

Review article

Natural rubber latex allergy

Turjanmaa K, Alenius H, Mäkinen-Kiljunen S, Reunala T, Palosuo T.
Natural rubber latex allergy.

Allergy 1996; 51: 593–602. © Munksgaard 1996.

**K. Turjanmaa¹, H. Alenius²,
S. Mäkinen-Kiljunen³,
T. Reunala^{3,4}, T. Palosuo²**

¹Department of Dermatology, Tampere University Hospital and Medical School, University of Tampere, Tampere; ²National Public Health Institute, Helsinki; ³University Hospital for Skin and Allergic Diseases, and ⁴Department of Dermatology, University of Helsinki, Helsinki, Finland

Dr K. Turjanmaa, MD
Department of Dermatology
Tampere University Hospital
FIN-33520 Tampere
Finland

Accepted for publication 25 April 1996

The history of natural rubber latex (NRL) allergy is relatively short; the first case reports appeared in 1979–80 in the European (1, 2) and in 1989 in the North American literature (3–5). During the last 10 years, NRL allergy has been acknowledged as a major occupational problem among glove-wearing health-care workers. In addition, several authors have noted that NRL allergy also occurs frequently outside the health-care environment. Populations at increased risk include not only glove-wearing kitchen workers and housekeeping personnel (6–8) but also children who may exhibit allergic reactions when blowing up balloons (9, 10). Even patients allergic to various fruits, such as banana and avocado, may experience allergic reactions from NRL and vice versa (11–14). The wide spectrum of symptoms of NRL allergy range from mild contact urticaria to asthma and anaphylactic reactions (3, 15–17). Severe allergic reactions are frequently reported to occur intraoperatively in children with spina bifida (18, 19). It has recently been emphasized that NRL allergens become easily airborne with glove powder and that persons sensitized to NRL may also suffer from occupational asthma (20–23).

The presence of specific IgE in NRL-allergic patients may be verified by skin prick tests (SPT) or by serologic methods such as RAST (24–27). The limited knowledge of the relevant NRL aller-

gens has been a major hindrance in developing optimal tests for diagnostic and rubber-product-monitoring purposes. Recently, however, several major NRL allergens have been characterized at the molecular level (28–32). This progress will soon yield better diagnostic tests and perhaps also tools for immunotherapy. This information will also enable rubber manufacturers and governmental regulatory authorities to ensure that potentially harmful NRL gloves, medical devices, and consumer products are withheld from the market.

Epidemiology and risk factors

At present, the incidence of NRL allergy is still unknown, but several prevalence studies have been published. In European health-care workers screened with SPT, the prevalence of NRL allergy has ranged from 2.8% to 10.7% (Table 1). High prevalences have also been found in physicians (9.9%) and operating-room nurses (8.2%) examined in Canada and the USA (33, 34). In agreement with SPT screening, a recent serologic study based on RAST found a 5.5% prevalence of NRL allergy among 381 hospital workers in the USA (35). Children with spina bifida have shown the highest prevalence of NRL allergy (Table 1). The frequency has ranged from 32% to 51% in SPT screenings (36–38) and from 34% to 47% in serologic IgE

Table 1. Prevalence of NRL allergy in various populations

Population	Subjects studied (n)	Prevalence* (%)	Country/reference
Health-care workers			
Hospital employees	512	2.8	Finland/Turjanmaa 1987 (16)
Hospital employees	273	4.7	Belgium/Vandenplas et al. 1995 (23)
Hospital employees	224	16.9	USA/Yassin et al. 1994 (44)
Hospital and dental-care employees	202	3.5	Sweden/Wrangsjö et al. 1994 (56)
Hospital physicians	101	9.9	Canada/Arellano et al. 1992 (33)
Operating-room nurses	197	10.7	France/Lagier et al. 1992 (95)
Operating-room nurses	547	8.2	USA/Turjanmaa et al. 1995 (34)
Other glove-wearing workers			
Hairdressers	41	9.7	The Netherlands/van der Walle & Brunsvelde 1995 (96)
Multioperated patients			
Spina bifida children	25	32.0	France/Moneret-Vautrin et al. 1993 (36)
Spina bifida children	83	50.6	USA/Kelly et al. 1993 (37)
Other populations			
Adult allergy and asthma patients*	224	4.5	Canada/Hadjiladis et al. 1995 (54)
Atopics in allergy clinic	100	3.0	Canada/Arellano et al. 1992 (33)
Adult surgical patients	804	0.12	Finland/Turjanmaa et al. 1995 (42)
Nonatopics in allergy clinic	272	0.4	France/Moneret-Vautrin et al. 1993 (36)

* NRL allergy diagnosed by skin prick testing.

** 11% health-care workers.

measurements (19, 39, 40). In contrast to these studies, a low prevalence rate of 4.3% was reported for Venezuelan children with spina bifida (41). The occurrence of NRL allergy has not been systematically surveyed among the general population, but the prevalence seems to be clearly less than 1% (Table 1). NRL allergy was found in only one (0.12%) of 804 unselected adult Finns prick-tested before surgery (42). A low prevalence rate of 0.4% was also found in French nonatopic subjects prick-tested in an allergology clinic (36). In atopic populations, the frequency of NRL allergy seems to be higher. The prevalence was 0.85% in 4708 Finnish patients prick-tested under suspicion of atopic symptoms (42) and 3% in 100 atopic patients studied in Canada (33). A serologic screening study has been performed with the AlaSTAT method (Diagnostic Products Corporation, Los Angeles, CA, USA) in blood donors (43). The prevalence of latex-specific IgE antibodies was as high as 6%, but the clinical relevance of this finding should be evaluated in further studies.

In addition to repeated exposure to gloves and other NRL products, atopy seems to be the principal determinant for the development of NRL sensitization. In agreement with this, NRL-allergic health-care workers are atopic 2.2–4.2 times more often than their coworkers without NRL allergy (16, 23, 33, 36, 44). Hand eczema disrupts the skin barrier, and, together with personal atopy, this condition is one of the main predisposing factors

for NRL allergy (6, 8, 20, 25, 45). The prevalence of hand dermatitis has been as high as 67–82% in NRL-allergic patients (6, 8). In addition to contact with gloves, the patients may also react to airborne NRL in their working environment (23, 46). At present, it is not known whether pre-existing asthma may be a risk factor for NRL allergy (47).

Children with spina bifida form a well-known, prominent risk group for NRL allergy (3, 21, 36, 39, 40). There are also children without history of major operations who may exhibit NRL allergy symptoms from balloons, rubber toys, and pacifiers (9, 10). Many of these NRL-allergic children have had associated food allergy to cereals, banana, and other fruits (10, 48). These findings suggest that a pre-existing food allergy could be an additional risk factor for NRL allergy in children.

Clinical manifestations of NRL allergy

The clinical symptoms of NRL allergy usually arise from direct contact with an NRL product but may also result from inhalation of airborne allergens bound to substances such as glove powder. The most frequently reported manifestation is contact urticaria, followed by rhinoconjunctivitis (Table 2). Mucosal swelling is a typical symptom after oral, vaginal, or rectal exposure to NRL products, such as balloons, gloves, and condoms. The systemic reactions consist of generalized urticaria, asthma, and anaphylactic shock (49, 50). While serious

Table 2. Frequency of symptoms of NRL allergy in two European patient series

	Finnish series* (n=124)	German series** (n=70)
Contact urticaria	75%	100%
Conjunctivitis	22%	44%
Rhinitis	15%	51%
Asthma or dyspnea	3%	31%
Severe systemic reactions	8%	6%

* Turjanmaa et al. 1995 (42).

** Jäger et al. 1992 (20).

reactions may occur under various conditions, the great majority have occurred within the health-care system, especially intraoperatively (38, 49). Anaphylaxis can, however, be induced also outside the health-care system; e.g., in NRL-allergic children when blowing up toy balloons (9).

NRL allergens have caused occupational asthma in a surgical glove-manufacturing plant (46). Positive inhalation challenge tests have been shown to occur in NRL-allergic patients (20), and, recently, Vandenplas et al. (23) focused attention on the frequent occurrence of NRL-induced asthma among health-care workers. After specific NRL inhalation challenges, they found a 2.5% prevalence of occupational asthma among 273 hospital employees. This and the other recent studies (21, 22, 51) suggest that the widespread use of powdered gloves and the airborne spread of NRL allergens should be considered a significant health problem among hospital personnel.

In addition to immediate cutaneous symptoms, i.e., contact urticaria, glove-wearing NRL-allergic patients can also present with persistent hand eczema (6, 8, 33, 45). Turjanmaa (6) found hand eczema in 67% of NRL-allergic hospital employees. Interestingly, the eczema disappeared in several patients after withdrawal of NRL gloves although the patients did not have type IV contact allergy to rubber chemicals. This finding suggests that chronic hand eczema may be one manifestation of NRL allergy, and, if so, the pathogenetic mechanism could be similar to type I protein contact dermatitis, a well-known occupational problem among food handlers allergic to fish or vegetables (52).

Diagnosis of NRL allergy

The diagnosis of NRL allergy is based on clinical history and laboratory tests (Table 3). Careful history is important when diagnosing NRL allergy, but even a thorough history will not necessarily identify all NRL-allergic persons (7). The patient may or may not belong to the known risk groups,

Table 3. Diagnosis of NRL allergy

Method	Comment
Clinical history	Will not identify all allergic patients
Skin prick testing	Rapid and safe; commercial allergens available; sensitivity >90%
Glove use or challenge tests (skin, lungs)	Highly allergenic glove brand required; potentially dangerous; emergency treatment facilities needed
<i>In vitro</i> tests (RAST, AlaSTAT, etc.)	Commercial tests available; sensitivities and specificities variable

and the symptoms may be typical of NRL allergy or totally absent. In health-care workers and other glove-wearing personnel, NRL allergy can easily remain unrecognized (6). Especially in atopic patients who frequently have dry skin, the cutaneous symptoms of NRL allergy are easily masked by skin irritation and itching caused by glove powder or the occlusion effect of the glove. On the other hand, several screening studies have shown that as many as 30–60% of SPT-positive, NRL-allergic health-care workers report no symptoms at primary examination. In children with spina bifida, a detailed history seems to be the most sensitive means of detecting NRL-allergic patients at risk of anaphylaxis (39). In contrast to this patient group, clinical history remains negative in about one-third of NRL-allergic children who have associated food allergy (10, 48).

The diagnosis of NRL allergy should be confirmed by *in vivo* or *in vitro* tests (6, 49, 53). In 1984, we started to use SPT with aqueous NRL glove extracts, and this method has yielded satisfactory results when several thousand patients were screened for NRL allergy (42). During the last years, we have used the same highly allergenic glove brand (1:5 w/v, Triflex, Baxter, lot 06 92L12DPGN) and a special lancet (ALK a/s, Hørsholm, Denmark) in the testing. Although anaphylactic events have been reported after SPT with NRL and multipointed lancets (37), most investigators agree that SPT is the best method of screening and diagnosing NRL allergy (42, 54). Lack of standardized NRL allergens has been the major disadvantage of the SPT method. A standardized commercial NRL allergen has now become available in Europe (Stallergènes, SA, Fresnes, France). In addition, a few nonstandardized SPT preparations (ALK a/s, Denmark; Bencard, Mississauga, Ontario, Canada) are marketed in Europe and Canada. Recently, we evaluated all these three preparations in 110 previously diagnosed NRL-allergic patients and compared the results to those obtained with our standard glove extract. The sensitivities were 88% for Stallergènes, 54% for

ALK, 92% for Bencard SPT allergens, and 92% for the reference glove extract (55).

Use tests with latex gloves or pulmonary inhalation tests have been suggested as decisive steps to judge whether a relevant clinical allergy to NRL really exists (42, 47). The glove use test frequently produces contact urticaria if it is performed with highly allergenic gloves. The use test has caused anaphylactic reactions in a patient with severe hand eczema, and, for safety reasons, the use test should be started with a finger piece of a glove (42, 56). To avoid false-positive results in milk-allergic subjects, the use test should be performed with a glove brand without casein (57). Recent studies have shown that the bronchial challenge test, either by handling NRL gloves or with aqueous extracts, can identify health-care workers with NLR-induced occupational asthma (20, 23, 58).

At present, *in vitro* measurement of NRL-specific IgE can be performed by RAST, AlaSTAT, and various ELISA methods and other IgE-binding assays, such as immunoelectrophoresis, immunospot, and immunoblotting. The sensitivities and specificities of these tests are not yet optimal, possibly due to deficiencies in NRL allergen source materials and their cross-reactivity with other IgE antibodies (13, 24, 27, 37). The commercial latex CAP-RAST (Pharmacia, Uppsala, Sweden) has proven rather sensitive (80–90%), but, at least in children, the specificity may not be adequate (48, 56). Latex RAST seems to detect well highly allergic patients although one study reported anaphylactic reactions in NRL-allergic patients with negative RAST (59). IgE antibodies to purified NRL allergens such as hevein have also been measured by ELISA methods that show 100% specificity (32, 60). Their use is currently restricted to scientific purposes, but, when appropriate mixtures of purified allergens are available, such reagents can provide exquisitely specific and sensitive means of *in vitro* diagnosis of NRL allergy.

NRL allergens

Numerous studies based on immunoblotting and other immunoelectrophoretic methods have described a large variety of NRL proteins binding IgE from sera of NRL-allergic patients, but, hitherto, little consensus has existed on which of these proteins should be considered major or clinically significant allergens. However, substantial progress has recently been made in the purification and molecular characterization of several NRL allergens, an advance which has facilitated the assessment of their significance and allowed proper comparison of the results obtained by different researchers.

IgE-binding proteins in NRL characterized by immunoblotting

A 14-kDa protein has been identified in several immunoblotting studies as one of the major NRL allergens (20, 61–65); in particular, almost all NRL-allergic patients with spina bifida had IgE antibodies combining with a protein of this size (63, 65). However, in two-dimensional electrophoresis, as many as 26 IgE-binding polypeptides with molecular mass of about 14 kDa and isoelectric points ranging from pI 4.2 to 6.5 could be detected in NRL, indicating that the 14-kDa band is composed of a multitude of polypeptides with various isoelectric points (66). In addition to the 14-kDa band, most NRL-allergic patients with spina bifida also had IgE antibodies against an NRL protein with an apparent molecular mass of 27 kDa. Interestingly, other NRL-allergic patients did not recognize this allergen (65, 66).

Alenius et al. (67) showed that the most frequently recognized NRL allergen among adult patients presenting primarily cutaneous symptoms was a 20-kDa protein. IgE antibodies to this protein were found in sera from 17/22 (77%) patients in this particular patient group, whereas only 36% of the same patients had antibodies to the 14-kDa protein (67). Akasawa et al. recently reported that most of their NRL-allergic patient sera showed IgE antibodies to an 18-kDa protein (68) which could be the same as the 20-kDa NRL allergen described above (67). Several other NRL proteins, such as those with apparent molecular masses of 25.6, 30, 46, 54, and 75 kDa, may also be important allergens (65, 67–69).

Molecular characterization of NRL allergens

A number of NRL proteins have earlier been characterized at the primary structure level, and some of them have recently been shown to represent significant allergens (Table 4). Hevein is a chitin-binding protein believed to be involved in the coagulation of latex and to play a role in the protection of rubber tree wounds by inhibiting the growth of several chitin-containing fungi (70, 71). Hevein is synthesized as preproprotein (also known as prohevein) that is post-translationally processed into amino-terminal hevein (43 amino acids) and the carboxy-terminal 138-amino acid C domain (Fig. 1) (72). Hevamine, another major NRL protein, has been shown to exhibit chitinase and lysozyme activity, and it may also be antifungal (73). Another two rubber proteins are believed to play a role in the elongation of polyisoprene chains: rubber elongation factor (REF), which is tightly bound to the surfaces of rubber particles, and

Table 4. Basic properties of molecularly characterized NRL allergens

Allergen	Mol. mass (kDa)	Length (amino acids)	Information on primary structure	Functions, sequence homologies	Ref.
Hevein	4.72	43	C**	Chitin-binding, homology to WGA***	32, 71
Hevein C-domain	14	138	C	Homology to WIN1 in potato	32, 71
REF (Hev b 1)	14.6	137	C	Elongation of polyisoprene chains	78, 60, 74
Prohevein	20	187	C	Hevein preproprotein	30, 71
27-kDa protein	27*	Unknown	P	Function unknown, homology to REF	29
Hevamine	29.6	273	C	Chitinase, lysozyme	30, 73
36-kDa protein	36*	Unknown	P	Endoglucosidase or rubber tree (?)	30
46-kDa protein	46*	Unknown	P	Function unknown	69

* Apparent molecular mass based on electrophoretic mobility.

** C=complete amino acid sequence known.

P=partial sequence known.

*** Wheat germ agglutinin.

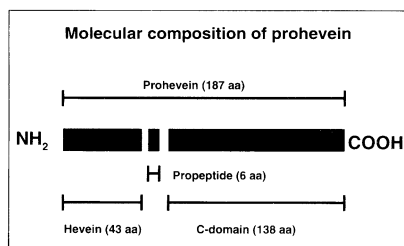


Fig. 1. Schematic composition of prohevein (hevein preproprotein), a major NRL allergen, aa=amino acid.

prenyltransferase, which is found both free in the cytosol and in association with rubber particles (74, 75).

Rubber elongation factor (14.6 kDa). REF has been identified as the major allergen in NRL (Hev b 1) and the only allergen present in one latex surgical glove brand analyzed (28). In this study, REF was reported to induce symptoms in NRL-allergic patients and in ELISA to block completely NRL-specific IgE antibodies in all 13 patient sera tested. However, these findings have not been confirmed by other authors. When REF was purified by electroelution from rubber particles and analyzed for its IgE-binding ability by immunoblotting, 4/6 sera from NRL-allergic children with congenital anomalies but only 1/30 other NRL-allergic patients showed IgE antibodies against the highly purified REF preparation (60). Likewise, in ELISA, only 8/45 (18%) NRL-allergic patients had IgE antibodies to purified REF (Table 5). Essentially similar results were reported by Akasawa et al. (68), who found that 23% of their NRL-allergic patient sera reacted in immunoblotting with a

Table 5. Occurrence of IgE antibodies to molecularly characterized and purified NRL proteins measured by ELISA (Alenius et al. 1996 (32, 60))

Purified NRL protein	Positive/patient sera studied
Hevein	24/43 (56%)
Prohevein C-domain	11/52 (21%)
REF	8*/45 (18%)
Prohevein	36/52 (69%)

* Includes four children with spina bifida.

14.6-kDa NRL protein band identified as REF by amino acid analysis. These data suggest that REF is one, but not the most, significant allergen among the NRL proteins.

Prohevein (20 kDa) and hevein (4.7 kDa). A 20-kDa NRL protein, previously shown to be the most important allergen for adult NRL-allergic patients (65, 67), was identified by amino acid sequencing as prohevein (30). In immunoblotting, purified prohevein bound IgE from 24/29 (83%) and in ELISA from 36/52 (69%) sera of NRL-allergic patients (30, 60) (Table 5). Purified prohevein also elicited positive SPT reactions in 6/7 NRL-allergic patients and was considered to represent a major NRL allergen (30). In line with these findings, Beezhold et al. (69), showed that the amino acid sequences of two NRL protein bands excised at the 14- and 18-kDa regions were homologous to prohevein. However, the authors did not assess the IgE reactivity of patient sera against purified proteins.

Attempts have also been made to localize IgE-binding epitopes of prohevein. Alenius et al. (32) recently reported that around 70–80% of NRL-allergic patients had IgE antibodies to purified prohevein, whereas a minority (15–20%) of these patients had IgE against the purified prohevein C-domain in ELISA and immunoblot assays (Table 5).

Moreover, the IgE-binding peptides purified from a brand of highly allergenic NRL gloves were shown to be hevein molecules since they showed amino acid sequences identical to those of the prohevein N-terminus and had a molecular mass corresponding to that of hevein (4719.1 Da), a 43-amino acid N-terminal fragment of prohevein (Fig. 1). In ELISA, 56% of 45 NRL-allergic patient sera showed IgE antibodies to purified hevein, and hevein elicited positive SPT reactions in patients showing IgE to the N-terminus of prohevein. The same study also showed that purified hevein inhibited 72% of IgE binding from pooled sera of NRL-allergic patients to solid-phase glove extract in ELISA inhibition. The authors concluded that the main allergenic epitope of prohevein is located in its N-terminus, and that the immunologically active fragments carrying this epitope, known as hevein, are found in a highly allergenic latex glove. A recent study by another group (76) has confirmed hevein as a major NRL allergen.

Twenty-seven-kDa NRL protein. Alenius et al. reported primary structure data on a 27-kDa protein (29), recognized characteristically by IgE in sera from NRL-allergic patients with spina bifida (65, 66). Most of the purified tryptic peptides obtained from the 27-kDa protein revealed no significant homology to any of the published protein sequences, indicating that this protein has not previously been described at the primary structure level. However, partial homology to REF was observed. Interestingly, the IgE reactivity to the 27-kDa allergen among patients with spina bifida was very similar to their reactivity against REF. It is possible that this co-occurrence of IgE antibodies is partially explained by the homology between REF and the 27-kDa protein.

Lu et al. (31) recently characterized a 23-kDa NRL protein which reacted with the IgE from 13/17 (76%) NRL-allergic spina bifida patients. The purified 23-kDa protein also induced significant proliferation of lymphocytes from spina bifida patients, but not from health-care workers. The amino acid sequences of tryptic peptides from the 23-kDa protein showed significant though only partial homology with REF. Since the amino acid sequences of the tryptic peptides derived from the 27-kDa and the 23-kDa proteins were virtually identical in the studies of Alenius et al. (29) and Lu et al. (31), and since the IgE reactivity against both proteins seemed to be restricted to NRL-allergic patients with spina bifida, it could be assumed that these proteins are the same or that they represent different isomers or modifications of the same protein (Alenius, unpublished observations). Differences in the estimated molecular

mass of the proteins are probably due to differences in the laboratory methods used. The exact mass of the proteins needs to be established by mass spectrometric analysis or by calculations based on their complete amino acid sequences.

Hevamine (29.6-kDa), a 36-kDa glucanase, and a 46-kDa NRL protein. A 30-kDa NRL protein, purified and identified as hevamine (30) (Table 5), showed IgE binding in 1/29 (3%) NRL-allergic patient sera. Beezhold et al. (69) had also reported that the N-terminal amino acid sequence of an excised NRL protein band at 29 kDa was homologous to hevamine, but none of their 40 patients showed IgE binding in immunoblotting to proteins of this size. These results suggest that hevamine is not an important NRL allergen. Alenius et al. (30) described a 36-kDa NRL protein which showed high homology to several plant endo-1,3- β -glucosidases. This 36-kDa protein bound IgE from 6/29 (21%) NRL-allergic patient sera and was therefore considered to be a significant NRL allergen. In addition, Beezhold et al. (69) showed that NRL protein bands with apparent molecular masses of 46-kDa and 110-kDa had identical, previously unrecognized N-terminal amino acid sequences. IgE antibodies from NRL-allergic patient sera seemed to bind frequently to the 46-kDa-size protein. This protein should, however, be purified before its significance as a novel and important NRL allergen can be confirmed.

Allergens in NRL products

Immunoblot assays have been used to analyze IgE-binding proteins in NRL products. In a study of eight different glove brands, a total of 14 protein bands, ranging from 11 to 200 kDa, could be identified (77). Five brands showed positive immunoblot reactions when tested with IgE antibodies from sera of NRL-allergic patients. The strongest reactions were to 14- and 30-kDa allergens. However, the authors speculated that, because of the limitations of the immunoblot assay, it is possible that the glove extracts contained IgE-binding low-molecular mass (<10 kDa) peptides that may have escaped detection. It is possible that new allergenic epitopes are formed during glove manufacturing. Evidence of this was provided by Mäkinen-Kiljunen et al. (78), who demonstrated by immunoelectrophoresis that one allergen was present in the glove extract, but not in NRL. In general, allergen patterns are notably simpler in glove extracts than in NRL, but it should be kept in mind that IgE-binding proteins detected in immunoblotting after sodium dodecyl sulfate polyacrylamide gel electrophoresis may also be split-down products of larger

stem molecules. Information on molecularly characterized NRL allergens that have been demonstrated in gloves is currently still very limited. Most of the IgE-binding capacity of one highly allergenic glove was attributable to hevein in a recent study (32), and both REF and a 23-kDa protein have been identified in certain glove brands (28, 31).

An attempt can be made to measure the "total" allergenicity of manufactured NRL products *in vivo* by SPT or *in vitro* by specific IgE inhibition assays. In 1988, Turjanmaa et al. (79) used SPT to study the allergenicity of 19 surgical and household NRL gloves and found great variation among them. Later, Yunginger et al. (80) studied 71 glove brands by RAST inhibition, and similarly demonstrated great variation (more than 3000-fold differences) in their allergen contents. Overall, the NRL gloves, especially the powdered ones, contained higher levels of extractable allergens than the other rubber products tested. In 1994, the Finnish National Research and Development Centre for Welfare and Health conducted a study of 20 brands of internationally sold surgical and examination gloves covering over 90% of the Finnish medical glove market. The allergenicity of glove extracts was assessed by three methods: SPT, RAST inhibition, and ELISA inhibition. Highly significant correlations ($r=0.94-0.96$) between the methods were observed, indicating that the ELISA method can also be used for reliable NRL allergen quantification (81). On the basis of these results, NRL gloves could be divided into three groups containing low (<10 arbitrary units [AU] per ml; nine gloves), moderate (10–100 AU/ml; three gloves), or high (>100 AU/ml, eight gloves) levels of NRL allergens. Both powdered and nonpowdered brands were found among gloves with low allergen content. It is well established that cornstarch glove powder can absorb NRL allergens from the gloves (51, 82, 83), and air-sampling studies have shown that NRL aeroallergen concentrations are high in areas where powdered "highly allergenic" gloves are frequently used (21, 22). At present, however, it is not known which of the main NRL allergens contaminate the glove powder.

Latex allergen cross-reactivity

Since the first report suggesting allergen cross-reactivity between NRL and banana (11), a number of studies dealing with possible cross-reactivity between NRL and various food allergens have been published (13, 14, 84–90). RAST inhibition and immunospot and immunoblot inhibition have been used to verify cross-reacting IgE antibodies to latex and banana (13, 90), but 100% inhibition has not been observed in any experiment, indicat-

ing that only a few of the NRL and banana allergens are cross-reactive. The presence of at least one common allergen in NRL and banana has been verified by immunoelectrophoresis (13). In addition, there is evidence that sensitization to banana may result in the production of IgE antibodies which cross-react with allergens in native NRL, but not with allergens in gloves (13). Allergens in native NRL may be denatured during the storage of NRL in ammonia or be otherwise modified during glove manufacture.

Immunoblot inhibition has demonstrated cross-reacting IgE antibodies to several proteins in NRL and banana (90). Lavaud et al. (14) and Vallier et al. (91) have suggested that 15- and 30-kDa proteins are important cross-reacting allergens in NRL and banana. One 15-kDa protein is profilin, an actin-regulating protein, shown to be an important cross-reacting allergen of several plant sources such as tree, grass, and weed pollens and fresh fruits and vegetables (92). Profilin has been demonstrated in NRL and banana, but not in NRL glove extracts (91). Latex RAST positivity was not correlated with birch, mugwort, or timothy pollen RAST (13), but cross-reactivity has been reported among NRL, ragweed, and blue grass allergens (93).

About half of the NRL-allergic patients have experienced symptoms after eating banana, and 35% have had positive skin test results to fresh banana (13, 87). Among 47 NRL-allergic patients, 26 (55%) had IgE antibodies also to banana, and of the 31 latex RAST-positive patients, 25 (81%) also had positive banana RAST (13). Besides banana, other foods, such as avocado, chestnut, tomato, kiwi, melon, pineapple, peach, and papaya, have been thought to cross-react with NRL. Follow-up studies are needed to evaluate the clinical importance of the frequent occurrence of NRL IgE antibodies in food-allergic patients. Furthermore, the role of fruits and early contact with NRL pacifiers (94) as possible primary sensitizers in infancy should be elucidated.

Future prospects

NRL gloves and other products are and will be ubiquitous in medical and nonmedical environments. Several crucial questions have to be answered to solve the current problem of NRL allergy. The risk groups and various symptoms have been identified rather well, but asymptomatic NRL-allergic subjects present a diagnostic challenge to every physician. In addition, the mechanisms of NRL sensitization are still poorly understood. It is important to elucidate especially the significance of airborne NRL exposure in health-care workers (48). More research is also

needed to assess the consequences of the coexistent food and NRL allergy reported to occur frequently both in children and adults.

Considerable progress has recently been made in identifying and characterizing at molecular level several important NRL allergens. Prohevein and hevein are major allergens for health-care workers, whereas REF and a 27-kDa NRL protein are important allergens for multioperated children (29–32, 60). Knowledge of the whole spectrum of NRL allergens will help researchers to develop more specific *in vivo* and *in vitro* tests for diagnostic purposes. Furthermore, the production of purified NRL allergens could provide tools for immunotherapy. The mechanisms behind the frequently observed cross-allergies will be better understood once the relevant allergenic epitopes have been identified. In particular, it is important to know whether sensitization to food allergens, such as banana, could facilitate the development of NRL allergy in childhood.

The prevention of NRL allergy is the ultimate goal for researchers, clinicians, and regulatory authorities. The Food and Drug Administration (FDA) in the USA and the European Committee for Standardization (CEN) have acknowledged the measurement of total protein as a simple option for glove manufacturers to monitor their products. Recent research has yielded specific methods for measuring NRL allergen levels in the gloves, and this progress has already led the Finnish authorities to inform consumers of the highly allergenic glove brands in the market. The international rubber manufacturers may also benefit from these new methods of developing less allergenic gloves and other NRL products. Advances in this field will inevitably lead to a safer environment for glove-wearing health-care workers and their patients.

References

- Forström L. Contact urticaria from latex surgical gloves. *Contact Dermatitis* 1989;6:33–4.
- Nutter A. Contact urticaria to rubber. *Br J Dermatol* 1979; 101:597–8.
- Slater J. Rubber anaphylaxis. *N Engl J Med* 1989; 320:26–31.
- Spaner D, Dolovich J, Tarlo S, Sussman G, Butto K. Hypersensitivity to natural latex. *J Allergy Clin Immunol* 1989;83:1135–7.
- Taylor J, Cassettari J, Wagner W, Helm T. Contact urticaria and anaphylaxis to latex. *J Am Acad Dermatol* 1989; 21:874–7.
- Turjanmaa K. Latex glove contact urticaria. Thesis, University of Tampere, 1988. *Acta Universitatis Tamperensis series A*, vol. 254, 1–86.
- Sussman G, Beezhold D. Allergy to latex rubber. *Ann Intern Med* 1995;122:43–6.
- Taylor J, Praditsuan P. Latex allergy. Review of 44 cases including outcome and frequent association with allergic hand eczema. *Arch Dermatol* 1996;132:265–71.
- Axelsson I, Eriksson M, Wrangsjö K. Anaphylaxis and angioedema due to rubber allergy in children. *Acta Paediatr Scand* 1988;77:314–16.
- Sorva R, Mäkinen-Kiljunen S, Suvelto K, Juntunen-Backman K, Haahela T. Latex allergy in children with no known risk factor for latex sensitization. *Pediatr Allergy Immunol* 1995;6:36–8.
- M'Raihi L, Charpin D, Pons A, Bongrand P, Vervloet D. Cross-reactivity between latex and banana. *J Allergy Clin Immunol* 1991;87:129–30.
- Blanco C, Carrillo T, Castillo R, Quirarte J, Cuevas M. Avocado hypersensitivity. *Allergy* 1994;49:454–9.
- Mäkinen-Kiljunen S. Banana allergy in patients with immediate-type hypersensitivity to natural rubber latex: characterization of cross-reacting antibodies and allergens. *J Allergy Clin Immunol* 1994;93:990–6.
- Lavaud F, Prevost A, Cossart C, Guerin L, Bernard J. Kochman S. Allergy to latex, avocado, pear, and banana – evidence for a 30 kD antigen in immunoblotting. *J Allergy Clin Immunol* 1995;95:557–64.
- Axelsson J, Johansson S, Wrangsjö K. IgE-mediated anaphylactoid reactions to rubber. *Allergy* 1987;42:46–50.
- Turjanmaa K. Incidence of immediate allergy to latex gloves in hospital personnel. *Contact Dermatitis* 1987; 17:270–5.
- Leynadier F, Pecquet C, Dry J. Anaphylaxis to latex during surgery. *Anaesthesia* 1989;44:547–50.
- Slater J. Medical rubber anaphylaxis [Letter]. *Lancet* 1991;337:187.
- Kelly K, Pearson M, Kurup V, et al. A cluster of anaphylactic reactions in children with spina bifida during general anesthesia: epidemiologic features, risk factors, and latex hypersensitivity. *J Allergy Clin Immunol* 1994;94:53–61.
- Jäger D, Kleinhan D, Czuppon A, Baur X. Latex-specific proteins causing immediate-type cutaneous, nasal, bronchial, and systemic reactions. *J Allergy Clin Immunol* 1992;89:759–68.
- Swanson M, Bubak M, Hunt L, Yunginger J, Warner M, Reed C. Quantification of occupational latex aeroallergens in a medical center. *J Allergy Clin Immunol* 1994;94:445–51.
- Tarlo S, Sussman G, Contala A, Swanson M. Control of airborne latex by use of powder-free latex gloves. *J Allergy Clin Immunol* 1994;93:985–9.
- Vandenplas O, Delwiche JP, Evrard G, et al. Prevalence of occupational asthma due to latex among hospital personnel. *Am J Respir Crit Care Med* 1995;151:54–60.
- Turjanmaa K, Reunala T, Räsänen L. Comparison of diagnostic methods in latex surgical glove contact urticaria. *Contact Dermatitis* 1988;19:241–7.
- Wrangsjö K, Wahlberg J, Axelsson I. IgE-mediated allergy to natural rubber in 30 patients with contact urticaria. *Contact Dermatitis* 1988;19:264–71.
- Slater J, Mostello L, Shaer C. Rubber specific IgE in children with spina bifida. *J Urol* 1991;146:578–9.
- Hamilton R, Charous B, Adkinson N, Yunginger J. Serologic methods in the laboratory diagnosis of latex rubber allergy: study of nonammoniated, ammoniated latex, and glove (end-product) extracts as allergen reagent sources. *J Lab Clin Med* 1994;123:594–604.
- Czuppon AB, Chen Z, Rennett S, et al. The rubber elongation factor of rubber trees (*Hevea brasiliensis*) is the major allergen in latex. *J Allergy Clin Immunol* 1993;92:690–7.
- Alenius H, Kalkkinen N, Lukka M, et al. Purification and partial amino acid sequencing of a 27 kD natural rubber

- allergen recognized by latex allergic children with spina bifida. *Int Arch Allergy Immunol* 1994;106:258-62.
30. Alenius H, Kalkkinen N, Lukka M, et al. Prohevein from the rubber tree (*Hevea brasiliensis*) is a major latex allergen. *Clin Exp Allergy* 1995;25:659-65.
31. Lu L, Kurup V, Hoffman D, Kelly K, Murali P, Fink J. Characterization of a major latex allergen associated with hypersensitivity in spina bifida patients. *J Immunol* 1995;155:2721-8.
32. Alenius H, Kalkkinen N, Reunala T, Turjanmaa K, Palosuo T. The main IgE-binding epitope of a major latex allergen, prohevein, is present in its N-terminal 43 amino acid fragment, hevein. *J Immunol* 1996;156:1618-25.
33. Arellano R, Bradley J, Sussman G. Prevalence of latex sensitization among hospital physicians occupationally exposed to latex gloves. *Anesthesiology* 1992;77:905-8.
34. Turjanmaa K, Cacioli P, Thompson R, Simlote P, Lopez M. Frequency of natural rubber latex allergy among US operating room nurses using skin prick testing [Abstract]. *J Allergy Clin Immunol* 1995;95:214.
35. Kaczmarek R, Silverman B, Gross T, et al. Prevalence of latex-specific IgE antibodies in hospital personnel. *Ann Allergy Asthma Immunol* 1996;76:51-6.
36. Moneret-Vautrin DA, Beaudouin E, Widmer S, et al. Prospective study of risk factors in natural rubber latex hypersensitivity. *J Allergy Clin Immunol* 1993;92:668-77.
37. Kelly K, Kurup V, Zacharisen M, Resnick A, Fink J. Skin and serologic testing in the diagnosis of latex allergy. *J Allergy Clin Immunol* 1993;91:1140-5.
38. Slater J. Latex allergy [Review]. *J Allergy Clin Immunol* 1994;94:139-49.
39. Tosi L, Slater J, Shaer C, Mostello L. Latex allergy in spina bifida patients: prevalence and surgical implications. *J Pediatr Orthop* 1993;13:709-12.
40. Pittman T, Kiburz J, Gabriel K, Steinhardt G, Williams D, Slater J. Latex allergy in children with spina bifida. *Pediatr Neurosurg* 1995;22:96-100.
41. Capriles-Huleit A, Sanchez-Borges M, Von-Scazoni C, Medina J. Very low frequency of latex and fruit allergy in patients with spina bifida from Venezuela: influence of socioeconomic factors. *Ann Allergy Asthma Immunol* 1995;75:62-4.
42. Turjanmaa K, Mäkinen-Kiljunen S, Reunala T, Alenius H, Palosuo T. Natural rubber latex allergy - the European experience. In: Fink J, editor. *Latex allergy*. Philadelphia: Saunders, Immunol Allergy Clin North Am 1995;15:71-88.
43. Ownby D, Ownby H, McCullough J, Shafer A. The prevalence of anti-latex IgE antibodies in 1000 volunteer blood donors [Abstract]. *J Allergy Clin Immunol* 1994;93:282.
44. Yassin M, Lierl M, Fischer T, O'Brien K, Cross J, Steinmetz C. Latex allergy in hospital employees. *Ann Allergy* 1994;72:245-9.
45. Charous B, Hamilton R, Yunginger J. Occupational latex exposure: characteristics of contact and systemic reactions in 47 workers. *J Allergy Clin Immunol* 1994;94:12-8.
46. Tarlo S, Wong L, Roos J, Booth N. Occupational asthma caused by latex in a surgical glove manufacturing plant. *J Allergy Clin Immunol* 1990;85:626-31.
47. Vandenplas O. Occupational asthma caused by natural rubber latex [Review]. *Eur Respir J* 1995;8:1957-65.
48. Ylitalo L, Turjanmaa K, Reunala T. Natural rubber latex (NRL) allergy in food allergic children [Abstract]. *J Allergy Clin Immunol* 1996;97:321.
49. Levy D, Charpin D, Pecquet C, Leynadier F, Vervloet D. Allergy to latex [Review]. *Allergy* 1992;47:579-87.
50. Sussman G, Tarlo S, Dolovich J. The spectrum of IgE-mediated responses to latex. *JAMA* 1991;265:2844-7.
51. Tomazic V, Shampaine E, Lamanna A, Withrow T, Adkinson N, Hamilton R. Cornstarch powder on latex products is an allergen carrier. *J Allergy Clin Immunol* 1994;93:751-8.
52. Maibach H, Johnson H. Contact urticaria syndrome. *Arch Dermatol* 1975;111:726-30.
53. Ownby D, McCullough J. Testing for latex allergy. *J Clin Immunology* 1993;16:109-13.
54. Hadjiladis D, Khan K, Tarlo S. Skin test responses to latex in an allergy and asthma clinic. *J Allergy Clin Immunol* 1995;96:431-2.
55. Turjanmaa K, Alenius H, Mäkinen-Kiljunen S, Palosuo T, Reunala T. Commercial skin prick test preparations in the diagnosis of rubber latex allergy [Abstract]. *J Allergy Clin Immunol* 1995;93:299.
56. Wrangsjö K, Osterman K, van Hage-Hamsten M. Glove-related skin symptoms among operating theatre and dental care unit personnel. II. Clinical examination, tests and laboratory findings indicating latex allergy. *Contact Dermatitis* 1994;30:139-43.
57. Mäkinen-Kiljunen S, Reunala T, Turjanmaa K, Cacioli P. Is cow's milk casein an allergen in latex-rubber gloves? [Letter]. *Lancet* 1993;342:863.
58. Pisati G, Baruffini F, Bernabeco F, Stanizzi R. Bronchial provocation testing in the diagnosis of occupational asthma due to latex surgical gloves. *Eur Respir J* 1994;7:332-6.
59. Leynadier F, Dry J. Allergy to latex [Review]. *Clin Rev Allergy* 1991;9:371-7.
60. Alenius H, Kalkkinen N, Turjanmaa K, Mäkinen-Kiljunen S, Reunala T, Palosuo T. Significance of the rubber elongation factor as a latex allergen. *Int Arch Allergy Immunol* 1996;109:362-8.
61. Morales C, Basomba A, Carrreira J, Sastre A. Anaphylaxis produced by rubber glove contact: case reports and immunological identification of the antigens involved. *Clin Exp Allergy* 1989;19:425-30.
62. Alenius H, Turjanmaa K, Palosuo T, Mäkinen-Kiljunen S, Reunala T. Surgical latex glove allergy: characterization of rubber protein allergens by immunoblotting. *Int Arch Allergy Appl Immunol* 1991;96:376-80.
63. Slater J, Chhabra S. Latex antigens. *J Allergy Clin Immunol* 1992;89:673-8.
64. Chambeyron C, Dry J, Leynadier F, Pecquet C, Tran X. Study of the allergenic fractions of latex. *Allergy* 1992;47:92-7.
65. Alenius H, Palosuo T, Kelly K, et al. IgE reactivity to 14-kD and 27-kD natural rubber proteins in latex-allergic children with spina bifida and other congenital anomalies. *Int Arch Allergy Immunol* 1993;102:61-6.
66. Alenius H, Kurup V, Kelly K, Palosuo T, Turjanmaa K, Fink J. Latex allergy: frequent occurrence of IgE antibodies to a cluster of 11 latex proteins in patients with spina bifida and histories of anaphylaxis. *J Lab Clin Med* 1994;123:712-20.
67. Alenius H, Turjanmaa K, Mäkinen-Kiljunen S, Reunala T, Palosuo T. IgE immune response to rubber proteins in adult patients with latex allergy. *J Allergy Clin Immunol* 1994;93:859-63.
68. Akasawa A, Hsieh LS, Lin Y. Serum reactivities to latex proteins (*Hevea brasiliensis*). *J Allergy Clin Immunol* 1995;95:1196-1205.
69. Beezhold D, Sussman G, Kostyal D, Chang N. Identification of a 46-kD latex protein allergen in health care workers. *Clin Exp Immunol* 1994;98:408-13.
70. Gidrol X, Chrestin H, Tan H, Kush A. Hevein, a lectin-like protein from *Hevea brasiliensis* (rubber tree), is involved in the coagulation of latex. *J Biol Chem* 1994;269:9278-83.
71. Broekaert I, Lee H, Kush A, Chua N, Raikhel N. Wound-

- induced accumulation of mRNA containing a hevein sequence in laticifers of rubber tree (*Hevea brasiliensis*). Proc Natl Acad Sci U S A 1990;87:7633-7.
72. Lee H, Broekaert W, Raikhel N, Lee H. Co- and post-translational processing of the hevein preproprotein of latex of the rubber tree (*Hevea brasiliensis*). J Biol Chem 1991;266:15944-8.
73. Jekel P, Hartmann B, Beintema J. The primary structure of heveamine, an enzyme with lysozyme/chitinase activity from *Hevea brasiliensis* latex. Eur J Biochem 1991;200:123-30.
74. Dennis M, Henzel W, Bell J, Kohr W, Light D. Amino acid sequence of rubber elongation factor protein associated rubber particles in *Hevea* latex. J Biol Chem 1989; 264:18618-26.
75. Light D, Dennis M. Purification of a prenyltransferase that elongates cis-isoprene rubber from latex of *Hevea brasiliensis*. J Biol Chem 1989;269:9278-83.
76. Chen Z, Posch A, Raulf-Heimsoth M, Baur X. Isolation and identification of hevein as a major IgE-binding polypeptide in latex from *Hevea brasiliensis* [Abstract]. J Allergy Clin Immunol 1996;97:428.
77. Alenius H, Mäkinen-Kiljunen S, Turjanmaa K, Palosuo T, Reunala T. Allergen and protein content of latex gloves. Ann Allergy 1994;73:315-20.
78. Mäkinen-Kiljunen S, Turjanmaa K, Palosuo T, Reunala T. Characterization of latex antigens and allergens in surgical gloves and natural rubber by immunoelectrophoretic methods. J Allergy Clin Immunol 1992;90:230-5.
79. Turjanmaa K, Laurila K, Mäkinen-Kiljunen S, Reunala T. Rubber contact urticaria. Allergenic properties of 19 brands of latex gloves. Contact Dermatitis 1988;19:362-7.
80. Yunginger J, Jones R, Fransway A, et al. Extractable latex allergens and proteins in disposable medical gloves and other rubber products. J Allergy Clin Immunol 1994;93:836.
81. Turjanmaa K, Mäkinen-Kiljunen S, Alenius H, Reunala T, Palosuo T. *In vivo* and *in vitro* evaluation of allergenicity of natural rubber latex (NRL) gloves used in health care: a nation-wide study [Abstract]. J Allergy Clin Immunol 1996;97:325.
82. Turjanmaa K. Update on occupational natural rubber latex allergy. Dermatol Clin 1994;12:561-7.
83. Beezhold D, Beck W. Surgical glove powders bind latex antigens. Arch Surg 1992;127:1354-7.
84. Ross B, McCullough J, Ownby D. Partial cross-reactivity between latex and banana allergens J Allergy Clin Immunol 1992;90:409-10.
85. Rodriguez M, Vega F, Garcia MT, et al. Hypersensitivity to latex, chestnut, and banana. Ann Allergy 1993;70:31-4.
86. De Corres L, Moneo I, Munoz D, et al. Sensitization from chestnuts and bananas in patients with urticaria and anaphylaxis from contact with latex. Ann Allergy 1993;70:35-9.
87. Blanco C, Carrillo T, Castillo R, Quirarte J, Cuevas M. Latex-allergy: clinical features and cross-reactivity with fruits. Ann Allergy 1994;73:309-14.
88. Ahlroth M, Alenius H, Turjanmaa K, Mäkinen-Kiljunen S, Reunala T, Palosuo T. Cross-reacting allergens in natural rubber latex and avocado. J Allergy Clin Immunol 1995;96:167-73.
89. Baur X, Chen Z, Rozynek P, Duser M, Raulf-Heimsoth M. Cross-reacting IgE antibodies recognizing latex allergens, including Hev b 1, as well as papain. Allergy 1995;50:604-9.
90. Alenius H, Mäkinen-Kiljunen S, Ahlroth M, Turjanmaa K, Reunala T, Palosuo T. Cross-reactivity between allergens in natural rubber latex and banana studied by immunoblot and immunoblot inhibition methods. Clin Exp Allergy 1996;26:341-8.
91. Vallier P, Ballard S, Harf R, Valenta R, Deviller P. Identification of profilin as an IgE-binding component in latex from *Hevea brasiliensis*: clinical implications. Clin Exp Allergy 1995;25:332-9.
92. Valenta R, Duchene M, Ebner C, et al. Profilins constitute a novel family of function plant pan-allergens. J Exp Med 1992;175:377-85.
93. Appleyard J, McCullough J, Ownby D. Cross-reactivity between latex, ragweed, and blue grass allergens [Abstract]. J Allergy Clin Immunol 1994;93:182.
94. Mäkinen-Kiljunen S, Sorva R, Juntunen-Backman K. Latex dummies as allergens [Letter]. Lancet 1992;339:1608-9.
95. Lagier F, Vervloet D, Lhermet I, Poyen D, Charpin D. Prevalence of latex allergy in operating room nurses. J Allergy Clin Immunol 1992;90:319-22.
96. van der Walle H, Brunsveld V. Latex allergy among hairdressers. Contact Dermatitis 1995;32:177.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.