Risiken erkennen – Gesundheit schützen

# Allergies caused by consumer products and foods

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Around the world allergies are one of the biggest health problems. They impair the quality of life of a large part of the population and have major economic repercussions. The German Study on the Health of Children and Adolescents (KIGGS)[1] revealed that 40.8% of the children examined are sensitised to at least one allergen based on specific IgE antibodies to dietary and inhalation antigens. According to this study 16.7% of all children and adolescents currently suffer from allergic symptoms or disorders.

The number of allergic diseases is on the increase. In Germany it varies from region to region. There are different types of immunological-allergic responses. Airborne allergens and foods normally trigger a type I reaction which may manifest in seasonal or year-long common cold, nettle rash, bronchial asthma and allergic inflammation of the pulmonary alveoli. In rare cases hypersensitivity to certain substances may also trigger immediate life-threatening responses (anaphylactic shock). Skin allergies (type IV contact allergies) may be caused by various components in consumer products like cosmetics, clothing or toys. The Federal Institute for Risk Assessment (BfR) was asked by the Federal Ministry of Food, Agriculture and Consumer Protection (BMELV) to present the current level of scientific findings on allergies caused by consumer products and foods by way of preparation for the National Action Plan on Allergies.

## 1 Definitions

An allergy is understood to be a hypersensitivity reaction that is triggered by immunological mechanisms.

Allergic reactions can manifest as types I to IV allergies (based on the categories of Gsell and Coombs).

**Type I reactions** are IgE-mediated reactions involving the release of mediators (e.g. histamine) stored in mast cells, the release of newly formed mediators (e.g. leucotrienes, prostaglandins and platelet-activating factor) or the release of cytokines (e.g. IL-3, IL-4, IL-5, IL-6, GM-CSF). The clinical symptoms are rhinitis, asthma, urticaria, diarrhoea and anaphylactic shock.

The following diagrams illustrate the complex interactions involved in the triggering of an IgE-mediated type I asthma reaction and an allergic reaction in the gastrointestinal tract.

[1] KIGGS, conducted by the Robert Koch Institute, http://www.kiggs.de/

Figure 1: **Asthma induction**[2]

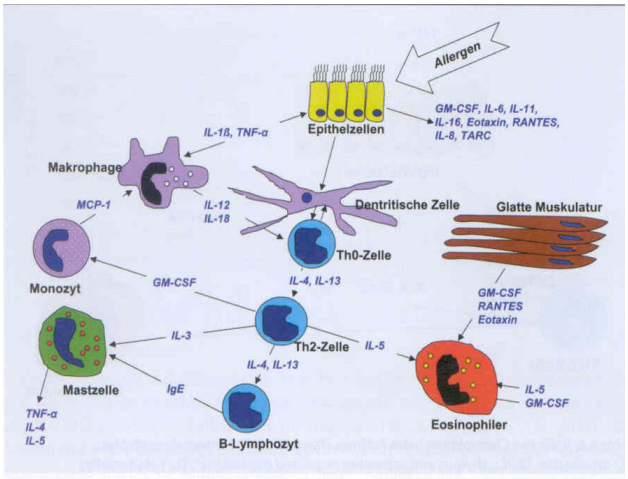
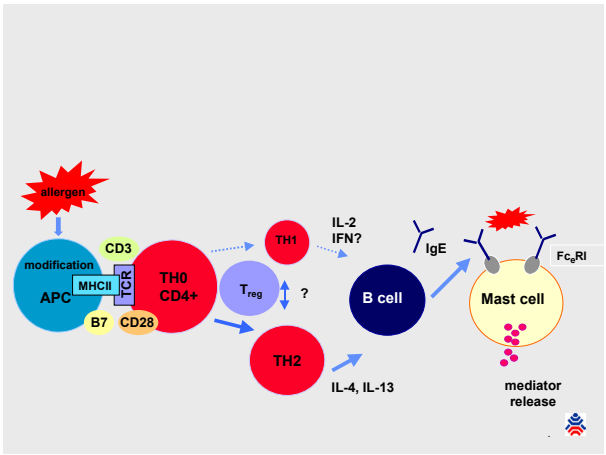



Abb. 2 ▲ Zytokinnetzwerk bei Asthma. (Nach [2]; TNF: Tumornekrosefaktor, IL: Interleukin, GM-CSF: Granulozyten-Makrophagen-Kolonie-stimulierender Faktor, RANTES: „regulated on activation T-cell expressed and secreted", MCP: Monozytenchemotaktisches Protein, TARC: „thymus and activation regulated chemokine", Th: T-Helferzelle)

(Terms in figure 1 in clockwise ordern)
Allergen, Smooth muscle, Eosinophile, B-lymphocyte, Mast cell, Monocyte, Macrophage, Epithelial cells, Dendritic cell)

(Subtitle in figure 1)
Cytokine network in eliciting asthmatic response. (According to [2]; TNF: tumour necrosis factor, IL: interleukine, GM-CSF: granulocyte macrophage colony-stimulating factor, RANTES: regulated on activation T-cell expressed and excreted; MCP: monocyte chemotactic protein, TARC: thymus and activation regulated chemokines; Th: T helper cell.

**Figure 2: Allergy in the gastrointestinal tract**[3]




[2] taken from: M. Schmidt (2006): Asthma bronchiale, Der Internist 47, 835-852, according to Barnes PJ (2003), Pathopysiology of asthma. Eur Respir Mon 23: 180-194.

[3] Taken from: Lecture by Professor Vieths, PEI, during the seminar "Assessment of the Allergenicity of Food Ingredients including Novel Foods at BfR on 12 September 2006."

**Type II reactions** are antibody-mediated cytotoxic reactions. The cytotoxic effect results from activation of complement, by binding to the $F_c$ receptors of killer cells and / or the promotion of immunophagocytosis. Type II reactions play a role in cytotoxic reactions affecting blood cells/cells of bone marrow, liver and thymus.

**Type III** allergies lead to glomerulonephritis, arthralgia, urticaria, and sometimes also to cytopenia. Immunocomplex responses are involved here in which polyvalent antigens lead to cross-linkage with antibodies and the antibodies formed are able to activate the complement system. When the complexes reach the tissue, localised inflammation is induced (Arthus phenomenon). If the complexes remain in the bloodstream, they can agglomerate in tissues where physiological filtration processes take place, for example in renal glomeruli.

**Type IV** allergies are not antibody-mediated reactions. Type IV reactions are triggered by T cells on whose surface an antigen is bound to receptors. Together with MHC II structures, CD4 cells are activated. In the context of the MHC I structures this leads to an activation of CD8 cells. Activated CD4 cells may release pre-inflammatory cytokines (IFN$\gamma$, GM-CSF, TNF$\beta$, IL-3, -4, -5, -8) whereas CD8 cells have a cytoxic effect on antigen-carrying cells. Contact sensitivity is the most well known example of an allergic type IV reaction.

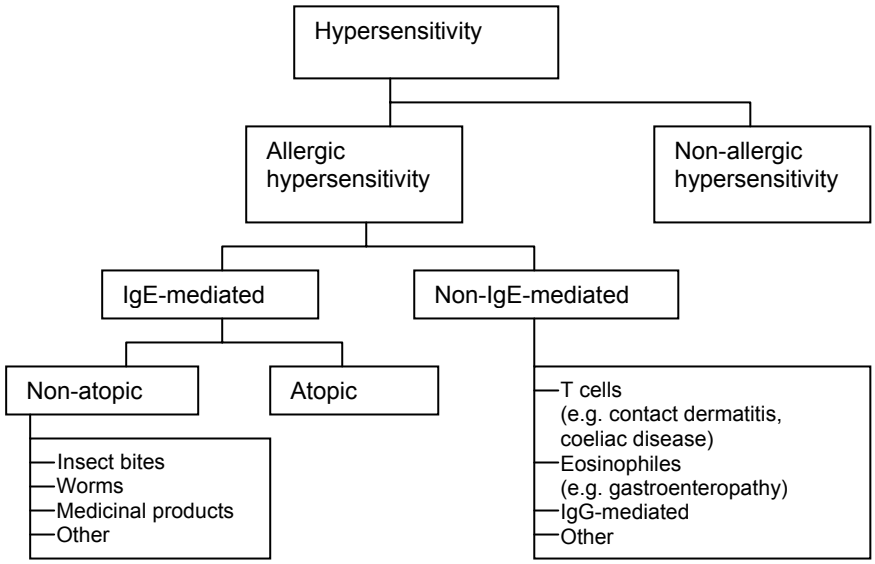
Allergens are **antigens** that stimulate the immunologically induced hypersensitivity. They are proteins which often possess a carbohydrate side chain.

**Atopia** is the term used to describe an individual or a familial predisposition to produce IgE in response to small doses of an allergen. The typical manifestations are asthma, rhinoconjunctivitis or eczematous dermatitis.

**Anaphylaxia** is a severe life-threatening generalised or systemic hypersensitivity reaction which may be triggered by allergic or non-allergic (so called pseudo-allergic) reactions. It may be fatal. There are reports of reactions to peanuts with fatal consequences.

The terms used below are based on the proposals of the World Allergy Organization, Nomenclature Review Committee (Johansson *et al.,* 2004) and the European Academy of Allergy and Clinical Immunology (Johansson *et al.,* 2001). According to these definitions all food intolerances come under the generic term “food hypersensitivity”. This can be broken down into allergic and non-allergic hypersensitivity (see Figure 3).

**Figure 3: Differences between allergic and non allergic hypersensitivity**




**Allergic hypersensitivity** is the term used to describe objectifiable and reproducible symptoms or signs caused by exposure to a specific stimulus at a dose which would be tolerated by healthy individuals.

In the case of **non-allergic hypersensitivity** immunological mechanisms are not detectable. The clinical term used for this is "**pseudo-allergy**".

In the following text as a rule the term allergic hypersensitivity reactions is used. Substances from consumer products may cause allergic contact dermatitis when they come into contact with the skin (type IV allergy). Substances released into the air from products may also lead to allergic hypersensitivities through skin contact (type IV allergy) or through contact with the respiratory tract (type I allergy). Substances in foods may also induce oral sensitisation (type I allergy). Non-allergenic reactions to food (ingredients) and reactions to food additives are also mentioned. These non-immunological reactions encompass the so-called pseudo-allergic reactions as well as reactions caused by biogenic amines or reactions due to enzyme deficiencies. In most cases the exact mechanism that led to non-immunological reactions is not known (EFSA, 2004).

The clinical appearance of pseudo-allergic reactions is similar to that of immune-mediated responses. Severe, sometimes life-threatening symptoms may occur. In both cases the same mediator systems (for instance mediators from tissue mast cells like histamine and leucotrienes) are involved. Whereas the mediator release is triggered in the case of the immune-induced response by an antigen-antibody reaction at the mast cell membrane, the mediators in the case of the pseudo-allergic reaction are released by pharmacological mechanisms (Kreft *et al.,* 1995). The so-called pseudo-allergy is non-specific for the causative agent. It may occur without prior sensitisation which means at the first contact. Pseudo-allergic reactions are generally triggered by low molecular substances which occur

naturally in or can be added to foods. Reports of hypersensitivity reactions linked to natural food ingredients or food additives, have been assessed by the former Scientific Committee on Food of the European Commission (SCF 1982, 1995) as well as by the Scientific Panel on Dietetic Products, Nutrition and Allergies (NDA) of the European Food Safety Authority (EFSA) on several occasions (EFSA, 2004).

## 2 Consumer products

Substances in products that come into contact with the skin play an important role as exogenous factors in the triggering of allergic contact eczemas (type IV allergies) at home but also at work. Occupational skin diseases have headed the list (approximately 25%) of all reported occupational diseases for many years in Germany and in other European countries.

The most important skin-contact products for consumers are cosmetics and clothing textiles. However, other products that have intensive skin contact like shoes, gloves and toys are also to be taken into account. Special mention should be made of tattoos where the skin's barrier function is switched off. Effective prevention is possible through the identification and elimination or limitation of the allergens. For instance, reducing exposure to nickel in costume jewellery (see below) in Denmark and Germany has led to a major drop in nickel allergies in young women and men (Jensen *et al.,* 2002). From the regulatory angle appropriate labelling of allergens is customary in cosmetics so that sensitised individuals can avoid skin contact.

Besides the substances which are taken up exclusively through skin contact, fragrances are also of importance. They are used in various ways in cosmetics and commodities including detergents and cleaning products and are taken up via the respiratory tract. Up to now it is unclear whether skin sensitising fragrances can lead, in conjunction with inhalation exposure, to respiratory allergies or to allergic contact eczemas. There have been reports that highly sensitive groups like asthma patients, atopics and individuals whose symptoms are linked to multiple chemical sensitivity and the sick building syndrome showed hypersensitivity reactions to fragrances. However, in the case of the two latter disorders opinions differ as to whether a primarily toxicological mechanism is involved. A background paper by the Federal Environmental Agency (UBA) refers to an epidemiological research project of the Information Network of Departments of Dermatology (IVDK, Göttingen) that examines reactions to fragrances (UBA, 2006). Furthermore, the influence of passive smoking on asthma development in children is of importance.

### 2.1 Epidemiological findings

The Information Network of Departments of Dermatology (IVDK) evaluates data from 40 dermatology departments in Germany, Austria and Switzerland. At regular intervals it draws up lists of allergens ranked by prevalence (Schnuch *et al.,* 2004; Straff and Schnuch, 2006). For instance based on the data from 1999, a manifest allergic contact eczema was diagnosed based on a positive epicutaneous test reaction in 1,648 out of 9,266 patients tested in dermatology departments. Depending on the model of extrapolation from the tested patient cohort to the normal population, this corresponds to an incidence (rate of new cases) of between three (medium case scenario) and seven (worst case scenario) cases per 1,000 a year. However, the incidences identified in selected professional groups are far higher.

There are only rough estimates of the incidence of allergic contact eczema in the general population. So far, no comprehensive studies have been conducted (Schnuch *et al.,* 2004). In the Health Survey 2000 non pre-selected patients were questioned by a dermatologist about the occurrence of an allergic contact eczema. Based on these survey results a lifetime

prevalence of around 15% and an annual prevalence of approximately 7% were identified (Hermann-Kunz, 2000). By contrast, based on epicutaneous tests conducted between 1992 and 2000 in a total of 78,067 patients, IVDK identified, using the different extrapolation models, a 9-year prevalence of 7% (medium case scenario) and of 16.6% (worst case scenario) for the overall population in the Federal Republic of Germany (Schnuch *et al.,* 2004). The analysis of sensitisations in this patient cohort, extrapolated to the total population, led to a ranking of substances which triggered sensitisation most frequently. Nickel was at the top of the list (2.3%), followed by a fragrance mixture (1.8%), Peru balsam (1.3%), p-phenylene diamine (0.7%) and potassium dichromate (0.6%). In 2004 the ten most frequent triggers of positive test reactions in patients with allergic contact eczema (hit list) were nickel, fragrance mixture, Peru balsam, cobalt chloride, potassium dichromate, colophonium, amerchol L 101 (wool wax alcohol), p-phenylene diamine, mercury amide chloride and methyl dibromoglutaronitrile/phenoxyethanol (Oppel und Schnuch, 2006).

## 2.2 Dose-response relationship

Risk assessment only permits quantitative statements to a very limited degree, including dose-response relationships and threshold levels when it comes to contact allergies and consumer products. The problem already starts with the definition of the exposure dose in humans. Links between the content of a substance in the product (concentration) and exposure are only possible in the case of preparations like paints, detergents and cosmetics. However the conditions of use must also be taken into account. In the case of consumer products like clothing and toys, it is only the proportion of the substance released from the product (migration) that is important for exposure assessment. At the present time, there are only few generally accepted methods (e.g. for phthalates in toys) for measuring migration and scarcely any data are available from appropriate measurements. A further problem is that the measurement data are not necessarily suitable for exposure assessment. The goal of the research project *Compilation, analysis and evaluation of data and methodologies to characterise qualitatively and quantitatively human exposure to chemicals released from consumer products/articles* (“ChemTest”) is to obtain suitable data and methods. BfR is involved in this project.

Moreover, for the purposes of a quantitative risk assessment, detailed knowledge is needed about the dose-response relationships in humans for both the sensitising and allergy-inducing effect of the substances concerned. When it comes to allergies special attention must be paid to the group of already sensitised individuals. Up to now, data on dose-response relationships have only been available for a few model substances. The established test methods in animal experiments normally only lead to semi-quantitative results. More dose-response relationships that also permit quantitative statements or render these more reliable could become available in the future through increased use of the lymph node test.

## 2.3 Important substance groups

The potential sources of exposure of the main allergenic substances in consumer products are presented below (selected by Schnuch *et al.,* 2004):

**Nickel**: Nickel is by far the most important contact allergen both around the world and in Germany. According to estimates, up to 4.5 million German people are sensitised to this allergen (Schnuch *et al.,* 2002). Exposure sources are jewellery, piercings and clothing accessories. For individuals who are already sensitised to nickel, oral exposure for instance from cooking utensils and electric kettles, may also be relevant (EFSA, 2006).

**Fragrances**: There are more than 5,000 fragrance substances. They are frequently used as mixtures, particularly in cosmetics (perfumes, shampoos, creams, shower gel, toothpaste), household products (for instance in room fresheners and in carpet shampoos), textiles, shoes, toys, etc.

**Peru balsam**: Peru balsam is a natural product which is made from the wound exudation of the Peru balsam tree. It is used as a fragrance in cosmetics (soaps, shampoos, lipsticks), shoes and tobacco.

**Chromium and potassium dichromate:** Chromium or potassium dichromate is found in cement and other building materials, glazings, paints, leather clothing, leather gloves and leather shoes as well as in material for uniforms.

**Colophonium**: Colophonium is a natural product made from the resin of conifers. It is used amongst other things for glues, paints and printing inks.

**Methyl dibromoglutaronitrile (MDBGN)**: This substance is used as a preservative in cosmetics (now banned), detergents and ultrasound gel.

**p-Phenylene diamine**: p-phenylene diamine is used in hair dyes, part of disperse dyes in textiles, antioxidants in rubber and in paints/varnishes, plastics and as a henna additive (temporary tattoos).

**Thiurames**: The substance mixture is used as a vulcanisation accelerator in rubber products like rubber gloves, spray and adhesive plasters or insect repellents.

**(Chloro)methyl isothiazolinone (isothiazolinone mixture CMI/MI)**: This substance is used as a preservative in glues, waxes, paints/varnishes, leather clothing, wood preservatives, mixed water dyes and cosmetics.

**Turpentine oil:** Turpentine oil is known as a solvent and diluting agent in varnishes, paints, shoe polish, resins, building materials, etc. There have been reports of a cross-allergy between turpentine oil and various fragrances and tea tree oil.

**Formaldehyde or formaldehyde liberators/resins:** This substance is used as a preservative in cosmetics, wash-and–wear textiles, paint/varnishes and chipboard.

## 2.4 Relevant products and materials

The following section describes important product areas for the triggering of allergies:

**Clothing textiles**
According to findings of the BfR Textile Working Group, between 1 and 2% of contact allergies in German dermatological clinics are triggered by textiles. The textile auxiliary catalogue contains approximately 7,000 preparations of textile auxiliaries and finishing agents. Furthermore, there are colourants (pigments or dyes). Roughly half of the 4,000 colourants are azo dyes. In some cases, carcinogenic and allergenic amines may be released from them during metabolism or on the skin. When it comes to the triggering of allergies, the highly sensitising disperse dyes like Disperse Blue 106 and 124 are of importance. They often occur together. After azo cleavage Disperse Blue 106 and 124 may

also release the highly allergenic substances p-phenylene diamine or p-aminoazobenzene. Around two thirds of all textile-related cases of allergy are attributed to disperse dyes (Hatch and Maibach, 1995). Other important allergens in clothing are potassium dichromate (leather clothes) formaldehyde-releasing resins (wash-and-wear finish) and rubber chemicals like thiurames, dithiocarbamates or benzothiazoles (in rubber bands) (Schnuch *et al.,* 2004).

**Leather clothing including gloves**
Potassium dichromate is one of the most important contact allergens. Azo dyes as well as p-tert-butyl phenol formaldehyde resin from adhesives may play a role as allergens in shoes.

**Cosmetics**
High sensitisation rates were identified for the following ingredients both for leave-on products on the skin and for cosmetics which are rinsed off: fragrance mixture, Peru balsam, MDBGN, wool wax alcohols, CMI/MI etc. (Schnuch *et al.,* 2004). In the case of hair products whose ingredients can lead to neck, head and face eczemas in consumers, besides fragrances and preservatives (MDBGN, CMI/MI), the most apparent are mainly typical "hairdresser substances" like ammonium per sulphate but also p-phenylene diamine and p-aminophenole as precursors or degradation products of hair dyes and thiurames as rubber ingredients (Schnuch *et al.,* 2004).

The competent scientific body of the European Commission (SCCNFP/SCCP) assessed specific fragrances because of their diverse application areas in cosmetics and other product groups. In its expert opinion dated 25 September 2001, it strongly recommends restricting the use of these, in some case highly sensitising, substances or imposing specific requirements on their use.

Hair dyes were examined by the Scientific Committee on Consumer Products (SCCP) of the European Commission. Some of the substances used were found to have highly sensitising properties. Appropriate labelling provisions are currently in place.

**Tattoos, permanent make up and henna tattoos**
According to IVDK, skin reactions in conjunction with tattoos are rare but are as a rule severe if they occur. Allergic reactions play the largest role. Besides metal-containing substances in dye mixtures a key role may also be played by the sensitising dyes as well as by amines which may occur as impurities or as cleavage products in tattooing agents.

Henna tattoos also called temporary tattoos or temptoos are a major problem when it comes to allergies. Because in this case, the dye mixture is applied to the skin, it is considered to be a cosmetic. Henna tattoos are frequently darkened with the sensitising p-phenylene diamine (black henna). In the EU p-Phenylene diamine is only permitted in cosmetics for use in oxidation hair dyes. Hence, its use in henna tattoos is prohibited. Nevertheless black henna is frequently used, particularly for body painting in children. Numerous individual case studies in the scientific literature confirm allergic reactions in conjunction with henna tattoos. A recent publication from Denmark describes serious skin reactions to hair dyes in eight children under the age of 16, of whom six had already suffered a reaction to black tattoos (Sosted *et al.,* 2006). As henna tattoos are mainly offered on markets or at holiday destinations, consumer awareness should be raised about this issue.

**Toys**
The Committee on Cosmetic Products and Non-Food Products (SCCNFP) of the European Commission had already proposed in its expert opinion in 1999 that manufacturers should refrain from using sensitising fragrances in toys on grounds of precautionary health

protection. Many of these sensitising fragrances were identified and quantified in seven out of ten products examined in the study presented in Denmark “Mapping of perfume in toys and children’s articles” (ENTR/TOYS/2006/36, dated 27 April 2006). Several non-sensitising fragrances are available as a substitute.

**Room fresheners**
A report by the Scientific Committee on Health and Environmental Risks (SCHER) of the European Commission is available on the emission of chemicals from air fresheners. This body sees a lack of clarity concerning the associations between disease symptoms and the emissions from air fresheners which have been observed particularly in highly sensitive groups of individuals (SCHER, 2006).

**Rubber products**
Two forms of allergies are generally known in conjunction with rubber products. The classical rubber allergy is a type IV allergy and is triggered by skin contact with the processing aids like vulcanisation accelerators (e.g. mercaptobenzthiazol). In recent years special attention has, however, also been paid to type I allergies (immediate type) which are triggered by natural latex components (proteins). This form of allergy has been observed in particular in children who have had several operations (intensive mucosa contact with rubber medical devices) and in hospital staff (use of powdered surgical gloves). Aerogenic exposure seems to be particularly important in the case of powdered gloves. The BfR Plastics Recommendation XXI, Consumer Products Based on Natural and Synthetic Rubber, contains the following passage: In order to prevent the risk of allergies, the content of soluble proteins is to be reduced to a minimum in consumer products in the special category and in other consumer products in accordance with §2 (6) Nos 3-6 Food and Feed Act (LFGB). In the case of products made from natural rubber latex the consumer products or their packaging must carry the following wording: “Natural rubber latex has been used in the production of this product which may cause allergies.”

**Passive smoking**
The report by the Surgeon General dated 27 June 2006 sums up the current level of scientific knowledge on the health risks from passive smoking. Besides other risks, it confirms that children exposed to passive smoking are more at risk of developing asthma, too (Department of Health and Human Services, 2006). Several studies from various countries all show that parental smoking increases the prevalence of asthma and respiratory symptoms like coughing and rhonchus in children under the age of eleven. A meta analysis of these studies revealed a statistically significant link between the number of smokers and the prevalence of the occurrence of the symptoms (odds ratio 1.47, both parents smoke). The report comes to the conclusion that the data sufficiently prove a causal relationship between parental smoking and asthma in children.

## 2.5 Research

The following research topics are currently being addressed by BfR:

- Toxicity of chemicals in consumer products and cosmetics in human keratinocyte cultures
- Studies on the allergenic potential and on the skin penetration of constituents from consumer products and cosmetics
- Studies on the metabolism of azo dyes in clothing and cosmetics
- Toxicological studies on substance mixtures from consumer products
- Cleavage of azo dyes by bacteria in the human skin *in vitro*

Need for experimental research:

- Support for the development of methods to measure exposure from consumer products
- Support for dermato-toxicological research projects (test for sensitising properties, test on skin penetration, test on dermal exposure, test on systemic availability and effect of tattoo dyes)
- Further development of existing test systems or development of new *in vitro* tests for skin sensitisation including molecular mechanisms of action (expression analysis / proteomics, morphological and molecular indicator tests).

Need for epidemiological research:

- Development in and continuous support for epidemiological studies on contact allergies in Germany with a focus on specific products (IVDK)
- Further studies and definitive clarification of the question whether and, if so, how exposure to passive smoking encourages asthma development in children.

## 2.6 Summary: Consumer products

It is difficult to say whether there is a growing trend towards contact allergies caused by consumer products. On the one hand, product ranges and consumer behaviour change very quickly; on the other, the identified risks are regularly reduced through intervention measures. However, the substitutes, as numerous examples have shown, can lead to new risks.

Quantitative statements on risk assessment along the lines of dose-response relationships and thresholds are only possible to a very limited degree in the area of “contact allergies and consumer products”.

Effective prevention of contact allergies is based on two things. First of all mention should be made of the testing of substances used in consumer products. This applies in particular to products which come into contact with the skin. The established tests can identify allergens. The lymph node test allows the classification of substances by potency. Human experience is also essential. With IVDK Germany has an effective system; however, its contribution to consumer health protection could and should be considerably improved. The methods mentioned above and IVDK are important sources of information for risk assessment and the resulting management options for regulation. Experience has shown that exposure-reducing measures (constraints on applications or concentrations, warnings for risk groups) effectively influence allergic incidents in the field of contact allergies. In the case of nickel, regulatory measures have reversed the trend. Labelling regulations for allergenic fragrances have been introduced for cosmetics and detergents. Regulations are currently being prepared for chromate in leather clothing and tattoos.

BfR believes there is a considerable need for research in the areas of exposure (release of substances), dermato-toxicology (method development) and epidemiology.

# 3 Food

## 3.1 Food and food ingredients

### 3.1.1 Overview of prevalence

The prevalence of food-induced allergies in the general population is estimated to be approximately between 1 and 3% of adults and 4 and 6% of children (EFSA, 2004) and up to 8% of children (Boden *et al.,* 2005; Lorenz *et al.,* 2001). Although in principle almost all foods can trigger isolated cases of food allergies, only relatively few foods are of particular clinical importance. For instance 75% of food allergy reactions in children occur in conjunction with the consumption of eggs, peanuts, dairy milk, fish and certain types of nuts whereas around 50% of allergies of this kind in adults can be traced back to fruits like kiwi, banana, apple, pear, plum and vegetables like carrots and celery as well as certain nuts and peanuts (EFSA, 2004).

A study conducted in Berlin involving a representative random sample of the population supplied concrete data on the incidence of food allergies (Roehr *et al.,* 2004; Zuberbier *et al.,* 2004). It should, however, be pointed out that these data apply solely to Berlin. It is not possible to apply them to the general population as the type and prevalence of hypersensitivity reactions of a population to foods depend on eating habits, climate and environment. This study is the first of its kind in the world to examine the prevalence of hypersensitivity reactions to foods in a non-selected random population sample while applying a precise diagnostic regimen. According to this study the ratio of reported to clinically proven cases of hypersensitivity is approximately 10:1 (Roehr *et al.,* 2004). There is a similar situation in other countries like the United Kingdom and Denmark (Pereira *et al.,* 2005; Osterballe *et al.,* 2005; Venter *et al.,* 2006).

Given the lack of longitudinal studies and reliable derived data, a sound scientific answer cannot be given to the question whether hypersensitivity reactions to foods have increased in recent years. The number of foods for which hypersensitivity reactions have been reported has increased. This may be due to the broader range of foods on offer, increased awareness or improved diagnostics. Ellman *et al*. (2002) reported for the United Kingdom that the sensitisation rate to foods had not increased in two groups of children and adolescents with atopic dermatitis, who were examined and then re-examined ten years later. They also reported that the foods concerned had largely remained the same with the exception of increased sensitisation to milk and peanuts.

### 3.1.2 Existing labelling provisions for the main allergens

Annex IIIa to EU Directive 2000/13/EC lists the foods that trigger allergies and certain intolerances most frequently. These so-called main allergens – “the allergenic dozen” – are linked to the most frequent allergies to foods in terms of numbers and must be indicated on the labels of (pre-packaged or mainly processed) foods: gluten-containing cereals (wheat, rye, barley, spelt, kamut or their hybridised strains, crustaceans, eggs, fish, peanuts, soybeans, milk, shell fruit (almonds, hazelnuts, walnuts, cashew nuts, pecan nuts, brazil nuts, pistachios, macadamia nuts, Queensland nuts), celery, mustard, sesame seeds and products derived from them as well as sulphur dioxide and sulphites at concentrations of more than 10 mg/kg or 10 mg/l expressed as $SO_2$ (EU Directive 2003/89/EC, amending Directive 2000/13/EC). This selection of ingredients that have to be listed on the label corresponds to the most frequent food allergies and intolerances in Europe. As some derivatives of known food allergens may not trigger any allergic reactions, certain exceptions

were formulated which are valid up to November 2007 (Annex to Directive 2005/26/EC of the Commission of 21 March 2005 establishing a list of food ingredients or substances provisionally excluded from Annex IIIa of Directive 2000/13/EC). To reflect the latest scientific findings, the Directive is to be continuously re-examined and, if necessary, updated.

The above-mentioned labelling provisions mainly refer to packaging labels on ready-to-eat products. Exceptions are so-called “loose products” like bread and bakery products, sausage and cheese which are sold over the counter in bakeries, butchers shops, canteens, at weekly open air markets etc. by sales staff to the consumer. This wording need not appear either on pre-packaged food like freshly prepared salads, which are prepared at the point of sale for immediate sale to the consumer and are handed over to the consumer by the sales staff. Foods, however, must be labelled if the customer purchases a salad, etc. in a self-serve outlet.

There are currently no limit values in Germany or the EU for mandatory listing of allergenic components on the label. Allergens which unintentionally reach the food need not be labelled either. The causes of unintentional contamination with allergenic (otherwise mandatory labelled) components (cross contamination) are mainly the (unwitting) use of contaminated ingredients and the carry-over of contaminated ingredients into the production process as a consequence of inadequate rinsing or inadequately separated production sections. Hence for reasons of product liability some manufacturers use the wording “May contain traces of XYZ (XYZ = allergens, e.g. hazelnuts)” in the labelling of their products.

When the wording “May … contain” is merely used for prophylactic reasons because suitable measures to reduce or even prevent cross-contamination would make production more expensive, this is not really in the interest of consumer protection as growing use of this wording further reduces the choices available to allergy sufferers. At all events, it is recommended that manufacturers quantitatively determine the degree of contamination and take technical steps to prevent it.

### 3.1.3 Examples of other relevant allergens that as yet need not be listed on labels

**Lupins**

There have been cases of hypersensitivity reactions to lupins and products made from lupins like lupin flour which have been reported several times in recent publications. Lupin products include lupin flour, which is used for the production of gluten-free bakery products and meals for the dietetic treatment of patients suffering from coeliac disease as well as numerous ready-to-eat products (quark, tofu, sausages, liquid spices, schnitzel, vegeburgers, spreads, pasta, all types of bakery goods, coffee substitutes) to which lupin flour, lupin protein concentrate, lupin bran or lupin fibre concentrates are added. These products are mainly intended for vegetarians and are sold in health food stores. There are no exact figures on the frequency of use or level of consumption of lupin products. Cases of hypersensitivity reactions to lupin flour and cross-reactivities with peanut allergies have been documented (e.g. Radcliffe *et al.,* 2005; Wüthrich *et al.,* 2004; Smith *et al.,* 2004; Faeste *et al.,* 2004). Lupin flour is normally listed as an ingredient in bakery products / baking mixtures and ready-to-eat products which are sold to coeliac disease patients and vegetarians. However, it may not always be listed when small amounts of lupin products (flour or protein / fibre concentrates) are used because of their emulsifying properties instead of food additives.

It would be appropriate and desirable for consideration to be given to the mandatory labelling of lupin products as ingredients because of the small amounts that suffice to trigger allergic symptoms and the possible severity of the symptoms of a lupin protein allergy even though,

at the present time, the prevalence of lupin protein allergies is nowhere near as high as that of peanut or soybean protein allergies. BfR refers to the EFSA Opinion on Lupins (EFSA, 2005).

**Seafood**
Seafood is seen as a relevant allergenic food (Osterballe *et al.,* 2005; Lorenz *et al.,* 2001) for which mandatory labelling is in place in Australia and New Zealand in addition to the known main allergens mentioned above (Boden *et al.,* 2005).

Molluscs are a large and diverse group of seafood that include roughly 100,000 species which live in salt water, fresh water and on land. Some molluscs are an important source of food. They are used as ingredients in processed foods like soups and sauces and in products like surimi. There have been reports of food allergy reactions to various molluscs like snails, oysters, mussels, clams, squid, abalones and octopus which were, in some cases, life-threatening. The prevalence of self-reported mollusc allergies extends from approximately 0.15% (4 in 2716) in school children in France up to around 0.4% (or 20% of all cases of seafood allergies) in a household study involving 14,948 people in the USA.

BfR considers that reflections on mandatory labelling for molluscs as ingredients in foods are called for and refers to the EFSA Opinion on the Assessment of Molluscs for Labelling Purposes (EFSA, 2006).

**Further foods or ingredients**
Other foods or ingredients which have been described as triggers of hypersensitivity are carrots, cucumber, oranges, pineapples, tomatoes, raw potatoes (Osterballe *et al.,* 2005) as well as stone and pomaceous fruit like peaches, kiwis, mangoes, and lychees (Besler, 2001). Peas are also included amongst the more important possibly allergenic foods (DGE, 2002).

Celery is one of the main allergens. It triggers allergies relatively frequently and plays a major role in the mugwort-celery-carrot-spice syndrome (Besler, 2001). There have also been reports of allergic reactions to various spices and herbs like aniseed, coriander, caraway, chamomile and paprika (Besler, 2001). Curry, pepperoni, parsley, oregano, green pepper and ginger may also be allergenic ingredients (Osterballe *et al.,* 2005).

**Cross-reactions**
When considering foods and ingredients that can lead to intolerance reactions, possible cross-reactions should be taken into account. Cross-reactions are based on structural similarities between the allergenic proteins of various foods or between pollen and food allergens. They extend the sensitisation spectrum in humans. A cross-reactivity has been observed between an allergy to latex and certain fruits like avocados, potatoes, bananas and tomatoes (Samartin *et al.,* 2000). Up to 80% of people who are sensitised to birch pollen also have a cross-reactivity to foods like apples, cherries, brazil nuts, celery, hazelnuts, kiwi, oranges, tomatoes, carrots and peaches (Osterballe *et al.,* 2005; Samartin *et al.,* 2000; Besler M, 2001; Burks/Ballmer-Weber, 2006) and, in some cases, to soya as well. In some cases allergens of fresh fruit and vegetables have proved to be heat labile which means that the allergenic potential can be reduced by heating the food.

The most frequent clinical manifestation of a pollen-associated food allergy is the oral allergy syndrome (OAS) which occurs directly after or within 30 minutes of eating the food. This mainly involves itching and swelling of varying degrees of the oral mucosa, lips and tongue, but severe systemic manifestations are also possible (Ballmer-Weber/Wüthrich, 2001; Vickerstaff Joneja, 1999; Burks/Ballmer-Weber, 2006).

**Non-immunologically mediated food intolerances**
Non-immunologically mediated food intolerances caused by a real or induced enzyme deficiency (e.g. lactase deficiency) or pseudo-allergies after mediator release are not triggered by the immune system. Other pseudo allergic phenomena, induced for instance by salicylates or the effects of certain biogenic amines like histamine, serotonin and tyramine are also not caused by the immune system (Raithel *et al.,* 2002). Dietary enteral histamine intake (for instance from certain types of cheese, anchovies, tuna fish) may lead to food-induced histaminosis with gastrointestinal symptoms, headache, flush, tachycardia and a drop in blood pressure. Fresh foods contain hardly any or only low amounts of biogenic amines as long as they are not exposed to any microbial influence. Fermented foods of plant and animal origin contain varying amounts of amines depending on the degree of processing and refining. Examples that can be mentioned here are cheese, in particular cheddar and blue cheese, sauerkraut and wine. Depending on the hygiene conditions (production, transport, warehousing, processing) excessive bacterial contamination may lead to spoilage processes with an ensuing increase in the amine content. High protein foods like fish, meat and sausages may be particularly affected (Siedentopp, 1997).

3.1.4 Summary

There are no robust prevalence data that would permit a ranking of the above-mentioned possible allergens. Any prioritising of the main allergens by the severity of their allergy-inducing potential is difficult as sensitivity varies considerably between individuals.

3.2 Contribution of pesticides and contaminants to the development of an allergy

Various organophosphates (diazinon, dichlorvos, fluazinam, parathion) are indicated as triggers of asthma at the workplace (www.asmanet.com). So far there have been no reports of pesticides and contaminants that have triggered allergies via the oral route.

3.3 Prevention measures, particularly in infant and child nutrition.

According to estimates, an atopic constitution – a genetic predisposition to sensitisation by allergens and to the production of IgE antibodies – contributes to between 70 and 80% of the manifest IgE-mediated allergic diseases.

Breastfeeding and an avoidance of exposure to tobacco smoke during pregnancy and after birth are recommended as the main prevention measures (Johansson und Haahtela, 2004). Breastfeeding does not have a 100% preventive effect; this seems to be restricted to allergic dermatitis and seems to merely postpone manifestation.

Exclusive breastfeeding and the avoidance of complementary food and dairy milk in the first four to six months of a baby's life are recommended for all children, irrespective of their genetic predisposition. The breastfeeding mother does not need to keep to an elimination diet except in the rare cases in which a food allergy has been identified in the breastfed infant by means of reliable diagnostic methods.

If an infant is not breastfed and there is a family history of allergic diseases in first-degree relatives, the infant should only be given formula with proven reduced allergenicity for at least four to six months (Muraro *et al*., 2004a, b, c; Halken, 2004). The hypo-allergenicity of these foods should not only be determined by characterising protein segments using chemical or immunological methods but should also be confirmed in controlled clinical trials. There are

scarcely any robust data on the recommended dietary regimen in the second half of a baby's first year of life in the case of a family predisposition. The gradual introduction of new foods under observation is recommended whereby foods (eggs, soya, fish, nuts, peanuts) which cause allergies very frequently in early childhood, should not be given to the child before it reaches the age of two.

A newborn baby has the most intensive contact with allergens via the gastrointestinal tract. In simple terms, there are two possible reactions: sensitisation or the development of an oral tolerance with an immunological response that is not characterised by inflammatory tissue messenger substances. So far, it has not been possible to identify the underlying mechanisms.

Besides a genetic predisposition (41 to 70% of all infants with a dairy milk allergy come from families with atopic diseases compared with 29 to 35% of non-allergic infants), the functioning immunity of the mucosa of the gastrointestinal tract plays a decisive role in protection against allergies. This mucosa-associated immune system consists of a non-specific (mucus) and a specific component with the capacity for immune exclusion. Immune exclusion for instance takes place through secretary antibodies or suppression mechanisms whereby local or systemic sensitisation to harmless food antigens is avoided. These specific mechanisms are not fully developed at birth. Their development depends on adequate microbial stimulation and also on the time and level of the first contact with food antigens (Hauer, 2006). One highly promising research area is the influence of food on the intestinal microbiota of infants (Penders *et al.,* 2006) and the administration of probiotic bacteria in the first six months of life in order to stimulate the development of the immune system in the expectation of effects on the onset of allergic diseases.

In the case of a proven food allergy (open exposure, DBPCFC, skin tests, serology), the standard treatment is still a diet in which the foods which have been proven to cause the allergy, are left out.

The specific induction of oral tolerance in individuals with an existing food allergy could be an alternative to the strict elimination diet which often constitutes a major burden for the people affected (Staden *et al.,* 2006). On the basis of specific oral tolerance induction, concepts could be developed for the targeted primary prevention of allergic diseases (Strid *et al.*, 2004) if the immunological processes involved could be elucidated, if the necessary allergen doses could be determined and if the decisive molecules for the production of oral tolerance could be identified (Niggemann *et al.*, 2006). For some years now experiments have been under way to induce a specific oral tolerance by slowly increasing intake (may take up to one year) of the foods that trigger the allergy symptoms and, in this way, bring about a supposedly active suppression of the immunological (IgE mediated) reaction. However, it has been shown that regular allergen intake is necessary to maintain tolerance (Rolinck-Werninghaus *et al.*, 2005). In the case of pollen-associated food allergies, the hyposensitisation treatment of allergic rhinitis or bronchial asthma can also alleviate the symptoms of food allergies (AWMF Guideline No. 061/011).

## 3.4 Summary

Annex IIIa to the EU Directive 2000/13/EC on the labelling of foods lists the foods which trigger allergies and certain food intolerances the most often. These so-called main allergens must be listed on the labels of (pre-packaged or mainly processed) foods. They are gluten-containing cereals (wheat, rye, barley, oats, spelt, kamut or hybrid strains of them), crustaceans, eggs, fish, peanuts, soybeans, milk, shell fruit (almonds, hazelnuts, walnuts,

cashew nuts, pecan nuts, brazil nuts, pistachios, macadamia nuts, Queensland nuts), celery, mustard, sesame seeds and products derived from them as well as sulphur dioxide and sulphites at concentrations of more than 10 mg/kg or 10 mg/l expressed as $SO_2$. As some derivatives of known food allergens may not trigger allergic reactions, some exceptions have been formulated which are valid up to November 2007.

This mandatory labelling does not apply to so-called “loose goods” like bakery products, sausage and cheese which are sold to the consumer over the counter (bakeries, butchers shops, canteens and at open air weekly markets). Foods in pre-packages which are produced at the point of sale for immediate sale to the consumer and are handed over to consumers, do not have to be similarly labelled either (like freshly prepared salads, which are packaged in the shop and handed to the consumer by sales staff).

Appropriate measures should be taken to prevent unintentional contamination with allergenic components subject to mandatory labelling which may occur during the production process (cross-contamination) of foods. This includes appropriate rinsing as well as the use of separate conduction systems and production segments to prevent/avoid carry over. Because of the different products and production processes, it is, however, difficult to apply the principles of good manufacturing practice or technological unavoidability when assessing these measures.

Some spices, herbs and peas have an allergenic potential which, however, seems to be less relevant in terms of numbers than the main allergens already mentioned in Annex IIIa to the Food Labelling Regulation (EU Directive 2000/13/EC Annex IIIa).

Individuals who are allergic to birch pollen are more at risk of developing additional intolerances to various foods – like apples, cherries, brazil nuts, celery, hazelnuts, kiwis, oranges, tomatoes, carrots, peach or soya (cross-reactivity with the triggering of an oral allergy syndrome). A similar situation was observed in conjunction with an existing allergy to latex and foods like avocados, potatoes, bananas and tomatoes. Patients who have been diagnosed as having a birch pollen allergy, should be informed by their attending physician about the possibility of a cross-reaction to a series of foods. Information on the various aspects of a birch pollen allergy, including possible cross-allergies that can cause an oral allergy syndrome (OAS) of varying degrees of severity, is available in various forms. Attending GPs, specialist associations and patient associations active in this area should provide sufferers with general and individual information.

## 3.5 Additives

### 3.5.1 Prevalence

Varying information is available on the prevalence of intolerance to food additives. Based on several studies the Scientific Committee on Food (SCF) for the European Commission came to the conclusion in 1981 that between 0.03 and 0.15% of the population are affected (SFC, 1982). In other studies from Holland (Jansen *et al.,* 1994), Denmark (Fuglsang *et al.,* 1993; Madsen 1994) and the United Kingdom (Young *et al.,* 1994), the prevalence of intolerance to additives was 0.13%, 1% and 0.026% respectively (SCF 1995). There are various reasons why prevalence can vary so markedly (Madsen 1994, EFSA 2004). The exact diagnosis of intolerance is not easy. Unlike the detection of real allergies, there are no simple blood or skin tests for the detection of pseudo-allergies. The prevalence of intolerance reactions to additives can only be reliably determined in extensive, placebo-controlled, double blind oral provocation tests. These requirements are only met by a few studies (Simon 2003).

Furthermore, specific groups like asthmatics or patients with urticaria or angioedemas were frequently examined who have a special sensitivity and are already undergoing medical treatment for corresponding symptoms. The results of studies of this kind can only be transferred in a limited manner to the overall population. Differing data on the prevalence of intolerance to additives can, therefore, be attributed to differences in the respective test populations but also to methodological difficulties in detecting pseudo-allergic reactions.

### 3.5.2 Examples of relevant additives

According to Kreft *et al.* (1995) and Simon (2003), some examples of additives mentioned in conjunction with pseudo-allergic reactions are:

the preservatives:
- sorbic acid and sorbates (E200-E203),
- sodium, potassium or calcium benzoates (E211-E213),
- parahydroxybenzoic acid esters (E214-E219) and sulphites (E220-E228),

the antioxidants:
- butylated hydroxy-anisol (BHA, E320) and butylated hydroxytoluene (BHT, E321),

the dyes:
- tartrazine (E102),
- sunset yellow S (E110),
- amaranth (E123),
- cochineal red A (E124),
- erythrosine (E127),
- patent blue V (E131) and indigo carmine I (E132)

the flavour-enhancer:
- monosodium glutamate (E621).

**Sulphites**
Adverse reactions to sulphites have been described in detail by the EFSA Scientific Panel on Dietetic Products, Nutrition and Allergies NDA (EFSA 2004). Sulphites are used as preservatives (E220-E228). They do, however, also occur naturally in foods as a consequence of fermentation processes, for instance in wine. They may be formed during the digestion of sulphur-containing amino acids, too. In 1994 SCF established an ADI (Acceptable Daily Intake) of between 0 and 0.7 mg $SO_2$/kg body weight. However, it stressed that compliance with this ADI did not mean that intolerance reactions like asthma induced through sulphite could be ruled out. While no information is available on the prevalence of intolerance to sulphites in the general population, data are available for asthma sufferers from various oral provocation studies indicating a range of between 4 % and 66 % (EFSA 2004). The main intolerance reactions are bronchial spasms which may occur within a few minutes of eating sulphite-containing foods. Other effects were also observed, too. The pathogenesis has not been clearly elucidated. Immune-mediated and non immune-mediated mechanisms are under discussion whereby the NDA Panel is of the opinion that the existence of immune-mediated mechanisms is very unlikely (EFSA 2004). According to Directive 2003/89/EC foods containing concentrations of more than 10 mg/kg or 10 mg/l (expressed as $SO_2$) of sulphur dioxides or sulphites must be correspondingly labelled. This value is based on the detection limit of the available methods for the determination of sulphur dioxide and sulphites. A threshold for intolerance reactions induced by sulphites is unknown; it could be lower than 10 mg/kg.

**Tartrazine**
In the past the dye tartrazine (E102) has frequently been linked to an asthma-inducing effect. According to Simon (2003) however, sensitivity to tartrazine in asthmatic patients is extremely unusual. Reports that up to 50 % of asthmatics who are sensitive to aspirin are also sensitive to tartrazine could not be confirmed in placebo-controlled, double blind studies (Simon 2003).

**Monosodium glutamate**
Monosodium glutamate, used as a flavour enhancer (E621), also occurs naturally in foods. It is linked to a series of symptoms. Since reports in the 1960s about intolerance reactions after eating glutamate-containing dishes in Chinese restaurants, they are also called “China Restaurant Syndrome” or “Sodium Glutamate Symptom Complex”. Glutamates have been evaluated several times by the expert committees JECFA (Joint FAO/WHO Expert Committee on Food Additives) and SCF and accepted for use in foods. These evaluations also took into consideration the possible occurrence of intolerance (WHO 1987, SCF 1991). An expert body of the Federation of American Societies for Experimental Biology (FASEB) assessed monosodium glutamate on behalf of the American Food and Drug Administration (FDA) and found that a low, non-identified percentage of the population reacts to the consumption of monosodium glutamate with certain symptoms which are usually transient and not life-threatening. In these cases reactions had been observed under non-typical consumption conditions and after the intake of larger amounts of monosodium glutamate (3g or more) on an empty stomach and in the absence of foods. The 1995 FASEB report suspected that individuals suffering from severe asthma may be especially sensitive to glutamate (FDA 1995). This could not, however, be confirmed in placebo-controlled, double blind studies (Simon 2003).

**Cochineal, carmine and carminic acid**
In most cases intolerance reactions to additives are pseudo-allergic reactions whereby some additives can also lead to immune-mediated reactions (SCF 1995). IgE-mediated immune responses may, for instance, be triggered by cochineal extract (E120). The terms cochineal, carmine and carminic acid are sometimes used as synonyms but refer to different substances. Cochineal is the term used for the dried bodies of female chochineal scale insects, *Dactylopius coccus Costa*, which contain an alkali protein compound of carminic acid. The insects which originate from Central America are grown inter alia in the Mediterranean region. Water soluble carminic acid is made from extracts of the dried scale insect. Carmine is the lake made from precipitation with aluminium salts (Lück und Kuhnert 1998). According to the purity criteria defined in Directive 95/45/EC these commercially available products also contain protein material from the insects. The use of cochineal as a colouring agent for foods has been assessed on several occasions by the expert bodies SCF and JECFA. In 1981 SCF established an acceptable daily intake (ADI) of between 0 and 5 mg/kg body weight (SCF 1983). In 1982 JECFA came to the same conclusion (WHO 1982). The allergenic potential was assessed by JECFA in 2001 (WHO 2001). There have been reports of reactions following occupational exposure, after skin contact and after consumption of foods containing these colours. The symptoms included urticaria, rhinitis, diarrhoea and anaphylaxis. There are several indications that proteins are the allergens, however, the structures of the proteins and the role of the protein-bound carminic acid in the allergic reaction are unknown (WHO 2001, Chung *et al.,* 2001, Tabar *et al.,* 2003). JECFA came to the conclusion that cochineal extract, carmine and possibly carminic acid in foods may lead to allergic, in some cases severe reactions (WHO 2001).

**Mannitol**
An IgE-mediated mechanism was observed in one patient with a mannitol intolerance (E421) (Hedge and Venkatesh 2004). However, this finding is not likely to apply in general.

### 3.5.3 Summary

The occurrence of intolerance reactions to specific additives cannot be ruled out. The current labelling regulations do, however, mean it is possible for individuals to avoid foods in the case of a known intolerance to specific additives.

### 3.5.4 Test requirements for food additives

For food additives there are no mandatory test requirements. The EFSA Scientific Panel AFC that deals with food additives, flavourings, processing aids and materials in contact with food, looks to the recommendations of the Scientific Committee on Food of the European Commission (Guidance on submissions for food additive evaluations by the Scientific Committee on Food (SCF 2001). Studies on tests of immunotoxicity, allergenicity and intolerance reactions are touched on in the SCF recommendations, but are not part of the core studies that normally have to be carried out. A decision is taken on whether studies of this kind are necessary in each individual case.

### 3.5.5 Test requirements for food enzymes (work ongoing)

Standard legal provisions for food enzymes are to be adopted in the EU in the foreseeable future. At the same time, guidelines are to be published for the testing and evaluation of food enzymes. These guidelines are currently being elaborated by the AFC Scientific Panel of EFSA (with the participation of scientists from BfR). They are also to contain requirements for testing for allergenic potential which will probably be based on the recommendations for the testing and evaluation of new proteins in genetically modified plants (EFSA 2004, see 3.6). BfR is of the opinion that the tests proposed are, in principle, helpful but does draw attention to the fact that the tests do not permit a definite statement about allergenicity of a protein in the case of oral intake but allow for an assessment of the allergenic potential. In principle, there is a need to develop further *in vitro* tests and animal models which, after successful validation, can refine or replace the range of methods currently available for assessing the allergenic potential.

Scientists agree that enzymes can trigger allergies in conjunction with inhalation and dermal exposure. This is primarily seen as a risk for individuals who are exposed to concentrated levels of enzymes at the workplace, for instance during production and use in the food-processing industry. There are no confirmed cases in which the consumption of enzyme-treated foods led to a sensitisation of consumers. However, it cannot be ruled out that allergic reactions may occur because of an earlier sensitisation (e.g. at the workplace) or because of cross-reactions.

## 3.6 Assessment of the allergenic potential of foods derived from genetically modified plants

In the case of foods derived from genetically modified plants the allergenic potential can be influenced by the introduction of new proteins but also by changes in the endogenous protein pattern. The following comments describe the procedure currently used by the EFSA Scientific Panel on Genetically Modified Organisms when assessing the allergenic potential (EFSA 2004). It is based on recommendations of expert groups of the World Health

Organisation and Food and Agriculture Organisation (WHO/FAO) and of the Codex Alimentarius Commission (CAC) (WHO/FAO 2001; CAC 2003).

### 3.6.1 Allergenicity of new proteins

Allergenicity is not a fully predictable inherent property of a protein as it is also influenced by the genetic background of the respective individual. There are no validated test methods to predict the allergenicity of a protein after oral intake. At the present time, a combination of different test methods is used to obtain various pieces of information which together allow an assessment of allergenic potential. The assessment is mainly based on comparisons of the protein with known allergens, on information on the allergenicity of the organism that was the donor of the genetic material used and on the results of immunological *in vitro* tests.

First of all a test for sequence homologies and / or structural similarities with known allergens is to be carried out. Bioinformatic analyses, in which the amino acid sequence of the protein in question is compared section by section with the sequences of known allergens stored in databases, can identify identities or similarities with linear IgE-binding epitopes. However, this method cannot be used to identify any epitopes which are formed by non-linear amino acids sequences (conformation epitopes) (Wal 1999).

A second step examines – with the help of immunological *in vitro* methods like immunoblot, RAST (Radio-Allergo-Sorbent-Test) or ELISA (Enzyme-Linked Immuno Sorbent Assay) – whether the protein is bound by specific IgE antibodies from sera of allergic patients. The procedure depends on whether the corresponding gene introduced into the plant comes from an allergenic or non-allergenic organism.

If the donor organism is considered allergenic but no sequence homology of the protein to a known allergen was demontrated, then specific serum screening should be undertaken. For this purpose sera from individuals who are sensitised to the donor organism are needed. In the case of a positive result the new protein may then be considererd very likely to be allergenic. If, by contrast, there is no IgE binding, additional studies should be conducted (see below).

If the donor organism is not known to be allergenic, but there are indications of a sequence homology to a known allergen, specific serum screening should be conducted with sera from patients who are sensitised to this allergen. Furthermore, additional tests should be conducted.

One recommended additional study involves testing the stability of the protein to the digestive enzyme pepsin in simulated gastric fluid (SGF). Some typical food allergens have proved to be relatively stable in this test; by contrast non-allergenic proteins are normally degraded within seconds (Metcalfe *et al.,* 1996). However, no absolute congruence exists (Fu *et al.,* 2002). Furthermore, targeted serum screening can be undertaken. For this sera of individuals are needed who are sensitised to foods broadly related to the donor organism of the genetic material. The use of this method and of specific serum screening is, however, constrained by the limited availability of suitable sera.

If the evaluation of the overall findings indicates that the protein has allergenic potential, then risk management steps must be taken to ensure that individuals with a genetic predisposition for allergic disorders can avoid exposure. In line with the specific requirements for the labelling of foods derived from genetically modified organisms consumers' attention must be drawn to the presence of the protein through appropriate labelling.

If the genetic material introduced into the plant comes from wheat, rye, barley, oats or related types of cereal, it should also be assessed whether the newly expressed protein plays a role in the triggering of gluten-induced enteropathy (coeliac disease) or in other enteropathies.

### 3.6.2 Endogenous plant allergens

If the unmodified plant is known to be allergenic, like soybean, or soybean derived foods, it should also be examined whether the endogenous allergen pattern was changed through the process of genetic modification. This is normally done by separating protein extracts obtained from the genetically modified plants using SDS polyacrylamide gel electrophoresis and the detection of allergenic proteins in immunoblots using sera from individuals with an allergy to soybeans. In future, profiling techniques (proteomics) in conjunction with immunological detection methods could also be used for the qualitative and quantitative analysis of endogenous proteins and peptides with allergenic potential.

### 3.6.3 Prevalence of allergies to foods derived from genetically modified organisms

Up to now there have been no reports at all of an allergy triggered specifically by foods derived from genetically modified organisms. However, in two cases, an allergenic potential of foods derived from transgenic plants was identified in the safety assessment. Based on the safety assessment these organisms were excluded from use in food production.

The allergen range of traditional soybeans was compared with transgenic varieties in a series of studies. Sten *et al.* examined 18 soya extracts (8 traditional and 10 genetically modified types) with serum samples from nine adults allergic to soybean. The immune test (RAST), histamine release *ex vivo* and also the skin test produced variable reaction patterns which, however, also occurred independently of the genetic modification (Sten *et al.,* 2004). In the sera of children with allergic asthma with rhinitis or a food allergy to maize or soybeans, no differences were detected either regarding the reaction to conventional or genetically modified types (Batista *et al.,* 2005).

## 3.7 Novel foods

The safety assessments of novel foods and food ingredients, which come under the scope of Regulation (EC) No. 258/97,are carried out in line with the guidelines of the Scientific Committee on Food (SCF) of the European Commission (European Commission 1997). It calls for an assessment of allergenic potential without, however, making any concrete proposals about the type of test. Given the great degree of heterogeneity of novel foods, the testing and assessments are always done on a case by case basis:

- In the case of individual substances, simple and complex mixtures, the procedure is the same as for food additives. A decision must be taken in each individual case whether and how a test for allergenic potential should be carried out (see section 3.5.4).

- No concrete test requirements were formulated either for complex novel products, which also include traditional foods from non European countries. In principle, it is a problem that new allergies to food ingredients normally only occur after lengthy consumption (with the exception of cross-reactions). In any case, there are no validated test methods for predicting allergenicity after oral exposure. If specific sera from allergic individuals are available, possible cross-reactions to already known

allergens should be examined by using immunological methods like ELISA or Western Blot.

### 3.8 Unanswered questions and the need for research

Up to now, the question about a possible increase in food allergies could not be unequivocally answered up to now as there are no longitudinal studies on allergy prevalence. One way of overcoming this lack of data could be to repeat the Berlin allergy study.

Nor has the question been clarified whether concentrations can be identified for food allergens which are below the threshold for allergy patients. Studies to establish threshold values for individual allergens would also be desirable for the labelling of foods.

The procedure used for the safety assessment of foods derived from genetically modified plants (see section 3.6.1) is also suitable for identifying known allergens in a new host. However, this method is only suited to a limited degree for identifying new allergens or the modified immunogenic properties of known proteins. In principle, there is a need to develop other *in vitro* tests and animal models which – after successful validation – can supplement or replace the spectrum of methods for assessing allergenic potential that are currently available.

In recent years, therefore, allergenicity test models have been developed on the basis of suitable experimental animals (Atherton *et al.,* 2002; Kimber *et al.,* 2003; Knippels *et al.,* 2003). They offer approaches to examine the sensitising potential of popular proteins. According to Prescott and Hogan the animal models must meet the following criteria (Prescott *et al.,* 2006):

- The animals should react with known symptoms to the standard allergens.
- The animals should already be specifically sensitisable to the oral administration of low amounts of the test protein without adjuvants.
- There should be both specific IgE formation as well as other $T_{H2}$ cell responses.
- The clinical picture of the reaction should correspond to the human allergy.
- The animals should be easy to keep, show high reproduction rates and have never been fed the protein that is being tested.

The Norwegian brown rat and Balb/c laboratory mice have proved to be particularly suitable.

The animal models developed in recent years are suitable in principle not only for testing the allergenicity of proteins but also for testing the ability to induce other immunological responses and tolerance. However, they can only be used within the framework of safety assessment after successful standardisation and validation.

There are still unanswered questions concerning the influence of thermal processing techniques on food allergenicity. Thermal processes do frequently reduce the allergenicity of foods. However, there have also been reports of increased allergenicity resulting from the roasting of peanuts (Maleki *et al.,* 2003). The systemic clarification of the influence of thermal processes on the allergenicity of individual allergens down to clinical end points would be desirable. Furthermore, it would be sensible to analyse the critical control points of production processes in order to minimise contamination with allergens by developing quality concepts.

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