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# Latex Allergy

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## INTRODUCTION

Natural rubber latex (NRL) allergy was clearly identified in 1979 in Europe (1) and in 1989 in North America (2,3), although adverse reactions to natural rubber materials had occasionally been described earlier (4). Over the past 15 years, NRL has been increasingly acknowledged as a major cause of IgE-mediated allergy in occupational and nonoccupational environments (5,6). NRL materials can cause a wide spectrum of immediate hypersensitivity reactions, ranging from mild urticaria to extensive angioedema and life-threatening anaphylaxis after cutaneous, mucosal, or visceral exposure. In addition, it has been shown that NRL proteins can bind onto glove powder and can then act as airborne allergens causing rhinitis and asthma (7).

## NATURAL RUBBER LATEX

### Composition

In the chemical industry, the term latex applies to any emulsion of polymers, including synthetic rubbers and plastics. NRL refers specifically to products derived from the milky fluid, or latex, produced by the laticifers of the tropical rubber tree *Hevea braziliensis* (botanical family of Euphorbiaceae). Laticifers are specialized structures that consist of anastamosed latex-producing cells. Upon wounding, the cytoplasmic content of these cells is expelled and coagulates in order to seal and protect the wounded sites.

Using high-speed centrifugation, NRL can be separated into three components: the "rubber cream" containing the rubber particles, the latex serum (C-serum),

and the "bottom fraction" which consists mainly of vacuolar structures called *lutoids*. Rubber particles are spherical droplets containing polymers of *cis*-1,4 polyisoprene coated with a layer of hydrophilic colloid (proteins, lipids, and phospholipids). Lutoids are vacuoles with an acidic content that are involved in the coagulation of latex through the release of proteins interacting with rubber particles. Fresh NRL consists of about 30% to 40% rubber hydrocarbon and 2% to 3% protein. A number of NRL proteins have been purified and sequenced. Prenyltransferase (38 kDa) is found in the cytosol as well as in association with rubber particles. Rubber elongation factor (14.6 kDa) is bound to the surface of rubber particles. These two enzymes are thought to play a role in the elongation of polyisoprene chains (8). The lutoid bodies contain defense-related proteins. Hevein (4.7 kDa), a major protein of the lutoid bodies, is synthesized as a preproprotein (or prohevein, 20 kDa) that is post-translationally processed into an amino-terminal fragment, hevein, and a carboxyl-terminal domain (14 kDa). Hevein is a lectin-like protein that may be involved in the coagulation of latex by bridging rubber particles (9). Hevein inhibits the growth of chitin-containing fungi through chitin-binding properties (10). Hevein shows structural homology to wheat germ agglutinin and other chitin-binding proteins, while the carboxyl-terminal domain demonstrates homology to wound-inducible proteins in various plants, such as WIN 1 and WIN 2 (11). Hevamine (29 kDa), an enzyme with lysozyme and chitinase properties, has been isolated from the lutoids (12). The lutoid bodies contain glycoproteins that can form complex microfibrils and microhelices.

## Processing

Ammonia is added to the fresh latex obtained during tapping of the rubber tree to prevent premature coagulation and bacterial growth. The resulting emulsion is concentrated to obtain a 60% rubber content by centrifuging. Further processing of concentrated NRL varies considerably according to the desired properties of the finished product, but usually includes the following three steps: compounding, coagulation, and vulcanization. Compounding involves the addition of a variety of chemicals including sulfur compounds, antioxidants (e.g., paraphenylenediamine), accelerators (e.g., zinc oxide, thiurams, dithiocarbamates, mercaptobenzothiazole, etc.), fillers, pigments, emulsifiers, and other ingredients. Some of these compounding agents, particularly the accelerators, can cause delayed type-IV hypersensitivity (13). The concentrated liquid NRL is converted to a solid form during the coagulation, or curing, process by dehydration and/or addition of acids, metal ions, or surface-active agents. Vulcanization consists of a heat-catalyzed cross-linking of the *cis*-1,4 polyisoprene chains by sulfur bridges; this process imparts the characteristic property of rubber elasticity. NRL articles are produced either by dipping or by extrusion/compression molding. Typically, gloves are manufactured by dipping porcelain formers, pretreated with a coagulant (e.g., calcium nitrate) and a releasing agent (cornstarch powder), into the compounded liquid NRL. The gloves are then passed through ovens to complete coagulation of NRL and through water baths to extract water-soluble proteins and processing chemicals. Finally they undergo vulcanization and addition of donning powder. For powder-free gloves, the residual releasing agent can be subsequently removed from the gloves through a chlorination wash process.

## PATHOGENESIS

There is convincing evidence from both in vitro and in vivo experiments that immediate hypersensitivity reactions caused by NRL materials are mediated through specific IgE antibodies directed against NRL proteins that persist in manufactured products (5,6). Exposure to the NRL proteins occurs by direct contact with the latex product and by inhalation of NRL-contaminated powder aerosolized from powdered gloves. Significant amounts of rapidly elutable endotoxin can contaminate NRL gloves and are also present in glove-generated aerosols (14). Animal models have shown mixed results regarding the role of glove-associated endotoxin. In presence of high dose endotoxin (250,000 EU), the production of Hev b 5 specific IgE was augmented (15). Coexposure to nonammoniated latex (NAL) and low levels of endotoxin (up to 25,000 EU) decreased NRL-specific IgE but enhanced nonspecific airway hyperreactivity (16). Given the nature of these findings, further research to investigate the effects of endotoxins on IgE responses to NRL is necessary.

### NRL Allergens

Immunoblotting studies conducted by numerous investigators have identified IgE-binding proteins with molecular weights ranging from 2 to 200 kDa in raw NRL and eluates from NRL-manufactured products (17–27). Antigens with molecular weights of 14, 20, 24, 27, 30, 36, and 46 kDa have been consistently identified. Variations in specific antigen reactivity may be due to differences in source materials, including fresh latex or NAL, ammoniated latex, and finished products. Ammonia treatment and other manufacturing procedures can cause aggregation and/or precipitation of NRL peptides (27–30). Antigenic variability may also result from the methods used for extracting and identifying antigens from NRL products as these methods can lead to conformational alteration and degradation of NRL proteins (30–32). Furthermore, significant differences can be detected in the pattern of IgE reactivity between subjects with NRL allergy (24,26,27,32,33), possibly as a result of differences in the patients' mode of sensitization. Although most studies have failed to demonstrate a correlation between the pattern of IgE reactivity to NRL proteins and clinical manifestations of NRL allergy, some investigations suggest that spina bifida is often associated with the development of IgE antibodies against 24-kDa and 27-kDa proteins (29,34).

Substantial progress has been made in the purification and molecular characterization of NRL allergens. To date, 13 allergens have been officially named by the International Union of Immunological Societies Allergen Nomenclature Committee (35), and several of these exist in multiple isotypes (Table 1) (26,29,30,36–47). Using a proteomic approach, 47 IgE binding proteins were analyzed, resulting in the identification of several known allergen (Hev b 6, 7, 9, and 11) and five new allergen candidates (UDP-glucose pyrophosphorylase, isoflavone reductase, rotamase, thioredoxin, and citrate binding protein) (48). Except for Hev b 4, the named NRL allergens have been cloned and produced by recombinant technologies. The recombinant proteins have been characterized, and for several of the allergens, the T and B cell epitopes have been identified (49–52). Detailed information regarding these allergens can be found in recent reviews (53–55). The use of recombinant or highly purified natural proteins in both laboratory and clinical studies has lead to information on the relative importance of the various individual allergens. By skin-prick testing

**Table 1** Natural Rubber Latex (NRL) Allergens

| Allergen | Common name | Molecular weight (kDa) | Plant allergen family | Potential cross-reacting allergens | Accession no. | References |
|---|---|---|---|---|---|---|
| Hev b 1 | Rubber elongation factor | 58/14.6 | | Papain, fig | AY120685 | 29,30,36 |
| Hev b 2 | β 1-3-glucane | 34/36 | PR-2 | | AF311749 | 37,38 |
| Hev b 3 | Small rubber particle protein | 24 | | | O82803 | 29 |
| Hev b 4 | Cyanogenic glucosamide | 100–115 | | | BI729486 | 38 |
| Hev b 5 | Acidic protein | 16 | | Kiwi | U42640 | 30,39 |
| Hev b 6.01 | Hevein preprotein | 20 | | | M36986 | 11 |
| Hev b 6.02 | Hevein | 5 | PR-3 | Banana, avocado Kiwi | P02877 | 37 |
| Hev b 6.03 | C-terminal domain | 14 | PR-4 | Potato | P02877 | 26,37,40 |
| Hev b 7.01 | Patatin homolog (B-serum) | 42 | | | U80598 | 41 |
| Hev b 7.02 | Patatin homolog (C-serum) | 44 | | Potato | AJ223038 | 26 |
| Hev b 8 | Profilin | 14 | Profilin | Pollen, celery | AJ243325 | 42 |
| Hev b 9 | Enolase | 51 | | Molds | AJ132580 | 43 |
| Hev b 10 | Mn-superoxide dismutase | 26 | | Molds | L11707 | 44 |
| Hev b 11 | Class I chitinase | 33 | PR-3 | Banana, avocado | AJ238579 | 45 |
| Hev b 12 | Lipid transfer protein | 9.4 | PR-14 | Stone fruits, peach | AY057860 | 46 |
| Hev b 13 | Early nodule-specific protein | 42 | | Patatin | P83269 | 47 |

*Note*: Allergens are named according to the International Union of Immunological Societies nomenclature. Representative accession numbers are given. Additional information can be obtained at www.allergen.org.
*Abbreviation*: PR, pathogenesis-related proteins.

the NR-allergic health care workers with recombinant Hev b 2, 3, 5, 6, 7, and 8, it was found that Hev b 5 (62%), Hev b 6 (66%), and Hev b 7 (41%) were the most common allergens for health care workers (56). More recently, health care workers were skin tested with purified native NRL proteins Hev b 1, 2, 3, 4, 6, 7, and 13 and with recombinant Hev b 5 (57). In this study, Hev b 2 (63%), 5 (65%), 6 (63%), 7 (45%), and 13 (63%) were found to be the most reactive. Interestingly, reactivity of native Hev b 2 (63%) and rHev b 2 (7%) differed significantly between these studies suggesting that the glycosylation on the native protein (compared to the nonglycosylated recombinant

form) may play an important role in reactivity to individual Hev b allergens. The contribution of glycosylation to the reactivity/potency of specific NRL allergens has not been well studied.

## Assessment of Exposure to NRL Allergens

NRL is widely used in the manufacturing of medical devices (gloves, catheters, drainage tubes, anesthetic masks, tourniquets, dental dams, etc.) as well as in the production of a variety of everyday articles, including household gloves, toys, balloons, condoms, baby pacifiers, sports equipment, elastic straps, mattresses, tires, and adhesives. Various in vitro methods have been used to estimate the allergenic content of NRL materials, including total protein measurements and ELISA and RAST inhibition methods. Total protein assays are easy to perform, but they lack sensitivity and specificity. The results of these assays are strongly influenced by the presence of various chemicals in NRL products that can interfere with these tests (58). Unless precipitation techniques are used to remove interfering substances (59), the results of these tests are unreliable. A modified Lowry test was standardized by the American Society for Testing and Materials (ASTM, D5712) with a protein precipitation step using trichloroacetic acid and phosphotungstic acid to eliminate the interfering substances. This method results in a reasonable estimate of the total protein in the NRL product. ASTM standards recommend that all examination and surgical gloves should contain less than $200\,\mu g/dm^2$ of total protein when assessed by this standard test (60).

Many studies have found a marked discordance between the total amount of protein eluting from NRL devices and their allergenic potential, as assessed by skin-prick testing (61–64). For some studies this was due to the failure in removing interfering chemicals, but the lack of correlation may also be due to the nonallergenic nature of some proteins found in NRL products. Immunochemical assays provide a more sensitive and biologically relevant method for determining allergen levels in NRL products (58). ELISA and RAST inhibition methods have been used to estimate the antigen content in NRL products (58,63,65). These methods have shown considerable variations in the allergen content between different brands of gloves and even between different batches of the same brand of gloves (58,63,65). The ASTM has developed a standardized method for quantifying the allergenic potential of latex materials using an inhibition ELISA (ASTM D6499 assay). This test uses a well-characterized rabbit–antilatex reference antisera and an ammoniated NRL protein reference standard, prepared as industry reference materials, to measure antigen levels. The ASTM recommends the presence of less than $10\,\mu g/dm^2$ of antigenic protein on examination and surgical gloves when assessed by this standard method. IgE inhibition assays (RAST inhibition) commonly used by individual laboratories are affected by the source of specific IgE and the quality of allergen reference standard. Current work at the ASTM is focused on standardizing monoclonal antibody assays that measure specific allergens. A commercial kit using monoclonal antibodies is available to measure Hev b 1, 2, 5, and 6 as individual ELISA determinations and then combine the results as an indicator of allergenicity. A recent report suggests that measuring only Hev b 5 and Hev b 13 produces a reliable estimate of the allergenic potential (66). While additional work is necessary to standardize an allergen assay, in vivo and in vitro methods have shown that the total protein and allergen content of NRL gloves can be significantly reduced by washing the gloves during the manufacturing process (62,67).

Exposure to NRL allergens can occur from direct contact of NRL materials with the skin, and mucosal and serosal membranes. It has also been demonstrated that NRL protein allergens can bind to powder particles on gloves (or on any powdered rubber product, such as toy balloons) and can become potent airborne allergens (20,60,68–70). Using an inhibition assay, Swanson et al. (71) quantified airborne NRL allergens collected using personal and area samplers at various work sites in a hospital. The amount of airborne NRL allergens correlated with the frequency of glove use, although considerable variation was found among subjects with the same type of job. Substantial amounts of allergens were recovered from coats and surgical scrub suits, suggesting that resuspension from clothing and settled dust may lead to secondary or even remote inhalation exposure. Twenty percent of airborne powder particles were in a respirable size and therefore capable of causing asthma. In a prospective study, NRL aeroallergen levels were strongly correlated with the use of powdered NRL gloves in the operating room and were similar to that found in nonsurgical days when low-allergen gloves were used (72). Another study found that powdered surgical gloves generated lower levels of airborne allergens than did examination gloves, and the allergen was primarily associated with larger particles of size more than 10 μm (73). In contrast, powdered examination gloves produced a higher proportion of allergenparticles in the respirable range (73).

## EPIDEMIOLOGY

### Incidence and Prevalence

The incidence of NRL allergy has changed significantly in many occupational settings since the previous edition of this book in 1999. From 1989 to 1999 a number of studies had documented a high incidence of NRL allergy in individuals with occupational exposure to NRL. Most affected were glove wearers and manufacturers (74–81), and patients undergoing multiple surgical procedures (82), particularly in early infancy, such as children with spina bifida and urogenital abnormalities (83–87). Epidemiological studies documented NRL allergy in about 10% of workers manufacturing medical gloves (74) and NRL toys (88). Prevalence figures for NRL allergy had ranged from 2.8% to 17% among health-care workers, including physicians, nurses, laboratory technicians, hospital housekeepers, and dental-care providers (75–80). The highest prevalence rates, ranging from 29% to 65%, were found in children with spina bifida (83–87). In addition, NRL allergy due to gloves was increasingly described in workers in nonmedical environments, including those exposed to chemicals (89), hairdressers (90), and greenhouse workers (81). Few reports have assessed the incidence of NRL allergy. In dental hygiene apprentices reported by Gautrin et al. (91), 110 students were followed after entering the program between 1993 and 1995. On follow-up up to 32 months after entry, seven developed skin sensitization to NRL (6%), while the cumulative incidence of probable occupational rhinoconjunctivitis was 1.8% and probable occupational asthma was 4.5%.

The increasing incidence and prevalence of NRL allergy during that 10-year period were attributed in part to the advent of Standard Precautions in the last half of the 1980s, which resulted in increased use of NRL devices as a protective barrier against viral infections. The increased demand for, and production of, NRL gloves may also have played a role, with the potential for saturation of NRL proteins in the leeching fluid during production and other changes in manufacturing processes (92).

The increased need for tapping of rubber trees and, in some cases, the treatment of Hevea trees with phytohormones to stimulate the production of latex could have enhanced the biosynthesis of some proteins by laticifers, especially defense-related proteins (9,93). Increased recognition of NRL allergy by exposed workers and physicians is also likely to have contributed to the apparent increase in the prevalence of the disease during that time.

Because exposure appears to be the most significant risk factor for developing NRL allergy, it is not surprising that with recognition and intervention measures, the incidence has fallen. Work-related allergic responses from NRL carried by glove powder should no longer be a problem in most occupational settings. As noted, the most reported occupational sensitization was in health-care workers, primarily from the use of high-protein, powdered NRL gloves (6). With this understanding, the protein content of NRL gloves has been significantly reduced by many manufacturers (94), and low-powdered or nonpowdered gloves are available. Several recent studies suggest that when instituted, such changes are very effective in reducing the risk of occupational sensitization in health care workers (95–101). Despite the reductions in incidence of NRL allergy reported from health care facilities where glove changes have been made, it is likely that a significant proportion of facilities have not made specific changes in glove usage. Efforts have been made by NRL glove producers to reduce powder and NRL protein content of NRL gloves used for health care (94). However there is no clear published report to suggest overall effectiveness of this in facilities that have not specifically purchased low-protein, powder-free gloves. Recent reports from various areas of the world indicate that prevalence rates of latex sensitization range from 5.4% to 9.7% among hospital employees with daily NRL contact (102–104). Similarly, it may be expected that improvements in powdered gloves may be slower in non–health care occupations (105,106).

## Risk Factors

Although exposure to NRL is intuitively the most relevant risk factor for the initiation of NRL allergy, a clear dose–response relationship between occupational exposure to NRL and IgE-mediated sensitization has not been consistently demonstrated in prevalence surveys. This is because assessment of exposure based on self-reported use of NRL gloves does not reflect the actual level of exposure, as colleagues working in the same environment represent a significant source of airborne allergen (107,108). In addition, cross-sectional studies may be affected by survival bias, because workers with NRL sensitization may tend to use fewer NRL gloves (109). Two epidemiological surveys have provided direct evidence supporting a causal role of exposure to NRL gloves. In a cross-sectional survey of dental students and staff, Tarlo et al. (80) documented a progressive increase in risk of sensitization to NRL by years of exposure as shown by skin-prick test responses to a low-ammoniated raw NRL solution. None of the year 1 or 2 students tested were sensitized (before significant clinical use of NRL gloves), whereas 6% of year 3 students, 10% of year 4 students, and 25% of the staff were sensitized. Symptoms of asthma, rhinoconjunctivitis, and contact urticaria associated with NRL glove exposure were significantly more frequent among those with positive skin tests to NRL. In a prospective cohort study of apprentices, Gautrin et al. (110) found that the cumulative incidence rate of skin reactivity to NRL was significantly higher among dental hygiene students using NRL gloves on a regular basis (6.3%) than among animal health technologists (1%) or pastry makers (1.6%).

The prevalence of sensitization among workers exposed to NRL has never been compared adequately with the figures observed in the general adult population. Prevalence rates of skin reactivity to NRL extracts varied from 0.6% to 4.9% in apprentices assessed before starting occupational exposure (111) and in individuals attending a health-screening visit (112), a preoperative visit (82), or an allergy clinic (113). The figures for clinical allergy to NRL were usually lower, ranging from 1.2% to 3.1% (82,112,113). Higher prevalence rates of NRL sensitization have generally been reported in studies that assessed the levels of NRL-specific IgE antibodies among blood donors (from 3.6% to 7.6%) (114–117). In a population-based survey derived from the Third National Health and Nutrition Examination Survey (1988–1991), Garabrant et al. (118) found that the prevalence of NRL-specific IgE antibodies was not higher among health care workers than among the general population. The reported prevalence rate of NRL sensitization in the general population was, however, much higher (18.4%) than the figures reported in other unexposed populations, raising concern about the specificity of the method used for measuring specific IgE antibodies.

In addition to repeated exposure to NRL products, atopy seems to be the principal determinant for the development of NRL sensitization. Atopy (defined either by immunological tests to common inhalant allergens or by the history) is two- to five-fold more frequent in health care personnel with NRL allergy than in their coworkers without NRL allergy (75,76,78–80,119,120). However, the predictive value of atopy with regard to the development of immunological sensitization and occupational asthma due to NRL is low (79). In a recent study, sensitization to hevein (Hev b 6.02) was associated with the HLA class II alleles DQB1*0302 (DQ8) alone and DQB1*0302(DQ8)-DRB1*04 (DR4) haplotype among health-care workers with NRL allergy (121). Pre-existing dermatitis of the hands is thought to enhance the risk of NRL allergy by facilitating the transcutaneous passage of NRL proteins (122). Hand eczema has been found more frequently in subjects with NRL allergy than in their nonallergic coworkers (75,78–80). In spina bifida children, the development of NRL allergy is associated with atopy and the number of surgical procedures (84,87). Exposure to NRL in infancy is likely to be the crucial factor leading to the high prevalence of NRL sensitization in spina bifida children as compared with adults affected by similar neurological disorders and NRL exposure (123). Reports suggest that allergy to foods can develop before the onset of clinical allergy to NRL products (124), although the role of food allergy as an independent risk factor for the initiation of NRL allergy remains uncertain.

## CLINICAL MANIFESTATIONS

### Skin and Systemic Reactions

The severity of clinical manifestations of NRL allergy varies according to the route of exposure. Cutaneous exposure to NRL causes local urticaria usually restricted to the site of NRL contact, although systemic reactions have been occasionally reported (3,125,126). In glove wearers, skin symptoms take the form of pruritus, erythema, and hives beginning 20 to 30 minutes after donning NRL gloves. Symptoms of glove-induced itching and redness of the hands have, however, a low predictive value with regard to the presence of NRL allergy, because questionnaire surveys have shown that a high proportion (up to 50%) of health care workers experience glove-related skin symptoms consistent with contact dermatitis in the absence of

any demonstrable allergic sensitization to NRL (75,77–79,91). In addition to immediate skin reactions, NRL-exposed workers can also present with persistent dermatitis related to irritant contact dermatitis or delayed hypersensitivity reaction to rubber additives, disinfectants, or drugs (13). Delayed skin reactions to patch tests with NRL suggest that allergic contact eczema to NRL proteins can develop in subjects with or without concomitant urticaria (105,122,127).

Mucosal, visceral, and parenteral exposures to NRL are associated with the greatest risk for developing severe systemic reactions. Anaphylactic reactions have been documented during surgical procedures (2,85,128), deliveries (129), gynecological examinations (130), dental treatment (128), barium enema using balloon-tipped catheters (131,132), and condom-protected sexual intercourse (133). NRL has become the second most common cause of perioperative anaphylactic reactions, accounting for 16% of such adverse events (134). NRL-induced reactions during surgery are characterized by a delayed onset after induction of anesthesia (2). There is also some suggestion that intravenous exposure to NRL allergens can result from injection ports in intravenous lines, plungers on syringes, and stoppers on medication vials (135). Systemic reactions have also been described after ingestion of foods contaminated by NRL allergens when handled by personnel wearing gloves (136). Finally, it should be kept in mind that urticaria and anaphylaxis can occur after remote exposure to NRL allergens transferred from the workplace on hands and clothes (137). Fatal anaphylactic reactions induced by NRL seem, however, to be a rare consequence of NRL allergy (132,138), although a recent survey of U.K. theatre managers found that 18 major anaphylactic reactions and four deaths had occurred among about 500 NRL-allergic patients after they had undergone surgery (139).

### Respiratory Symptoms

In the early 1990s, it was demonstrated that exposure to airborne NRL allergens bound to powder particles of gloves (or to any dusted rubber products, such as toy balloons) could result in allergic respiratory reactions, including rhinoconjunctivitis and asthma (7,20,140). These respiratory symptoms have been described primarily among workers manufacturing or using NRL gloves (74,79). A survey of hospital employees showed that asthma is a common manifestation of NRL allergy, and this has been documented through specific inhalation challenges in approximately half of the participants who demonstrated skin sensitization to NRL (i.e., 2.5% of all employees) (79). Surveillance programs and medicolegal statistics indicate that NRL has become one of the leading causes of occupational asthma in the 1990s (141,142). However, only 39% to 68% of subjects with NRL-induced occupational asthma identify NRL gloves as the cause of their asthma, since the work relatedness of respiratory symptoms can be obscured by several factors (143,144). Thus, exposure to airborne NRL allergens is most often intermittent and indirect, resulting from inhalation of NRL allergens disseminated in the air by coworkers handling NRL gloves (107). As a result, subjects who do not use NRL gloves but who experience asthma at work tend to ascribe their asthma to substances other than NRL.

The possibility of respiratory allergy to NRL should be also considered in nonmedical occupations. Rhinoconjunctivitis and asthma caused by NRL gloves have been reported in greenhouse workers (81), hairdressers (105), food processors (145), laboratory workers (146), and pharmaceutical industry workers (89). Although powdered NRL gloves are the most frequent source of exposure to airborne NRL,

respiratory reactions have occasionally been described in workers exposed to NRL dust generated by grinding dolls (88) and by processing elasticized fabrics (147). In nonoccupational environments, respiratory symptoms can result from exposure to deflating or bursting toy balloons. One report has suggested that NRL can cause eosinophilic bronchitis, which is characterized by NRL-related cough and sputum eosinophilia in the absence of demonstrable airflow obstruction or nonspecific bronchial hyperresponsiveness (148). At present, it remains unknown whether this syndrome progresses to typical asthma.

### Food Allergy

It was recognized early on that individuals with NRL allergy experience allergic reactions after ingestion of banana, kiwi, avocado, and chestnut with an unusually high frequency. In recent years, the list of plant-derived foods causing allergic reactions in NRL-allergic subjects has been extended to include potato, tomato, passion fruit, melon, fig, pineapple, mango, peach, plum, almond, and pepper (124,149–151). Approximately 30% to 50% of individuals with NRL allergy show clinical hypersensitivity to some plant-derived foods, while an even higher proportion (about 70%) demonstrates IgE antibodies against these allergens (124,149,150). The association between allergy to NRL and to plant-derived foods is usually referred to as the "latex-fruit syndrome." The symptoms that are experienced by individuals with the latex-fruit syndrome range from itching of the throat to oral and facial swelling, rhinoconjunctivitis, and anaphylactic shock. It is noteworthy that these hypersensitivity reactions to foods may develop after cessation of occupational exposure to NRL (151). In addition, several reports have described an association between NRL allergy and sensitization to latex from the weeping fig (*Ficus benjamina*) (152), to enzymes extracted from the latex of papaya (*Carica papaya*) (124,153,154), and to pollen (150,155,156). Conversely, a substantial proportion of subjects with fruit allergy show IgE-mediated sensitization to NRL, although only a minority of them will develop clinical hypersensitivity reactions to NRL products (157,158). Several proteins have been identified to be involved in this immunological cross-reactivity between NRL and phylogenetically distant plants, including class I chitinases containing an N-terminal hevein-like domain (Hev b 6.02), a beta-1,3-glucanase (Hev b 2), a patatin-like protein (Hev b 7), and the pan-allergen profilin (Hev b 8) (50,149,155,156,159–161).

## DIAGNOSTIC PROCEDURES

### Immunological Tests

Most studies have shown that in vitro measurement of NRL-specific IgE using RAST or ELISA methods is less reliable than skin testing (20,122,162–164). There are three FDA-cleared commercial in vitro assays whose diagnostic performance has been carefully compared with skin testing (165). The CAP system (Pharmacia Inc.) and the Alastat microtiter plate assay (Diagnostics Products Corp.), the most commonly used tests, perform comparably, with sensitivities around 75% and specificities of about 97%. The Hy-Tech assay (Hycor) has a greater sensitivity (92%) but a lower (73%) specificity (166). Although anaphylactic events have been reported after skin tests with NRL extracts (162), most investigators agree that skin testing can be performed safely and should be, for the time being, the recommended procedure for demonstrating IgE sensitization to NRL. The use of homemade

extracts of NRL materials is not recommended for routine testing, because these extracts are of variable allergenic activity (167). Standardized and validated extracts of NRL are becoming commercially available (168). Further characterization of relevant NRL allergens will make it possible to achieve proper allergen standardization.

## Inhalation Challenges

Recent studies have provided evidence that clinical history and immunological testing are sensitive but not specific tools for diagnosing NRL-induced occupational asthma (Table 2) (143,144,169). Among workers investigated for possible occupational asthma caused by NRL gloves, the nature of reported symptoms, including the presence of work-related urticaria and rhinitis, and their timing in relation to workplace exposure do not discriminate between subjects with and without NRL-induced asthma. Awareness of a specific temporal relationship between exposure to NRL gloves and the development of asthma symptoms is more frequently reported by subjects with NRL-induced asthma (143,144). Skin-prick tests to NRL are positive in almost all subjects who demonstrate an asthmatic response to inhalation challenge with NRL gloves, providing a high negative predictive value for the presence of NRL-induced occupational asthma. Conversely, positive immunological tests do not necessarily indicate that NRL is involved in the development of asthmatic reactions. The combination of skin-prick tests with the clinical history increases the sensitivity from 87% to 94% and the negative predictive value from 50%

**Table 2** Validity of Procedures for Diagnosing NRL-Induced Occupational Asthma as Compared with Specific Inhalation Challenges

| | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | References |
|---|---|---|---|---|---|
| Clinical history | 92 | 32 | 24 | 94 | 169 |
| | 87 | 14 | 75 | 50 | 143 |
| | 89 | 50 | 77 | 71 | 144 |
| NSBH | 90 | 7 | 68 | 25 | 143 |
| | 90 | 10 | 65 | 33 | 144 |
| Skin-prick tests | 100 | 21 | 74 | 100 | 143 |
| to NRL | 100 | 20 | 70 | 100 | 144 |
| Specific IgE to NRL | 95 | 40 | 75 | 80 | 144 |
| Clinical history + skin test to NRL | 94 | 36 | 76 | 71 | 143 |
| NSBH[a] + skin test to NRL | 84 | 70 | 84 | 70 | 144 |

*Note*: The prevalence rates of NRL-induced occupational asthma, as ascertained by specific inhalation challenges in the studies by Baur et al., Vandenplas et al., and Quirce et al. were 19% (12/62), 69% (31/45), and 63% (19/30), respectively.

[a]Methacholine $PC_{20}$ value less than 4 mg/mL.

*Abbreviations*: PPV, positive predictive value; NPV, negative predictive value; NSBH, baseline nonspecific bronchial hyperresponsiveness; NRL, natural rubber latex.

*Source*: From Refs. 143, 144, 169.

to 71%, while the positive predictive value remains unchanged (from 75% to 76%). According to the study by Quirce et al. (143,144) the best specificity (70%) and positive predictive value (84%) are provided by a positive skin-prick test response and an airway hyperresponsiveness. These findings indicate that a diagnostic approach combining the clinical history with immunological testing remains less reliable than the specific inhalation challenges. On the other hand, monitoring of peak expiratory flow rates does not allow for precise identification of the agent causing occupational asthma, because workers may be exposed to multiple asthmogenic agents. Thus, inhalation challenges with NRL should be recommended when the highest level of accuracy is required to establish or exclude a diagnosis of occupational asthma in workers exposed to airborne NRL.

Specific inhalation challenges with NRL should be performed only in specialized centers with facilities to treat severe asthmatic reactions and anaphylactic responses (170–172). However, these tests have proved to be a simple and safe technique, provided that safety requirements and stringent protocols of exposure and monitoring are carefully observed. It has recently been shown that repeated challenge exposures to glove powder do not provoke an increase in immunological sensitization to NRL allergens (173). SIC can be performed either by handling NRL gloves (140,143,144,169,174), by inhaling NRL-loaded cornstarch particles collected from powdered latex gloves (172,173), or by administering aqueous extracts of gloves (175). At present, however, no standardized methodology exists for performing SIC with NRL, because standardization of these tests would require quantification of the amount of NRL allergen delivered and comparison of these levels with those measured at work. The "handling" method is more likely to mimic the mode of exposure encountered at the workplace (i.e., airborne particles) than is the inhalation of nebulized glove extracts. It has been shown that this "realistic" method allows for generating steady concentrations of airborne NRL allergens after a few minutes (144). These findings indicate that the cumulative dose of NRL administered to the patients is mainly determined by the duration of challenge exposure. The dose of NRL allergens required to induce an asthmatic response varies widely from one subject to another, ranging from 25 to 1500 ng (144,174).

## MANAGEMENT AND OUTCOME

Pharmacotherapy with antihistamines and corticosteroids does not completely remove the risk of life-threatening anaphylactic reactions to NRL (176). There is some suggestion, from case reports (177–179) and a limited number of placebo-controlled studies (180,181), that immunotherapy with NRL extracts could lead to a reduction in NRL-related symptoms (cutaneous, nasal, and ocular), medication score, and skin and conjunctival reactivity to NRL. Immunotherapy is, however, associated with a high risk of severe local and systemic adverse effects and should be considered unacceptable in its current form. Modified recombinant allergens (182,183), T cell epitope peptides (184), or DNA vaccines (185) could be promising tools for delivering safe and effective NRL allergen immunotherapy (186). A preliminary report suggests that omalizumab, a recombinant and humanized anti-IgE monoclonal antibody, induces an improvement in conjunctival and skin reactivity to NRL (187). At present, avoidance of exposure to NRL-containing products still remains the primary method for management of NRL allergy. Once the diagnosis has been firmly established, NRL-allergic patients should receive complete information about the potential sources of

exposure to NRL and the possibility of cross-reactivity with plant-derived foods. All surgical procedures, diagnostic investigations, and dental treatments should be performed strictly in NRL-free environments, regardless of the severity of reactions induced by skin exposure (5,6,188). NRL-allergic individuals should wear a MedicAlert® bracelet or another "allergy identification" device. Those patients who report a history of anaphylactic reaction should be prescribed an autoinjectable epinephrine kit and carefully instructed on how to use it.

In occupational settings, management options include relocation of the worker to an NRL-free work area or conversion of the worker's current area to an NRL safe area. Complete avoidance of exposure to NRL is difficult in health-care environments, as it implies both personal and institutional policy changes. NRL-allergic health-care workers should be instructed to use only NRL-free gloves. However, personal avoidance of NRL gloves is not sufficient to prevent exposure to airborne NRL allergens, because the continued use of powdered NRL gloves by coworkers may disseminate significant amounts of NRL-contaminated powder particles, which are capable of triggering respiratory reactions in allergic workers (71,72,108,189). Thus, every effort should be made to avoid or to minimize indirect airborne exposure to NRL. Nonpowdered gloves with low protein content are effective in reducing the concentration of airborne NRL allergens (71,72,174,190,191) and the level of NRL-specific IgE (191,192), and in preventing the development of asthmatic reactions in health-care workers with NRL-induced asthma (64,174,190). However, the safety of low-protein NRL glove used by coworkers should be properly evaluated on an individual basis, as highly sensitive subjects may still develop asthmatic reactions after prolonged exposure to low-protein gloves (64,174).

There is limited information pertaining to the health and economic outcomes of NRL allergy. A few reports indicate that occupational NRL allergy is associated with a substantial adverse impact on work ability and career options in health-care workers (193,194), particularly in those with NRL-induced asthma (195). A recent follow-up study of workers with NRL-induced occupational asthma found a similar degree of improvement in NRL-related symptoms and nonspecific bronchial hyperresponsiveness in workers who avoided exposure to NRL as compared with those who only reduced exposure (151). These findings indicate that reduction of exposure to NRL can be considered a reasonably safe alternative in those subjects for whom complete NRL avoidance is not feasible. In addition, reduction of exposure to NRL was associated with fewer adverse socioeconomic consequences than complete avoidance. Further investigation is required to determine whether subjects with urticaria and/or rhinitis will develop asthma if they remain exposed to low levels of airborne NRL. It remains unknown whether asymptomatic subjects who demonstrate skin or serological evidence of NRL sensitization will progress to clinical allergy on exposure to NRL products. Nevertheless, it is wise to recommend NRL-free environments during surgical procedures in these individuals with subclinical sensitization to NRL allergens.

## PREVENTION

The use of NRL-free materials is undoubtedly the most effective means of preventing sensitization to NRL, as has been reviewed (5). Most NRL devices for medical or consumer purposes can be easily replaced by latex-free materials with similar properties, with the notable exception of medical gloves. At present, the widespread

use of NRL-free medical gloves does not appear to be feasible, because synthetic elastomer gloves with satisfactory mechanical and tactile properties are much more expensive than NRL gloves. Vinyl gloves are not as strong as latex gloves, nor do they provide a satisfactory tactile feel. Nevertheless, vinyl or other synthetic gloves should be used where possible for nonsterile procedures, as examination gloves are a significant source of exposure to airborne NRL allergens outside operating rooms. Unless mandated by accepted Standard Precautions, the routine use of NRL gloves by workers and other individuals, such as food handlers and housekeeping personnel, should be discouraged (188).

Because the NRL allergens are closely associated with the donning cornstarch powder (189,196), airborne exposure can be reduced by powder-free or low-powdered gloves or by reducing NRL-allergen content of gloves. Although manufacturers of NRL gloves for health care use have generally reduced the protein and powder content of such gloves to varying degrees (94), widespread switching to NRL gloves with a low allergen and powder content in all exposed health care workers is the logical intervention to reduce exposure to NRL allergens. This approach has been demonstrated to be effective in preventing the development of NRL allergy among health care workers (95–101). In a school of dentistry in Ontario, powdered NRL gloves were substituted with low-protein, powder-free NRL gloves as a result of a cross-sectional survey conducted in 1995 (80). In a repeat survey of the same school in 2000 (97), none of the 57 participating third- and fourth-year students had a positive skin test to NRL, and the only positive skin test responses were in three dental assistants who had not participated in the earlier study. The frequency of contact urticaria and/or pruritus associated with glove use was significantly reduced, and there was a trend toward reduced rates of asthma and rhinoconjunctivitis associated with NRL gloves among all participants. Similarly, in a large Ontario hospital, after changing from powdered NRL gloves to low-protein, low-powdered examination gloves in 1995 and to sterile NRL gloves in 1997 (95), there was a marked fall in the annual rates of "incident reports" and newly diagnosed NRL allergy. Incident reports, which had peaked at 45 in 1994, fell to 0 in 1999, and in that year, only one hospital worker (whose symptoms began in 1997) was newly diagnosed with NRL allergy. Therefore glove changes effectively eliminated the problem of new NRL allergy in this hospital and dental school. Of note, the overall cost of gloves in this hospital did not increase as a result of these changes. Instead of each hospital department ordering gloves individually, glove orders were for the most part consolidated through one supplier, and the bulk ordering led to similar overall costs despite the generally higher costs of safer gloves (95).

Very similar findings in relation to NRL allergy in health-care workers have been reported from the Mayo Clinic by Hunt et al. (98) after changing over to NRL gloves with low or undetectable allergen content. That hospital did not place a restriction on powdered NRL gloves, but it was found that the reduction in glove allergen content was sufficient to reduce airborne NRL allergens carried by the glove cornstarch. Hunt et al. (98) found that NRL-induced symptoms of rhinoconjunctivitis and asthma rarely occurred at sites where the airborne concentration of NRL allergen was below 10 $ng/m^3$. They reported that measured concentrations of NRL allergens in the Mayo Clinic after the glove changes were usually below 1 $ng/m^3$ and consistently below 10 $ng/m^3$ (98), in contrast with previous reports of concentrations 10 to 500 $ng/m^3$ in settings where high-allergen gloves were used (190,197). They also reported that since the glove changes, there were no new reports to the Employee Health Department of change in work area due to NRL allergy (98). As in the

previously cited study (95), costs did not significantly increase with glove changes. More generalized population studies also support the effectiveness of glove changes in reducing occupational NRL allergy. Allmers (99,100) has reported a dramatic reduction in NRL allergy in Germany concurrent with glove changes, and in Ontario, Canada, reductions in compensation claims for NRL-induced occupational asthma have coincided with glove control measures (96), consistent with current recommendations (5). There is less information published as to the implementation of preventive measures for non–health care workers and any impact on sensitization and clinical allergy incidence. Levels of NRL allergen have been reported to be very high in glove-making facilities as recently as in 2000 (198), but current understanding of the risks of sensitization should allow better occupational hygiene measures to reduce skin and airborne exposure of workers to NRL allergen.

Although the total protein content of gloves may not accurately reflect their allergen content (62–64), this does not appear to have been a practical concern in ameliorating the problem of sensitization. Regulatory agencies should establish international standards for the labeling of NRL-containing devices and for measurement of their protein and allergen content. Published data regarding allergen and protein levels in gloves may also prove to be a valuable tool to guide procurement decisions (67,94). Although cost considerations are frequently cited as an objection to converting to non-NRL or low-allergen NRL gloves, reports from North American medical centers have documented no increase in glove costs (95,98). Furthermore, indirect costs such as workers' compensation, disability, loss of work, and medical treatment resulting from NRL exposure must be added into any strict accounting of costs incurred to reduce NRL exposure (199).

The continuing high prevalence of NRL allergy among exposed workers in centers where the use of high-protein NRL gloves is still continued justifies regular medical surveillance by questionnaire and immunological assessment in such settings until the recommendations to change the gloves to low-allergen gloves are implemented. There is also a need for ongoing vigilance and screening for a history of possible NRL allergy in high-risk patients who are undergoing relevant procedures. A positive screening history should be followed up with formal allergy assessment, and when positive or in doubt, NRL-free protocols should be implemented. Children requiring early frequent surgical and medical procedures due to spina bifida or other congenital abnormalities are at such high risk for developing NRL allergy that complete avoidance of exposure to NRL products is needed from birth (200,201).

## CONCLUSION, RESEARCH NEEDS, AND PERSPECTIVES

Over the last two decades NRL allergy has become a major cause of medical concern among individuals exposed to NRL-containing materials in medical and nonmedical environments. Intense research efforts have led to the identification of NRL allergens and characterization of pathophysiological mechanisms of the disease. Translation of research findings into workplace practice has significantly altered the course of the NRL allergy outbreak. NRL allergy should be regarded as one of the few conditions where control of exposure is feasible and seems to be effective in reducing the burden of the disease. Further characterization of relevant NRL allergens should allow for developing quantitative assessment of clinically relevant allergens in NRL products and implementing more precise quality standards.

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# ASTHMA IN THE WORKPLACE

## *And Related Conditions*

## THIRD EDITION

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