Natural rubber latex allergy increasingly has been recognized during the past decade [1]. It now is considered to be the most frequent cause of occupational allergy in healthcare workers [2]. Natural rubber products can trigger urticaria, angioedema, and anaphylaxis after cutaneous, mucosal, or visceral exposure, and in the case of disposable medical gloves, latex allergens that are adsorbed to glove-donning powders can trigger rhinoconjunctivitis and asthma [3].

Natural rubber latex

Natural rubber is derived from the cytosol, or latex, of the commercial rubber tree *Hevea brasiliensis* [4]. It is important to distinguish natural rubber from synthetic elastomers, which include butyl rubber (a petroleum-based product), polymers of 2-chlorobutadiene (Neoprene, DuPont Dow Elastomers LLC, Wilmington, DE), and copolymers of butadiene and acrylonitrile [5]. Synthetic rubber products pose no risks to persons who have been sensitized to natural rubber proteins.

Rubber processing

Ammonia is added to natural rubber latex to prevent autocoagulation during harvesting. About 90% of harvested latex is processed by subsequent acid
coagulation into dry sheets or crumbled particles for manufacture of vehicle tires, rubber thread products, rubber seals and diaphragms, or other dry rubber products. The remaining 10% of harvested rubber is concentrated to 60% (vol/vol) by centrifugation, after which various compounding materials are added for manufacture of dipped latex products, such as gloves, condoms, or balloons [4]. Dipped latex products are responsible for most allergic reactions to natural rubber latex.

**Rubber chemistry**

Rubber particles are composed of *cis*-1,4-polyisoprene, which contains an outer layer of protein, lipid, and phospholipid that provides structural integrity [4]. The latex cytosol contains most of the enzymes that are necessary for the conversion of sucrose into *cis*-1,4-polyisoprene. The protein content of raw latex is 10 to 15 mg/mL, about 27% of which is associated with the rubber particles [4].

**Natural rubber latex allergens**

Several natural rubber proteins are allergenic (Table 1) [6]. These proteins are involved in rubber biosynthesis, disease resistance, or structural or housekeeping activities. Hev b 1 (rubber elongation factor) and Hev b 3 are associated with the polyisoprene particles and, along with Hev b 7, are major allergens for persons

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Molecular weight (kD)</th>
<th>Biologic function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hev b 1</td>
<td>14.6</td>
<td>Rubber elongation factor; involved in polyisoprene biosynthesis</td>
</tr>
<tr>
<td>Hev b 2</td>
<td>35.1</td>
<td>Endo-1,3-β-glucanase; involved in defense against fungal pathogens</td>
</tr>
<tr>
<td>Hev b 3</td>
<td>22.3</td>
<td>Involved in polyisoprene biosynthesis</td>
</tr>
<tr>
<td>Hev b 4</td>
<td>50–57</td>
<td>Component of microhelix protein complex</td>
</tr>
<tr>
<td>Hev b 5</td>
<td>16</td>
<td>Structural protein; partial homology with acidic protein from kiwi fruit and potato</td>
</tr>
<tr>
<td>Hev b 6.01</td>
<td>20</td>
<td>—</td>
</tr>
<tr>
<td>Hev b 6.02</td>
<td>4.7</td>
<td>Involved in latex coagulation</td>
</tr>
<tr>
<td>Hev b 6.03</td>
<td>14</td>
<td>—</td>
</tr>
<tr>
<td>Hev b 7</td>
<td>42.9</td>
<td>Patatin-like protein with lipid acylhydrolase and phospholipase A2 activity; inhibitor of polyisoprene biosynthesis</td>
</tr>
<tr>
<td>Hev b 8</td>
<td>13.9</td>
<td>Profilin; supports actin polymerization</td>
</tr>
<tr>
<td>Hev b 9</td>
<td>47.7</td>
<td>Enolase</td>
</tr>
<tr>
<td>Hev b 10</td>
<td>22.9</td>
<td>Manganese superoxide dismutase; protection from reactive oxygen species</td>
</tr>
<tr>
<td>Hev b 11</td>
<td>33</td>
<td>Class I chitinase; involved in plant-pathogen interaction</td>
</tr>
</tbody>
</table>

with myelodysplasia [7,8]. Healthcare workers are more likely than patients with myelodysplasia to be sensitized to Hev b 5, an acidic protein in latex serum, and Hev b 6 [9,10].

**Cross-reactive allergens**

Clinical associations have been reported between latex allergy and allergy to several fruits and vegetables (Box 1), most commonly bananas, kiwi fruit, chestnut, avocados, papayas, potatoes, and tomatoes [11]. In the clinical history

<table>
<thead>
<tr>
<th>Box 1. Foods that are cross-reactive with natural rubber latex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foods that frequently cause clinical allergy in persons with latex allergies</td>
</tr>
<tr>
<td>Avocado</td>
</tr>
<tr>
<td>Kiwi fruit</td>
</tr>
<tr>
<td>Banana</td>
</tr>
<tr>
<td>Potato</td>
</tr>
<tr>
<td>Tomato</td>
</tr>
<tr>
<td>Chestnut</td>
</tr>
<tr>
<td>Papaya</td>
</tr>
</tbody>
</table>

| Passion fruit         |
| Fig                  |
| Melon                |
| Mango                |
| Pineapple            |
| Peach                |
| Pear                 |
| Celery               |
| Pineapple            |
| Cantaloupe           |
| Apple                |
| Cherry               |
| Wheat                |
| Turnip               |
| Spinach              |
of some patients, the latex allergy has preceded the food allergy, whereas the converse is true in other patients. Structural homologies exist between Hev b 6 and wheat germ agglutinin [12] and between endochitinases in avocado [13] and banana [14].

**Epidemiology**

Although latex sensitization can occur in the general population, occupational allergy to latex has been described mainly in persons who manufacture or use disposable latex gloves. Most data concerning the prevalence of latex sensitization are derived from large cross-sectional studies that assess sensitivity and self-reported symptoms. These studies are confounded by the different serologic assays and skin test reagents that are used, concomitant sensitization to cross-reacting fruits and vegetables, differences in latex exposure levels in the study populations, and the unreliability of self-reported symptoms [15].

**Prevalence of latex sensitization**

**General population**

The prevalence of latex sensitization in the general population ranges between 5% and 10%. Positive skin tests to latex were noted in 9.5% of 325 consecutive adult hospital inpatients awaiting surgical or urologic procedures [16]. Elevated levels of latex-specific immunoglobulin E (IgE) antibodies were measured in 6.5% of 1000 volunteer blood donors [17] and in 6.7% of 996 ambulatory surgical patients [18].

**Manufacturing workers**

Occupational asthma that is caused by latex allergy has been reported in workers who manufacture latex gloves. In a Canadian study, the prevalence of positive skin tests to latex were noted in seven of 64 workers (11%), and latex-induced occupational asthma was documented by spirometry and questionnaires in 3 of 81 workers (3.7%) [19]. In contrast, the prevalence of latex sensitization, assessed by prick skin testing, was only 1.3% in latex harvesters and 1.7% in workers from a latex glove factory in Thailand, despite personal mean exposures to latex aeroallergens greater than 1000 ng/m³ [20]. Two of 22 workers in a manufacturing plant that produces latex dolls were noted to have flushing, rhinoconjunctivitis, and wheezing when exposed to sanded doll parts [21]. In a study of 35 current or former workers in a Swedish condom packaging factory, 10 workers reported work-related rhinoconjunctivitis, and 3 workers had occupational asthma [22]. Only one worker had elevated levels of latex-specific IgE antibodies, whereas eight workers were sensitized to *Lycopodium clavatum* (staghorn club moss) spores, which were used to lubricate the rolled condoms. In a cross-sectional survey of 418 greenhouse workers who wore rubber gloves
daily, the prevalence of positive latex prick skin tests was 5%, and the prevalence of elevated levels of latex-specific IgE antibodies was 4% [23].

**Healthcare workers**

Healthcare workers, particularly those who are atopic, show an increased prevalence of latex sensitization. In surveys involving questionnaires and either latex skin testing or immunoassays for latex-specific IgE antibodies, 0.5% [24], 5.0% [25], and 17% [26,27] of various hospital employee groups were documented as latex sensitive [28]. To compare the prevalence rate of latex sensitization in healthcare workers with the rates in other population groups, Garabrant and colleagues measured latex-specific IgE antibodies that were collected from 5512 adults who participated in the Third National Health and Nutrition Examination Survey (1988–1991) [29]. The prevalence of latex sensitization (latex-specific IgE antibody > 0.35 IU/mL) ranged from 9% in secretaries to 18% in healthcare workers to 38% in other machinists. These findings suggest that glove use was not associated with latex sensitization in healthcare workers or in other jobs in which latex glove use was common; however, this study was limited by the relatively low response rate of participants concerning present occupation and glove use, raising issues of reliability and reporting bias [30]. The study also used serologic tests, which significantly overestimate true sensitization rates in low-prevalence populations [31].

**Incidence of latex sensitization and latex allergy**

In contrast to the many cross-sectional studies of the prevalence of latex sensitization [32], there are few studies on the incidence of latex sensitization or latex allergy. Annual incidence rates for contact urticaria in healthcare workers have been estimated to be 1.9 of 10,000 workers according to a questionnaire survey [33] and between 1.3 and 11.8 of 10,000 workers according to a review of a national registry [34]. Archambault and colleagues prospectively studied 122 dental hygiene students at the beginning and end of their 3-year training period and found a cumulative incidence rate of 6.4% for skin sensitization to latex [35]. This rate was significantly higher than that found in two comparison groups (animal health apprentices, 1.0%; pastry-making apprentices, 1.6%) [36]. Among the dental hygiene students, the cumulative incidence rates were 4.5% for latex-induced occupational asthma and 1.8% for latex-induced rhinoconjunctivitis.

In an incidence study, Sussman and colleagues first determined the baseline prevalence of latex sensitization (12.1%) among 1351 healthcare workers at two hospital sites [37]. At one site, the use of moderate-to-high protein latex gloves was continued, whereas powder-free latex gloves were introduced at the other site, and the cohort members were restudied after 1 year. Only four persons with initially negative latex skin test results converted to positive results after 1 year, two of whom were in the powdered-glove group (1.0% incidence rate) and two of whom were in the powder-free–glove group (0.9% incidence rate); only the former two persons were symptomatic.
Clinical manifestations

Cutaneous reactions

Cutaneous reactions to natural rubber latex most often involve dermatitis of the hands, wrists, or forearms [38,39]. These reactions include irritant contact dermatitis, allergic contact dermatitis, protein contact dermatitis, or contact urticaria. Although other latex-containing products may contribute to these problems, most latex-related problems arise from natural rubber latex gloves [38].

Irritant contact dermatitis

Most skin complaints that are associated with wearing gloves are assumed to be caused by skin irritation, but few studies in the literature document this assumption [40]. Irritant contact dermatitis usually is caused by multiple irritants, such as hand washing, moisture trapped inside gloves, occlusion, friction, glove-donning powder, or other irritating chemicals [39,41]. Irritant contact dermatitis is not an immunologic reaction; it results from direct injury of the epidermis [40]. Irritant contact dermatitis most often involves the webbed spaces between the fingers and the dorsal surface of the hand, where the stratum corneum is thinner. Acute irritant dermatitis can occur with a single exposure to a substance that impairs epidermal function, whereas chronic irritant dermatitis occurs after repeated exposures to the same substance or a series of irritants. In the latter case, cumulative damage to the skin may continue after exposure to the irritant ceases [42]. Irritant contact dermatitis may predispose the individual to subsequent allergic reactions to latex [38].

Allergic contact dermatitis

The most common immune-mediated reaction to latex gloves is allergic contact dermatitis, a delayed hypersensitivity reaction to chemical additives that generally occurs 1 to 2 days after exposure, but can occur from several hours to several days after exposure [38]. The most common culprits are accelerators, especially thiurams and carbamates [39,43,44]. The para-phenylenediamine group includes the most common sensitizers for allergic contact dermatitis to industrial rubber (eg, the rubber tire industry) [39]. In a report from the North American Contact Dermatitis Group, carbamate sensitivity was reported more frequently than thiuram sensitivity [44].

Protein contact dermatitis

Protein contact dermatitis is a chronic, recurrent dermatitis that is caused by proteins rather than chemicals [45]. The reaction most often occurs in an occupational setting and can occur with latex. The urticarial or vesicular eruption occurs 30 minutes to 6 hours after contact with the allergenic protein [39,46].

Contact urticaria

Contact urticaria is the most common and often is the only manifestation of IgE-mediated latex allergy in healthcare workers, 60% to 80% of whom report
contact urticaria involving the hands [47,48]. Urticarial lesions occur in the
distribution of contact with a latex item within 30 minutes of contact [41].

**Respiratory reactions**

Inhalation of latex allergen-coated cornstarch particles from powdered gloves
can evoke rhinoconjunctivitis and asthma in latex-allergic healthcare workers
[49,50]. Occupational asthma has been described in employees at a rubber-glove
manufacturing facility [19]. Most individuals with latex allergies are highly
atopic and have histories of seasonal allergic rhinitis caused by pollens or allergic
asthma caused by house dust mites or animal danders [51]. Of the 29 healthcare
workers with latex-induced asthma reported by Hunt and colleagues, however,
14 had no history of asthma, suggesting that latex-induced wheezing may occur
as an isolated phenomenon [2].

**Anaphylaxis**

Latex-allergic persons can experience anaphylaxis in a variety of medical care
situations [52]. Anaphylaxis can be triggered by toy balloons [53], squash racquets
with rubber handles [54], and latex padding in children’s play areas [55]. Fatal
latex-induced anaphylaxis has been attributed to a rubber balloon rectal catheter
[56], a urethral catheter [57], and a latex-containing hair adhesive [58].

**Diagnosis**

**Patch testing**

Patch testing is the diagnostic method of choice for latex-induced allergic
contact dermatitis. Various rubber additives are applied to the patient’s back for
48 hours, after which the test sites are read at 48 and 96 hours. The thin layer
rapid use epicutaneous (T.R.U.E.) test (Kabi Pharmacia Service A/S, Hillerod,
Denmark) is a panel of 24 allergens that are most widely available in the United
States and includes four rubber screening mixes and mercaptobenzothiazole.
More comprehensive rubber allergen series are available worldwide (Box 2).
Pieces of latex gloves or ammonia-free natural rubber latex also can be applied
for testing.

**Measurement of latex-specific IgE antibodies**

**Skin testing**

Skin testing with natural rubber latex is the diagnostic procedure of choice in
Europe and Canada, where commercial extracts are available for this purpose. In
the United States, no licensed commercial latex extracts are available for
diagnostic use. Allergists frequently perform puncture skin testing with extracts
of finished rubber products (usually latex gloves), which vary widely in their
Box 2. Materials for diagnostic patch testing for rubber additives

Thiuram mix

- Tetramethylthiuram disulfide
- Tetramethylthiuram monosulfide
- Tetraethylthiuram disulfide
- Dipentamethylenethiuram disulfide

Black rubber mix

- N-cyclohexyl-N-phenyl-4-phenylenediamine
- N,N'-diphenyl-4-phenylenediamine
- N-isopropyl-N-phenyl-4-phenylenediamine

Mercapto mix

- 2,2'-Benzothiazyl disulfide
- N-cyclohexylbenzothiazyl sulphenamide
- 4-Morpholinyl-2-benzothiazyl disulfide

Carba mix

- 1,3-Diphenylguanidine
- Zinc diethyldithiocarbamate
- Zinc dibutyldithiocarbamate

Other materials

- N,N-di-C-naphtyl-4-phenylenediamine
- N-phenyl-2-naphtylamine
- Hexamethylenetetramine
- Diaminodiphenylmethane
- Diphenylthiourea
- Dibenzothiazyl disulfide
- Zinc dimethylthiocarbamate
- 2,2,4-Trimethyl-1,2-dihydroquinoline
- Diethylthiourea
- Dibutylthiourea
- Dodecylmercaptan
- N-cyclohexylthiophthalimide

Data from Chemotechnique Diagnostics, Dormer Laboratories, Ontario, Canada.
allergen contents [3,59]. Systemic reactions have been reported with use of these nonstandardized preparations [60]. Skin testing with glove extracts, ammoniated latex, or nonammoniated latex that have standardized protein contents is safe and efficient [61].

**Immunoassays for latex-specific IgE antibodies**

Three FDA-licensed immunoassays for latex-specific IgE antibodies are available from diagnostic reference laboratories. When skin tests and immunoassays are performed in the same patient groups, only 50% to 90% of persons with positive skin test results have latex-specific IgE antibodies that are measurable by immunoassay [62]. The sensitivity of these immunoassays can be improved by spiking latex with recombinant latex proteins [63].

**Challenge studies**

A fitted face shield and hood system has been developed to perform graded inhalation challenge studies with latex allergen-coated cornstarch particles [64]. The allergenicity of powdered gloves has been tested by having patients don and remove powdered gloves inside a small provocation chamber [65]. Nasal and bronchial inhalation challenge tests have been used to document the allergenicity of crude latex or individual latex proteins [7,66,67].

Latex allergy can be confirmed by the use test, in which the fingers of latex gloves are cut off and applied to the wet fingers of persons with suspected contact urticaria to rubber [25]. After 30 minutes (sooner if intense itching occurs), the glove finger is removed, and the reaction is graded. If the finger challenge test is negative, a further challenge can be conducted using the whole glove. The usefulness of this test is limited by the widely varying allergen contents of gloves from different manufacturers or from different lots [59].

**Management of workers with latex allergies**

Workers with possible occupational allergy to latex should receive a complete medical, occupational, and allergy history; should receive a physical examination; and should undergo appropriate laboratory studies to confirm the diagnosis. The magnitude of latex aeroallergen exposure can be measured using high-volume air samplers (3 L/s) or personal breathing-zone samplers (4 L/min) that are equipped with polytetrafluorooethylene (Teflon E.I. DuPont de Nemours and Co., Wilmington, DE) filters [68]. Exposed filters are extracted with small volumes of buffer, and latex allergens in the extracts are measured by inhibition immunoassay using pooled, IgE antibody-containing sera from several latex-sensitized healthcare workers. Alternatively, an inhibition immunoassay that uses polyclonal rabbit antiserum [69] or a monoclonal, antibody-based ELISA for individual latex proteins [70] can be used to measure latex aeroallergens or the latex allergen contents of finished rubber products. Such assays are vital to
objectively assess baseline exposure levels to latex aeroallergens, to evaluate the results of subsequent environmental changes that have been designed to reduce workplace aeroallergen exposures, and to select latex products with low allergen content when no substitute synthetic elastomer product is available.

**Latex-safe environments for healthcare workers and patients**

Because most IgE-mediated reactions to rubber have been described in healthcare workers or in latex-sensitive individuals undergoing medical or dental procedures, emphasis has been placed on providing latex-safe clinics and hospitals [71]. In addition to reducing or eliminating use of powdered latex gloves, cleaning of carpets and upholstered furniture can eliminate reservoirs of latex allergens [72]. A cost-analysis study suggested that healthcare facilities are likely to benefit from becoming latex-safe, even if latex-related disability rates among employees are low [73].

A team approach is critical to implementing environments for medical care delivery that are latex-safe [47,74]. Such teams should include industrial hygienists, who are trained to deal with work-related illnesses and injuries [75]. High-risk work areas, where large quantities of latex gloves are used, can be identified by review of purchasing and stockroom records or by review of worker compensation or Occupational Safety and Health Administration injury records. The goals of the team should include: (1) identification and elimination of powdered gloves with high allergen content, (2) definition and labeling of latex-safe areas within the medical center, (3) establishment of a mechanism for periodic retesting of purchased latex products to ensure that they are safe, (4) selection and introduction of latex alternatives into the medical center. Whereas some latex-sensitive workers, such as food service workers, safely can use non-latex gloves without an increased risk for infection or disease transmission, the superior barrier protection of natural rubber latex may dictate that workers such as nurses or emergency medical technicians use low-protein, powder-free latex gloves [76]. Internal policies should be established for latex-sensitive employees and patients. These policies should address: (1) the responsibilities of management and employees in identifying the signs and symptoms of latex allergy, (2) the provision and maintenance of latex-safe carts for patients with latex allergies, (3) requirements for testing new latex products, and (4) goals for staff and patient education. Establishment of early intervention protocols may reduce lost-time and medical claims for latex-sensitized workers [77].

**Reduction or prevention of latex sensitization**

In 36 latex-sensitive workers with well-documented occupational asthma who reduced or avoided latex exposure, significant lessening of asthma and decreased bronchial hyperreactivity were noted after a median follow-up of 56 months [78]. Latex-specific IgE levels decreased in six of seven healthcare workers who avoided use of powdered latex gloves for 12 months [79]. Twenty latex-
sensitized anesthesiologists (12 symptomatic, 8 symptomatic) who avoided use of latex gloves for 10 to 15 months became asymptomatic, and 16 of these doctors had decreased levels of latex-specific IgE [80]. Latex skin test titration endpoints did not change appreciably, however, suggesting that a longer period of avoidance of latex gloves or tighter environmental-control measures may be necessary to achieve maximal immunologic improvement. In a long-term follow-up study of 71 healthcare workers and 89 non-healthcare workers with well-documented latex allergy (primarily hand eczema), the use of latex gloves with low allergen content or non-latex gloves substantially reduced the prevalence of hand eczema [81]. All of the healthcare workers and 98% of the non-healthcare workers continued working. In two cross-sectional surveys of dental students and staff at one medical school that were performed 5 years apart and after the school began purchasing low-protein, powder-free latex gloves, latex-related symptoms and positive latex skin test responses were reduced significantly in the second survey [82].

After active efforts to reduce workplace exposure to latex allergens and to increase use of non-latex gloves and powder-free, low-protein latex gloves, workers compensation claims resulting from latex-induced asthma have declined in Ontario, Canada, since 1994 [83]. During the same period, the number of new cases of occupational allergy to latex declined substantially at two large teaching hospitals in Toronto that have approximately 8000 employees [84]. The publication of guidelines to prevent latex allergy and the subsequent increased use of powder-free latex surgical and examination gloves in German acute care hospitals was associated with significant declines in the numbers of occupational allergy and asthma cases reported to the agency responsible for accident insurance and worker’s compensation measures [85].

Summary

Allergy to natural rubber latex is an important cause of occupational allergy in healthcare workers. Disposable medical gloves are the major reservoir of latex allergens, particularly powdered gloves, in healthcare delivery settings. Diagnosis of latex allergy requires a history of exacerbation of cutaneous, respiratory, ocular, or systemic signs and symptoms after exposure to natural rubber latex products; and evidence of sensitization by patch testing, skin testing, measurement of latex-specific IgE antibodies, or challenge testing. Optimal management of latex allergy involves education concerning cross-reacting allergens, reduction of cutaneous or mucosal contact with dipped rubber products, and minimization of exposure to latex aeroallergens in work environments.

References


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