Eur J Dermatol 2016; 26(6): 523-30

Marie-Noëlle CREPY

Department of Occupational Diseases,
Paris University Hospital,
Centre Hôtel-Dieu, AP-HP 1,
Parvis Notre-Dame, 75004 Paris,
France

Reprints: M.-N. Crepy
<marie-noelle.crepy@orange.fr>

Article accepted on 1/4/2016

Rubber: new allergens and preventive measures

Natural rubber latex (NRL) and rubber accelerators are well-known causes of occupational skin diseases. The latest epidemiological data on rubber allergy show that rubber additives are still among the allergens most strongly associated with occupational contact dermatitis, however, a decrease in NRL allergy has been confirmed. A review of recent publications on rubber allergens based on the Pubmed database is presented. New glove manufacturing processes have been developed, such as low-protein natural rubber gloves, vulcanisation accelerator-free gloves, or specific-purpose gloves containing antimicrobial agents or moisturisers. Several websites provide information on allergens found in gloves and/or glove choice according to occupation.

Key words: rubber, latex, allergy, allergen, glove, contact dermatitis

The word caoutchouc (commonly called rubber in English) is derived from the Amerindian phrase cao (wood) tchu (crying). In 1839, Charles Goodyear's discovery of the vulcanisation of rubber revolutionised the use and applications of rubber. Over 20,000 plant species can produce latex but *Hevea brasiliensis* (Willd. Ex A. Juss), a plant belonging to the Euphorbiaceae family, remains the main worldwide source of natural rubber latex [1]. The proportion of synthetic rubber is increasing; in 2011, global natural rubber production reached 10 million tons a year, while that of synthetic rubber was over 15 million tons [1].

There are many recent technological innovations and these go far beyond the field of dermato-allergology. This article is a review of the latest epidemiological data on rubber allergy and an update on rubber allergens and new manufacturing processes of gloves, since these data can be of interest to dermatologists, allergists, and occupational physicians. The data suggest that some examples of alternative gloves should be recommended to allergic subjects.

Update on epidemiology

Rubber additives

A descriptive study based on the national register of occupational diseases was carried out in Denmark in 2010. It included 1,504 patients and found that rubber additives are the main causes of allergic contact dermatitis (ACD). Rubber additives and epoxy were reported to induce 40% of the cases of occupational ACD [2, 3].

Pesonen *et al*. analysed the patch test results to the allergens in the European baseline series in 44,277 patients with and without occupational contact dermatitis; the data was collected from the European Surveillance System on Contact Allergy (ESSCA) from 2002 to 2010 [4]. Rubber additives are the allergens most strongly associated with occupational contact dermatitis; the results are shown in *table 1*. Positive patch test reactions to thiuram mix are found mostly in workers who wear waterproof (occlusive) protective gloves, such as domestic helpers, cleaners, healthcare workers, housekeepers, restaurant workers, bricklayers, and stonemasons.

The information provided by glove manufacturers and the search for the constituents of medical gloves show that most international rubber glove companies have replaced thiurams by dithiocarbamates and/or mercaptobenziothiazole derivatives [5, 6]. However, thiurams remain the rubber allergens that most frequently yield positive patch test results [7]. In a retrospective study (2002-2010) of patients suffering from occupational dermatitis carried out in Germany by Geier *et al*., 3,448 (24.4%) were tested for suspected glove allergy [8]. Among these, healthcare workers represented the largest group (n=1,058). The allergens most frequently yielding positive patch test results were thiurams (13%), dithiocarbamates (3.5%), 1,3-diphenylguanidine (3%), mercaptobenziothiazole and/or its derivatives (3%), and thioureas (0.4%). When comparing their results with those from 1995 to 2001, the authors concluded that the situation has remained unchanged. On the contrary, other more recent studies have shown a decrease in the prevalence of positive patch tests to thiuram mix [9-12].

In the UK, Warbuton *et al*. analysed cases of occupational allergic contact dermatitis induced by rubber additives reported to EPIDERM (an occupational skin disease surveillance network) between 1996 and 2012 [12]. The British baseline series includes thiuram mix 1% pet. (containing tetramethylthiuram disulphide or TMTD, tetramethylthiuram monosulfide or TMTM, tetraethylthiuram disulphide or TETD and dipentamethylenethiuram or PTD), carba mix 3% pet. (containing zinc diethyldithiocarbamate or ZDEC, zinc dibutyldithiocarbamate or ZDBC and 1,3-diphenylguanidine), mercapto mix 2% pet. (containing 2-mercaptobenzothiazole or MBT, N-cyclohexyl-2-benzothiazolesulfenamide or CBS, morpholinylmercaptobenzothiazole or MOR, and dibenzothiazyl disulfide or MBTS), mercaptobenzothiazole (MBT) 2% pet., and N-isopropyl-N′-phenyl-p-phenylenediamine or IPPD 0.1% pet. The other allergens tested vary from

doi:10.1684/ejd.2016.2839

To cite this article: Crepy MN. Rubber: new allergens and preventive measures. *Eur J Dermatol* 2016; 26(6): 523-30 doi:10.1684/ejd.2016.2839

Table 1. Risk of occupational contact dermatitis (OCD) associated with allergy to test substances; Pesonen *et al.* [4].

Allergens	OCD + (%+)	OCD - (%+)	PR (95% CI)
Thiuram mix	5.63	1.35	4.23
2-MBT	1.42	0.52	2.91
N-isopropyl-N′-phenyl-p-phenylenediamine (IPPD)	1.05	0.41	2.62
Mercapto mix (CBS, MBTS, and MOR)	1.32	0.62	2.46

CBS: N-cyclohexyl-2-benzothiazylsulfenamide; MBTS: dibenzothiazyle disulphide; MOR: morpholinylmercaptobenzothiazole.

one dermatologist to another. Thiurams remain the agents that most frequently cause ACD (603 cases), followed by carba mix (219 cases), mercapto mix (177 cases), IPPD (84 cases), N-cyclohexylthiophtalimide (a vulcanisation retarder) in 14 cases, hexamethylenetetramine (five cases), thioureas (four cases), diaminodiphenylmethane (two cases), and dithiodimorpholine in one case. The authors reported a decreasing incidence in ACD induced by thiurams, mercapto mix, and mercaptobenzothiazole, while the incidence of ACD induced by carba mix, which contains 1,3-diphenylguanidine, increased. Several studies have confirmed the increasing prevalence of positive patch test results with 1,3-diphenylguanidine [7]. It has been suggested that this was due to rubber latex gloves being replaced by synthetic rubber gloves [7, 13].

Latex

Preventive measures against latex allergy, in particular the use of low-protein, low-allergen, powder-free natural rubber latex (NRL) gloves, has markedly reduced latex allergies in healthcare workers [12, 14-16]. Recently, Blaabjerg *et al*. investigated the prevalence of NRL sensitisation between 2002 and 2013 in an allergy centre in Denmark (n=8,580) [15]. Latex sensitisation was defined by positive prick test results, whereas clinical NRL allergy was defined by immediate symptoms when exposed to NRL (contact urticaria, angioedema, rhinoconjunctivitis, asthma, gastrointestinal symptoms, anaphylaxis, worsening of hand eczema, or pruritus) combined with a positive prick test reaction. The prevalence of clinical NRL allergy decreased from 1.3% in 2002-2005 to 0.5-0.6% in 2006-2013 ($p<0.004$). Similarly, based on prick tests, the prevalence of NRL sensitisation decreased from 6.1% in 2002-2005 to 1.9% in 2006-2009, and then to 1.2% in 2010-2013 ($p<0.0001$). Of the NRL-sensitised patients, 64% also had a positive prick test reaction to birch pollen and 52% had a history of reaction to oral intake of fruit or vegetables (mainly kiwis, bananas, tomatoes, carrots, and avocados). Gloves (75%) and balloons (33%) were the main culprit materials.

Latest news on allergens

Rubber vulcanisation additives and antioxidants

The real haptens in thiurams and dithiocarbamates remain unknown. Hansson *et al*. tested 24 patients with known contact allergy to rubber accelerators (thiurams, dithiocarbamates, and/or mercaptobenzothiazoles) with a series of 21 compounds identified based on the chemical analyses of vulcanised rubber products (*table 2*) [6]. Diphenylguanidine, p-phenylenediamine oxidants, and thioureas were not included in the study. The baseline series included allergens usually found in the TRUE Test® or Chemotechnique® series, as well as potentially sensitising molecules (*table 2*). Zinc dibenzyldithiocarbamate in 1% pet. from the former Trolab® series, currently marketed by SmartPratice®, was not tested. Thiuram monosulfides induced stronger and more frequent patch test reactions than the corresponding thiuram disulfides. In this study, a positive reaction to a dithiocarbamate was always accompanied by a positive reaction to the corresponding thiuram, except in one case.

Table 2. List of allergens tested with the rubber series of Hansson *et al.* [6].

Chemical family	Marketed allergens	Additional allergens
Thiurams	Tetramethylthiuram monosulfide (TMTM) Tetramethylthiuram disulfide (TMTD) Tetraethylthiuram disulfide (TETD) Dipentamethylenethiuram disulfide (DPTD)	Tetraethylthiuram monosulfide (TETM) Dipentamethylenethiuram monosulfide (DPTM) Tetrabutylthiuram monosulfide (TBTM) Tetrabutylthiuram disulfide (TBTD)
Dithiocarbamates	Zinc dimethyldithiocarbamate (ZDMC) Zinc diethyldithiocarbamate (ZDEC) Zinc dibutyldithiocarbamate (ZDBC)	Methyl N,N-dimethyldithiocarbamate (MeDMC) Methyl N,N-diethyldithiocarbamate (MeDEC) Zinc pentamethylene-dithiocarbamate (ZPD)
Benzothiazoles	2- mercaptobenzothiazole (MBT) N-cyclohexyl-2-benzothiazylsulfenamide (CBS) Morpholinylmercaptobenzothiazole (MOR) Dibenzothiazyle disulphide (MBTS)	2- (methyl)mercaptobenzothiazole (MBT)
Products of thiurams and mercaptobenzothiazoles during vulcanisation		Dialkylthiocarbamyl benzothiazole Sulfide (DMTBS) Diethylthiocarbamylbenzothiazole sulfide (DETBS)

Thiuram disulfides and dithiocarbamates constitute a redox pair, thus during oxidation of a dithiocarbamate, the corresponding thiuram disulphide is formed, while during reduction of thiuram disulphide, a dithiocarbamate is formed. Today, dithiocarbamates are the main accelerators used in rubber gloves. However, positive patch test reactions to thiurams remain more frequent than positive patch test reactions to dithiocarbamates, which confirms the results from previous studies that showed that thiurams are better markers for sensitisation to the dithiocarbamate/thiuram redox pair. The study also confirms that butyl-substituted thiurams and dithiocarbamates have lower reactivity. Dialkylthiocarbamyl benzothiazole sulfides, formed between thiurams and mercaptobenzothiazoles during vulcanization, showed strong test reactions in almost all patients who were sensitive to dithiocarbamates, thiurams, or mercaptobenzothiazoles. Dialkylthiocarbamyl benzothiazole sulfide is the best marker of rubber allergy to substances of any of the three groups (thiurams, dithiocarbamates, and mercaptobenzothiazoles). The authors suggest that it should be evaluated in a multicentre study.

Several one-off cases of ACD induced by thiurams and dithiocarbamates have been published over the past few years. Creytens *et al*. reported the first case of connubial airborne contact dermatitis caused by a thiuram, *i.e.* disulfiram (tetraethylthiuram) in an atopic patient [17]. The patient had eczema on his face, neck, upper chest, shoulders, and elbow folds. Patch test results were positive to thiuram mix, carba mix, and methylisothiazolinone 0.05% aq. The patient's history revealed that he had crushed Antabuse® tablets (disulfiram) for his wife. His symptoms completely resolved after he started using a pill crusher. Pföhler *et al*. reported a case of occupational allergic contact dermatitis of the ears in a female working as a secretary [18]. She had been typing dictated letters for over 30 years and she wore a headset for over five hours a day, five days a week. Patch tests showed positive reactions to thiurams and rubber parts of the headset. After her headset was replaced by a rubber-free headset, her symptoms resolved completely.

Mercaptobenzothiazoles

Mercaptobenzothiazole sensitisation is mainly associated with ACD of the feet [19]. Recently, Munk *et al*. reported four cases of patients who developed ACD on their feet after wearing Keds® canvas sneakers. Patch test results showed positive reactions to thiuram mix, as well as to pieces of their shoes. High-performance liquid chromatography (HPLC) identified MBT in the canvas of the shoes, but no thiurams nor dithiocarbamates. Symptoms resolved after the patients stopped wearing the shoes. Information on the chemical composition of the shoes was difficult to obtain. The company's website mentions that the shoe is manufactured from an unvulcanised rubber sole attached to a canvas fabric, which is subsequently vulcanised in order to attach the top and bottom of the shoe.

Guanidines

The prevalence of positive patch results to 1,3-diphenylguanidine has been increasing over the past few years. In 2013, Baeck *et al*. [20] reported five cases of ACD caused by 1,3-diphenylguanidine. The authors hypothesised that this was due to the replacement of natural rubber latex gloves by synthetic rubber ones, as part of a "latex-free hospital". The same authors have reported 32 unpublished cases of ACD induced by 1,3-diphenylguanidine in synthetic rubber gloves since 2011 (Baeck, personal communication). In Sweden, Pontén *et al*. investigated 16 patients with ACD induced by sterile synthetic polyisoprene rubber gloves among surgical operating theatre personnel. Chemical analysis was carried out on five different brands of gloves using HPLC [7]. Rubber chemicals yielding positive patch test results were 1,3-diphenylguanidine (12 patients), thiurams (eight patients), and ZDEC (two patients). It is worth noting that although no thiurams were detected in any of the gloves, eight patients with a clinical history suggesting glove allergy had positive patch test results to thiurams. For two of the gloves, the concentrations of 1,3-diphenylguanidine on the inside were ten times higher than those on the outside of the gloves.

Dahlin *et al*. reported two cases of ACD induced by triphenylguanidine (CAS no.101-01-9) in synthetic rubber surgical gloves in a female surgeon and a scrub nurse [21]. Chemical analysis of synthetic rubber surgical gloves confirmed the presence of triphenylguanidine (gas chromatography/mass spectrometry (GC-MS) and liquid chromatography). Over 122 patients were tested using a rubber series including triphenylguanidine (1.35% pet.) between 2011 and 2013. Two other cases were positive to triphenylguanidine. All patients with positive patch test results to triphenylguanidine also had positive patch test results to 1,3 diphenylguanidine. There are at least three different guanidine-type accelerators that are used in the production of rubber, *i.e*. 1,3-diphenylguanidine, triphenylguanidine, and di-o-tolylguanidine (CAS no. 97-39-2). 1,3-diphenylguanidine is now a well-known sensitiser; it is tested in the rubber series (1% pet.) and elicits positive reactions in up to 3% of patients [8]. It is currently unknown whether there is cross-reactivity between triphenylguanidine and 1,3-diphenylguanidine.

Hamnerius *et al*. studied the influence of exposure time to gloves and the use of skin disinfectants on the amount of 1,3-diphenylguanidine released by synthetic rubber gloves [22]. They used HPLC to measure the amount of 1,3-diphenylguanidine released from the inside of the gloves after exposure to artificial sweat. After approximately 10, 30, 60, and 180 minutes, 73%, 79%, 82% and 87% of the total amount of 1,3-diphenylguanidine was released from the inside of the gloves (measured by HPLC), respectively. The remaining amount of extractable 1,3-diphenylguanidine was estimated by washing the inside of the gloves with ethanol for 10 minutes. The authors also evaluated the amount of 1,3-diphenylguanidine on the hands exposed to 3 ml of skin disinfectant and then after wearing gloves for 60 minutes, and compared this with a control group which did not use disinfectant. The amount of 1,3-diphenylguanidine released was higher in the group of patients whose hands were exposed to disinfectant.

Thioureas

Diphenylthiourea (DPTU), diethylthiourea (DETU), and dibutylthiourea (DBTU) are used in the series of rubber additives as the three diagnostic markers for polychloroprene rubber allergy [23]. In experimental studies, thiourea compounds are classified as weak sensitisers. Recently, it was found that DPTU was activated to metabolites including phenylisothiocyanate (PITC) and phenylisocyanate (PIC), which are strong sensitisers [24]. The authors carried out a chemical analysis with measures of DPTU, DETU, and DBTU in three main categories of products made of polychloroprene and likely to have prolonged contact with water, *i.e*. medical devices, and sports and diving gear. Only DETU was detected. DETU is by far the most common thiourea compound used in the manufacturing of polychloroprene goods. At 37°C, DETU is continuously degraded into ethyl isothiocyanate (ETIC). The authors concluded that DETU can be considered as a prehapten which, at room temperature, degrades into a strong sensitiser, *i.e*. EITC. EITC could thus account for severe ACD induced by polychloroprene rubber. ACD to thioureas in wetsuits was the subject of two presentations at the 2014 ESCD congress. Poreaux *et al*. reported a case of generalised eczema in a sea lion trainer [25]. Symptoms appeared after he started wearing a new Spandex wetsuit and persisted even after he returned to his previous wetsuits. Patch test results were positive for thioureas from the plastic-glue series (DETU and DBTU). Patch tests with 2.5 × 2.5-cm pieces of wetsuits were negative but positive with 5 × 5-cm pieces of wetted wetsuits. Chemical analysis of the wetsuits confirmed the presence of higher thiourea quantities than in the Spandex wetsuit.

Ghys and Goossens reported another case in a six-year-old child wearing a jet ski wetsuit [26]. Since she was three, she had been suffering from a recurrent generalised papular and urticarial eruption associated with the wearing of a wetsuit. Patch test results showed positive reactions to DETU and disperse dye mix from the European standard series, as well as to red, blue, and black pieces of the wetsuit. The lesions decreased when she started wearing cotton clothes under her wetsuit.

Liippo *et al*. [27] reported two cases of ACD induced by thioureas in the neoprene handles of cleaning trolleys in two cleaners with hand dermatitis. Patch test results were positive for thiourea mix (consisting of 0.5% [wt/wt] DETU, 0.5% DBTU, and 0.5% DPTU in petrolatum), DETU, and the handles of the trolleys.

Dyes

Reckling *et al*. reported a case of ACD of the hands in a male nurse induced by the dye of a blue nitrile glove [28]. Patch test results were positive for the blue nitrile gloves and phthalocyanine blue PB15. Thin layer chromatography of the blue nitrile glove confirmed the presence of PB15. Symptoms resolved after the patient changed to identical white nitrile gloves.

Other allergens

Benton *et al*. reported a case of ACD induced by a rubber respirator. The patient developed lesions limited to the face after he had worn the respirator for his military training. Patch test results were positive to pieces of the respirator and methyl hydroxystearate (1% pet.), a compound supplied by the manufacturer. Methyl hydroxystearate is derived from hydrogenated castor oil and is used as a processing aid as it reduces the coefficient of friction and surface tack.

Vanden Broecke *et al*. reported a case of severe ACD of the right hand in a retired farmer after he had cleaned his garden shed, wearing a rubber glove coated with a moisturiser on the inside (Vileda Comfort and Care, Comfort plus, extra-absorbent®; Vileda, Verviers, Belgium) [29]. He had severe dermatitis on the right hand, wrist, and forearm and a more discrete reaction on his left hand. He had been wearing the glove for about two hours, on his right hand only. The patient had a history of dermatitis induced by moisturisers and positive patch test results to cetrimide, a quaternary ammonium compound (cetyltrimethylammonium bromide), isopropanol, iodine, and povidone iodine. Patch testing was performed with the European baseline series, the rubber series, chamomile, the ingredients of the creams he had used, and with pieces of the inner and outer sides of the gloves. Positive results were yielded with cetyl alcohol and the pieces of the gloves. Chemical analysis of the gloves with GC-MS showed the presence of fatty alcohols, as well as docecytrimethylammonium chloride, a compound closely related to cetrimide. Quarternary ammoniums are surfactants used as stabilisers or wetting agents. They are found in the baths used on the glove production lines (Palu, personal communication). Additional patch tests with the ingredients from the gloves showed strong positive reactions to stearyl alcohol and behenyl alcohol (which includes various unsaturated and polyunsaturated alcohols). Dodecyltrimethylammonium chloride identified in the glove was not tested as it was not available, however, patch testing with benzalkonium (or alkyldimethylbenzylammonium chloride) yielded positive reactions.

In Pontén *et al*.'s study mentioned above (16 cases of ACD induced by sterile synthetic polyisoprene rubber gloves), cetylpyridinium chloride was positive in seven patients [7]. Since 2010, cetylpyridinium chloride has been tested at 0.1% (wt/wt) in water. The authors recommend patch testing with fully dissolved cetylpyridinium chloride at room temperature as, when stored in a refrigerator, it crystallises in the bottom of the test tube. The content of cetylpyridinium chloride was also analysed using HPLC, and was shown to be higher on the inside of the glove than on the outside of the glove.

Contamination

Ohata *et al*. reported severe itchy bullae and erythema on the feet, ankles, and lower legs in a farmer related to wearing rubber boots [30]. Patch tests showed positive results for the inner surface, the outer surface, and the sole of the boots. Patch tests performed with the constituents of the boots provided by the manufacturer, as well as with pieces of identical new boots, gave negative results. The patient recalled spraying dazomet in his fields 17 days before the onset of the first symptoms. He was then wearing his rubber boots, which he wore again later. Dazomet was detected by gas chromatography in the different parts of the boots. Dazomet decomposes into methyl isothiocyanate, a strong irritant compound. The authors concluded that the patient had allergic contact dermatitis caused by methyl isothiocyanate, as patch test results were positive in the patient and negative in 10 volunteers using the patient's boots.

Latex proteins

There are currently 15 latex proteins internationally considered as allergens. They are referred to as Hev b and are

Table 3. Sensitising latex proteins [1].

Hev b 1	Rubber elongation factor (REF)
Hev b 2	Beta-1,3-glucanases
Hev b 3	Small rubber particle protein (SRPP)
Hev b 4	Lecithinase homologue
Hev b 5	Acidic latex protein
Hev b 6	Hevein precursor
Hev b 7	Patatin homologue
Hev b 8	Profilin
Hev b 9	Enolase
Hev b 10	Superoxide dismutase (MnSOD)
Hev b 11	Class I endochitinase
Hev b 12	Non-specific lipid transfer protein type 1
Hev b 13	Esterase / early nodule specific protein
Hev b 14	Hevamine (lysozyme/chitinase)
Hev b 15	Serine protease inhibitor Latex

listed in *table 3*. The following website provides information on latex allergens: http://www.allergome.org or http://www.allergen.org.

Molecular allergy diagnosis can help to differentiate between patients with a severe risk of anaphylaxis and those with asymptomatic polysensitisation (carbohydrate determinants or CDD) [31-33]. EAACI recently published a position paper on food allergy and immunological cross-reactions [34]. Hev b 5, Hev b 6.01, and Hev b 6.02 are considered to be major allergens involved in latex sensitisation, in particular, in healthcare workers [34]. Hev b 1 and Hev b 3 affect patients who undergo surgery frequently (*e.g.* patients with spina bifida) [34]. Hev b 2, Hev b 6.01, Hev b 6.02, Hev b 6.03, Hev b 7, Hev b 8, and Hev b 11 are cross-reactive allergens that cause latex-fruit syndrome [34]. CDD have little or no clinical relevance [34]. Canonica *et al.* published a consensus document in 2013 [32]. Sensitisation to Hev b 8 (profilin), a cytoskeletal protein found in many plants (also a panallergen), is not related to clinical latex allergic reactions [32]. Patients with positive IgE against latex with negative prick test results with latex, monosensitisation to Hev b 8, and who show no latex-specific symptoms, are not considered allergic to latex and can thus undergo medical and surgical procedures (using latex gloves) without any risk [33, 35]. Hev b 8 is considered as a marker of asymptomatic latex sensitisation. Hev b 13, another allergen, can also be used to identify other cases of latex allergy, though in a lower percentage of cases [31]. Prick tests with latex standardised extracts are used to confirm latex sensitisation. Gabriel *et al.* analysed the protein and allergen composition of natural latex extracts from seven different manufacturers: Alk-Abelló, Allergopharma, Bial-Aristegui, Leti, Lofarma, Q-Pharma, and Stallergènes [36]. They analysed the protein content using sodium dodecylsulfate polyacrylamide gel electrophoresis and quantified four major allergens (Hev b 1, Hev b 3, Hev b 5, and Hev b 6.02) involved in latex allergy using an enzyme immunoassay. Allergenic capacity was assessed using microarray inhibition assays and prick tests in 11 patients with known latex allergy. Results showed large differences in protein profiles between the seven standardised latex extracts. A 65-fold variation in the protein content was observed, ranging from 8.0 μg/mL to 526.5 μg/mL. The levels of the four main latex allergens were also highly variable, particularly Hev b 3 and Hev b 5, as these were below the detection limit in some extracts. Similarly, allergenic capacity assessed using microarray inhibition assays and prick tests showed large differences between the extracts. Almost all patients allergic to latex had at least one negative prick test result (<3 mm) to one of the seven extracts. One of the patients had a prick test with a wheal diameter >8 mm with one extract, but no other visible skin reaction with the two others. The authors suggested that if latex allergy is suspected, prick tests should be carried out using at least two extracts from different companies in order to reduce the risk of false negative results.

Preventive measures: updates on rubber glove manufacturing

Over the past few years, new manufacturing processes have been developed resulting in low-protein rubber gloves, vulcanisation accelerator-free gloves or specific-purpose gloves, such as gloves containing antimicrobial agents or moisturisers.

Medical gloves

Low-protein latex gloves

Several methods are used to reduce the amount of allergenic proteins in Hevea latex; the use of deproteinised and purified naturel rubber latex (obtained by adding proteolytic enzymes and/or surfactants), chlorination, and mostly high-temperature post-washing [14, 37].

Rubber accelerator-free gloves

It is now possible to manufacture accelerator-free gloves, particularly single-use gloves. *Table 4* provides a list of examples of accelerator-free, single-use gloves. Different materials can be used, for instance:

– polychloroprene, as Gammex® in latex-free sensitive touch surgical gloves (sensoprene® process), or Gammex® PF Dermaprene by Ansell or Biogel® NeoDerm by Mölnlycke Health Care.
– nitrile, as in the MICRO-TOUCH® gloves Nitrile accelerator-free by Ansell.
– polyisoprene. Sempermed, a member of the Semperit group, has developed a photocross-linking process for rubber, quite different from vulcanisation that does not require rubber accelerators. This company sells Syntegra UV surgical gloves. This manufacturing process provides the same elasticity as in polyisoprene gloves.
– thermoplastic elastomer gloves (SEBS; a saturated styrene elastomer). These gloves are formulated without accelerators or cross-linking additives. Their manufacturing process is reported to produce glove films with fewer micropunctures than latex (Hoerner, personal communication). Hutchinson used to sell SEBS gloves (such as G-derm) before Lucenxia took over and developed the manufacturing process to sell Flexylon gloves (Finessis

Table 4. Examples of accelerator-free rubber gloves that can be recommended to allergic patients.

Use	Brand	Material	Manufacturer
	Gammex® latex-free, sensitive touch	Polychloroprene	Ansell www.anselleurope.com
	GAMMEX PF DermaPrene	Polychloroprene	Ansell www.anselleurope.com
Surgical gloves	Biogel NeoDerm	Polychloroprene	Mölnlycke Health Care biogel@molnlycke.com
	Sempermed® Syntegra UV	Polyisoprene photocrosslinked (no vulcanisation)	Sempermed sempermed(at)semperitgroup.com
	Finessis Corium®	SEBS (styrene elastomer)	Lucenxia
Single-use examination gloves	MICRO-TOUCH Nitrile accelerator-free	Nitrile	Ansell www.anselleurope.com

Corium® & Finessis Zero®). Flexylon is a very elastic material made of thermoplastic elastomer and liquid paraffin.

Another manufacturing process developed by Budev (http://www.budev.com) consists of subjecting the gloves to a wash in a strong alkaline solution to remove the rubber accelerators (Cleantexx gloves treated with MPXX®).

Specific purpose gloves

The risk of transmission of pathogens from healthcare workers to patients, but also from patients to healthcare workers, is well-known and has been the subject of an update by Cleenewerck at the GERDA conference in 2009 (update on medical and surgical gloves) [38]. The contamination rate with the risk of developing surgical site infections depends on the type of surgery carried out and can reach up to 50% during specific procedures, such as with the use of aortic balloon pumps [39]. In 2009, the World Health Organisation (WHO) published guidelines on hand hygiene in health care. After surgery, 18% (range: 5-82%) of gloves have punctures, which, in more than 80% of cases, go unnoticed by the surgeon [40]. Punctured gloves double the risk of surgical site infections [40]. Double gloving is one of the effective measures to reduce hand contamination, but does not totally eliminate the risk of transmission of pathogens [41]. Glove manufacturers have provided the market with antimicrobial surgical gloves. Gammex® Powder-free with ATM, manufactured and sold by Ansell, contains antimicrobial coating with chlorhexidine gluconate on the inside. These gloves are classified as a type III (highest risk) medical device in Europe. In July 2015, Lucenxia introduced Finessis Aegis®, an improved version of Hutchinson's G-VIR gloves. The antimicrobial agent, didecyldimethylammonium chloride, is normally not in contact with the skin as it is contained in a layer of the glove, and is only released when the glove is punctured. Protection from infection is enhanced in case of accidental blood exposure, moreover, this glove also reduces the risk of bacterial transfer from the surgeon's hand to the patient should micropunctures go unnoticed. Mölnlycke® developed another system, the Biogel® puncture indication system; a coloured indicator glove is worn under a neutral glove that allows unnoticed punctures to be detected more rapidly. If the top glove is punctured, fluid penetrates between the two gloves and a dark patch alerts the wearer to the puncture.

Guayule examination gloves

As a result of the decreasing acreage of rubber plantations, due to the fact that they have to compete with oil palm plantations, the growing demand for rubber and the potential severity of latex protein immediate allergy have promoted the research and development for alternatives to *Hevea brasiliensis* latex, particularly guayule (*Parthenium argentatum Gray*) and Russian dandelion (*Taraxacum kok saghyz*). Guayule is a latex-producing perennial shrub that grows in Mexico and the semi-arid areas of southwestern Texas, and belongs to the asteraceae family. Guayule can also be grown in the Mediterranean region. The processing technology and industrial development are currently US-based and operated by Yulex®. A European partnership has also been set up in France and includes the French Agricultural Research Centre of International Development (CIRAD) and the Le Mans Technology Transfer Centre (CTTM). Vulcanised natural guayule polyisoprene films have the same mechanical properties as Hevea polyisoprene. Several studies reported by S. Palu, at the 2011 Gerda conference in Montpellier, confirmed the good tolerance of guayule latex products in patients with Hevea latex protein allergy [42-44]. Guayule latex contains less than 1% of the protein content of Hevea latex [43]. Experimental studies in mice and rabbits, as well as studies in humans, have shown the absence of cross-reactivity between guayule and Hevea latex proteins [43]. However, guayule contains contact allergens called guayulins A and B [45, 46]. The examination gloves made with patented Yulex® guayule latex received clearance from the American Food and Drug Administration (FDA) in 2008. However, so far, no guayule latex gloves have been commercialised (Cornish, personal communication). Yulex® commercialises Patagonia® wetsuits in guayule latex. The composition and quality of Russian dandelion rubber are highly similar to Hevea latex and cross-reactivity reactions were found between Russian dandelion proteins and Hevea proteins [43]. Thus, Russian dandelion latex cannot be used for medical applications as a substitute for patients with latex allergy, however, it is being developed in the tyre industry (Continental, Pirelli, Bridgestone) [43].

Gloves that provide protection from chemicals

It is more difficult to manufacture vulcanisation accelerator-free gloves that provide protection from chemicals. As a reminder, gloves providing protection from chemicals marketed in Europe are regulated by directive 89/686/CEE on the design of personal protective equipment and bear the CE marking [47]. It is essential to differentiate two glove pictograms for chemical protection: the "chemical resistant" glove pictogram and the "low-chemical resistant" glove pictogram. According to standard EN 374 2003, to be awarded the "chemical resistant" pictogram, a glove must have a breakthrough time of at least 30 minutes against three chemicals from a list of 12 standard defined chemicals (methanol, acetone, acetonitrile, dichloromethane, carbon disulphide, toluene, diethylamine, tetrahydrofurane, ethyl acetate, n-heptane, sodium hydroxide 40%, and sulphuric acid 96%). This pictogram is different from the type III "low-chemical resistant" or "waterproof" glove pictogram used for gloves that do not achieve a breakthrough time of at least 30 minutes against at least three chemicals from the defined list, but which comply with the penetration test.

Some PVC, vulcanisation accelerator-free, thick gloves are type III gloves, bearing the marking "protection from chemicals". They are waterproof, comply with standard EN 374 2003, and have a breakthrough time of at least 30 minutes against three chemicals from the defined list. However, users should check that they provide protection from the chemicals used at work.

Websites

Several websites provide useful information on preventive measures, and in particular provide lists of the allergens found in gloves and avoidance lists.

The German website of BG BAU provides a list of gloves sorted by manufacturer and indicates the presence of the following allergens: thiurams, dithiocarbamates, thioureas, mercaptobenzothiazoles, and their derivatives. Additional allergens may be mentioned, such as 1,3-diphenylguanidine, N,N'-Diphenyl-p-phenylenediamine (an antioxidant found in rubber formulations such as bromobutyl), p-phenylenediamine in butyl rubber, hexahydro-1,3,5-triethyl-s-triazine (a formaldehyde releaser found in protection gloves), colophony, nickel, and hexavalent chromium. The website address is: http://www.bgbau.de/gisbau/service/allergene/allergeneliste-nach-hersteller-1

Ann Goossens's website provides detailed bibliographic information on glove manufacturers based on allergens, as well as retailers' contact information (http://contactallergy.uzleuven.be/). A Swiss website provides information on how to choose gloves based on the occupation of the person involved (http://www.2mains.ch/fr/professions/by_field). ■

Disclosure. *Acknowledgements: The author wishes to thank the following people for their help and advice: Mr. S. Palu (research fellow at the French Agricultural Research Centre of International Development, Montpellier), Mr. Dorget (Le Mans Technology Transfer Centre), Mrs. K. Cornish (The Ohio State University, Ohio Agricultural Research and Development Center), Mr. R. Virdi (Robac Rubber Technology, Robinson Brothers), Mrs. A. Van den Borre and Mr. P. Jacobs (Ansell), Mr. P. Hoerner (ABS Health Consulting), Mr. C. Francois-Saint-Cyr (Semperit), Mrs. E. Pruvost (Mölnlycke Health Care), Mrs. N. Oger (Mapa Spontex), Dr. M. Rittmeier (UVEX SAFETY Gloves), and Mr. S. Lenoble (Shield scientific). Conflict of interest: none. Financial support: none.*

References

1. Berthelot K, Lecomte S, Estevez Y, Peruch F. *Hevea brasiliensis* REF (Hev b 1) and SRPP (Hev b 3): an overview on rubber particle proteins. *Biochimie* 2014; 106: 1-9.

2. Carøe TK, Ebbehøj N, Agner T. A survey of exposures related to recognized occupational contact dermatitis in Denmark in 2010. *Contact Dermatitis* 2014; 70: 56-62.

3. Clemmensen KBC, Carøe TK, Thomsen SF, *et al.* Two-year follow-up survey of patients with allergic contact dermatitis from an occupational cohort. Is the prognosis dependent on the omnipresence of the allergen? *Br J Dermatol* 2014; 170: 1100-5.

4. Pesonen M, Jolanki R, Larese Filon F, *et al.* Patch test results of the European baseline series among patients with occupational contact dermatitis across Europe – analyses of the European Surveillance System on Contact Allergy network, 2002-2010. *Contact Dermatitis* 2015; 72: 154-63.

5. Geier J, Lessmann H, Uter W, Schnuch A, & Information Network of Departments of Dermatology (IVDK). Occupational rubber glove allergy: results of the Information Network of Departments of Dermatology (IVDK), 1995-2001. *Contact Dermatitis* 2003; 48: 39-44.

6. Hansson C, Pontén A, Svedman C, Bergendorff O. Reaction profile in patch testing with allergens formed during vulcanization of rubber. *Contact Dermatitis* 2014; 70: 300-8.

7. Pontén A, Hamnerius N, Bruze M, *et al.* Occupational allergic contact dermatitis caused by sterile non-latex protective gloves: clinical investigation and chemical analyses. *Contact Dermatitis* 2012; 68: 103-10.

8. Geier J, Lessmann H, Mahler V, *et al.* Occupational contact allergy caused by rubber gloves – nothing has changed. *Contact Dermatitis* 2012; 67: 149-56.

9. Bhargava K, White IR, White JML. Thiuram patch test positivity 1980-2006: incidence is now falling. *Contact Dermatitis* 2009; 60: 222-3.

10. Uter W, Hegewald J, Pfahlberg A, *et al.* Contact allergy to thiurams: multifactorial analysis of clinical surveillance data collected by the IVDK network. *Int Arch Occup Environ Health* 2010; 83: 675-81.

11. Knudsen B, Lerbaek A, Johansen JD, Menné T. Reduction in the frequency of sensitization to thiurams. A result of legislation? *Contact Dermatitis* 2006; 54: 170-1.

12. Warburton KL, Urwin R, Carder M, *et al.* UK rates of occupational skin disease attributed to rubber accelerators, 1996-2012. *Contact Dermatitis* 2015; 72: 305-11.

13. Cao LY, Taylor JS, Sood A, *et al.* Allergic contact dermatitis to synthetic rubber gloves: changing trends in patch test reactions to accelerators. *Arch Dermatol* 2010; 146: 1001-7.

14. Palosuo T, Antoniadou I, Gottrup F, Phillips P. Latex medical gloves: time for a reappraisal. *Int Arch Allergy Immunol* 2011; 156: 234-46.

15. Blaabjerg MSB, Andersen KE, Bindslev-Jensen C, Mortz CG. Decrease in the rate of sensitization and clinical allergy to natural rubber latex. *Contact Dermatitis* 2015; 73: 21-8.

16. Stocks SJ, McNamee R, Turner S, *et al.* Assessing the impact of national level interventions on workplace respiratory disease in the UK: part 1 – changes in workplace exposure legislation and market forces. *Occup Environ Med* 2013; 70: 476-82.

17. Creytens K, Swevers A, De Haes P, Goossens A. Airborne allergic contact dermatitis caused by disulfiram. *Contact Dermatitis* 2015; 72: 405-7.

18. Pföhler C, Körner R, Müller CSL, Vogt T. Occupational allergic contact dermatitis of the ears caused by thiurams in a headset. *Contact Dermatitis* 2011; 65: 242-3.

19. Landeck L, Uter W, John SM. Patch test characteristics of patients referred for suspected contact allergy of the feet – retrospective 10-year cross-sectional study of the IVDK data. *Contact Dermatitis* 2012; 66: 271-8.

20. Baeck M, Cawet B, Tennstedt D, Goossens A. Allergic contact dermatitis caused by latex (natural rubber)-free gloves in healthcare workers. *Contact Dermatitis* 2013; 68: 54-5.

21. Dahlin J, Bergendorff O, Vindenes HK, *et al.* Triphenylguanidine, a new (old?) rubber accelerator detected in surgical gloves that may cause allergic contact dermatitis. *Contact Dermatitis* 2014; 71: 242-6.

22. Hamnerius N, Pontén A, Persson C, Bergendorff O. Factors influencing the skin exposure to diphenylguanidine in surgical gloves. *Contact Dermatitis* 2014; 70: 59-60.

23. Ramzy AG, Hagvall L, Pei MN, *et al.* Investigation of diethylthiourea and ethyl isothiocyanate as potent skin allergens in chloroprene rubber. *Contact Dermatitis* 2015; 72: 139-46.

24. Samuelsson K, Bergström MA, Jonsson CA, *et al.* Diphenylthiourea, a common rubber chemical, is bioactivated to potent skin sensitizers. *Chem Res Toxicol* 2011; 24: 35-44.

25. Poreaux C, Penven E, Langlois E. Occupational contact dermatitis at the zoo. *Contact Dermatitis* 2014; 70: 51.

26. Ghys K, Goossens A. Diethylthiourea, also a contact allergen in a young sporty child. *Contact Dermatitis* 2014; 70: 91.

27. Liippo J, Ackermann L, Lammintausta K. Occupational allergic contact dermatitis caused by diethylthiourea in a neoprene handle of a cleaning trolley. *Contact Dermatitis* 2011; 64: 359-60.

28. Reckling C, Sheraz A, Engfeldt M, Bruze M. Occupational nitrile glove allergy to pigment blue 15. *Br J Dermatol* 2014; 171: 132.

29. Vanden Broecke K, Zimerson E, Bruze M, Goossens A. Severe allergic contact dermatitis caused by a rubber glove coated with a moisturizer. *Contact Dermatitis* 2014; 71: 117-9.

30. Ohata C, Yoneda M. Allergic contact dermatitis due to dazomet absorbed by agricultural rubber boots. *Acta Derm Venereol* 2013; 93: 81-2.

31. Ebo DG, Hagendorens MM, De Knop KJ, *et al.* Component-resolved diagnosis from latex allergy by microarray. *Clin Exp Allergy* 2010; 40: 348-58.

32. Canonica GW, Ansotegui IJ, Pawankar R, *et al.* A WAO–ARIA–GA^{2}LEN consensus document on molecular-based allergy diagnostics. *World Allergy Organ J* 2013; 6: 17.

33. Luengo O, Cardona V. Component resolved diagnosis: when should it be used? *Clin Transl Allergy* 2014; 4: 28.

34. Werfel T, Asero R, Ballmer-Weber BK, *et al.* Position paper of the EAACI: food allergy due to immunological cross-reactions with common inhalant allergens. *Allergy* 2015; 70: 1079-90.

35. Quercia O, Stefanini GF, Scardovi A, Asero R. Patients monosensitised to Hey b 8 (*Hevea brasiliensis* latex profilin) may safely undergo major surgery in a normal (non-latex safe) environment. *Eur Ann Allergy Clin Immunol* 2009; 41: 112.

36. Gabriel MF, Tavares-Ratado P, Peixinho CM, *et al.* Evaluation and comparison of commercially available latex extracts for skin prick tests. *J Investig Allergol Clin Immunol* 2013; 23: 478-86.

37. Ansell white paper on gloves NRL allergen contents. Available at: http://www.anselleurope.com/medical/downloads/NRL_allergen_white_paper.pdf [cited 19th June 2015].

38. Cleenewerck M-B. Update on medical and surgical gloves. *Eur J Dermatol* 2010; 20: 434-42.

39. Assadian O, Kramer A, Ouriel K, *et al.* Suppression of surgeons' bacterial hand flora during surgical procedures with a new antimicrobial surgical glove. *Surg Infect* 2013; 15: 43-9.

40. WHO guidelines on hand hygiene in health care. Available at: http://www.who.int/gpsc/5may/tools/9789241597906/en/ [cited 1st June 2015].

41. Mischke C, Verbeek JH, Saarto A, *et al.* Gloves, extra gloves or special types of gloves for preventing percutaneous exposure injuries in healthcare personnel. *Cochrane Database Syst Rev* 2014; 3: CD009573.

42. Palu S. Allergie au latex d'Hévéa, développement de la production d'un latex naturel non allergique à partir du guayule (*Parthenium argentatum Gray*) en remplacement du latex d'*Hevea brasiliensis* (projet européen EU-PEARLS). In: *Progrès en dermato-allergologie*. Montpellier: John Libbey Eurotext, 2011, p. 71-88.

43. Cornish K. Assessment of the risk of type I latex allergy sensitization or reaction during use of products made from latex derived from guayule and other alternative rubber producing species. *Rubber Sci* 2012; 25: 139-55.

44. Siler DJ, Cornish K, Hamilton RG, *et al.* Absence of cross-reactivity of IgE antibodies from subjects allergic to *Hevea brasiliensis* latex with a new source of natural rubber latex from guayule (*Parthenium argentatum*). *J Allergy Clin Immunol* 1996; 98: 895-902.

45. Stumpf DK, Ray DT, Schloman WW. Identification of a contact allergen in guayule latex and formulated guayule latex products. *J Am Oil Chem Soc* 2001; 78: 217-8.

46. Rodriguez E, Reynolds GW, Thompson JA. Potent contact allergen in the rubber plant guayule (*Parthenium argentatum*). *Science* 1981; 211: 1444-5.

47. Nouveau guide sur les normes européennes en matière de protection des mains. Available at: http://www.anselleurope.com/industrial/pdf/en_guide/ENFR.pdf [cited 16th June 2015].