



Current state of occupational latex allergy

Monika Raulf

Purpose of review

During the 1980s, natural rubber latex (NRL) emerged as a major cause of occupational allergy and asthma, especially in healthcare workers using powdered NRL gloves. Increased recognition of NRL allergies and transfer of research findings into prevention strategies resulted into an almost elimination of this health problem. Here, the current knowledge on allergens, their use in diagnostics, prevalence data of occupational NRL allergy and the status of prevention strategy are summarized.

Recent findings

While the current studies conducted in high-income countries show that prevention measures have reduced NRL allergy, this does not yet apply worldwide. For latex allergy diagnosis, it is important that recombinant allergens as reliable tools are available, because in several European countries and the United States, NRL skin prick test extracts and powdered latex gloves for bronchial challenge test are no longer commercially available, leading to a deficit in diagnostic tools. Due to the fact that latex is suitable with good properties as a raw material for gloves, alternatives with significantly lower protein content and without cross-reactive structures to latex proteins are sought.

Summary

Awareness of the sensitization risk associated with the use of latex gloves should still be present in all occupational settings.

Keywords

component-resolved diagnosis, healthcare workers, natural rubber latex, occupational allergy, prevention strategy

INTRODUCTION AND HISTORY OF NRL ALLERGY

The white milky sap of the rubber tree *Hevea brasiliensis* – a native of Amazon Basin – is the source of the production of commercially natural rubber latex (NRL) devices. The main constituent of NRL is the polymeric hydrocarbon 1,4 cis-poly-isoprene, and only 1–2% of the fresh weight of *Hevea* latex is made up of proteins, which are heterogeneously distributed in the latex sap [1].

These latex proteins are the source of IgE-mediated sensitization which may develop into IgE-associated type I allergy with corresponding clinical manifestations. Depending on the route of exposure and the type of latex contact whether by direct skin contact or inhalation, or via mucous membranes or vascular system the clinical manifestation range from localized urticaria to extensive angioedema and life-threatening anaphylaxis. Especially in healthcare, NRL was used not only in medical devices, but also in personal protective equipment, for example, examination and surgical gloves. A setting in which powdered NRL gloves are used, latex proteins bound to the cornstarch particles of the glove

powder which served as a vehicle for airborne transmission of the NRL proteins. The dust aerosol that was created when donning and removing powdered gloves provokes allergic symptoms (asthma, rhinoconjunctivitis), especially via uptake through the respiratory tract. In the late 1980s and 1990s, the airborne latex allergen exposure was the major source of latex sensitization and allergic symptoms in healthcare workers (HCWs) and allergy to NRL reached in this time period epidemic proportions, especially in western industrial countries. Additionally, NRL allergy has been described in several other occupations in which protective gloves are used (e.g.

Institute of Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr-Universität Bochum (IPA), Bochum, Germany

Correspondence to Monika Raulf, Institut für Prävention und Arbeitsmedizin der Deutschen Gesetzlichen Unfallversicherung, Institut der Ruhr-Universität Bochum (IPA), Kompetenz-Zentrum Allergologie/Immunologie, Bürkle-de-la-Camp-Platz 1, 44789 Bochum, Germany.
Tel: +49 30 13001 4310; fax: +49 30 13001 864310;
e-mail: raulf@ipa-dguv.de

Curr Opin Allergy Clin Immunol 2019, 19:000–000

DOI:10.1097/ACI.0000000000000611

KEY POINTS

- By strict allergen avoidance including the implementation of powder-free and NRL-gloves with low protein levels occupational NRL allergy can be prevented.
- Not only in the healthcare facilities but also in other workplaces attention and appropriate preventive measures should be introduced to reduce the risk of NRL sensitization and allergy.
- The deficit in diagnostic tools of NRL allergy based on unavailability of skin prick test extracts and powdered latex gloves for bronchial challenge test can be partly minimized by the application of recombinant latex allergens in the sequence of the proposed diagnostic algorithm.

housekeeping personnel, hairdressers, greenhouse workers and workers in textile factories). The high prevalence rates of NRL allergy with tremendous health and economic implications not only in HCWs but also in other populations with high exposure to NRL devices, for example, children with spina bifida or patients with other urogenital malformations requiring multiple surgical interventions at an early age, resulted in intensive research efforts to identify the allergen source, characterize the sensitization mechanisms, improve the diagnosis and delineate preventive strategies. Education about this allergy in healthcare facilities combined with the introduction of powder-free gloves with reduced protein levels has been associated with a decline in the number of suspected cases of NRL allergies in the late 1990s.

RELEVANT NRL ALLERGENS AND DIAGNOSIS OF NRL ALLERGY

More than 240 polypeptides were detected by two-dimensional electrophoresis in latex, and 60 IgE-binding structures were identified. At present, 26 *Hevea brasiliensis* allergens including isoforms and variants with molecular weight between 4.7 and 60 kDa have been listed by the WHO/International Union of Immunological Societies (IUIS) Allergen Nomenclature Sub-Committee as Hev b 1–15. (www.allergen.org) [2]. Hev b 15 – a serine protease inhibitor – was the last Hev b allergen included in the list [3]. Sufficient evidence exists suggesting that various risk groups are sensitized by different NRL allergens. It is also quite obvious that the mode of contact with the allergenic proteins is of enormous importance for the development of a sensitization. HCWs can be sensitized by airborne latex allergens

that are adsorbed on the glove powder and get into the air by putting on and taking off the powdered gloves. Patients with, for example, spina bifida or multiple surgeries, on the contrary, will be sensitized by the direct contact of latex-containing devices with their body fluids and mucous membranes. Whereas Hev b 5 and Hev b 6.01 (especially the hevein domain Hev b 6.02) were recognized as major allergens in HCWs, patients with spina bifida have predominantly IgE-reactivity to Hev b 1, Hev b 3 and Hev b 5. All other allergens are of minor relevance, but may help to complete and elucidate the diagnostic picture in individual cases. With the exception of Hev b 2, 4, 13 and 14, the Hev b-allergens are available in recombinant form and commercial coupled to ImmunoCAP (rHev b 1, 3, 5, 6.02, 8 and 11), and five of them (rHev 1, 3, 5, 6.01 and 8) are on the multiplex specific-IgE screening platform [Immuno Solid-phase Allergen Chip (ISAC)], both of them provided by Thermo Fisher Scientific (Uppsala, Sweden). All of these recombinant Hev b allergens have proved successful in the in vitro-diagnostic of NRL. With the ISAC chip, it is possible to determine simultaneously specific IgE against these five allergens with only 20 µl of serum, but the sensitivity of this assay with respect to the detection of NRL sensitization was lower compared to the conventional currently available ImmunoCAP k82 spiked with rHev b 5 and other methods like cellular antigen stimulation test (CAST) [4]. By using the recombinant single allergens in a component-resolved approach, identification of specific sensitization profiles of various risk groups is possible.

An accurate diagnosis of NRL-induced occupational asthma is an important step to prevent the progression and worsening of symptoms or to initiate a successful intervention. The specific IgE measurement with NRL extract is an important method to diagnose latex sensitization and could be significantly improved by addition of the major allergen rHev b 5 as a stable recombinant protein to the NRL extract preparation ('spiking' NRL extract) [5]. A study of [6] demonstrated that high levels of IgE specific for rHev b 5 combined with rHev b 6.01 or 6.02 are the most accurate predictors of a bronchial response to NRL showing better diagnostic efficiency than the NRL-(k82)-sIgE ImmunoCAP. This is important because in several European countries and the United States, NRL skin prick test extracts and powdered latex gloves for bronchial challenge test are no longer commercially available, leading to a deficit in diagnostic tools [7].

If a positive NRL-specific IgE result occurs in patients without clinical symptoms on exposure to NRL, determination of sIgE against cross-reactive carbohydrate determinants (CCD) can be performed

to clarify the origin of the IgE-binding to latex (protein epitopes versus glyco-peptides). On the basis of these data, a diagnostic algorithm has been developed to discriminate between patients with most likely clinical-relevant NRL sensitization (in this cases avoidance of latex products is necessary) and polysensitized patients in which the IgE-reactivity to NRL is based on CCD or Hev b 8 (the profilin) or the nonspecific lipid transfer protein (Hev b 12) and avoidance of latex devices is not necessary [8].

Lamberti *et al.* [9] studied the molecular profile of sensitization in healthcare students with occupational exposure to latex for less than 5 years. They confirmed the importance of Hev b 5 and Hev b 6.01 as clinically relevant and found that the combination of Hev b 5, Hev 6.01 and Hev b 8 identified 92% of the latex-allergic patients in their series. 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.

A recent study by Nowakowska-Swirta *et al.* [10²²] confirmed the importance of using recombinant latex allergens (Hev b 5, Hev b 6.01/6.02 and Hev b 8) to discriminate between a group of 26 HCWs with occupational asthma and 18 HCWs with work-exacerbated asthma. Saleh *et al.* [11] compared specific latex IgE levels of skin test-positive from a historic cohort (1995–2001) and a current group (2014–2015), and found that NRL-specific IgE levels were significantly higher in former patients with suspected latex allergy than in former latex-sensitized individuals without allergy. Unfortunately, no recombinant allergens were tested in this study. However, these authors also point out that the determination of the NRL-specific IgE alone is not sufficient for a correct diagnosis of latex allergy.

CURRENT PREVALENCE AND INCIDENCE DATA

Data on reported prevalence of latex sensitization and allergy among HCW, HCW students, dental students and dentists by Wu *et al.* [12] calculated from studies performed in different countries published between 2009 and 2015 showed 9.7% prevalence of latex allergy and 12.4% for latex sensitization (the total number of study participants used for calculation was 19 233, and the majority of the studies were from outside Europe and USA). A pooled analysis of 11 epidemiological surveys published between 2006 and 2015 evaluating the prevalence of NRL among HCWs with data on IgE sensitization to NRL from different countries (eight of these studies were conducted in developing countries) provided mean [95% confidence interval (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 [7]. A study from Albania [13] could show that among 240 dental students, 25% were suspicious for latex gloves hypersensitivity, skin prick test revealed a latex sensitization on 20% and airborne challenge with NRL gloves confirmed the allergic sensitization in 7.5% of the participants. In a Danish study [14] focused on all patients prick tested for NRL at the hospital ($n=8580$) over time from 2002 to 2013, the prevalence of NRL sensitization (and clinical NRL allergy, respectively) significantly declined from 6.1% (1.3%) in 2002–2005 to 1.9% (0.5%) in 2006–2009, and then to 1.2% (0.6%) in 2010–2013. Atopic diseases were found in 84% of the NRL-sensitized patients, and regarding occupational status, 31% of the patients allergic to NRL were HCWs and 54% had other jobs (e.g. teachers, hairdressers and chauffeurs); for 15%, the occupation was not recorded. In a present study from southern Thailand, the amount of proteins and the effects of NRL gloves on the pulmonary functions of 340 female nurses were evaluated [15²³]. The prevalence of respiratory effects self-attributed to NRL glove use and of NRL sensitization were 6.5 and 4.7%, respectively, in this study. Four of the 16 sensitized nurses (25%) reported respiratory symptoms. Furthermore, examination gloves contained protein levels in the range of 111–250 mg/dm². Different types of NRL gloves contained different amount of proteins. NRL sensitization was more prevalent in nurses with high concentrations of proteins in NRL gloves. The authors concluded that the use of gloves with low proteins can reducing NRL allergen exposure in these hospitals, which may reduce the risk of developing respiratory problems and NRL sensitization. In general, taking all limitations into account, these studies, pooled analysis and evaluations were able to show that in some countries occupational latex sensitization and allergy remains a problem [7].

PREVENTION STRATEGY

Because there are no health-based exposure limit values for sensitizing agents, the minimization requirement applies to prevention, that is, exposure to a potentially sensitizing agent should be reduced or avoided. Substitution of the allergen or allergen source can also be an effective prevention strategy. In the case of an allergic type I reaction, a distinction must be made between allergen concentrations which lead to sensitization and those which trigger allergic symptoms. In an already sensitized person, even any subsequent exposure to the allergen can

trigger the allergic symptoms. In the case of NRL, the risk of sensitization or allergic reaction to NRL can be reduced by minimizing the amount of leachable and especially airborne allergenic protein to which a subject is exposed. In Germany, for example, NRL-powdered NRL gloves or NRL gloves with high protein content were no longer allowed to be used at workplaces since 1997 [1]. The effectiveness of these primary preventive measures has been shown through a clear association between powder-free and NRL gloves with low protein levels and the decline in the number of suspected cases of occupational NRL on a nationwide scale [16]. In addition, the present study from Thailand [15²²] demonstrated that NRL gloves with a high protein content elicit a higher percentage of positive responses in latex-sensitized individuals than gloves with lower protein residues. In January 2017, a ban on the manufacture and sale of most powdered medical gloves in the United States was imposed [17].

Due to the fact that latex is suitable as a raw material for gloves and has very good properties, new manufacturing processes, for example, by use of deproteinized and purified NRL, chlorination and mostly high-temperature postwashing, have been developed resulting in low-protein rubber gloves [18]. On the contrary, research and development are looking for alternatives to *H. brasiliensis* latex. Guayule (*Parthenium argentatum*) latex, in particular, which contains less than 1% of the protein content of Hevea latex and has no cross-reactivity to Hevea allergens, has proved to be a suitable alternative [18].

CONCLUSION

In most western countries with high income, it can be concluded that latex allergy is a very good model for a 'new' allergy – especially an occupational one – which suddenly arises and has become a health problem with social and economic implications, but through targeted and evidence-based primary prevention strategies with appropriate controls (e.g. strict allergen avoidance), the prevalence could be significantly reduced in a relatively short period of time. This showed that especially the fruitful cooperation between clinicians, researchers, glove manufacturers and authorities was successful. On the contrary, particularly in low-income countries and workplaces that have not yet focused attention on NRL allergy prevention and, for example, still used powdered latex gloves, the disease continues to be a global concern. Although the use of gloves to protect against infections is part of everyday working life, especially in the health sector, other working areas in which latex gloves are also used, but risk

awareness is not present, should receive attention and appropriate preventive measures should also be introduced there. NRL allergy has also attracted attention in molecular allergy diagnostics, the so-called 'component-resolved diagnostic (CRD)', because it is an excellent model for the useful application of recombinant single allergens for improvement of routine diagnostics (via spiking of the latex extracts with rHev b 5) and discrimination between clinical relevant latex allergy and sero-positivity based on cross-reactivity to panallergic components (via application of major allergens recognized in different risk groups).

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

M.R. received speaker's honoraria from ThermoFisher Scientific in the past, but there are no conflicts of interest with regards to this publication.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Raulf M. The latex story. *Chem Immunol Allergy* 2014; 100:248–255.
2. Raulf M. Allergen component analysis as a tool in the diagnosis of occupational allergy. *Curr Opin Allergy Clinical Immunol* 2016; 16:93–100.
3. Rihs HP, Sander I, Heimann H, *et al.* The new latex allergen Hev b 15: IgE-binding properties of a recombinant serine protease inhibitor. *J Invest Allergol Clin Immunol* 2015; 25:160–162.
4. Seyfarth F, Schliemann S, Wiegand C, *et al.* Diagnostic value of the ISAC® allergy chip in detecting latex sensitizations. *Int Arch Occup Environ Health* 2014; 87:775–781.
5. Huss-Marp J, Raulf M, Jakob T. Spiking with recombinant allergens to improve allergen extracts: benefits and limitations for the use in routine diagnostics: part 19 of the Series Molecular Allergology. *Allergo J Int* 2015; 24:236–243.
6. Vandenplas O, Froidure A, Meurer U, *et al.* The role of allergen components for the diagnosis of latex-induced occupational asthma. *Allergy* 2016; 71:840–849.
7. Vandenplas O, Raulf M. Occupational latex allergy: the current state of affairs. *Curr Allergy Asthma Rep* 2017; 17:14.
8. Raulf M, Rihs HP. Latex allergens: source of sensitization and single allergens. *Molecular Allergy Diagnostics*; (eds), Kleine-Tebbe J, Jakob T 2017:459–470.
9. Lamberti M, Buonanno R, Ritonnaro C, *et al.* Molecular profile of sensitization in subjects with short occupational exposure to latex. *Int J Occup Med Environ Health* 2015; 28:841–848.
10. Nowakowska-Swirta E, Wiszniewska M, Walusiak-Skorupa J. Allergen-specific IgE to recombinant latex allergens in occupational allergy diagnostics. *J Occup Health* 2019; 61:378–386.
- Component-resolved diagnostic performed with NRL allergens confirming the usefulness of recombinant latex allergens.
11. Saleh MM, Forkel S, Schön MP, *et al.* Profile shift in latex sensitization over the last 20 years. *Int Arch Allergy Immunol* 2019; 178:83–88.
12. Wu M, McIntosh J, Liu J. Current prevalence rate of latex allergy: why it remains a problem? *J Occup Health* 2016; 58:138–144.
13. Bakiri A, Krja D, Skenderaj S, *et al.* Hypersensitivity to natural rubber latex gloves among albanian dental students: the role of exposure duration. *Int J Med Health Sciences Research* 2017; 4:45–49.

14. Blaabjerg MSB, Andersen KE, Bindslev-Jensen C, Mortz CG. Decrease in the rate of sensitization and clinical allergy to natural rubber latex. *Contact Dermatitis* 2015; 73:21–28.
 15. Supapvanich C, Povey AC, de Vocht F. Evaluation of proteins in natural rubber latex gloves and pulmonary function amongst female nurses in two tertiary hospitals in southern, Thailand. *Asian Pac J Allergy Immunol* 2019; doi: 10.12932/AP-310319-0530 [Epub ahead of print]
- Interesting study confirming that a successful prevention measure is the implementation of gloves with low protein content in tertiary hospitals in Thailand.
16. Allmers H, Schmengler J, Skudlik C. Primary prevention of natural rubber latex allergy in the German healthcare system through education and intervention. *J Allergy Clin Immunol* 2002; 110:318–323.
 17. Kelly KJ, Sussman G. Latex allergy: where are we now and how did we get there? *J Allergy Clin Immunol Pract* 2017; 5:1212–1216.
 18. Crepy M-N. Rubber: new allergens and preventive measures. *Eur J Dermatol* 2016; 26:523–530.