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Occupational Latex Allergy: the Current State of Affairs

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Abstract
Purpose of review Allergy to natural rubber latex (NRL) reached epidemic proportions during the nineties and led to intense preventive efforts. The aim of this review was to provide a comprehensive compilation of the current status of occupational NRL allergy.
Recent findings Recent advances led to the characterization of 15 NRL allergens and the development of assays for measuring the allergen content of NRL materials and specific IgE antibodies against NRL allergen components. Preventive measures aimed at reducing workplace exposure to NRL allergens were associated with decreasing incidence rates of NRL allergy. However, a pooled analysis of epidemiological surveys published during the last 10 years provided prevalence estimates of NRL sensitization and allergy similar to those derived from studies conducted before 2003.
Summary Substantial progress has been made in the understanding and prevention of NRL allergy, although the disease may still remain a worldwide cause of concern.

Keywords Latex allergy · Latex allergens · Occupational diseases · Specific IgE

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Abbreviations

HCW	Healthcare workers
Hev b	*Hevea brasiliensis* allergen
NRL	Natural rubber latex
OA	Occupational asthma
sIgE	Specific IgE antibodies
SPT	Skin prick test

Introduction

Natural rubber latex (NRL) allergy was first documented through skin testing in 1979, although adverse reactions to NRL materials had occasionally been described earlier [1–3]. In the late 1980s, NRL proteins were increasingly acknowledged as a major cause of immediate IgE-mediated allergy reactions ranging from localized urticaria to extensive angioedema and life-threatening anaphylaxis [1–3]. In addition, it was demonstrated that NRL proteins bind onto glove powder particles and can then act as airborne allergens causing rhinoconjunctivitis and asthma [1, 3].

Epidemiological surveys documented high prevalence rates of NRL allergy in populations with high exposure to NRL gloves and other NRL materials, particularly in healthcare workers (HCW) and children with spina bifida or other urogenital malformations requiring multiple surgical interventions at an early age [1, 3]. This epidemic of NRL allergy resulted in intense research efforts to identify the allergen source, improve the diagnosis, and delineate preventive strategies. A turning point came with the introduction of powder-free, low-protein/allergen NRL glove, which was associated with a sharp reduction in the incidence of NRL allergy, at least in Western industrialized countries.

The aim of this review was to provide a comprehensive compilation of the current knowledge on occupational NRL

allergy. The literature selection was based on a PubMed search for articles with an English abstract published during the last 10 years (January 2006 to October 2016) using the broad keyword "latex hypersensitivity." The retrieved abstracts ($n = 454$) were scrutinized in order to identify articles providing relevant information pertaining to the various aspects of occupational NRL allergy.

NRL Allergens

The milky sap of the rubber tree *Hevea brasiliensis* is the source for the production of NRL devices and is collected by tapping the rubber trees. Fresh Hevea latex contains only 1–2% proteins which are heterogeneously distributed in the latex sap. These proteins are involved in the biosynthesis of the polyisoprene associated with the coagulation of NRL and in the defense of the plant against various diseases. After ultra-centrifugation of the fresh latex sap, basically three main fractions (rubber phase, C-serum, and bottom fraction [B-serum]) are easily discerned. The C-serum fraction contains more than 200 polypeptides, and some of them are enzymes associated with the rubber biosynthesis. Since the identification of the first major NRL allergen, the "rubber elongation factor" (Hev b 1), in 1993 by Czuppon et al. [4], 15 NRL allergens have been characterized and assigned official numbers in the nomenclature list of the International Nomenclature Committee of Allergens (http://www.allergen.org) (Table 1) [3, 5–8]. Most of them are available as recombinant allergens, with the exception of Hev b 2, 4, 13, and 14. Most of the recombinant NRL allergens are produced in *Escherichia coli* due to the fact that they have none or no important posttranslational modification(s). The clear advantage of recombinant proteins in contrast to native proteins is that it is possible to produce large-scale quantities with a high reproducible quality, but they have to be validated against native proteins for equivalence in allergenic reactivity before they can be adopted in clinical practice. In contrast, the correlation between IgE reactivity to recombinant Hev b 2 and native Hev b 2 is very poor. Although IgE from a large proportion of NRL-allergic patients binds to native Hev b 2, the same IgE is unreactive, or only poorly reactive to the recombinant version produced in *E. coli*. Conformational differences or posttranslational modifications are likely to be responsible for such differences [9, 10]. Nevertheless, recombinant Hev b 2 synthesized in yeast (which perform glycosylation) does not bind IgE, although it is not clear if the yeast carbohydrate is similar to that of the native protein. A disadvantage of native allergens can result from the impurity of the protein separation, and data produced by different batches of native proteins (e.g., Hev b 13) have lead to divergent results. In the case of Hev b 4 and Hev b 14, allergens with only minor relevance, the interest to produce them in recombinant form does not exist.

Several NRL proteins have been identified to be involved in the immunological cross-reactivity between NRL and phylogenetically distant plants (the so-called "latex-fruit

Table 1 Allergens of the rubber tree *Hevea brasiliensis*. Immunological and clinical properties of characterized latex allergens

Allergenic molecule	Biochemical name	Molecular weight (kDa)	Clinical relevance[a]
Hev b 1	Rubber elongation factor	14	Major allergen in SB
Hev b 2	β-1,3-Glucanase	34	Uncertain[a]
Hev b 3	Small rubber particle proteins	24	Major allergen in SB
Hev b 4	Lecithinase homologue	53–55	Minor allergen[a]
Hev b 5	Acidic structural protein	16	Major allergen in HCW and important in SB
Hev b 6.01/6.02	Prohevein/hevein	20	Major allergen in HCW
Hev b 7	Patatin-like protein (esterase) from latex-B- and C-serum	44	Minor allergen
Hev b 8	Profilin (actin-binding protein)	14	Minor allergen
Hev b 9	Enolase	51	Minor allergen
Hev b 10	Manganese superoxide dismutase (MnSOD)	26	Minor allergen
Hev b 11	Class I chitinase	30	Minor allergen
Hev b 12	Nonspecific Lipid Transfer Protein type 1 (nsLTP1)	9	Minor allergen
Hev b 13	Esterase	42	Uncertain[a]
Hev b 14	Hevamine	30	Minor allergen[a]
Hev b 15	Serine protease inhibitor	7.5	Minor allergen

SB spina bifida patients, *HCW* healthcare workers, *NA* not available

[a] Not available in recombinant form

syndrome"), including class I chitinases containing an N-terminal hevein-like domain (Hev b 6.01 and 6.02), a beta-1,3-glucanase (Hev b 2), a patatin-like protein (Hev b 7), a homologous of the kiwi fruit protein pKIWI501 (Hev b 5), the pan-allergen profilin (Hev b 8), and the nonspecific lipid transfer protein (Hev b 12) [5, 6, 8, 11].

Exposure to NRL Allergens

Exposure to the NRL allergens can occur through both direct contact with the NRL materials and inhalation of NRL-contaminated powder aerosolized from powdered gloves (or any dusted NRL material, such as toy balloons). The establishment of the D5712 modified Lowry assay (according to the American Society for Testing and Material, ASTM) for total protein measurement in 1995 was the first step in standardization of NRL content measurement. In recent years, substantial progress has been made in the development of immunoassays for measuring the "total" allergen content and, more recently, the individual allergen concentrations in NRL products and in healthcare environments [12••]. Studies demonstrated that powdered gloves have a substantially higher allergen content compared with powder-free gloves, and non-sterile examination gloves contain higher amounts of NRL allergens compared with surgical gloves [13, 14]. Powdered examination gloves generate higher levels of airborne NRL allergens and produced a higher proportion of allergens on particles in the respirable range than powdered surgical gloves [15].

Currently, commercial tests are available to quantify individual NRL allergens (Hev b 1, Hev b 3, Hev b 5, and Hev b 6.02) by capturing ELISA-based assays using monoclonal antibodies and purified or recombinant allergens. Palosuo et al. [16] found that the sum of four clinically relevant NRL allergen (i.e., Hev b 1, Hev b 3, Hev b 5, and Hev b 6.02) concentrations >0.15 μg/g discriminated "moderate-to-high-allergenic" gloves (i.e., those containing more than 10 allergen units [AU]/ml and eliciting a positive skin prick test (SPT) response) from the "low-allergenic" gloves (<10 AU/ml) with a sensitivity of 0.90 and a specificity of 0.93. The explanatory role of the individual allergens was 74, 24, 11, and 0.3% for Hev b 6.02, b 5, b 3, and b 1, respectively.

Quantitative information on the allergenic potency of NRL gloves served as guidance for manufacturers in order to produce gloves with low NRL allergen content. Therefore, there is some published evidence from serial surveys of medical gloves marketed in Finland that the protein and allergen content of NRL gloves has declined in the mid to late 1990s [12••]. However, establishing permissible airborne exposure limits to NRL allergens in healthcare environments remains elusive because detailed evidence for exposure-response relationships and threshold exposure levels that induce no adverse health effects are currently lacking.

Clinical Manifestations of NRL Allergy

NRL materials can cause a wide spectrum of immediate IgE-mediated hypersensitivity reactions ranging from mild urticaria to extensive angioedema and life-threatening anaphylaxis in NRL-allergic individuals. Mucosal, visceral, and parenteral exposures to NRL are associated with the greatest risk for developing severe systemic reactions. NRL allergy may remain an important cause of anaphylaxis [17]. A national survey of perioperative anaphylactic reactions recorded during the period 1997–2007 in France indicated that NRL was still involved in approximately 20% of reported adverse reactions [18, 19]. NRL allergy shows two prominent clinical characteristics: the highly prevalent association with cross-reactive food allergy (the so-called latex-fruit syndrome) and the high frequency of occupational rhinoconjunctivitis and asthma in workers exposed to NRL gloves.

Approximately 30–50% of individuals with an NRL allergy show an associated allergy to fruits, most commonly to avocado, banana, kiwi, chestnut, and tomato, but also to a variety of other species [20]. The symptoms that are experienced by individuals with the latex-fruit syndrome range from oral allergy syndrome to rhinoconjunctivitis, angioedema, and severe anaphylaxis. Notably, these hypersensitivity reactions to foods may develop after cessation of occupational exposure to NRL [21].

In the early 1990s, it was demonstrated that NRL proteins can bind onto the cornstarch powder of gloves (or any dusted NRL product, such as toy balloons) and can then act as airborne allergens causing rhinitis and asthma [22, 23]. Epidemiological surveys of workforces exposed to NRL gloves showed that a substantial proportion (28 to 54%) of NRL-sensitized workers also develop occupational rhinitis and OA due to airborne NRL allergens [24–26].

Diagnosis of NRL Allergy

Overall, glove-related symptoms have a low predictive value with regard to the presence of NRL allergy. Questionnaire surveys have shown that a high proportion of HCWs experience glove-related skin symptoms (e.g., itching and redness) in the absence of any demonstrable IgE sensitization to NRL [27–32]. Accordingly, documentation of IgE-mediated sensitization to NRL through SPT with NRL extracts or the assessment of sIgE against NRL is a key step in the diagnosis of NRL allergy.

In a recent European evaluation of five commercial NRL extracts for SPTs in workers who reported skin symptoms due

to NRL gloves, the sensitivity of SPT as compared to the determination of sIgE against NRL extract was 89% for four out of the five extract solutions and the specificity was >92% for all extracts investigated [33]. The measurement of sIgE antibodies against NRL is another important method to document NRL sensitization. The method has been significantly improved by the addition of the major allergen rHev b 5 as a stable recombinant protein to the NRL extract. Several studies reported that the ImmunoCAP test with the Hev b 5-amplified NRL extract (k82) showed a higher sensitivity and should be the most appropriate tool to evaluate sensitization to NRL [34].

An accurate diagnosis of NRL-induced OA is a crucial step in implementing appropriate interventions aimed at minimizing the adverse health and socioeconomic impacts of the disease [35]. The clinical history is highly sensitive (87–89%), but not specific (14–50%) for diagnosing NRL-induced OA [36, 37]. On the other hand, a substantial proportion (32–61%) of subjects with NRL-induced OA fails to identify NRL gloves as the cause of their asthma [36, 37]. In published clinical studies of NRL-induced OA ascertained by specific inhalation challenges with NRL gloves in tertiary centers, SPT with commercial NRL extracts yielded high sensitivity (100%) and negative predictive value (100%), but a low specificity (20%) and positive predictive value (70–74%) in predicting the result of the challenge [36, 37]. In a recent retrospective study of a large cohort of workers evaluated for possible OA through a specific inhalation challenge with NRL gloves, the determination of sIgE against NRL (k82, Thermo Fisher Scientific, Phadia AB, Uppsala, Sweden) provided a high sensitivity (~95%) and a low specificity (40–48%) for diagnosing NRL-induced OA [38]. The low negative predictive value (71%) indicated that the absence of NRL-sIgE does not allow for excluding a diagnosis of NRL-induced OA without performing additional investigations. Conversely, this study showed that increasing the cutoff value for a positive sIgE test (i.e., ≥5.41 kU_A/l) increases the specificity and positive predictive value above 95%, although at the expense of a lower sensitivity (49%) [38]. Therefore, using a higher cutoff value for a positive NRL-sIgE result would be useful in selecting the patients for whom additional diagnostic procedures, such a specific inhalation challenges, would be required to achieve the highest level of confidence in establishing a diagnosis of NRL-induced OA.

The assessment of sIgE antibodies against recombinant or natural purified single NRL allergens has been investigated in recent years. Component-resolved diagnosis studies based on the traditional singleplexed sIgE assays and multiplex microarray techniques have demonstrated that panels of NRL allergens that include Hev b 1, 3, 5, and 6.01/6.02 identify almost all NRL-allergic patients [10, 39, 40]. Studies also indicated that different risk populations, such as patients with spina bifida and HCWs, show different sensitization profiles, resulting from different routes of exposure (i.e., direct blood/mucosal contact vs. inhalation exposure) [41]. In HCWs suffering from occupational NRL allergy, the most relevant allergens are Hev b 5 and Hev 6.01 or Hev b 6.02. On the other hand, Hev b 1 and Hev b 3 are often recognized by specific IgE in spina bifida patients, but are only minor allergens in HCW with NRL allergy [10, 42]. Lamberti et al. [32] found that the combination of Hev b 5, Hev 6.01, and Hev b 8 identified 92% of the NRL-allergic subjects. Positivity to rHev b 8 in their study was not an isolated IgE response and always associated with positivity to rHev b 6.01 and rHev b 5. The Immuno Solid-phase Allergen Chip (ISAC®) (Thermo Fisher Scientific, Phadia AB, Uppsala, Sweden), a multiplex system for sIgE-measurement, enables the simultaneous determination of sIgE antibodies against five NRL allergens (Hev b 1, Hev b 3, Hev b 5, Hev b 6.0, and Hev b 6.02) with only 20 μl of serum. However, the sensitivity of the ISAC® assay with respect to the detection of NRL sensitization was lower compared the conventional ImmunoCAP® k82 spiked with rHev b 5 [43].

In addition, the component-resolved approach may be useful to discriminate between genuine NRL allergy and IgE cross-reactivity due to the profilin component of NRL (Hev b 8) [40, 44] or to carbohydrate epitopes [44, 45]. If a positive NRL-sIgE result occurs in subjects without clinical symptoms on exposure to NRL, determination of sIgE against "cross-reactive carbohydrate determinants" (CCD) should also be performed to discriminate between IgE binding to protein epitopes and glyco-epitopes with low clinical relevance [3].

Based on these data, a diagnostic algorithm to discriminate between patients with NRL allergy and those polysensitized patients with a positive sIgE to NRL has been developed [8]. In patients with sIgE to Hev b 5, Hev b 6.01, or Hev b 1 and/or Hev b 3, a clinically relevant NRL sensitization is highly likely and avoidance measures are mandatory. On the other hand, in patients without sIgE to the abovementioned major latex allergens which show sIgE to CCDs or against panallergens such as latex profilin (Hev b 8), a clinically relevant NRL allergy is unlikely and therefore avoidance of latex products is not necessary [46, 47].

With regard to the diagnosis of NRL-induced OA, the study by Vandenplas et al. [38] demonstrated that the sum of sIgE concentrations against the recombinant allergens rHev b 5 and rHev b 6.01 or 6.02 was the most accurate predictor for a bronchial response to NRL and showed a higher diagnostic efficiency than the determination of sIgE against the whole NRL extract measured using the ImmunoCAP k82 (Thermo Fisher Scientific, Phadia AB, Uppsala, Sweden). This is a relevant finding because in several European countries, NRL extracts for SPT and powdered NRL gloves for inhalation challenge test are no longer commercially available, leading to a deficit in diagnostic tools. Nevertheless, none of the subjects with a positive inhalation challenge with NRL gloves and a negative NRL-sIgE result in this series showed IgE

binding to any of the tested recombinant NRL allergen components. Accordingly, the determination of sIgE against the currently available recombinant NRL allergens failed to improve the negative predictive value of the NRL-sIgE assay.

Epidemiology

Prevalence/Incidence

During the nineties, high prevalence rates of NRL allergy and NRL-induced OA have been reported in individuals with occupational exposure to NRL gloves, mainly in healthcare facilities. Occupational allergy and OA caused by NRL have also been described in workers manufacturing medical gloves and in non-medical occupations with NRL glove exposure, such as food processors, chemical and pharmaceutical workers, hairdressers, cleaners, and greenhouse workers [1]. OA induced by exposure to NRL dust has also been occasionally reported in workers manufacturing NRL toys and in those braiding NRL threads in the textile industry [48, 49].

A meta-analysis of epidemiological surveys among HCWs published up to 2003 reported prevalence estimates of 7.1% (95% confidence interval [CI] 6.7–7.5%) for IgE-mediated sensitization to NRL documented by a positive SPT response to NRL extracts, 6.3% (5.7–6.9%) for positive sIgE against NRL, and 4.3% (4.0–4.6%) for NRL allergy [50••]. Very few longitudinal studies have assessed the incidence of NRL allergy. In a prospective cohort of dental hygiene apprentices over 32 months, the cumulative incidence rate was 6% for the development of skin response to NRL, 1.8% for probable occupational rhinoconjunctivitis, and 4.5% for probable OA [26].

Surveillance programs and compensation statistics showed that NRL became the leading cause of occupational contact urticaria [51] and OA accounting for 3 to 24% of reported cases [52] during the nineties. However, more recent data from surveillance programs for occupational diseases have documented a marked decline in the incidence of contact urticaria and OA due to NRL. The French national network of occupational health surveillance and prevention (*Réseau National de Vigilance et de Prévention des Pathologies Professionnelles*, *RNV3P*) demonstrated a significant decline in the incidence of NRL-induced OA over the period 2001–2009 [53]. Notifications to a voluntary UK regional reporting scheme of OA (SHIELD, West Midlands) over a 21-year period (1991–2011) also showed a marked decrease in incident cases of OA due to NRL after 1995 [54]. Analysis of occupational skin diseases reported to the EPIDERM part of The Health and Occupation Research network in the UK found that the number of incident cases of contact urticaria related to NRL significantly declined between 1996 and 2012 with an average annual reduction in reported cases of 7.8% (95% CI −9.9 to −5.6%) [55]. A retrospective study of 8580 patients who completed skin prick testing at a Danish university Department of Dermatology and Allergy during the period 2002–2013 reported that the prevalence of NRL sensitization declined from 6.1% in 2002–2005 to 1.9% in 2006–2009 and to 1.2% in 2010–2013 [20]. Similarly, the prevalence of clinical NRL allergy declined from 1.3% of tested patients in 2002–2005 to 0.5–0.6% in 2006–2013.

The bibliographic search for the last 10 years identified 17 epidemiological surveys evaluating the prevalence of NRL allergy among HCWs. Six of these studies were excluded because data on IgE sensitization to NRL were lacking or incomplete. The findings of the remaining 11 studies are summarized in Table 2 [27–32, 56–60]. Notably, eight of these studies were conducted in developing countries. A pooled analysis of these studies provided mean (95% CI) prevalence estimates of IgE-mediated sensitization (i.e., positive SPT and/or positive sIgE) and clinical NRL allergy of 5.1% (3.1–7.4%) and 4.2% (3.0–5.6%), respectively (Table 2). These figures did not significantly differ from those reported in the above-quoted meta-analysis by Bousquet et al. [50••], indicating that NRL allergy still remains a significant cause of concern in some countries. However, a major methodological limitation in interpreting these recent data results from the use of prevalence instead of incidence rates as outcome measures, which does not allow for distinguishing "historical" cases from "recent" incident cases of NRL sensitization or allergy.

Risk Factors

Early on in the history of NRL allergy, it became apparent that the rapid emergence of NRL allergy during the late 1980s and early 1990s coincided with a steep upsurge in the use of NRL gloves in healthcare settings as a protective barrier against transmittable infections, particularly HIV infection and hepatitis [1–3]. This sudden high demand for NRL products probably lead to changes in the production processes of raw NRL that may have contributed to the development of NRL allergy [12••]. For instance, a shorter time from collection of NRL by tapping the *H. brasiliensis* trees to the manufacture of gloves may have resulted in higher protein content in the final product. Also, more frequent tapping of rubber trees and treatments with phyto-hormones may have induced an increase in the production of potentially allergenic defense-related proteins.

Although the high prevalence of NRL sensitization and allergy among HCWs has intuitively been attributed to widespread exposure to NRL gloves, attempts at identifying exposure-response relationships have produced conflicting results. The above-quoted meta-analysis by Bousquet et al. [50••] demonstrated that the prevalence rates of IgE-mediated sensitization to NRL and clinical NRL allergy were significantly higher among HCWs than in the general adult population. However, this meta-analysis failed to reveal an association between NRL exposure and the risk of IgE-

Table 2 Epidemiological surveys of NRL sensitization and allergy among healthcare workers (2006–2015)

Reference	Population, country (study period)	No. of surveyed subjects[a]	NRL IgE-mediated sensitization	NRL allergy[b]
Chaiear, 2006 [27]	Sample of 1 tertiary hospital staff ($n = 470$); Thailand (unknown timing)	412 (88%)	▶ SPT: 6/295 tested (2.0%) ▶ SPT: 6/412 (1.5%)	▶ 6/6 SPT + ve ▶ 6/412 (1.5%)
Buss, 2007 [28]	Sample of HCWs from 23 public health units ($n = NA$); Brazil (2004–2005)	140 (NA)	▶ SPT: 6/140 tested (4.3%)	▶ 6/6 SPT + ve ▶ 6/140 (4.3%)
Diegez, 2007 [29]	Hospital staff ($n = 2551$); Spain (unknown timing)	841 (33%)	▶ SPT: 28/154 tested (18.2%) ▶ SPT: 28/841 (3.3%)	▶ 28/28 SPT + ve ▶ 28/841 (3.3%)
Miri, 2007 [56]	Operating room staff from 13 general hospitals ($n = 512$); Iran (2001–2003)	512 (100%)	▶ SPT: 18/59 with Sx ▶ sIgE: 45/49 with Sx ▶ SPT and/or sIgE: 49/59 with Sx ▶ SPT and/or sIgE: 49/512 (9.6%)	▶ 49/512 (9.6%)
Wan, 2007 [57]	Nurses from operating rooms and ICU ($n = 500$); Taiwan (unknown timing)	130 (26%)	▶ sIgE: 3/130 tested (2.3%)	▶ 3/3 sIgE + ve ▶ 3/130 (2.3%)
Lin, 2008 [58]	6 hospital staff ($n = NA$); Taiwan (unknown timing)	1253 (NA)	▶ SPT: 152/1253 tested (12.1%)	▶ 79/152 SPT + ve ▶ 79/1253 (6.3%)
Galindo, 2011 [59]	Primary care providers ($n = 620$); Spain (2007–2008)	341 (55%)	▶ SPT: 18/170 tested ▶ SPT: 18/341 (5.3%)	▶ 10/170 tested ▶ 10/341 (2.9%)
Risenga, 2013 [30]	Sample of HCWs from high-risk areas in 1 hospital ($n = 200$); South Africa (2011)	158 (79%)	▶sIgE: 7/59 with Sx ▶ SPT: 5/38 with Sx and SPT –ve ▶ SPT and/or sIgE: 12/158 (7.6%)	▶ 12/158 (7.6%)
Köse, 2014 [60]	Tertiary hospital staff wearing gloves ($n = 1860$); Turkey (unknown timing)	1115 (60%)	▶ sIgE: 47/1115 tested (4.2%)	▶ 47/47 sIgE + ve ▶ 47/1115 (4.2%)
Supapvanich, 2014 [31]	Female nurses from 2 tertiary hospitals ($n = 665$); Thailand (unknown timing)	363 (55%)	▶ sIgE: 16/363 tested (4.4%)	▶ 8/16 sIgE + ve ▶ 8/363 (2.2%)
Lamberti, 2015 [32]	Medical and nursing students ($n = 723$); Italy (unknown timing)	619 (86%)	▶ SPT: 18/25 with Sx ▶ sIgE: 12/25 with Sx ▶ SPT and/or sIgE: 20/25 with Sx ▶ SPT and/or sIgE: 20/619 (3.2%)	▶ 20/619 (3.2%)
	Pooled mean (95% CI)[c]		+ve SPT and/or sIgE: 5.1% (3.1–7.4%) ($n = 5884$)	4.2% (3.0–5.6%) ($n = 5884$)

NRL natural rubber latex, *HCW* healthcare worker, *Sx* symptom, *sIgE* specific IgE antibodies against NRL, *SPT* skin prick test with NRL

[a] Participation rate within parentheses

[b] NRL allergy defined by the presence of both symptoms consistent with NRL allergy and positive sIgE assay or skin prick test to NRL. The denominator used to estimate the prevalence of NRL sensitization and allergy was the total number of surveyed subjects irrespective of whether the participants completed both the questionnaire and the assessment of sIgE-mediated sensitization to NRL

[c] Pooled analysis using a random effect model (MedCalc 16.8.4, Mariakerke, Belgium)

mediated sensitization to NRL. More recently, Kelly et al. [61] convincingly documented a quantitative exposure-response relationship by showing that the proportion of HCWs sensitized to NRL increased with the concentration of NRL allergens sampled in air ducts of their hospital work area from 2.2% for participants in low exposure areas (i.e., <10 μg of NRL allergens per g of dust) to 7.9% for intermediate exposure areas (i.e., between 10 and 100 μg/g) and 16.4% for high exposure areas (i.e., >100 μg/g).

In addition to frequent exposure to NRL gloves and other NRL materials, atopy has consistently been documented as a significant risk factor for the development of sensitization and allergy to NRL [1]. Other factors that have been associated with an increased risk include genetic factors (HLA-DR phenotypes and interleukin-13 and interleukin-18 promoter polymorphisms [62]), fruit allergy, and hand dermatitis that compromises the skin barrier and can contribute to enhanced penetration of NRL proteins [1].

Prevention

Despite the lack of quantitative evidence about the relationship between exposure to NRL allergens and the development of NRL sensitization, early initiatives to prevent the development of NRL allergy (i.e., primary prevention) have been taken at the local, national, and international levels since the early nineties, as reviewed by Wrangsjö et al. [63••]. The use of NRL-free materials is undoubtedly the most effective means of preventing sensitization to NRL. However, the complete substitution of sterile NRL gloves with gloves made from other materials remains controversial and a rational use of NRL gloves and synthetic alternatives should be promoted [12••]. Indeed, apart from effective biological impermeability, NRL gloves afford superior mechanical and tactile properties to most synthetic alternatives, and NRL is an environmentally sustainable material. Advancements in the identification of NRL allergens and in the glove manufacturing technology have led to the production of powder-free (i.e., containing less than 2 mg of powder per glove) and low-protein/allergen NRL gloves [12••]. Standards for medical gloves made of various materials have been issued in the USA and in Europe to give guidance to both manufacturers and purchasers of gloves [12••, 63••].

A systematic review of eight primary prevention intervention studies on NRL published between 1990 and 2004 [64••] concluded that there was adequate evidence that substitution of powdered NRL gloves with low-protein, low-powder or powder-free NRL gloves, or NRL-free gloves reduces the level of NRL aeroallergens as well as the rate of NRL sensitization and NRL-induced OA in HCWs. Since this review, further evidence supporting the effectiveness of primary preventive interventions has been provided by studies with different designs leading to variable causal inference ratings. A retrospective review of claims for NRL-related illness between 1997 and 2005 in a US healthcare institution found a 3.6-fold (95% CI 1.8–5.3) lower annual incidence of claims after the transition to powder-free NRL gloves in 2001 as compared to the period during which powdered NRL gloves were used [65]. The authors stated that the increase in the cost of gloves was partially offset by a decrease in the direct cost of workers' compensation, while the impact of decreasing NRL-related illness on work productivity could not be taken into account. In a retrospective study of all claims submitted to the Belgian Workers' Compensation Board up to 2004, incident cases of definite and probable NRL-induced OA were identified through the review of medical files and were correlated with the changes in glove usage characterized through a questionnaire survey of Belgian hospitals [66]. When categorized by the year of the onset of OA, the incident cases of NRL-induced OA markedly decreased from 1999 onwards. This downward trend was temporally associated with a decreasing use of powdered NRL; the proportion of powdered NRL gloves among all gloves purchased fell from 81% in 1989 to 18% in 2004. Powdered NRL gloves were predominantly substituted with NRL-free gloves for non-sterile procedures; of note, the changes in the pattern of glove usage occurred in the absence of any regulation-enforced preventive policy. A prospective cohort study of 805 HCWs at two US academic hospitals investigated the annual rate of NRL sensitization through SPT and NRL-related symptoms 12 months before and an average of 33 months after both hospitals implemented the substitution of powdered NRL gloves by non-powdered NRL sterile gloves and non-NRL examination gloves [61]. This high-quality study showed that the rate of incident NRL sensitization declined 16-fold after the intervention. The conversion rate decreased from 1.3% of SPT-negative participants per year of work during the pre-intervention phase to 0.08% of SPT-negative participants per year after the intervention. An analysis of cases of contact urticaria related to NRL reported to the UK surveillance scheme EPIDERM showed a downward trend during the period between 2000 and 2007 only among HCWs (incidence rate ratio 0.72 [95% CI 0.52–1.00]) as compared to the period before the implementation of preventive interventions (1996–1998) [67]. Larese Filon et al. [68] conducted a prospective cohort study from 2000 to 2009 of 2053 HCWs (9660 person-years) who started using non-powdered NRL gloves in 2000. Among the HCWs employed before 2000, positive sIgE to NRL was present in 5.2%, contact urticaria in 3.6%, and rhinitis in 2.0% at initiation of the study, while in those who started working after the introduction of non-powdered NRL gloves the corresponding cumulative prevalence rates over the 2000–2009 period were 0.2 and 0.2%, respectively.

Based on available evidence [64••, 69••], several practical recommendations for the primary prevention of NRL allergy can be issued:

- The use of NRL gloves should be restricted as far as possible to specific purposes; non-NRL gloves should be recommended for most non-sterile healthcare procedures that do not require high tactile sensitivity and manual dexterity.
- Sterile powdered NRL gloves should be substituted with powder-free, low-protein/allergen NRL gloves or non-NRL gloves.
- The use of NRL gloves by workers without exposure to contaminated biological fluids should be strongly discouraged.

Management and Outcome

Strict avoidance of exposure remains the optimal treatment for NRL allergy. Patients with an established diagnosis of IgE-mediated NRL allergy should be given detailed information concerning the nature of the disease and appropriate avoidance measures, especially during healthcare procedures. Educational resources for patients with NRL allergy can be found, for instance, on the American Latex Allergy Association website (http://latexallergyresources.org). Subjects with a history of severe reaction to NRL should be supplied with an epinephrine (adrenaline) auto-injector for emergency treatment.

In occupational settings, the management options include relocation of the worker to an NRL-free work area or conversion of the worker's area to an NRL safe area. However, complete avoidance of exposure to NRL is however difficult to implement in healthcare environments, as it implies both personal and institutional policy changes. HCWs with documented IgE-mediated NRL allergy should be instructed to use only NRL-free gloves. Nonetheless, personal avoidance of NRL gloves is not sufficient to prevent exposure to airborne NRL allergens, since coworkers who use powdered NRL gloves may disseminate significant amounts of NRL-contaminated powder particles capable of triggering respiratory reactions in allergic workers. Thus, every effort should be made to avoid or to minimize indirect airborne exposure to NRL from coworkers, although there is no clear guidance on how this is best achieved. The available options include: (1) the use of non-NRL gloves by both the affected worker and her/his colleagues or (2) the use of non-NRL gloves by the affected worker while colleagues use powder-free, low-protein/allergen NRL gloves. Early reports have demonstrated that powder-free, low-protein/allergen gloves are effective in preventing asthmatic reactions in HCWs with NRL-induced OA, although highly sensitive subjects may still develop rhinitis and after prolonged exposure to such gloves [70, 71]. A systematic review identified eight original reports on workplace-based intervention studies for workers with IgE-mediated NRL allergy published between 1990 and 2010 [72••]. Although the studies were heterogeneous in terms of the interventions and reported outcomes, the authors concluded that there was "moderately strong and consistent evidence that individual avoidance of powdered NRL gloves in the workplace reduces both symptoms and markers of sensitization in NRL-allergic individuals irrespective of whether coworkers use non-NRL gloves or powder-free, low-protein NRL gloves." This review also indicates that it is reasonable to allow HCWs with NRL allergy to use powder-free, low-protein NRL gloves, provided that coworkers also use non-NRL gloves or powder-free, low-protein NRL gloves.

Subsequent follow-up studies of subjects with NRL allergy confirmed that the use of non-NRL gloves and/or powder-free, low-protein NRL gloves was associated with a substantial improvement in work-related symptoms and quality of life [73–75], although in one German study work-related nose, eye, or airways symptoms were still experienced by 23% of participants [74]. After substitution of powdered NRL gloves by non-NRL gloves and/or powder-free, low-protein NRL gloves, 25 to 29% of previously sensitized employees reverted to negative SPT to NRL [61, 73]. It remains unknown however whether those subjects who "loose" NRL sensitization will develop symptoms on repeated exposure to NRL. Therefore, in subjects with documented IgE-mediated NRL allergy, preventive measures should be maintained in occupational and nonoccupational environments irrespective of changes in the apparent sensitization status over time.

In the quoted studies [73–75], 11 to 29% of the subjects had to leave their job as a result of the diagnosis of NRL allergy. Only one older study compared the health and socioeconomic outcome of patients with NRL-induced OA after complete cessation or reduction of exposure to NRL (i.e., affected workers used only non-NRL gloves while colleagues used either low-protein, low-powder NRL sterile gloves and non-NRL examination gloves or only occasionally NRL powdered gloves). Both reduction and complete avoidance of exposure to NRL were associated with a similar improvement in asthma severity and nonspecific bronchial hyperresponsiveness to histamine. However, complete avoidance of exposure to NRL was associated with asthma-related work disability (69%) and loss of income (62%) more frequently than was reduction of exposure (35 and 30%, respectively).

Current evidence is too weak to support the use of immunotherapy to treat NRL allergy in the workplace when avoidance measures are not feasible or not effective [34, 72••, 76]. Sublingual immunotherapy achieved the best risk to benefit ratio, although further properly controlled studies are needed and recombinant DNA technology could achieve a more accurate standardization of NRL extracts [77]. A single double-

blind, randomized, placebo-controlled study investigated the benefits of anti-IgE therapy (omalizumab) in 18 HCWs suffering from rhinoconjunctivitis and mild-to-moderate asthma [78]. After a 16-week treatment, omalizumab resulted in a significant reduction in conjunctival and skin reactivity to NRL compared to placebo, although the authors failed to provide information on NRL-related symptoms.

Conclusions

NRL allergy is instructive in many respects. The story of NRL allergy demonstrated that potent allergens such as NRL proteins can cause the rapid development of IgE-mediated sensitization and clinical allergy, reaching epidemic proportions in highly exposed populations. Intense research led to the elucidation of the allergen sources as well as the characterization, purification, and production of NRL allergens. Scientific and technological advances resulted in the development of specific assays for quantifying the allergen content of NRL materials and sIgE antibodies directed against the relevant NRL allergens for diagnostic purposes. Translation of research findings into preventive strategies markedly altered the course of the NRL allergy outbreak within about 15 years. Fruitful collaboration between clinicians, researchers, glove manufacturers, and public authorities allowed for the production of NRL gloves with a low-protein/allergen and powder content and the widespread substitution of powdered NRL gloves with these powder-free, low-protein/allergen NRL gloves and non-NRL gloves in healthcare settings. These preventive measures were not only associated with a marked reduction in the risk of sensitization to NRL, but they also allow the management of workers with NRL allergy without the need for redeployment to other work areas or career changes, thereby minimizing the socioeconomic burden of the disease. In this respect, NRL allergy should be regarded as one of the few conditions where reduced workplace exposure to allergens alone proved highly effective in the primary prevention and management of an occupational allergy. However, the evidence pertaining to the prevention of NRL allergy is prominently derived from studies conducted in HCWs in high-income countries and its generalizability to other workers exposed to NRL gloves and to HCWs in economically developing settings must be assumed with caution and recent studies outline the need for ongoing vigilance.

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Compliance with Ethical Standards

Conflict of Interest Dr. Vandenplas declares no conflicts of interest relevant to this manuscript. Dr. Raulf has received speaker's honoraria from Astellas Pharma GmbH, ThermoFisher Scientific, and HAL Allergy.

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