German Federal Institute for Risk Assessment

Science Report

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Allergies: background and facts

Allergies affect a large part of the population. According to estimates, more than 30% of people in Germany will develop an allergy in their lifetime. This involves a hypersensitive reaction of the immune system to certain substances that are foreign to the body. These substances, known as allergens, are found, for example, in plant pollen, insecticidal toxins, and food. In addition, medications and chemicals, such as cleaning agents or cosmetics, can also cause allergic reactions. Common symptoms of allergies include itching, welts, reddening, and swelling. Allergic rhinitis leads to a blocked or runny nose as well as to sneezing. Food allergens can also cause skin rashes, in addition to gastro-intestinal disorders, shortness of breath, and fatigue. Particularly severe cases may result in life-threatening anaphylactic shock.

The work of the German Federal Institute for Risk Assessment (BfR) focuses primarily on allergies connected to food and chemicals. This report offers a comprehensive overview of the most important aspects relating to these topic as well as plenty of additional general information about allergies. Through detailed explanations and references, this report supplements the FAQ written in accessible language.

Contents

1 General

1.1 Definition of allergies

An allergy is a hypersensitive reaction, mediated by **immunological mechanisms**. It is triggered by substances known as **allergens** (see also **1.2** and **1.3**), which affected persons were previously exposed to and sensitised by (*1*). Allergen detection is characterised by a very precise interaction between parts of the allergen structure (antigens) and antibodies and/or T cells, which are important components of the body's acquired immune defence.

An allergy can usually be subdivided into two phases. First, the initial **sensitisation phase** to an allergen, which is "clinically silent" (asymptomatic), but leads to what is termed an immunological memory. Substances that can cause such an immune response are also called sensitising. Subsequent contact with the allergen can then lead to the **elicitation phase** involving clinical symptoms, based on the immune memory created. Symptoms can vary: from skin wheals, reddening, and swelling, to sneezing or gastrointestinal problems, shortness of breath, fatigue, or severe allergic shock (see **1.4** and **1.6**). Allergies are divided into various types (see **1.5**). Type I allergies, facilitated by immunoglobulin E (IgE) antibodies, and type 4 allergies, facilitated by T cells, are the most common types and are the focus of this scientific report (*2, 3*).

1.2 Definition of allergens

All substances capable of triggering an allergic reaction are called allergens. Some people's immune systems identify allergens as "foreign" and this induces a hypersensitive (allergic) reaction. Contact with an allergen often occurs via the skin, the respiratory system, or the digestive system as well as through injections (e.g. insecticidal toxins). The amount of an allergen needed to tip the balance from tolerance to the manifestation of acute symptoms can vary greatly from one person to another.

Based on their chemical nature, **proteins** or peptides, e.g. from plants, pollen or mould spores, can be allergens. Animals proteins, for example from house dust mite excrement or animal hair (e.g. from dogs or cats) are also common allergens. In addition, **metals** such as nickel (Ni^{2+} ions), cobalt (Co^{2+} ions) or chromium (Cr^{3+} ions) as well as numerous **organic molecules** of natural or synthetic origin (e.g. medication) are sensitising substances that can trigger an allergic immune response (see **1.3**).

1.3 Number of known allergens

The World Health Organisation (WHO) lists **1,113 protein allergens** (http://www.allergen.org/, last accessed on 14/05/2024). It is still not known why some proteins act as allergens while others do not andresearch is ongoing.

The Regulation on the Classification, Labelling and Packaging of Chemicals (CLP Regulation) (*4*) currently lists more **than 1,200 substances** that are classified in the EU as potentially skin-sensitising (known as harmonised classification, https://echa.europa.eu/de/hot-topics/skin-sensitising-chemicals). Also in accordance with harmonised classification, 120 substances are additionally or exclusively classified as respiratory sensitisers. In addition, many additional substances were classified by the manufacturers, importers, or downstream users as sensitisers (self-classification). Furthermore, many other sensitisers are known that are not yet registered under chemicals legislation. For example, the book

"Patch testing" by Anton De Groot lists over 4,900 substances for diagnosing a contact allergy (*5*) (see **1.4**).

Alongside these known allergens, there are others for which a sensitising effect is either believed to exist or has already been demonstrated in certain cases. These allergens are mostly not included in databases and/or diagnostic testing has not (yet) been established.

1.4 Common allergies in the general population

According to survey data from the Robert Koch Institute, supplemented by laboratory data on sensitisation, more than 20% of children and 30% of adults develop an allergy in their lifetimes.
(https://www.rki.de/DE/Content/Gesundheitsmonitoring/Themen/Chronische_Erkrankungen/Allergien/Allergien_node.html; last accessed 28/02/2024)
However, there is a lot of uncertainty surrounding such surveys, as they are rarely based on any clear diagnosis.

People often come into contact with the following allergens in their everyday lives, listed here according to route of exposure:

Inhaled allergens, also known as aeroallergens, enter the body through respiration. Natural allergen sources include pollen from trees and grass, fungal spores, wood dust, and flour dust; people often encounter the latter two allergens via their work. Household dust contains animal allergen sources, e.g. mite excrement or suspended matter from animal epithelia (i.e. from the outer skin layers). Chemical vapors or volatile components from plastic and coatings can also trigger allergy symptoms.

Injected allergens enter the body via injections. Examples include insecticidal toxins, such as from honeybees, bumblebees or wasps, as well as injected medications and contrast agents.

If ingested, **food allergens** can trigger allergic reactions in people who have been sensitised. In Germany, up to 3 to 6% of the population have a food allergy clinically determined by a doctor or a provocation test. Self-reported allergic reactions are around six times more common and require medical confirmation (*6-8*).

Food allergies should be differentiated from other food hypersensitivities. One example is lactose intolerance. Here, the body is hypersensitive to lactose (milk sugar) and not, as with a cow milk allergy, to milk proteins. In affected indivdiuals, lactose is not broken down in the person's body due to a reduction in or lack of activity of the enzyme lactase. Fructose intolerance is due to fructose malabsorption, wherein the absorption of fructose from the small intestine is not sufficiently effective.

Common triggers of primary IgE-mediated food allergies (see **1.5**) during childhood include chicken eggs, cow milk, peanuts, nuts including hazelnuts or cashews, wheat, fish, and soy (*6, 9*). Children with atopic dermatitis have an increased risk of developing a food allergy (*10*). While many children with chicken egg or cow milk allergies develop a natural oral tolerance, peanut allergies and other nut allergies often continue into adulthood (*6, 9, 11*). For adolescents and adults, pollen-associated food allergens from stone and pomaceous fruits as well as nuts and vegetables (e.g. apple, hazelnut, carrot, or celery) are among the most prevalent triggers. Often, these reactions can be traced back to cross-reactivity following a sensitisation to inhaled allergens such as birch pollen. Crustaceans and shellfish as well as wheat are further food allergens in adults (*6*). Current data from the European

Anaphylaxis Registry show that during childhood peanuts, cow milk and cashews are the most common triggers of food-induced anaphylactic reactions, while wheat, shellfish, hazelnuts, and soy are the most common triggers for adults (*12*).

Contact allergens are typically substances with a relatively small molecular mass (such as metal ions, fragrances, or dyes). The metal nickel (Ni^{2+} ions) remains the most common contact allergen. According to estimates, around 11% of the general European population have a hypersensitivity reaction to nickel in diagnostic patch tests (*13*). Many other metals can also trigger allergies, for example cobalt, chromium, or palladium, which are found in jewellery, leather clothing, and implants (*14*). There are also many non-metallic, organic sensitising chemicals, including preservatives and fragrances, disinfectants, and medications (such as antibiotic ointments). Among other things, the BfR is studying possible allergy triggers in tattoo inks, which are a complex mixture of substances. Several (particularly red) pigments which have hitherto been used in tattoo inks are suspected of being capable of triggering contact allergies (*15*) (see **3.5**). Plants, too, can naturally contain contact allergens. For instance, pollen from plants of the composite family such as the drought-tolerant *Ambrosia artemisiifolia* or a protein found in ficus trees (*Ficus benjamina*) which is similar to the latex allergen can trigger allergies. The frequency of contact allergies among tested patients is collectively documented in Germany, Austria, and Switzerland by the Information Network of Departments of Dermatology (IVDK), which comprises 56 clinics (https://dkg.ivdk.org/). At the European level, this task falls to the European Surveillance System on Contact Allergies (ESSCA) (*16*).

Risk assessments and research, including at the BfR, help determine the most important allergens and allergen sources for the population in the domains of chemicals, food contact materials, and foodstuffs, thereby forming an important foundation for measures for exposure reduction (see **5.1** and **5.2**).

1.5 Allergy reaction types

Allergic reactions can be divided into different reaction types with different immunological mechanisms. In reality, the reaction types frequently occur as a mixture.

Type I to type III allergies are mediated by antibodies. In **type I allergies**, **IgE antibodies** are involved. These antibodies can trigger a reaction to, for example, food allergens or inhaled allergens within seconds to minutes through the release of histamine or other messenger substances from mast cells and basophilic granulocytes (“immediate hypersensitivity reaction”) (*1*). In the most serious cases, this can lead to anaphylactic shock.

Type II and III allergies involve other effector mechanisms, such that reactions only occur after approximately six to 12 hours. Examples of type II allergies include undesired medication effects; type III allergies include vasculitis, serum sickness, and farmer's lung.

T cells mediate the immune response in **type IV allergies**. The full elicitation of this immune reaction takes longer, typically 12 to 72 hours. Therefore, this type is commonly referred to as “delayed hypersensitivity reactions”. Allergic contact eczema is a classic example of a type IV allergy. However, T cells can also be involved as the main effectors in medication reactions.

In late 2023, the European Academy of Allergy and Clinical Immunology (EAACI) updated and expanded the reaction types to include other mechanisms. These include, for example,

damage to the body's barriers such as the skin or the mucous membranes of the lungs or intestines (e.g. through contact with cleaning agents), which can make allergic reactions more likely (*1*).

1.6 Allergy symptoms

Allergy symptoms vary widely. They depend, among other things, on the route of exposure, the amount of allergen, the reaction type, and the speed of elimination and/or breakdown of allergens. Symptoms range from light to life-threatening or chronic and may occur at the site of contact with the allergen (local) or independent of the site of contact (systemic). Anaphylaxis (anaphylactic reaction) refers to an acute, systemic reaction with symptoms of an immediate hypersensitivity reaction which can affect the entire body and be potentially life-threatening (*17*). The most severe form of anaphylaxis is anaphylactic shock.

If ingested through the lungs (**inhaled allergens**), allergens can cause seasonal or year-round allergic rhinitis (also called hay fever), bronchial asthma, allergic inflammation of the pulmonary alveoli, or even life-threatening cardiovascular collapse (anaphylactic shock).

Injected allergens can also cause potentially life-threatening allergic reactions (including anaphylactic shock and severe skin reactions).

After oral exposure to food allergens, symptoms can occur in various organ systems. Skin or mucous membrane symptoms, for example itching, redness, swelling, and hives, are most common (*6*). If atopic dermatitis is already present, aggravation of eczema can occur. The digestive system can also be affected, with symptoms such as nausea, stomach aches, vomiting, and diarrhoea. Symptoms of the respiratory pathways include rhinitis and coughing as well as shortness of breath or wheezing up to respiratory distress. The cardiovascular system can be affected, too. For example, people may experience dizziness or elevated heart rate. In the most severe case, ingestion of an allergy-triggering food allergen can lead to anaphylactic shock (*6*). Pollen-associated food allergies primarily lead to oral allergy syndrome (OAS). Itching or light swelling of the mouth and throat are typical symptoms (*6*).

After **skin contact** with sensitising substances, for instance through use of cosmetics, **allergic contact eczema** can occur in sensitized individuals after one to several days, typically at the site of contact with the product.

1.7 Allergy diagnosis

After gathering a comprehensive medical history, type I allergies (for example to foods, pollen, insect toxins) are generally first diagnosed with a sensitisation test, i.e. a skin prick test or IgE detection in the blood. For a skin prick test, drops of each test allergen solution are placed next to each other onto the inner side of the forearm. The skin is then pricked with a lancet. To diagnose food allergies, (native) foodstuffs are also used (*6*). The formation of wheales at the individual prick sites after about 15 to 30 minutes suggests a corresponding sensitisation, which is scored by the attending doctor according to severity. Additionally, the concentrations of allergen-specific IgE antibodies in a blood sample can be determined. There are also other methods of allergy detection, such as basophil activation tests (BAT), although this method has yet to become an established part of clinical routines. The presence of a sensitisation – determined by a prick test or an IgE detection in serum – does not automatically mean that symptoms will necessarily occur and does not constitute

confirmation of clinical relevance. For this reason, in particular when a patient's medical history is not a clear indicator, provocation tests play a significant role in diagnosing or determining allergies and are the gold standard when it comes to food allergies (see https://www.allergieinformationsdienst.de/provokationstests.html) (*6*).

Contact allergies (type IV) are determined using patch tests. Test substances are applied to the patient's back for 48 hours and covered with a plaster. Subsequent skin reactions (redness, swelling, blistering, eczema) are generally diagnosed after 48 to 72 hours and scored according to severity. Of 4,900 established patch tests (*5*), only some (currently around 120 test compositions) are authorized in Germany. Alternative *in vitro* tests have yet to become an established part of routine diagnosis, although they are, for example, performed in specialised laboratories for diagnosing allergies to implants (*14, 18*). The selection of allergens for standard tests or advanced tests is aided by national and European professional associations. For patch tests, these include the German Contact Allergy Group (DKG, https://dkg.ivdk.org/testreihen.html).

Sensitisation tests or patch tests can lead to false negative results, meaning they can fail to detect existing allergies. Positive results are also possible without the actual presence of clinical relevance. Clinical relevance for patch tests is defined according to a current guideline as follows: "The allergic test reaction is deemed to be relevant when the determined sensitisation 'explains' the current or a past episode of allergic contact eczema due to exposure to the allergen." (*19*). The reaction sensitivity can change across a patient's lifetime.

1.8 Cross allergies and the role of pollen

A cross allergy occurs if, for example, a person allergic to **birch pollen** triggered by inhalation suddenly develops a reaction after eating **apples, hazelnuts, and celery** (*6, 20*). Cross-reactions can be attributed to allergens or substances (proteins or chemicals) which are structurally similar and which activate the immune system in the same way, meaning they interact with the same T cells and/or antibodies. Pollen plays a special role here, because the allergens found therein are often very similar to proteins in foods. Other examples include cross-reactions between allergens from house dust mites and crustaceans (e.g. shrimp) or cross-reactions among chemical allergens, such as between nickel and palladium ions (*21, 22*). Often, however, it is unclear whether cross-reactivity is present (meaning the same antibodies or T cells react) or whether the case is instead a co-sensitisation (different antibodies/T cells react since two or more allergies are present in parallel). The molecular foundations, for instance in relation to potential cross-allergies to insects as novel foods, are being studied, including at the BfR (see **5.2**).

External link: https://www.ecarf.org/en/information-portal/allergies-overview/celery-cherry-and-more-cross-reactivity/.

1.9 Factors influencing allergy development

By now, several factors are known that potentially impact the development of allergies. **Genetic predisposition** plays a role for inhalation and food allergies. If both parents have allergies, it is more likely that their child will also develop an allergy (*23, 24*). Genetic variants might play a role in contact allergies, for example mutations of the filaggrin gene leading to a damaged skin barrier, which is suspected of making the development of contact allergies more likely (*25*). Other **life circumstances and environmental influences** can also

impact the development of allergies. Particularly in the past six decades, reports of allergy cases have increased (*26*). According to the "diversity hypothesis", a lack of exposure to certain, not yet clearly defined bacteria might make the development of allergies in early childhood more likely (*27*). Tobacco smoke also seems to contribute to the development of allergies in some people. Furthermore, damage to the body's barriers, such as due to frequent hand-washing with soaps or detergents, might influence the development of skin allergies (*26, 28*).

Certain **professions** are correlated with a higher risk for the development of allergies, since they involve a higher degree of **contact with allergy-triggering substances**. The most common allergy-triggering substances in professional contexts include flour dust, metals, preservatives, substances used in hairdressing (such as hair dyes), methacrylates (plastics manufacturing), and epoxy resin systems (flooring, painting) (*29*).

Current research is focused on the causes of allergy development and the in some instances still rising rates of allergies (e.g. inhaled and food allergens) (*30-32*).

1.10 Protection against sensitisation

It is **not really possible to prevent** the development of an allergy or a sensitisation to allergens common in the environment and it is **hard to predict** on an individual basis if a person will develop an allergy. Current knowledge regarding the prevention of atopic diseases, specifically atopic eczema, food allergies, allergic rhinitis, and (allergic) asthma, is summarised in a recently published guideline (*33*). In addition to smoke-free and low-pollution environments, recommendations are also made regarding diet for mothers and infants in their first year of life as well as biodiversity within households. There are, for example, new discoveries showing that early exposure to adequately cooked chicken egg in complementary feeding is more likely to lead to tolerance than to a chicken egg allergy (*33*). Some studies suggest that having a dog in the household might prevent the development of allergies (*34*).

Preventative occupational safety in Germany is the task of the German Federal Institute for Occupational Safety and Health (BAUA, https://www.baua.de). In general, contact with known sensitising substances should be reduced by means of appropriate occupational safety measures, for instance through avoiding or minimising skin contact or inhalation. This should predominantly be ensured through technical and organisational measures at workstations (e.g. extraction systems) as well as through personal protective equipment such as appropriate gloves, respiratory masks, or protective clothing in cases where replacing hazardous substances with safer ones is not possible.

1.11 Protection against and treatment of allergic reactions

Once an allergy has been diagnosed, further contact with the allergen should be avoided. For example, certain foods or problematic cosmetics should be avoided (**allergen avoidance**) for protection against allergic reactions. However, this is only possible if the critical allergen has been identified and if the (professional) circumstances of the affected person allows for avoidance (e.g. hairdressers). Labelling requirements for foods and products such as cosmetics can help people avoid allergens (see **2.1** and **3.1**).

Hyposensitisation therapy or specific immune therapy (desensitisation) allows for a controlled introduction of allergen exposure in order to enable the body to develop

tolerance (*35*). Such therapies are already available for individual allergens and routes of exposure for IgE-mediated allergic diseases. For others, research and development is still ongoing (*36*). Specific immune therapy with approved compositions can be particularly effective for inhaled allergens such as grass pollen or dust mites (*35, 36*). Over time, individual reactivity to an allergen can change and hyposensitisation or desensitisation is not equally effective for everyone.

2 Further information on food allergies

2.1 Labelling food allergens in Germany and the EU

In the EU, in accordance with Regulation No 1169/2011 (*37*), the **14 most common substances or products** which may trigger allergies and intolerances must be labelled on foods in which they are used as ingredients. This regulation specifies grains with gluten (specifically wheat such as spelt and Khorasan wheat, rye, barley, oats, or hybrid strains), crustaceans, eggs, fish, peanuts, soy beans, milk, nuts (specifically almonds, hazelnuts, walnuts, cashews, pecans, Brazil nuts, pistachios, and macadamia and Queensland nuts), celery, mustard, sesame, sulphur dioxide and sulphites (from 10 mg per kg or l), lupins, and molluscs (e.g. snails, muscles, oysters, squid).

Allergens inadvertently introduced into foods, however, do not need to be labelled. Corresponding labels ("May contain traces of...") are voluntary and are often used by manufacturers as a precautionary measure. For this reason, consumers cannot rely on the presence or absence of such labels to know if and in what amounts allergens are truly present in foods. The EU and the WHO are therefore currently discussing mandatory labelling on the basis of reference doses that includes unintentional allergen introduction (*38*).

2.2 Insects as a food source

From 2021 to 2023, **four species of insect** were approved in the EU as **novel foods**: the larvae of the yellow mealworm (*Tenebrio molitor*), the European locust (*Locusta migratoria*), crickets (*Acheta domesticus*), and the larvae of the lesser mealworm (*Alphitobius diaperinus*) (*39-41*). Other insects have been submitted for approval as foodstuffs.

The extent to which primary sensitisation to insects occurs is still unclear. Due to protein pattern similarity to house dust mites and crustaceans, cross-reactivity might be responsible for the elicitation of allergic reactions (*42*). For this reason, foods must be labelled if they contain insect components. A handful of human studies out of Laos and China have reported symptoms of food allergies in sections of the populations which consume insects (*43*). The applicability of these findings to the European context is still unclear.

The BfR is of the opinion that much research is necessary and is therefore conducting its own studies to assess the allergic potential of insects in Europe (see **5.2**).

3 Further information on allergies to chemicals

3.1 Regulation of the use of sensitising chemicals in Germany and the EU

In the EU, chemicals with hazardous properties are classified according to the CLP Regulation (*4*) and must be labelled accordingly. There is currently a harmonised classification of around 1,200 substances as skin sensitisers; a far smaller number is classified as respiratory sensitisers. Mixtures containing classified substances in concentrations above certain (sometimes substance-specific) thresholds must also be labelled, provided a test of the mixture does not demonstrate the opposite. In general, **generic concentration limits** (GCL) apply for the use of sensitising substances in mixtures. For particularly potent sensitisers, the Committee for Risk Assessment (RAC) of the European Chemicals Agency (ECHA) can propose specific concentration limits (SCL). All harmonised classifications and the GCL/SCL determinations are made legally binding by the European Commission (EC).

The Regulation concerning Registration, Evaluation, Authorisation and Restriction of Chemicals (**REACH Regulation)** (*44*) requires each manufacturer or importer of chemicals above a traffic volume of one tonne per year to submit a registration dossier to the ECHA. This includes, among other things, information about the toxicological properties of the registered substances, including potential sensitising properties. In addition to consideration of the harmonised classification, there are also multiple self-assessments and notifications. In Annex XVII of the REACH Regulation, certain uses of individual sensitising chemicals, including nickel or chromium VI, are restricted. Limits for skin sensitisers in tattoo inks have been in force since early 2022.

For **cosmetics,** Regulation (EC) No 1223/2009 on cosmetic products (*45*) applies and is supplemented in Germany by the German Cosmetics Regulation. The EU regulation's annexes list prohibited substances (negative list) and approved substances (positive list) and include amount limits and packaging warning label requirements for some, such as for sensitising chemicals like the hair dye *p*-phenylendiamine. Currently, 81 fragrances require individual labels on the packaging of cosmetic products if they are present in certain concentrations (*46*) (https://www.bvl.bund.de/DE/Arbeitsbereiche/03_Verbraucherprodukte/02_Verbraucher/03_Kosmetik/02_KennzeichnungKosmetik/bgs_kosmetik_kennzeichnung_node.html;jsessionid=28A3EE52B3C44AB4FB3BC996269631DE.internet971).

Biocides are subject to the Biocidal Products Regulation (*47*) at the EU level and are approved as products nationally by the Member States. Potential skin-sensitising properties are also evaluated. Plant protection products are regulated by the EU Plant Protection Products Regulation (*48*) , which also requires testing for skin sensitising properties.

The **EU Toy Safety Directive (*49*)** is intended to prevent harm through toys. In Annex II, the directive lists prohibited allergenic fragrances (traces < 100 mg/kg allowed) and fragrances requiring labelling as well as maximum amounts of allergenic metals (e.g. for nickel: 75 mg/kg in dry toy materials).

3.2 Preventative testing for sensitising properties of chemicals

Sensitising properties of chemicals are determined using animal experiments (*in vivo*) such as local lymph node assay (LLNA) or using **new approach methods** (NAMs), e.g. *in vitro*. For

ethical, economic, and scientific reasons, new approach methods receive priority funding and development, including at the BfR (see **5.1** and **5.2**). The European Commission's Cosmetics Regulation spearheaded these efforts, prohibiting animal experiments for cosmetic ingredients in 2013, which in turn led to the development of new *in vitro* tests.

Several NAMs for testing for sensitising properties have already been validated by the Organisation for Economic Co-operation and Development (OECD) and the European Commission (Joint Research Centre, JCR) and have been established in the REACH Regulation as well as the regulations for biocides and plant protection products as **standard information requirements**. *In vivo* tests are now only permitted if alternative methods are not feasible or if their results are not meaningful.

Hitherto unknown allergens can also be discovered through clinical research, for example when patients develop eczema as a reaction to previously unknown triggers which can then be identified. There is not yet a validated testing method for determining allergenic effect following oral exposure (although some indirect tests for potential protein allergens do exist).

3.3 Examples of successful regulation of sensitising chemicals

The oldest example of successful regulation in the EU is the restriction on the use of **nickel** in jewellery, which led to a significant decline in sensitisation rates in Europe. It was particularly possible to prevent sensitisation for young people, although nickel remains the most common allergen and Europe-wide studies are not always conclusive (*13, 50*).

Examples of chemical allergens which have caused higher rates of contact eczema include Methylisothiazolinone **(MIT)** and hydroxymethyl pentylcyclohexene carboxaldehyde **(HICC)**. MIT is used as a preservative, for example in wall paint, cosmetics, and household cleaning products, while HICC is used as a fragrance in perfumes, soaps, and deodorants. Both chemicals, which have been subject to harmonised classification as skin sensitisers in the EU, were identified as potential allergy-triggering substances by the Scientific Committee on Consumer Safety (SCCS).

Since around the year 2000, MIT had found increasing use as the sole preservative in industrial products. This led to cases of allergic contact eczema clearly tied to MIT, typically from wall paint (*51*). In 2005, use of up to 100 ppm of MIT was permitted in cosmetics (compared to the previous maximum of 3.75 ppm in combination products). In Germany and across Europe, the increased exposure to MIT led to an epidemic of allergic contact dermatitis due to MIT. There was an increase in confirmed allergies in tested persons from 1.9% (2009) to 4.4% (2011) (*52*).

Between 2005 and 2008, HICC was identified as the triggering allergen for 7.3% of patients with suspected contact allergies (*46*).

Both substances were placed in the category 1A (extreme/strong sensitiser) according to the CLP Regulation in regards to skin sensitisation. Scientific discoveries about both skin sensitisers lead to a ban on HICC and a limit of 0.0015% for MIT amounts in cosmetic products (in rinse-off products). No safe concentration was determined for leave-on cosmetic products, which remain on the skin, for either substance. As a result, their use therein was prohibited. These limits led to a drastic decrease in corresponding new allergies

within the population and contributed to the improvement of preventative risk assessment (*45, 53*).

3.4 Allergens in toys or clothes

According to the EU Toy Regulation(*49*), various allergenic fragrances are prohibited or must be labelled. Thresholds also exist for the most prevalent metal allergens. Textiles are regulated by the European General Product Safety Regulation (*54*) in combination with the REACH-Regulation (*44*). Allergic reactions in the form of contact allergies are rather rare when it comes to textiles (https://www.allergieinformationsdienst.de/vorbeugung-und-schutz/kleidung). European agencies exchange information about hazards relating to consumer products using the European rapid alert system Safety Gate (formerly RAPEX). Consumers can also find information here (https://ec.europa.eu/safety-gate-alerts/screen/webReport).

3.5 Allergens in tattoo inks

Tattoo inks consist of many individual substances which are introduced into the skin. There, the inks come into contact with immune cells and lymph fluid, which can lead to a specific reaction of the immune system – possibly intensified by the skin damage caused during tattooing. Tattoo inks can contain known sensitising substances, such as formaldehyde or heavy metals like nickel. There is evidence suggesting that certain colour pigments, especially red colours, more readily cause allergic reactions (*55*). Additionally, ingredients in tattoo inks can be transformed into new chemical compounds over time due to the impact of light or by being broken down by enzymes within the body. Laser removal, too, can lead to new chemical components. These new substances can potentially have an allergenic effect and may occur after significant delay. Allergic reactions to tattoo inks can therefore occur both directly after the tattooing and years later.

Substances with known health-hazardous effects including potential sensitising properties in tattoo inks and permanent make-up are limited by the REACH-Regulation (Entry 75, Annex XVII) (*44, 56*). This regulation sets maximum concentrations for such substances (further information: https://echa.europa.eu/hot-topics/tattoo-inks). Future research will show the effect of the new legislation on the occurrence of allergic reactions in connection with tattoos.

3.6 Nickel allergies and nickel in foods

Exposure to nickel through food primarily occurs via plant-based foods. Large amounts of nickel are found in pulses, nuts, oilseeds (approx. 2 mg/kg), chocolate products (approx. 3.8 mg/kg), and cocoa beans and products (approx. 9.5 mg/kg). By comparison, baked goods as well as meat and sausage products contain less nickel. The German Federal Office of Consumer Protection and Food Safety (BVL) publishes an annual report on food safety, which includes an overview of nickel content in foodstuffs in Germany (https://www.bvl.bund.de/DE/Service/01_Infothek/03_berichte/infothek_berichte_node.html).

Current data has not shown the development of nickel allergies following oral exposure to nickel. Once a person has been sensitised, it seems that the triggering of symptoms through nickel in foods may be possible in extreme, outlier cases (*57*). Generally, however, consumption of nickel is not a problem for people with a nickel allergy.

4 Further information on other allergies

4.1 Artificial enzymes in everyday products

Artificial enzymes are used in foods as well as household cleaning products, such as detergents. These include known allergens. In this context, artificial means biotechnologically manufactured – potentially also in a slightly modified, optimised form. The extent to which biotechnological manufacturing can lead to new, unexpected allergenic potential has yet to be fully researched.

5 BfR's activities on the topic of allergies

5.1 Risk assessment and committee activities

Through the **preparation of dossiers** for the harmonised classification and labelling of sensitising substances according to the EU **CLP Regulation** as well as within the scope of the EU biocide regulations and the EU regulations for plant protection products, the BfR actively contributes to improving consumer protection.

The BfR also participates in the toxicological **assessment** of respiratory and skin sensitisers, in the coordination of test requirements for substances with inadequate data, and in the development of proposals for **regulatory measures** in accordance with the EU **REACH Regulation**, e.g. for limiting the use of sensitising chemicals in consumer products.

The contributions of employees of the BfR in expert committees for assessment, further development of assessment guidelines, and testing strategies at the European and the international level, such as in the SCCS and the OECD, are as much part of protecting the population from allergens as their advisory work on allergen labelling together with other stakeholders.

Additionally, the BfR takes part in information exchange in expert dialogues under the auspices of the head of the German Federal Office for Chemicals (BfC) with participation of associations, industry, and other interest groups. Participation in and organisation of scientific events with various stakeholders such as industry associations, agencies of the German federal states ('Laender'), or monitoring laboratories strengthen scientific exchange regarding health risks which can arise from consumer products.

5.2 Research projects (selection)

The BfR conducts intensive research on the topic of allergies within the scope of various projects (https://www.bfr.bund.de/en/allergies-54481.html). Both research projects within the institute and third party-funded projects are conducted. In order to prevent economic interests from influencing research, it is exclusively funded by third-party funding from public national and European institutions. A selection of research topics is listed below:

Allergies to foods

- Development of a testing system for insect-protein-based novel food products for detecting adverse endpoint oral sensitisation, anaphylactic potential, and (cross-) allergies to insect proteins

Allergies to chemicals

- Studies on Methylisothiazolinone as a preservative in cosmetics and other consumer products, development of immunotoxicological tests, studies into (allergenic) azo dyes
- Participation in and assessment of third-party research results in committee work, e.g. on human allergy data, and in *in vitro* test development in the OECD
- Studies on contact allergen-specific T cells in human tissue
- Studies on cross-reactivity of chemical-specific T cells as well as on the unique properties of the T cell receptor repertoire and the development of new blood-based *in vitro* tests on chemical-specific T cell activation for diagnostic and regulatory applications as an alternative to animal experiments
- Identification of "alternatives to skin-sensitising substances in consumer mixtures" as part of the socio-economic analysis of possible restrictions (REFOPLAN Project)

6 Abbreviations

BAT	**B**asophil **A**ctivation **T**est
BfR	German Federal Institute for Risk Assessment, Ger. ***B****undesinstitut* ***f****ür* ***R****isikobewertung*
CAS	**C**hemical **A**bstracts **S**ervice
CLP	**C**lassification, **L**abelling and **P**ackaging
DACH	Germany, Austria, and Switzerland
ECHA	**E**uropean **C**hemical **A**gency
EFSA	**E**uropean **F**ood **S**afety **A**uthority
ESSCA	**E**uropean **S**urveillance **S**ystem on **C**ontact **A**llergies
EU	**E**uropean **U**nion
FAQ	**F**requently **A**sked **Q**uestions
FG	Unit, Ger. ***F****ach****g****ruppe*
GCL	**g**eneric **c**oncentration **l**imits
HICC	4-(4-**H**ydroxy**i**sohexyl)-3-**c**yclohexene-1-**c**arbaldehyde, CAS 31906-04-4
IVDK	Information Network of Departments of Dermatology, Ger. ***I****nformations****v****erbund* ***d****ermatologischer* ***K****liniken*
LNNA	**l**ocal **l**ymph **n**ode **a**ssay
MIT	2-**M**ethyl-4-**i**so**t**hiazolin-3-one, CAS 2682-20-4
NAMs	- **n**ew **a**pproach **m**ethodologies
OECD	**O**rganisation for **E**conomic **C**o-operation and **D**evelopment
RAC	**C**ommittee for **R**isk **A**ssessment
REACH	**R**egistration, **E**valuation, **A**uthorisation and Restriction of **Ch**emicals
SCCS	**S**cientific **C**ommittee on **C**onsumer **S**afety
SCL	**s**pecific **c**oncentration **l**imit
BVL	German Federal Office of Consumer Protection and Food Safety, Ger. ***B****undesamt für* ***V****erbraucherschutz und* ***L****ebensmittelsicherheit*
WHO	**W**orld **H**ealth **O**rganization

7 External information and links

- European Academy of Allergy and Clinical Immunology (EAACI), https://eaaci.org

- World Allergy Organization (WAO), https://www.worldallergy.org
- German Allergy and Asthma Society (*Deutscher Allergie- und Asthmabund*, DAAB), https://www.daab.de/
- Allergy Information Service, https://www.allergieinformationsdienst.de/
- White Book of Allergies in Germany (*Weißbuch Allergie in Deutschland*) https://link.springer.com/book/10.1007/978-3-89935-313-6
- German Pollen Information Service Foundation https://www.pollenstiftung.de/
- European Society of Contact Dermatitis (ESCD) https://escd.org/
- German Society for Allergology and Clinical Immunology, https://dgaki.de/
- European Centre for Allergy Research Foundation (ECARF) https://www.ecarf.org/
- BfR Expert Opinion No. 001/2007 https://www.bfr.bund.de/cm/349/allergies_caused_by_consumer_products_and_foods.pdf

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About the BfR

The German Federal Institute for Risk Assessment (BfR) is a scientifically independent institution within the portfolio of the Federal Ministry of Food and Agriculture (BMEL) in Germany. The BfR advises the Federal Government and the States ('Laender') on questions of food, chemicals and product safety.
The BfR conducts independent research on topics that are closely linked to its assessment tasks.

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