but most likely involves hyperreactivity to inhaled SO_2 in the great majority of cases[80], however, there are reports of IgE mediated reactions[94] and other sulfite sensitive asthmatics have been found with low levels of sulfite oxidase[95]; necessary to oxidise endogenous sulfite to sulfate. It is possible that patients with sulfite-induced urticaria present more commonly an IgE-mediated reaction.

Sulfite-induced asthma

Most patients with sulfite-asthma have severe chronic asthma, often corticosteroid-dependent[80]. Usually, but not always, the patient is non-atopic but may suffer from chronic vasomotor rhinosinusitis. These individuals are differentiated from aspirin-sensitive asthma because they lack nasal polyps and eosinophilia. However, some aspirin sensitive asthmatics present also a dyspnoea after ingestion of wine or foods containing sulfites[96,97]. Fatal asthma has been reported after ingestion of sulfite-containing foods or drinks. There is no link between sulfite sensitivity and the degree of airways hyperresponsiveness[98].

Due to the lack of reliable skin or in vitro tests, the diagnosis of an intolerance to sulfites is still based on placebo-controlled oral provocation tests. Sulfite-challenge may cause a severe asthmatic reaction so it should be carried out by trained investigators and when the patient is in a stable state.

A screening challenge should be conducted in a single-blind, open fashion, and when positive, confirmed by a double-blind challenge[99]. Doses of ingested sulfites should be increased cautiously. However, sulfite-sensitive subjects with asthma will not necessarily react after ingestion of sulfited foods. The likelihood of a reaction is dependent on the nature of the food, the level of residual sulfite, the sensitivity of the patient, and perhaps on the form of residual sulfite and the mechanism of the sulfite-induced reaction[100].

Other symptoms

Delayed eczematous and immediate urticarial reactions due to sulfites in foods have been demonstrated[101,102]. However, sulfites represent a rare cause of urticaria[103]. Anaphylaxis-like reactions are exceptionally caused by sulfites[104]. Clinical cases of contact allergy due to sulfites have been observed[105].

Intolerance to other food additives

Tartrazine, azo and non-azo food colours

All food colours contain aromatic rings and some contain azo-linkage. Tartrazine, sunset yellow and carmoisine are the most widely used azo food colours. Non-azo food colours include brilliant blue, erythrosine and indigotin. Although azo and non-azo food colours have been implicated in a number of anecdotal hypersensitivity reactions, it has been concluded that they are rarely involved[106-108].

Following the study of Samter and Beers, for many years, tartrazine was thought to cross-react with aspirin and to cause asthma[109]. However, it has now been demonstrated that tartrazine is not a cyclooxygenase inhibitor[110] and several double-blind placebo-controlled challenges with tartrazine in aspirin-intolerant asthmatics have led to the conclusion that there was no cross-reactivity between cyclooxygenase inhibitors (aspirin and nonsteroidal anti-inflammatory agents) and tartrazine[108]. Tartrazine may cause asthma by itself but such a reaction is, at most, rare[111,112]. Tartrazine can however cause urticaria, atopic dermatitis or hyperkinesis in an occasional patient but their prevalence is again very small[108,113].

Aspartame

Aspartame is a food additive used as an intense sweetener. Neurologic, gastrointestinal, and allergic reactions have been reported but very few have been eventually confirmed[114,115]. Aspartame will be further discussed under the section on metabolic disorders (section 6).

Monosodium glutamate

Monosodium glutamate (MSG) is one of the most widely used food additives around the world. It has been involved in the "Chinese restaurant syndrome" which consists of the development within hours after a meal of headache, burning sensation along the back of the neck, chest tightness, nausea and sweating[116] and in delayed airways obstruction[117]. The prevalence of this syndrome was as high as 30% in some studies. However, double-blind challenge of individuals who identify themselves as suffering the 'syndrome' has often failed to confirm the role of monosodium glutamate as the provocative agent, and, when some common food materials are used in the same experimental setting, similar symptoms can be produced in a limited number of people[118]. Moreover, it has been observed that the occurrence of urticaria, angioedema or anaphylaxis after meals in Chinese or Indonesian restaurants is more often due to IgE-mediated Type I food allergy, caused by consumption of shrimp, peanut or spices, or herbs in particular those of the parsley family (e.g. coriander)[119]. Finally, glutamate sensitivity is exceptionally occurring in asthmatics[120].

Benzoates and esters of para-benzoic acid

Benzoic acid and sodium benzoate are widely used as antimycotic and antibacterial preservatives in foods and beverages. Esters of parabenzoic acid (parabens), are also used as preservatives in a limited number of foods. Adverse reactions to these compounds in patients who suffer from chronic urticaria have been extensively studied. It is clear that benzoates in foods can cause urticaria in adults (for review see:[121,122]) and in children[123]. However, double-blind placebo-controlled challenges have been rarely carried out and the exact prevalence of benzoate intolerance in chronic urticaria is still unknown, ranging from almost none to over 50%. These differences may be explained (i) by the difficulty to perform reliable challenges and interpret them[124], (ii) by the inability of many patients to confirm the positivity of the challenge by an effective benzoate-free diet , and, (iii) are also related to the day-to-day variability of symptoms.

The prevalence of hypersensitivity to benzoates in asthma is unknown since of the few studies that have been conducted, most were not adequately carried out. However, it is likely that benzoates are rarely inducing asthma[106,125].

Parabens have been shown to elicit IgE mediated hypersensitivity reactions when used as pharmaceutical preservatives; however, as with the other additives noted above, ingested parabens have only occasionally been associated with adverse reactions[122].

Other additives

Although any food additive may induce an untoward reaction, anecdotal reports confirmed by challenge have found some particular reactions. Two cases of chronic urticaria were found to be exacerbated by the antioxidant food preservatives, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT)[126].

Some allergenic enzymes from Aspergillus or other sources have been identified in flour and were shown to cause asthma in bakers but there is apparently no food allergy described.

Coeliac disease

Definition

Coeliac disease is an enteropathy due to an abnormal immune reaction to gluten. It may be considered as a form of food allergy although it is not IgE mediated.

Pathophysiology and genetics

There are evidences suggesting that the characteristic hyperplastic villous atrophy is secondary to an abnormal T-cell mediated response to gliadin, the alcohol soluble fraction of gluten, (and to related prolamines from rye, barley and oats) whose peptides (α, ß, γ and ω) contain 'toxic' sequences (Pro-Ser-Gln-Gln, Gln-Gln-Gln-Pro). This abnormal response occurs in genetically .susceptible individuals, bearing in their vast majority (≥ 90%) the major histocompatibility complex (MHC) DQ (α_1*0501, $ß_1$*0201) heterodimer[127]. In these individuals, some $CD4^+$T cells located in the lamina propria may initiate the pathological process leading to villous atrophy with increased intraepithelial $CD8^+$ and γ/δ TCR^+T lymphocytes.

Features

Although the onset of the disease occurs more commonly in children, nevertheless, adult onset coeliac disease also occurs. In toddlers, coeliac disease remains characterised by a classical malabsorption syndrome with loss of appetite, diarrhoea, loss of weight, abdominal distension, and finally growth retardation. The older the child, the less symptomatic the disease which may manifest merely as short stature in a teenager. Usual blood tests (RBC count, levels of plasma iron, folate, cholesterol, vitamins A and E) may be useful to show the nutritional consequences of malabsorption[128].

Adults usually present with anorexia, abdominal pain, diarrhoea and weight loss; but some present with unsuspected sideropaenic anaemia, folate deficiency, osteomalacia or depression[129].

The disease may be silent and should be looked for among first relatives of patients, in patients with diabetes (prevalence - 3%), IgA deficiency, IgA nephropathy, dermatitis herpetiformis and other immune mediated diseases[130].

Methods of investigations

Although one hour blood xylose test, and permeability tests may be helpful in indicating a proximal intestinal lesion, the best single test to perform before an intestinal biopsy is the assay of the anti-gliadin, -reticulin, or -endomysium IgA and/or IgG antibodies. When the three tests are performed together the positive predictive value of these antibodies is near 100%. Finally, the diagnosis rests on the intestinal biopsy which shows the characteristic hyperplastic flat mucosa[128].

Management

The gluten free diet remains the basis of the treatment, restoring health totally. It is usually a life long prescription. It has been shown in an English cohort that gluten free diet might decrease the risk of malignancies and particularly lymphoma in adults who adhere to it during more than 5 years[131]. The increased risk of malignancies, well shown in several former American, English and Swedish series, is not found in a recent Finnish study concerning adult patients supposedly following a gluten free diet in the proportion of 85%[132].

Inherited metabolic disorders

Introduction

Over 300 human diseases due to inborn errors of metabolism are now recognized, and this number is constantly increasing as new concepts and techniques become available. Until recently certain of these hereditary metabolic disorders (and in particular overload disorders) were untreatable. Progress made in (bone) marrow transplants or enzyme replacement therapy have, however, enabled encouraging results to be obtained in certain cases and high hopes are being entertained for gene therapy in order to compensate for enzyme deficits where no other form of treatment is available[133].

For many of the inherited metabolic disorders there is some scope for dietary management, whether this involves removing a source of carbohydrates from the diet (e.g. galactose in galactosemia or fructose in fructosemia), reducing fat intake as in certain fatty-acid-metabolism disorders, reducing overall protein intake, or specifically restricting the intake of certain essential amino acids (e.g. phenylalanine in phenylketonuria or branched-chain amino acids in maple syrup urine disease,

methylmalonic acidemia or propionic acidemia). The use of pharmacological doses of thiamine, pyridoxine or biotin may also constitute an effective treatment for vitamin-dependent disorders where the mutation in question affects the link between an enzyme or receptor with its co-factor[133].

Three inherited metabolic disorders are to receive special attention as part of food intolerance owing to the ubiquitous nature of the nutriments involved, their toxicity for the sufferers of deficits and, consequently, of the need to inform patients or their families of the presence or otherwise of these components in prepacked foods. Those disorders are phenylketonuria, galactosemia and fructose intolerance.

Lactose intolerance, which is very widespread among certain ethnic groups, is not as a rule due to a structural anomaly in a gene as in exceptional congenital lactose intolerance, but to deficiency of lactase synthesis after weaning, as normally occurring in practice in all mammalian species in which lactose is the main sugar in their milk[134,135]. It therefore does not strictly count among the innate metabolic malfunctions. The problems thus caused for victims are, moreover, of quite a different type since they manifest themselves via signs indicating intestinal fermentation (swelling, abdominal pains, or even diarrhoea) where excess lactose is ingested, but not via toxicity to the liver and/or brain as in the case of galactose, fructose or phenylalanine in patients suffering from galactosaemia, hereditary fructosemia or phenylketonuria respectively.

Phenylketonuria

Phenylketonuria (PKU) is caused by the mutation of the phenylalanine hydroxylase gene which suppresses the activity of the enzyme either fully (or almost so). More than 200 mutations have been recognized[136] which to varying degrees affect synthesis of the enzyme, its stability or catalytic site.

A random distinction can be drawn between three types, which differ via the degree of enzyme deficit, and whose repercussions on mental development are not the same: (i) classic PKU whereby the residual activity of the liver is less than 1% of normal, and which manifests itself via an increase in the level of plasma phenylalanine, upstream of the block, above 1.2 mmol/l (20 mg/100 ml) and a tolerance of less than 350-400 mg of phenylalanine/day in the diet; (ii) mild PKU whereby phenylalanine hydroxylase activity of roughly 1-3% persists and which is characterised by a phenylalaninemia lying between 0.6 and 1.2 mmol/l (10-20 mg/100ml) and a tolerance lying between 100 and 750mg of phenylalanine/day; (iii) moderate permanent hyperphenylalaninemias which corresponds to residual activities of more than 5% of the normal and whereby, by definition, the phenylalaninemia does not exceed 0.6 mmol/l (10 mg/100 ml) when a normal diet is followed. Where there is no neonatal screening and early treatment, only classic and mild PKUs involve a risk of mental retardation. The frequency of these forms to be treated varies within the European Union. The estimates are 1/4 500 in Ireland, 1/8-10,000 in Denmark, 1/10,000 in Belgium and 1/16,500 in France[136-138].

Phenylalanine represents, on average, 4-5% of the amino acids in all food protein. A normal diet (2-3g of proteins/kg bw) thus supplies roughly 1250mg to a one-year old child and almost twice this in a five-year old child, whereas the tolerance of the victims, which only increases very slightly with age, is several times lower than these values in the most severe cases. This situation demands the use of amino acid mixtures that contain no phenylalanine, but which are tyrosine enriched (tyrosine is essential in the absence of phenylalanine), or of protein hydrolysates from which most of the phenylalanine has been removed, for example by means of adsorption on activated charcoal. The nitrogen requirements and those for the other essential amino acids may thus be met, and the phenylalanine that is necessary for growth is basically obtained from fruits and vegetables.

Restriction of phenylalanine intake in amounts which enables the phenylalanine plasma level to be kept below 0.4 mmol/l (7 mg/100 ml) throughout life, or at least until adolescence, allows normal (or quasi normal) physical and intellectual development to take place in the children afflicted[138,139]. Aspartame which is a dipeptide made up of aspartic acid and phenylalanine is used as an intense sweetener to substitute sucrose in a whole range of "light" beverages and low-calorie products (e.g. yoghurts). It may constitute a significant source of phenylalanine for patients and prevent satisfactory checking of their rate of plasma phenylalanine[140,141]. It is therefore important that they be informed of this, and it would be highly desirable for an appropriate warning to have to be entered on the labels for food products containing these, as is already the case in certain Member states.

Fructosaemia

Three inherited abnormalities of fructose metabolism are known. Two of these are caused by a defect of one of the enzymes of the specialised fructose pathway: essential fructosuria and hereditary fructose intolerance - the former a harmless and the latter a potentially lethal condition. All three defects are inherited as autosomal recessive traits. Hereditary fructose intolerance is characterised by severe hypoglycaemia and vomiting shortly after the intake of fructose. Prolonged fructose ingestion in infants leads to poor feeding, vomiting, jaundice, haemorrhage, proximal renal tubular syndrome, and finally, hepatic failure and death. Patients develop a strong distaste for noxious food. Therefore, a chronic course is observed only in preschool-aged children. Fructose 1-phosphate aldolase of liver, kidney cortex and small intestine is deficient. Hypoglycaemia after fructose ingestion is caused by fructose 1-phosphate inhibiting glycogenolysis at the phosphorylase level and gluconeogenesis at the mutant aldolase level. Patients remain healthy on a fructose- and sucrose-free diet.

Galactosemia

Three inherited disorders of galactose metabolism have been described. The genetic disturbance (autosomal recessive) is expressed as a cellular deficiency of either galactokinase, galactose 1-phosphate uridyl-transferase or uridine diphosphate galactose 4-epimerase, which convert galactose to glucose. The clinical manifestations in infants are toxicity syndromes resulting from exposure to galactose. Toxicity symptoms include cataracts inanition, failure to thrive, vomiting, liver disease, cataracts, and developmental delay. Despite initiation of a lactose-free diet, which alleviates the acute toxicity, there are long-term complications in transferase-deficient patients. These consist of poor growth, speech abnormalities, mental deficiency, neurologic syndromes and ovarian failure in females.

Prevalence of adverse reactions to food

Prevalence of food allergy and putative food allergy

Although there is a better recognition of food allergy, its real prevalence has only been investigated in very few studies. Prospective, population-based studies are required to assess the true incidence of food-allergic diseases. The rate of food intolerance or of food allergy 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%[142]. However, when appropriate tests are used this percentage decreases sharply[143,144].

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%[145]. It seems, however, that a more realistic rate is ranging from 1 to 3%[146-149]. This variation mainly reflects differences in criteria for diagnosis, differences in study design, and possibly differences in diets accounting for geographical differences. Moreover, in many studies, allergy and non-immunologic intolerance was not differentiated[150-152].

A survey of 1,483 Dutch adults[143] revealed that the prevalence of perceived food additive intolerance/allergy was 1.6% with 13.3% reporting intolerance/allergy to any foodstuff. Of the 198 subjects with self-reported food intolerance/allergy 90 were subjected to clinical histories and to skin-prick testing. Of these, 54 had possible allergy or intolerance to foods (i.e. 3.6% of the population). Based on further investigation involving elimination diets and open food challenge, adverse reactions to foods could only be confirmed in 25 (1.7% of the population). Double-blind, placebo-controlled food challenge reduced the number to 12 or 0.08% of the population. Only two of these subjects had an adverse reaction to food additives giving prevalence of 13 per 10,000 of the population.

In a Danish study, 335 atopic children aged 4-15 years were questioned about hypersensitivity and 22.7% implicated food additives. An open challenge with food additives reduced this figure to 6.9% and a double-blind challenge reduced this further to 1.8%. A second and similar study investigated 173 children reporting hypersensitivity. In an open challenge with food additives 9.8% revealed a positive reaction while a double blind challenge of twelve of these positive children reduced the prevalence to 3.5%. The combined results revealed a prevalence of 2% with open challenge and the double blind challenges would indicate the true prevalence of intolerance to food additives to be 1%[153].

A survey of 18,582 subjects in the UK showed that 7.4% had a perceived adverse reaction to food including food additives with 1.4% reporting an adverse reaction only to food additives[154]. Of those who reported an adverse reaction to food additives, 89.1% indicated their willingness to attend for a further interview. Of the 649 who attended for interview, 132 subjects were submitted to a clinical evaluation of adverse reactions to food additives of which 81 completed the trial. Of these 81, three showed consistent reactions to low or high doses of food additives. On that basis, the population prevalence to food additives was put at 0.026% or about 3 people per 10,000 of 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[155]. The prevalence of positive skin tests to inhalant allergens was around 25% but 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.

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[156]. 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 lyophilised 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.

The prevalence of sulfite sensitivity in the general population is unknown and in asthma reports on a small number of patients have lead to a variable prevalence. Both adults and children can suffer from sulfite-induced asthma. It appears that patients with severe asthma, such as steroid-dependent bronchial asthma present a greater prevalence of sulfite sensitivity[157]. Some reports suggest a prevalence of sulfite sensitivity in at least 5% of the asthmatic population[158]. However, a very careful study proposed that on the basis of challenges, the best estimate of the prevalence of sulfite sensitivity in the asthmatic patients studied is 3.9%. This population, however, contained a larger number of steroid-dependent asthmatic patients than would be found in the general asthmatic population. It was concluded, therefore, that the prevalence of sulfite sensitivity in the asthmatic population as a whole would be less than 3.9% and that steroid-dependent asthmatic patients are most at risk[159].

These studies combine to indicate that using double-blind food challenge, the prevalence of food allergy is far below 1% of the population in adults and may be slightly greater in children[160]. However, this may be a 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.

The prevalence of food allergy is highly dependent on geographical area. In areas where sensitivity to birch and mugwort pollen is prevalent, 30 to 50% of these patients present 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 but since this food has been widely marketed throughout Europe it is now a major allergen both in the US and Europe. Shrimp allergy is common in Southern USA, fish allergy is common in the Nordic countries and 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[161].

Prevalence of metabolic disorders and coeliac disease

Lactose intolerance is widespread among certain ethnic groups. A deficiency of lactase is common in the Mediterranean, parts of Africa and in Asia[162].

Estimates of the prevalence of transferase deficiency galactosaemia based on the detection of heterozygotes in Wales, Denmark and the United States range from 1; 18,000 to 1: 180,000. The prevalence at birth has been 1: 70,000 in the British Isles. In a large-scale screening programme in New York State involving 141,000 infants, a prevalence of 1: 35,000 has been detected, while the frequency in Massachusetts is 1: 190,000[163]. The incidence in Belgium and Switzerland is approximately 1 in 62,000. Galactosaemia occurs with a frequency of 1 in 300 among the community of Irish travellers, and 1 in 20,000 in the general population in Ireland.

Cases of hereditary fructose intolerance have been reported from Europe, North America, India, Australia and other parts of the world. The true incidence is not known but may be as high as 1: 20,000 in Switzerland. Evidence is overwhelming that considerable numbers of children and adult patients must live undiagnosed in the general population[164].

Cumulative incidence rates of coeliac disease vary from 1 in 300 (in Sweden) to 1 in 3,500 in the South West of France (region of Toulouse), being around 1 / 1000 in England and Central Europe (Germany, Austria, Switzerland). Incidence rates vary also with time, decreasing in England, rising sharply in Sweden (from 1 / 100 to 1 / 300 during the last 10 years), stable elsewhere[165].

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OPINION ON MINERAL AND SYNTHETIC HYDROCARBONS

EXPRESSED ON 22 SEPTEMBER 1995

Terms of reference

To advise on the safety-in-use of mineral and synthetic hydrocarbon oils and waxes for use as food additives, in food processing and for use in food packaging materials.

Background

Types of mineral and synthetic hydrocarbons

Food grade mineral hydrocarbons are produced as by-products during the refining and distillation of crude mineral oils. Oils can be manufactured by two routes, the modern hydrogenation method and by the older acid (oleum) treatment. There are three main types of products; liquids, semi-liquids and solids, examples of each being mineral (white) oils, petroleum jellies and mineral waxes. Petroleum jellies are prepared by mixing oils and waxes so only mineral oils and mineral waxes need be considered when assessing the safety of mineral hydrocarbons.

There is a wide variation in the composition of these oils and waxes, resulting from the use of a range of crude oil starting materials, and most products are complex mixtures. This poses problems in developing meaningful specifications for these products, an issue which we address in more detail later. Mineral hydrocarbons may be straight chain (normal paraffins), branched chain (non-normal paraffins) or cyclic (naphthenics). For the paraffinics, the chain length may vary within the approximate range C_{15}-C_{80}. The oils are generally described according to the predominant type of material present, as either paraffinic or naphthenic, but paraffinic oils may contain some cyclic structures, and similarly naphthenic oils may contain some straight and branched chain paraffins. Mineral waxes contain mainly paraffinic hydrocarbons, with only very low levels of saturated cyclic naphthenic structures. It is the ratio of straight chain to branched chain paraffinic hydrocarbons, and to a certain extent molecular weight, which determine whether the wax is classified as a paraffin, intermediate or microcrystalline wax. Paraffin waxes contain mainly straight chain components with the proportion of branched chain components varying from as low as 5%; the proportion of branched chain components increases as average molecular weight increases. Intermediate waxes have higher average molecular weights than paraffin waxes and consist of approximately equal proportions of straight chain and branched chain alkanes. Microcrystalline waxes have the highest average molecular weight and contain mainly branched chain components with less than 30% straight chain alkanes.

Hydrocarbon waxes which are completely synthetic can also be produced by the Fischer-Tropsch process (passage of steam over hot coal). These too will be mixtures of components with varying chain length, but comprise mostly straight chain components only.

Uses

Mineral hydrocarbons have been widely used in many different applications which can potentially give rise to residues in food. Past or present uses include direct food additives (e.g. as glazing agents), constituents of chewing gum base, processing aids (e.g. lubricants), in food packaging materials (e.g. wax-coated cartons), in cheese wax, in pesticide formulations, as adjuvants in veterinary medicines, and in human medicines (e.g. liquid paraffin laxative). Within Europe, their uses as direct food additives have diminished and in some countries they are not permitted for food additive use.

Natural occurrence in food and environmental contamination of food

In addition to deliberate uses in foods, food processing and food packaging, the diet will also contain other hydrocarbons due to biosynthesis of hydrocarbons in terrestrial and marine plants and animal species and from environmental contamination of foods such as fish and shellfish resulting from geological activity, drilling of crude oil, oil and petroleum spillages and combustion of petroleum and other fossil fuels. Saturated and unsaturated n-alkanes with chain lengths of C_{15}, C_{17} and C_{21} are predominant in marine organisms, whilst saturated n-alkanes of chain lengths C_{27}, C_{29} and C_{31} are typical of terrestrial plants.

Previous Scientific Committee for Food (SCF) evaluation

The SCF considered the use of food-grade mineral hydrocarbons in May 1989 (1). At that time, two 90-day feeding studies in Fischer 344 (F344) rats, sponsored by industry, revealed that the two mineral oils tested, an oleum (acid) treated oil and an oil produced by the hydrogenation method, deposited in organs such as the spleen, liver and lymph node and were accompanied by histological abnormalities in these organs and consequential haematological abnormalities (2-4). During its review the Committee also noted that there were still many unresolved problems over the specifications for mineral hydrocarbon compounds. The SCF concluded that the available data did not permit an Acceptable Daily Intake (ADI) to be set, and that there was no toxicological justification for the continued use of mineral hydrocarbons as food additives. However, the Committee advised that there was no evidence of an acute health hazard to warrant urgent action to change the present pattern of the use of these compounds in food.

The Committee did use the 90-day studies to set two temporary Tolerable Daily Intakes (TDI) to cover residues in food arising from the use of mineral hydrocarbons in packaging materials. The t-TDIs were 0.005 mg/kg bw for oleum treated mineral hydrocarbons and 0.05 mg/kg bw for hydrocarbons produced by the hydrogenation method. The SCF stated that continued use of these materials was conditional on new short-term studies on well-specified mineral oils being performed by the end of 1990, followed by long-term studies completed within 5 years of the date of the SCF review (1).

Current review

Several new studies and reviews were sponsored by industry following requests for further data on these materials by the SCF and other regulatory bodies (5-15). The materials tested in these studies were chosen by the industry as being representative of mineral hydrocarbons currently used in food, in the sense that they had physical properties covering the range of the then used materials, from low viscosity oils through to waxes. A preliminary study on straight-chain, synthetic waxes has also been completed recently (12). We were also informed of another study carried out by industry on straight chain, synthetic waxes (known as Waxes A, B and C). Limited information but no study report has been made available to the SCF on these three waxes (13).

Since the Committee had only very limited data available to it on the likely exposure to mineral hydrocarbons from any of its food uses, it has not been possible to make any reliable estimates of intakes. We understand that in addition to work already published (16-20), the industry is gathering further information on migration of mineral hydrocarbons from food packaging materials into foods and is generating consumption data for the US population. We welcome this but in the absence at present of adequate exposure information relating to the EU, the opinion which follows is therefore a hazard assessment, not a risk assessment.

Evaluation of effects observed in animals and humans

The majority of animal studies have been carried out on the F344 rat which appears to be more sensitive to mineral hydrocarbons than other strains of rat. However, there is no information on whether humans may be more or less sensitive to mineral hydrocarbons than the F344 rat and we therefore considered it prudent to base our assessment on the results available in the F344 strain of rat.

From the available data on animals (2-12) and humans (21-32), it is clear that some mineral and synthetic oils and waxes not only accumulate with repeated dosing, but also give rise to effects which are not confined solely to localised foreign body reactions and provide clear evidence of toxicity in animals. In those oils and waxes which did show effects, the effects seen were similar in nature but differed in severity, i.e. some only gave rise to significant effects at a 2% level in the diet whereas others produced effects at 0.02%, with very occasional findings at 0.002%. The following effects were observed: increased organ weights, especially liver and lymph nodes; altered serum enzyme levels; increased monocyte and neutrophil counts; reduced red blood cells, haemoglobin, haematocrit, MCHC, MCH; and the accumulation of hydrocarbon material in tissues. The main histopathological findings were granulomata in the liver and focal collections of vacuolated macrophages (histiocytosis) in the lymph nodes. In animals dosed with certain of the waxes, an inflammatory lesion at the base of the mitral valve in the heart was observed. It was characterised by increased cellularity of the valve with destruction of the fibrous core. In some animals given these waxes, birefringent hydrocarbon material was detected in the mitral valve region, but the inflammatory lesion was not always accompanied by a significant level of hydrocarbon material in the valve; similarly, the presence of birefringent material was not always accompanied by an inflammatory lesion. None of the oils tested produced this lesion. In those studies which included a withdrawal phase, most of the toxic effects were still evident at the end of the withdrawal period but there was limited evidence that the severity of some of these effects had decreased during this phase. In all studies, female rats appeared to be more susceptible than male rats.

Samples of liver tissue from a small number of rats were analysed and the accumulated mineral hydrocarbons were found to be comparable but not identical to the original oil/wax administered. Lower and higher molecular weight hydrocarbons were under-represented in the liver extracts compared with the original test sample and the branched chain content of the residues was relatively higher than in the original test sample.

The data indicate that toxicity is correlated with accumulation. In animal studies, of those mineral and synthetic hydrocarbons which did accumulate, the degree of accumulation was generally highest in those showing most toxicity and lowest in those materials producing little or no accompanying toxicity. In all groups tissue levels declined following withdrawal of dosing. Two of the human population studies also showed a clear correlation between the extent of the lesions and the amounts of mineral hydrocarbons which could be extracted from the tissues (25,27).

It is not possible to predict the ultimate consequences for health of the reactions observed in some of the animal studies, such as the inflammatory reactions in the liver and the mitral valve of the heart. However, we consider that these and some of the other effects noted above are undesirable and further consider that there are sufficient parallels between the observations of accumulation and effects in animals and man to conclude that there is the potential, depending on the intake, for adverse effects on human health. For those hydrocarbons which have been shown to both accumulate and cause toxicity, for which a no adverse effect level is not yet known, (i.e. oils: N10(A), N15(H), P15(H), N70(H), N70(A); and waxes: LMPW, IMPW, M5, M5DO, C80, A, B and C), it is not possible from current information to set a safe level for intake from food. Further research might identify such levels.

One of the tested mineral hydrocarbon oils, the P100(H), showed minimal accumulation but no toxicity within the duration of a 90-day study. Whilst longer term studies would be necessary to ensure that such oils did not eventually give rise to toxicity, it seems likely, as a generalisation, that there may be low levels of accumulation of mineral and synthetic hydrocarbons which are of no toxicological significance. Indeed, it is clear from the animal tissue reversal studies that the body is able to metabolise and clear much of what is absorbed in the absence of any further intake. Unfortunately, there is no information on whether there might be an equilibrium point at which regular but low intakes of certain mineral and synthetic hydrocarbons with a lesser tendency to accumulate might be cleared successfully by the body without any long-term sequelae. Kinetic and dose/response information from tissue reversal studies would have helped elucidate this point but, to date, only 2% dietary dose groups have been studied at a single time point. In the absence of further information on this point at present, but bearing in mind the capacity of the body to clear smaller amounts of material and the lack of toxicity seen with the P100(H) oil, we consider P100(H) oil as temporarily acceptable, subject to a satisfactory specification and the submission of further data (see below). We understand that further *in vitro* and *in vivo* studies on the kinetics of mineral hydrocarbon absorption, metabolism and clearance are underway and we welcome this.

The P70(H) oil also deserves separate consideration. It showed accumulation in liver, lymph node and kidney which was slightly greater than that seen with the P100(H) oil but was not as extensive as that seen with the other oils which showed toxicity in 90-day studies. Whilst some organ weight, clinical chemistry and haematological changes were noted with the P70(H) oil, these changes were small in magnitude, with little or no evidence of relationship to dose, and no significant histological lesions such as granulomata in the liver or histiocytosis in the lymph nodes were seen. We therefore consider P70(H) as temporarily acceptable, to be included in a temporary Group ADI together with P100(H) oil (see below).

Two of the mineral hydrocarbons tested, the microcrystalline high sulphur wax (HSW) and high melting point wax (HMPW), neither accumulated nor showed any toxicity in the 90-day and reversal studies carried out. Similarly, the synthetic H2 wax showed no toxicity and, whilst it has not been tested in a tissue accumulation and reversal study, the physical parameters of its specification are comparable with those of the HSW and HMPW. We therefore regard the microcrystalline HSW and HMPW, and the synthetic H2 wax as acceptable for food use, provided a specification can be set for these materials which would exclude the likelihood of significant quantities of cumulative/toxic components being present (see below).

Specifications

Central to deciding whether to recommend some mineral hydrocarbons as acceptable for food use was the question of specifications. As mineral hydrocarbons are complex mixtures derived from varying sources, they can only be described loosely in chemical terms, rather than fully characterised chemically in the detailed manner of most other food additives. It is therefore necessary also to describe them by means of their physical characteristics. The loose chemical descriptions and physical characteristics describe products as sold. Thus we are aware that products with similar physical descriptions may differ in the detail of their chemical constituents; indeed, a single named product sold by one producer may vary over time. It follows that the mineral hydrocarbons used in the toxicity tests cannot be reproduced exactly for marketing. We have therefore considered very carefully the question of whether the toxicity observed with some materials could be caused by very small proportions of unusual, highly toxic components, whose presence in products defined mainly by physical characteristics could be unpredictable and uncontrollable. We consider that the totality of the evidence now available on both mineral and synthetic hydrocarbons is sufficient to enable us to reach a view that such a possibility is very unlikely. Rather we have concluded that it is largely the amounts of lower molecular weight, shorter chain-length substances, which are absorbed and only slowly cleared from the body, that most probably determine the occurrence or absence of toxicity. Accordingly, we consider that, for practical purposes for the time being, mineral and synthetic hydrocarbons could be defined by physical specifications which are sufficiently tightly drawn so as to ensure that only a small proportion of any product conforming to these specifications will have carbon chain-lengths in the absorbable range.

The envelope specifications proposed (see below) exclude all the mineral and synthetic hydrocarbons tested to date which showed some toxicity in 90-day studies, but include the P70(H) oil, P100(H) oil, HSW, HMPW and H2 wax which did not. However, we urge that further efforts are made to improve and refine the specifications within this envelope specification for any mineral or synthetic hydrocarbons which are marketed for food use.

Acceptable Daily Intakes and further research

We have considered the setting of Acceptable Daily Intakes (ADI). In addition to their diversity, complexity and the difficulties of chemical characterisation, mineral and synthetic hydrocarbons also differ from other more conventional food additives in the general lack of studies conducted to modern day standards on aspects of toxicity other than general toxicity and mutagenicity. We have again given this matter careful thought, noting that recent long-term rat and mouse carcinogenicity studies with a complex mixture of chlorinated paraffins, which produced similar effects such as lymph node histiocytosis, liver granulomata, congestion in the spleen and accompanying clinical chemistry and haematological changes, did not adversely affect survival or tumour rates (33).

We consider that since the envelope specification we propose for waxes largely excludes absorbable materials, the possibility of toxic effects other than those which would show up in a 90-day study is remote for waxes falling within that specification. Accordingly we have used the usual safety factor of 100 applied to the no-effect level for the waxes (i.e. 2% in the diet in 90-day studies) to set a Group ADI of 0-20 mg/kg bw for the highly refined microcrystalline and synthetic waxes which conform to the envelope specification. We require no further data on these waxes.

For white paraffinic mineral oils which conform to the envelope specification for oils, we have used a safety factor of 500 applied to the 90-day no-effect level of 2% in the diet for the P100(H) oil and the 90-day minimal effect level of 2% in the diet for increased liver weight for the P70(H) oil, in order to set a temporary Group ADI of 0-4 mg/kg bw. This ADI is temporary pending submission within 4 years of a 2-year chronic toxicity/ carcinogenicity study on P70(H) oil, to include a satellite group dosed for 1 year only and then left untreated for a further year. This would provide information on whether or not the very limited accumulation observed with these oils in the 90-day studies would give rise to any toxicity if administration was continued for a longer period and information on the reversibility of any effects observed. Pending these results, a higher safety factor has been chosen because of the indication that there is some absorption and minimal accumulation of the P100(H) and P70(H) oils compared with no detectable accumulation of higher viscosity waxes of similar or longer average carbon chain-length distributions. The additional factor chosen over and above the usual safety factor of 100 is 5, rather than 2 as is usual for temporary ADIs, because of the nature of these uncertainties about absorption when viewed alongside the gaps in the toxicological database.

Conclusions

(i) There are sufficient data to allocate a full Group ADI of 0-20 mg/kg bw for waxes conforming to the following specification:

Highly refined waxes derived from petroleum based or synthetic hydrocarbon feed stocks, with

Viscosity	not less than 11 mm^2s^{-1} (centiStokes) at 100°C
Carbon number	not less than 25 at the 5% boiling point
Average molecular weight	not less than 500

We do not require any further data on these waxes.

(ii) There are sufficient data to allocate a temporary Group ADI of 0-4 mg/kg bw for oils conforming to the following specification:

White paraffinic mineral oils derived from petroleum based hydrocarbon feed stocks, with

Viscosity	not less than 8.5 mm^2s^{-1} (centiStokes) at 100°C
Carbon number	not less than 25 at the 5% boiling point
Average molecular weight	not less than 480

We require a chronic toxicity/carcinogenicity study of 2 years duration on P70(H) oil, which includes a reversibility phase in which a satellite group dosed for 1 year is left untreated for a further year, to be submitted within 4 years.

(iii) We urge that further efforts are made to improve and refine the specifications within the above envelope specifications, particularly with respect to better chemical characterisation, for any mineral or synthetic hydrocarbons which are marketed for food use.

(iv) We would wish to see other relevant toxicological and exposure data which we understand are being generated on mineral hydrocarbons.

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