

Occupational asthma and rhinoconjunctivitis induced by natural rubber latex exposure

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A number of reports indicate that occupational exposure to natural rubber latex (NRL) in health care workers can elicit symptoms of rhinoconjunctivitis with or without asthma in selected individuals who are sensitized. The prevalence or risk of NRL-induced asthma in relation to rhinoconjunctivitis is small in comparison with other forms of occupational allergic respiratory disease. The lower risk of NRL-induced asthma appears to be related to poor penetration of the allergen into the lower respiratory tract because of the relatively large particle size of allergen-bearing cornstarch particles. Because of a lack of large prospective studies, little is known about the incidence and natural history of latex-induced respiratory disease. Because of heightened awareness of NRL allergy and changing patterns in glove manufacturing and glove use, it is likely that the occurrence of NRL-induced occupational respiratory disease will decline and its natural history will change. Nevertheless, because a large number of individuals are exposed to NRL in various occupations, the incidence, prevalence, and natural history of NRL allergy merit further monitoring. (*J Allergy Clin Immunol* 2002;110:S75-S81.)

Key words: *Natural rubber latex, occupational asthma, rhinoconjunctivitis*

Since Nutter¹ reported urticarial lesions from contact with natural rubber latex (NRL) gloves in 1979, there has been growing interest in the importance of NRL as a sensitizing agent, particularly in the occupational setting. In the late 1980s and early 1990s, several case reports and case series implicated NRL as a cause of rhinoconjunctivitis and asthma among health care workers.²⁻⁵ Although NRL gloves are used in a number of occupations, health care workers are by far the largest group with occupational NRL exposure in the United States.

Both asthma and rhinoconjunctivitis are common disorders, affecting approximately 14% and 6.5% of the US population, respectively.^{6,7} Further, it is estimated that as many as 15% of all cases of asthma represent disease of occupational origin.⁸ The mechanisms by which NRL induces rhinoconjunctivitis and asthma and the magnitude and natural history of these disorders are the focus of this discussion.

Abbreviation used

NRL: Natural rubber latex

MECHANISMS OF NRL RHINOCONJUNCTIVITIS AND ASTHMA

Natural rubber is a processed product derived from latex, the sap extracted from the rubber tree, *Hevea brasiliensis*. Latex itself has a complex composition consisting of spherical polyisoprene droplets coated with a layer of proteins. These proteins represent a family of water-soluble, thermostable proteins of varying molecular weights. Morales et al⁹ were among the first to demonstrate that extractable proteins from NRL could bind specific human IgE antibody. The characteristics of latex allergens are reviewed by Sussman et al (see p S33 in this issue).

Since the 1980s, the manufacturing of NRL gloves has involved the use of cornstarch powder for ease of donning. A review of these manufacturing processes and how they have changed over time is also provided by Yip and Cacioli (see p S3 in this issue). Tarlo et al³ were among the first to suggest that rhinoconjunctivitis and asthma were caused by airborne cornstarch particles bearing NRL allergens. Subsequently, it was demonstrated that latex proteins could bind to cornstarch particles and that NRL allergens could be extracted from glove powder.^{10,11}

On this basis, it is generally accepted that NRL-induced rhinoconjunctivitis and asthma are IgE-mediated processes initiated by the deposition of allergen-bearing airborne particles on the mucosal surfaces of the eyes and respiratory tract. Contact between NRL allergens and specific IgE antibody bound to mast cells results in cross-linking of IgE receptors and subsequent mast cell activation with release of granules containing biologically active mediators, as well as de novo generation of potent fatty acid mediators. Collectively, these mediators are responsible for the pathobiology of rhinoconjunctivitis and asthma. For example, release of histamine can lead to engorgement of venous sinusoids, resulting in congestion; stimulation of postcapillary venules and mucous glands, producing rhinorrhea; and activation of sensory nerve fibers, which causes sneezing, itching, and pain. Release of cysteinyl leukotrienes can further augment the degree of rhinorrhea through their action on postcapillary venules and mucous glands. The lower respiratory tract differs from the nasal airway insofar as the lower airways are surrounded by smooth muscle. Accordingly, the effects of

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mediator release in the lower respiratory tract include not only mucus secretion and microvascular leak with transudation and tissue edema but also contraction of airway smooth muscle, all of which lead to airway obstruction.

Unless shielded by protective gear, the ocular and nasal mucosal surfaces are fully exposed to suspended particulate matter in the environment, irrespective of the size of the airborne particles. By contrast, transport of particles from the ambient air into the lower respiratory tract involves a more complicated anatomic route. In general, particles $>10\text{ }\mu\text{m}$ are unable to penetrate below the level of the glottis.¹² Particles between 5 and $10\text{ }\mu\text{m}$ tend to be deposited on the mucosal surfaces of the trachea and large airways, whereas those $<5\text{ }\mu\text{m}$ diameter penetrate the more peripheral regions of the lungs. Thus, the eyes and nose have greater exposure to airborne allergens than the lungs. Because of these differences, there are notable differences in the prevalence and the time to onset of allergic symptoms involving the nasal airway and lower respiratory tract. For example, nasal symptoms caused by exposure to NRL and other occupational allergens have been shown to precede the development of lower respiratory tract symptoms by months or years.¹³⁻¹⁵ The delay in onset of asthma symptoms is likely to involve not only a decrease in the amount of exposure of the lower respiratory tract but also a delay in lower respiratory tract sensitization as a result of lower local allergen exposure.

The term *allergic sensitivity* signifies that an individual has produced specific IgE antibody in response to a defined exposure. Allergic sensitivity, by itself, is required, but it is not sufficient to manifest a clinically evident allergic reaction to a specific allergen (eg, rhinoconjunctivitis or asthma). It is well recognized that sensitivity to common aeroallergens is more prevalent than the occurrence of allergic respiratory disease.⁶ Similarly, among exposed health care workers with positive skin test responses to NRL, only 41% to 69% have reported respiratory symptoms with exposure.^{16,17} A clinically evident allergic reaction is the product of 3 factors: (1) the level of allergic sensitivity, (2) the level of allergen exposure, and (3) the level of target organ responsiveness.^{18,19} For example, for a given level of allergic sensitivity, a tissue response can be induced by a relatively low dose of allergen exposure in an individual with a high degree of end-organ tissue responsiveness. Conversely, an identical tissue response can be elicited in an individual with a lower level of tissue responsiveness, provided that the dose of allergen exposure is high enough. Although the pathophysiologic determinants of nasal tissue responsiveness are unknown, those of the lower respiratory tract appear to chiefly involve the bronchomotor response of the airways, including factors that are capable of regulating bronchomotor tone.

Thus, asthma and rhinitis reflect tissue responses to the deposition of airborne allergens on local mucosal surfaces. Although Vandenplas²⁰ has suggested that asthma may be part of a systemic reaction after dermal contact with NRL, we would argue that this is not true asthma, but rather a process caused by activation of mediators in the systemic

circulation that are more likely to result in alterations in vascular permeability and edema of the airways without the typical inflammatory response seen in asthma.

EPIDEMIOLOGY

Although there are well-characterized cases of NRL-related allergic rhinoconjunctivitis and asthma in the literature, these are largely presented in case reports or case series from which no epidemiologic information can be derived.^{3,4,21,22} Most information concerning the prevalence of latex allergy is derived from larger cross-sectional studies assessing sensitivity and self-reported symptoms in exposed health care workers. These studies are confounded by a number of issues including the use of different methods and reagents for testing skin or serologic sensitivity, differences in levels of exposure of the populations studied, and the unreliability of self-reported symptoms obtained with questionnaires.

Problems posed by a lack of standardization of methods for determining NRL sensitivity are discussed by Hamilton et al (see p S47 in this issue). When issues of methodological variability were taken into consideration, the reported prevalence of NRL sensitization varied between 4.5% and 22% in 12 cross-sectional studies that evaluated populations ranging in size from 135 to 741 subjects.²³⁻³⁴ Combining the populations of these studies yields a total of 6146 subjects with a pooled prevalence rate of 8.2%. Studies that included serologic tests of NRL sensitivity, which are thought to have less diagnostic sensitivity, have yielded a pooled prevalence rate of 7.5% in a combined population of 1505 exposed workers derived from 4 studies.^{32,35-37}

The prevalence rates of rhinoconjunctivitis and asthma are shown in Fig 1. In 7 separate studies, the prevalence of rhinoconjunctivitis in NRL-exposed health care workers ranged from 1.2% to 16.3% in populations ranging in size from 131 to 1472 subjects.^{17,28,29,31,35,37,38} The prevalence rate for those reporting symptoms of rhinoconjunctivitis with glove exposure in the pooled population ($n = 3567$) was 7.6%. The asthma prevalence in the same populations ranged from 0% to 6.8%, with a pooled prevalence rate of 1.4%.^{17,28,29,31,35,37,38} Thus, for those reporting symptoms of rhinoconjunctivitis caused by glove exposure in the workplace, the concurrent prevalence or risk of having asthma caused by glove exposure was approximately 1 of 5, or 18.4%.

Comparison of the prevalence of NRL-induced symptoms with the prevalence of symptoms in another form of occupational allergy provides insight into the magnitude of the problem. A relevant comparison is with dander allergen derived from small animals, an airborne protein allergen commonly found in the medical research setting.

The molecular weight of latex allergens, reported to be in the range of 14 to 27 kd,³⁹ is similar to the range of 10 to 38 kd reported for small animal dander allergens.⁴⁰⁻⁴² Moreover, the airborne levels of latex reported in workplace settings are comparable to those reported for dander allergens. For example, Swanson et al⁴³ reported latex

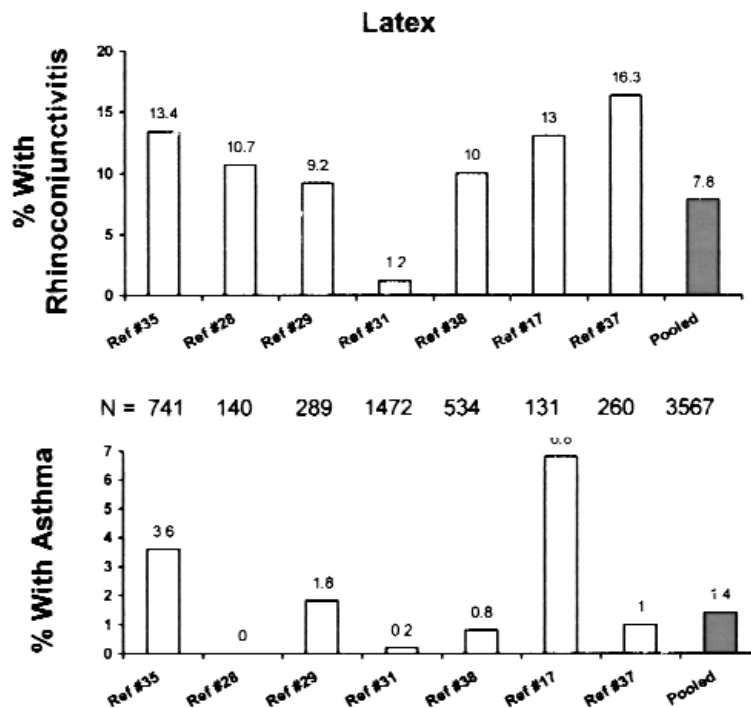


FIG 1. Prevalence of latex-induced asthma and rhinoconjunctivitis symptoms reported in 7 studies. Population sizes are listed in between graphs. Pooled prevalence is shown in shaded column.

aeroallergen concentrations ranging from 13.8 to 974 ng/m³, whereas others have reported concentrations in the range of 0.86 to 616 ng/m³ in areas where there is heavy use of powdered latex gloves.⁴⁴⁻⁴⁷ Ohman et al⁴⁸ found that animal dander allergen levels were similar, ranging from 16.6 to 563 ng/m³ in animal holding rooms. Likewise, Twiggs et al⁴⁹ reported airborne mouse dander allergen ranging from 1.8 to 825 ng/m³ in holding rooms, depending on the number of mice and degree of work activity.

The prevalence of sensitization to laboratory animal dander as determined by skin testing varied from 8.2% to 18.4% in 5 studies in populations ranging in size from 145 to 365 exposed workers.⁵⁰⁻⁵⁴ The pooled prevalence in the combined population of 1035 workers was 13% for animal dander compared with 8.2% for NRL sensitization. The prevalence of rhinoconjunctivitis and asthma in laboratory animal handlers is shown in Fig 2. For rhinoconjunctivitis, the prevalence varied from 14.7% to 37% in 7 studies with populations ranging from 138 to 5641 exposed workers.^{50-52,54-57} The pooled rhinoconjunctivitis prevalence in the combined population of 8003 was 18.7%. In the same studies, the prevalence of asthma ranged from 6.4% to 11.7%, with a pooled prevalence of 7.4% in the total population of 8003 workers. Thus, for exposed animal handlers, the prevalence of both rhinoconjunctivitis and asthma is higher than observed in workers reporting symptoms related to NRL exposure. Of particular interest is the finding that for animal workers reporting symptoms of rhinoconjunctivitis, the concurrent prevalence or risk of having asthma symp-

toms with exposure is 1 of 2.5, or 40%. This compares with a risk of 1 of 5 for NRL workers with rhinoconjunctivitis having asthma. Hence, for subjects reporting symptoms of rhinoconjunctivitis with workplace exposure, those exposed to NRL are approximately half as likely to also have symptoms of asthma as those exposed to animal dander (Fig 3). Similar differences between NRL and animal dander have been shown in prospective cohort studies examining the incidence of skin sensitization and occupational asthma.⁵⁸⁻⁶⁰ In these studies, the incidence of sensitization to dander was 3.56-fold greater than sensitization to NRL, and the incidence of probable occupational asthma was 1.5-fold greater with dander than with NRL.⁵⁸⁻⁶⁰

The lower asthma prevalence in NRL-exposed workers is most likely explained by the size of allergen-bearing particles. Using standard air sampling techniques combined with inhibition immunoassay techniques, Swanson et al⁴³ demonstrated that less than 20% of airborne NRL allergen was bound to particles <7 μ m. This is in contrast to mouse allergen, which is carried on particles ranging from 3.3 to 10 μ m,⁴⁸ and rat allergens, which are carried on particles ranging from 1 μ m to >20 μ m, with the majority on particles <7 μ m.^{61,62}

However, it is difficult to explain the lower prevalence of rhinoconjunctivitis with latex on the basis of exposure, because particle size is not an issue and the levels of airborne allergen in these occupations are similar. Prior atopy, a risk factor for the development of sensitivity to either NRL or dander,^{17,33,53,57} is also an unlikely expla-

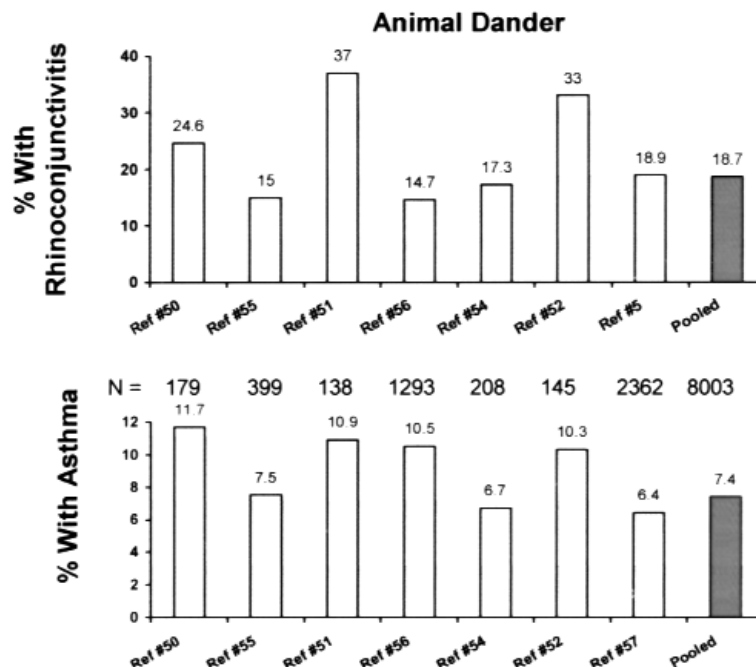


FIG 2. Prevalence of animal dander-induced asthma and rhinoconjunctivitis symptoms reported in 7 studies. Population sizes are listed in between graphs. Pooled prevalence is shown in shaded column.

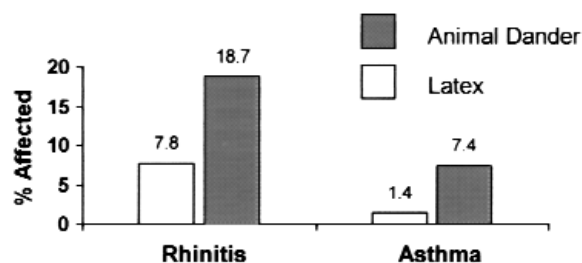


FIG 3. Relative prevalence of rhinoconjunctivitis and asthma caused by NRL (clear horizontal bars) versus laboratory animal dander (shaded horizontal bars).

nation, because prior atopy occurred in 18% to 50% of NRL-exposed workers and 22% to 39% of dander-exposed workers.*

One possible explanation is that the smaller particle size of dander allergen permits it to remain airborne for a longer time and to diffuse more widely in the workplace. This would allow for a greater duration of exposure and, perhaps, for a larger number of workers to be exposed.

DIAGNOSIS OF LATEX ALLERGIC RESPIRATORY DISEASE

The diagnosis of NRL-related rhinoconjunctivitis requires that the patient manifest signs and symptoms of rhinoconjunctivitis and that these findings be related to NRL exposure. Sneezing and rhinorrhea with itching and

watering of the eyes during periods of high exposure and improvement in these symptoms when away from exposure are highly suggestive of occupational allergy. It is important to rule out other factors in the workplace capable of causing such symptoms before confirming that symptoms are specifically due to NRL exposure. It is interesting to note that the prevalence of work-related rhinitis symptoms has exceeded the prevalence of skin sensitivity to NRL in a number of studies.^{23,29,37} Although this may be explained by a lack of sensitivity of skin testing methods, it is more likely that some individuals reported work-related symptoms that had another cause. For example, rhinitis symptoms can be induced by odors, bright lights, or even changes in temperature and humidity during movement in and out of the operating room. On the other hand, these latter stimuli are not usually associated with signs of inflammation or conjunctivitis. Thus, a careful examination to detect signs of allergic inflammation of the ocular and nasal mucous membranes is important in the diagnosis of occupational allergy.

Some investigators have attempted to document latex-induced allergic rhinitis by using nasal challenge techniques.^{65,66} In one study, nasal challenge with NRL glove powder elicited a response consisting of rhinorrhea, increased nasal obstruction, and increased nasal secretions in 1 of 7 workers reporting glove-related nasal symptoms.⁶⁵ Of the 7 workers, only the subject responding to the nasal glove powder challenge proved to be sensitive to NRL by skin testing. Unfortunately, there is too little information and too little experience with these techniques to assess either the sensitivity or the specificity, and thus the diagnostic usefulness, of nasal challenge with NRL.

*References 23, 29, 30, 33, 35, 36, 50, 52-55, 63, and 64.

The diagnosis of occupational asthma requires that the patient have asthma symptoms including chest tightness, cough, and wheezing in association with workplace exposure and remission when away from exposure. It also requires objective physiologic confirmation of airflow limitation. Asthma is characterized by variable airflow obstruction that is at least partially reversible by bronchodilators.⁶⁷ Because asthma symptoms are non-specific and could be related to other respiratory ailments, it is important to obtain physiologic documentation of reversible airflow obstruction. Documentation that asthma is related to a specific etiologic agent in the workplace often requires serial pulmonary function measurements. For example, results of pre- and post-shift spirometry, if positive, are usually confirmatory. However, this approach lacks sensitivity because of the variability of day-to-day exposure levels and the possibility of having a false-negative result. Serial measurements of peak expiratory flow rate with a portable monitor are more practical for longer-term monitoring of pulmonary function in relation to exposure.⁶⁸

Bronchial challenge testing has also been recommended as useful in the diagnosis of occupational asthma caused by latex or other agents.⁶⁹ For example, methacholine challenge testing has a high degree of sensitivity in patients with symptomatic asthma and therefore a high negative predictive value.^{18,19,70} By contrast, a positive methacholine challenge result (20% fall in FEV₁ at a concentration ≤ 10 mg/mL) may be found in 10% to 15% of nonasthmatic individuals with rhinitis only and in as many as 8% of healthy individuals.^{18,19} Although some have suggested that a positive methacholine challenge response in a subject with a history suggestive of occupational asthma and a positive skin test response confirm the diagnosis,⁶⁹ I would argue that the positive methacholine challenge response only makes the diagnosis more probable. Hence, I believe that a negative methacholine challenge response in a symptomatic worker is a far more powerful test for ruling out asthma. However, it is important to note that despite the high sensitivity of methacholine challenge in diagnosing asthma, there are reports of negative methacholine responses in sensitive workers who experience acute airway obstruction when exposed to toluene diisocyanate.⁷¹

Airway challenge with the specific etiologic agent has also been used in the diagnosis of occupational asthma.⁶⁹ However, because limited data are available, it is difficult to assess the sensitivity and specificity of this approach with most occupational agents. For example, latex glove handling under controlled conditions has been used to simulate workplace exposure for diagnostic purposes in a number of studies.⁷²⁻⁷⁶ Others have used soluble extracts prepared from NRL glove powder or glove components.^{15,77-80} However, the interpretation of a response to an aerosolized aqueous extract is problematic because several investigators have shown that soluble extracts of allergens can elicit airway reactions in sensitized subjects who have never experienced spontaneous symptoms of asthma.^{19,81,82} In these subjects, lower respiratory tract

mucosal reactions occur because of the inordinately high level of exposure to fine aerosol particles. Accordingly, I believe that asymptomatic subjects who are sensitized to NRL would respond to aqueous NRL aerosols, but such reactions, from a diagnostic point of view, are likely to reflect false-positive reactions. The specificity of challenges in which glove-handling techniques are used is seemingly greater to the extent that it reflects workplace conditions. However, even with these techniques, exposure levels can far exceed those encountered in the hospital setting. For example, Laoprasert et al⁷⁵ performed glove-handling challenges in a chamber with glove changes once every 3 minutes with powdered high-allergen gloves and found a mean airborne NRL protein level of 7600 ng/m³ with a range of 93 to 54,000 ng/m³. These levels, in most cases, exceed those reported in various locations of the hospital.^{43,45,46} A lack of specificity of simulated workplace challenges is suggested by reports of positive responses in 2 of 7 sensitized subjects without symptoms of asthma.²⁹

The sensitivity of challenges simulating workplace exposure has not been systematically evaluated. However, Baur et al⁸³ reported reactions to glove handling in less than 25% of workers having a history of work-related asthma symptoms. Laoprasert et al⁷⁵ similarly reported positive challenge responses in 4 of 9 subjects, whereas Vandenplas et al²⁹ found positive responses in 5 of 5 subjects tested. On the basis of these studies, it appears that simulated workplace challenges may not be as specific or sensitive as serial monitoring of lung function in confirming NRL-induced asthma.

NATURAL HISTORY

Lacking prospective studies in workers with documented NRL allergic respiratory disease, we know little about the natural history of these disorders. According to studies in workers who handle Western red cedar, it has been suggested that the natural history of occupational asthma varies according to the duration of exposure before onset of symptoms and the duration of symptoms before removal from the workplace.⁸⁴ When removed from Western red cedar dust exposure, approximately 50% of previously symptomatic workers experienced complete remission of symptoms with decreased methacholine responsiveness. Those with longer-term exposure had persistent asthma despite removal from exposure. Similar findings have been reported for asthma caused by toluene diisocyanate, another low-molecular-weight chemical.⁸⁵ The notion that asthma may be persistent in workers with long-term exposure before removal from the workplace is based on the thesis that a longer duration of airway inflammation may induce chronic airway hyperresponsiveness.⁸⁵ It should be emphasized that these observations pertain to low-molecular-weight chemical sensitizers and may not apply to high-molecular-weight protein allergens, particularly NRL allergens.

Reports of remission of asthma and rhinoconjunctivitis symptoms after switching to powder-free gloves sug-

gest a favorable prognosis.^{44,45} Although, Brugnami et al⁸⁶ suggested that latex-induced asthma could lead to permanent respiratory disability, their data suggest otherwise. They found that after 7 months to 7 years of follow-up, 3 of 6 subjects continued to have asthma on the basis of symptoms. However, their data reveal that only 1 of these 3 subjects had mildly abnormal pulmonary function with increased methacholine responsiveness. Another had borderline methacholine hyperresponsiveness but normal pulmonary function. In none of the subjects was there sufficient objective impairment to suggest that there could be permanent respiratory disability.

Because of heightened awareness of NRL allergy and changing patterns in glove manufacturing and glove use, it is likely that the occurrence of NRL-induced occupational respiratory disease will decline and its natural history will change. Nevertheless, because a large number of individuals are exposed to NRL in various occupations, the incidence, prevalence, and natural history of NRL allergy merit further monitoring.

REFERENCES

- Nutter AF. Contact urticaria to rubber. *Br J Dermatol* 1979;101:587-98.
- Seaton A, Cherrie B, Turnbull J. Rubber glove asthma. *Br Med J* 1988;296:531-2.
- Tarlo SN, Wong L, Roos J, Booth N. Occupational asthma caused by latex in a surgical glove manufacturing plant. *J Allergy Clin Immunol* 1990;85:626-31.
- Marcos C, Lazaro M, Fraj J, Quirce S, de la Hoz B, Fernandez-Rivas M, et al. Occupational asthma due to latex surgical gloves. *Ann Allergy* 1991;67:391-3.
- Baur S, Jager D. Airborne antigens from latex gloves [letter]. *Lancet* 1990;335:912.
- Nathan RA, Meltzer EO, Selner JC, Storms W. Prevalence of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997;99:S808-S814.
- United States Centers for Disease Control. Forecasted state-specific estimates of self-reported asthma prevalence. *Mor Mortal Wkly Rep CDC Surveill Summ* 1998;47:1022-5.
- Blank P. Occupational asthma in a national disability survey. *Chest* 1987;92:1354-7.
- Morales C, Bascombe A, Carreira J, Sasure A. Anaphylaxis produced by rubber glove contact: case report and identification of the antigens involved. *Clin Exp Allergy* 1989;19:425-30.
- Tomazic VJ, Shampaine EL, Lamanna A, Withrow TJ, Adkinson NF Jr, Hamilton RG. Cornstarch powder on latex products is an allergen carrier. *J Allergy Clin Immunol* 1994;93:751-8.
- Beezhold D, Beck WC. Surgical glove powders bind latex antigens. *Arch Surg* 1992;127:1354-7.
- Muir DCF. Particle deposition. In: Crystal RG, West JB, editors. *The lung: scientific foundations*. New York: Raven Press; 1991. p. 1939-43.
- Malo J-L, Lemiere C, Desjardins A, Cartier A. Prevalence and intensity of rhinoconjunctivitis in subjects with occupational asthma. *Eur Respir J* 1997;10:1513-5.
- Vandenplas O, Delwiche JP, Sibille Y. Occupational asthma due to latex in a hospital administrative employee. *Thorax* 1996;51:452-3.
- Marcos C, Lazaro M, Fraj J, Quirce S, de la Hoz B, Fernandez-Rivas M, et al. Occupational asthma due to latex surgical gloves. *Ann Allergy* 1991;67:319-23.
- Hunt LW, Fransway AF, Reed CE, Miller LK, Jones RT, Swanson MC, et al. An epidemic of occupational allergy to latex involving health care workers. *J Occup Environ Med* 1995;37:1204-9.
- Tarlo SM, Sussman GL, Holness DL. Latex sensitivity in dental students and staff: a cross-sectional study. *J Allergy Clin Immunol* 1997;99:396-401.
- Cockcroft DW, Murdock KY, Kirby J, Hargreave F. Prediction of airway responsiveness to allergen from skin sensitivity to allergen and airway responsiveness to histamine. *Am Rev Respir Dis* 1987;135:264-7.
- Fish JE, Peters SP. Bronchial challenge testing. In: Middleton E, Reed CE, Ellis EF, Adkinson NF, Yunginger JW, Busse WW, editors. *Allergy: principles and practice*. 5th ed. St Louis: Mosby; 1998. p. 454-64.
- Vandenplas O. Occupational asthma caused by natural rubber latex. *Eur Respir J* 1995;8:1957-65.
- Orfan NA, Reed R, Dykewicz MS, Ganz M, Kolski GB. Occupational asthma in a latex doll manufacturing plant. *J Allergy Clin Immunol* 1994;94:826-30.
- DeZotti R, Larese F, Fiorito A. Asthma and contact urticaria from latex gloves in a hospital nurse. *Br J Ind Med* 1992;49:596-8.
- Mace SR, Sussman GL, Liss G, Stark DF, Beezhold D, Thompson R, et al. Latex allergy in operating room nurses. *Ann Allergy Asthma Immunol* 1998;80:252-6.
- Liss GM, Sussman GL, Deal K, Brown S, Cividino M, Siu S, et al. Latex allergy: epidemiological study of 1351 hospital workers. *Occup Environ Med* 1997;54:335-42.
- Hamann CP, Turjanmaa K, Rietschel R, Siew C, Owensby D, Gruninger SE, et al. Natural rubber latex hypersensitivity: incidence and prevalence of type I allergy in the dental professional. *J Am Dent Assoc* 1998;129:1-12.
- Carrillo T, Blanco C, Quirarte J, Castillo R, Cuevas M, de Castro FR. Prevalence of latex allergy among greenhouse workers. *J Allergy Clin Immunol* 1995;96:699-701.
- Cornio L, Turjanmaa K, Talja M, Andersson LC, Ruutu M. Toxicity and immediate allergenicity of latex gloves. *Clin Exp Allergy* 1993;23:618-23.
- Douglas R, Czarny D, Morton J, O'Hehir RE. Prevalence of IgE mediated allergy to latex in hospital nursing staff. *Aust NZ J Med* 1997;27:165-9.
- Vandenplas O, Delwiche J-P, Evrard G, Aimont P, Van Der Brempt X, Jamart J, et al. Prevalence of occupational asthma due to latex among hospital personnel. *Am J Respir Crit Care Med* 1995;151:54-60.
- Arellano R, Bradley J, Sussman G. Prevalence of latex sensitization among hospital physicians occupationally exposed to latex gloves. *Anesthesiology* 1992;77:905-8.
- Leung R, Ho A, Chan J, Choy D, Lai CKW. Prevalence of latex allergy in hospital staff in Hong Kong. *Clin Exp Allergy* 1996;27:167-74.
- Kibby T, Akl M. Prevalence of latex sensitization in a hospital employee population. *Ann Allergy Asthma Immunol* 1997;78:41-4.
- Yassin MS, Lierl MB, Fischer TJ, O'Brien K, Cross J, Steinmetz C. Latex allergy in hospital employees. *Ann Allergy* 1993;72:245-9.
- Turjanmaa K. Incidence of immediate allergy to latex gloves in hospital personnel. *Contact Dermatitis* 1987;17:270-5.
- Grzybowski M, Ownby DR, Peyser PA, Johnson CC, Schork MA. The prevalence of anti-latex IgE antibodies among registered nurses. *J Allergy Clin Immunol* 1996;98:535-44.
- Kaczmarek RG, Silverman BG, Gross TP, Hamilton RG, Kessier E, Arrowsmith-Lowe JT, et al. Prevalence of latex-specific IgE antibodies in hospital personnel. *Ann Allergy Asthma Immunol* 1996;76:51-6.
- Page E, Esswein EJ. Health hazard evaluation report #98-0096-2737: Exemplar St. Joseph Hospital, Denver, Colorado. Washington, DC: US Government Printing Office; 1998.
- Kujala VM, Reijula KE. Glove-induced dermal and respiratory symptoms among health care workers in one Finnish hospital. *Am J Ind Med* 1995;28:89-98.
- Slater JE. Latex allergy. *J Allergy Clin Immunol* 1994;94:139-49.
- Newman Taylor AJ, Longbottom JL, Pepys J. Respiratory allergy to urine proteins of rats and mice. *Lancet* 1977;2:847-9.
- Ohman JL Jr, Lowell FC, Bloch KJ. Allergens of mammalian origin. II: Characterization of allergens extracted from rats, mouse, guinea pig, rabbit pelts. *J Allergy Clin Immunol* 1975;55:16-24.
- Price JA, Longbottom J. Allergy to mice. Further characterization of two major mouse allergens (Ag 1 and Ag3) and immunohistochemical investigations of their sources. *Clin Exp Allergy* 1990;20:71-7.
- Swanson MC, Bubak ME, Hunt LW, Yunginger JW, Warner MA, Reed CE. Quantification of occupational latex aeroallergens in a medical center. *J Allergy Clin Immunol* 1994;94:445-51.
- Allmers H, Brehler R, Chen Z, Raulf-Heimsoth M, Fels H, Baur X. Reduction of latex aeroallergens and latex-specific IgE antibodies in sensitized workers after removal of powdered natural rubber latex gloves in a hospital. *J Allergy Clin Immunol* 1998;102:841-6.
- Tarlo SM, Sussman G, Contala A, Swanson MC. Control of airborne latex by use of powder-free latex gloves. *J Allergy Clin Immunol* 1994;93:985-9.
- Sussman GL, Liss GM, Keal K, Brown S, Cividino M, Siu S, et al. Incidence of latex sensitization among latex glove users. *J Allergy Clin Immunol* 1998;101:171-8.

47. Heilman DK, Jones RT, Swanson MC, Yunginger JW. A prospective, controlled study showing that rubber gloves are the major contributor to latex aeroallergen levels in the operating room. *J Allergy Clin Immunol* 1996;98:325-30.
48. Ohman JL, Hagberg K, MacDonald MR, Jones RR Jr, Paigen BJ, Kacerig JB. Distribution of airborne mouse allergen in a major mouse breeding facility. *J Allergy Clin Immunol* 1994;94:810-7.
49. Twigg JT, Agarwal MK, Dahlberg MJE, Yunginger JW. Immunochemical measurement of airborne mouse allergens in a laboratory animal facility. *J Allergy Clin Immunol* 1982;69:522-6.
50. Cockcroft A, Edwards J, McCarthy P, Andersson N. Allergy in laboratory animal workers. *Lancet* 1981;1:827-30.
51. Venables KM, Tee RD, Hawkins ER, Gordon DJ, Wale CJ, Farrer NM, et al. Laboratory animal allergy in a pharmaceutical company. *Br J Ind Med* 1988;45:660-6.
52. Slovak AJM, Hill RN. Does atopy have any predictive value for laboratory animal allergy? A comparison of different concepts of atopy. *Br J Ind Med* 1987;44:129-32.
53. Newill CA, Prenger VL, Fish JE, Evans R III, Diamond EL, Wei Q, et al. Risk factors for increased airway responsiveness to methacholine challenge among laboratory animal workers. *Am Rev Respir Dis* 1992;146:1494-500.
54. Hollander A, Heederik D, Brunekreef B. Work-related changes in peak expiratory flow among laboratory animal workers. *Eur Respir J* 1998;11:929-36.
55. Gross NJ. Allergy to laboratory animals: epidemiologic, clinical, and physiologic aspects, and a trial of cromolyn in its management. *J Allergy Clin Immunol* 1980;66:158-65.
56. Lutsky I, Newman I. Laboratory animal dander allergy. I. An occupational disease. *Ann Allergy* 1975;35:201-5.
57. Aoyama K, Ueda A, Manda F, Matsushita T, Ueda T, Yamauchi C. Allergy to laboratory animals: an epidemiological study. *Br J Ind Med* 1992;49:41-7.
58. Gautrin D, Infante-Rivard C, Ghezzi H, Malo JL. Incidence and host determinants of probable occupational asthma in apprentices exposed to laboratory animals. *Am J Respir Crit Care Med* 2001;163:899-904.
59. Gautrin D, Ghezzi H, Infante-Rivard C, Malo JL. Incidence and determinants of IgE-mediated sensitization in apprentices. A prospective study. *Am J Respir Crit Care Med* 2000;162:1222-8.
60. Archambault S, Malo JL, Infante-Rivard C, Ghezzi H, Gautrin D. Incidence of sensitization, symptoms, and probable occupational rhinoconjunctivitis and asthma in apprentices in apprentices starting exposure to latex. *J Allergy Clin Immunol* 2001;107:921-3.
61. Platts-Mills TAE, Heymann PW, Longbottom JL, Wilkins SR. Airborne allergens associated with asthma: particle sizes carrying dust mite and rat allergens measured with a cascade impactor. *J Allergy Clin Immunol* 1986;77:850.
62. Corn M, Koegel A, Hall T, Scott A, Newill A, Evans R. Characteristics of airborne particles associated with animal allergy in laboratory workers. *Ann Occup Hyg* 1988;32:435-46.
63. Davies GE, McArdle LA. Allergy to laboratory animals: a survey by questionnaire. *Int Arch Allergy Appl Immunol* 1981;64:302-7.
64. Davies GE, Thompson A, Niewola Z, Burrows GE, Teasdale EL, Bird DJ, et al. Allergy to laboratory animals: a retrospective and a prospective study. *Br J Ind Med* 1983;40:442-9.
65. Kujala VM, Pirila T, Kurup VP, Reijula KE. Nasal challenge, skin tests, and serum antibodies in the diagnosis of latex-induced occupational rhinitis. *Am J Rhinol* 1996;10:67-72.
66. Kujala V, Pirila T, Niinimäke A, Reijula K. Latex-induced allergic rhinitis in a laboratory nurse. *J Laryngol Otol* 1995;109:1094-6.
67. National Heart Lung and Blood Institute. National Asthma Education and Prevention Program, Expert Panel Report 2. Guidelines for the diagnosis and management of asthma. Bethesda (MD): US Department of Health and Human Services; 1997. p. 1-146.
68. Moscato G, Godnic-Cvar J, Maestrelli P. Statement on self-monitoring of peak expiratory flows in the investigation of occupational asthma: Subcommittee on Occupational Allergy of European Academy of Allergy and Clinical Immunology. *J Allergy Clin Immunol* 1995;96:295-301.
69. Bernstein DI. Clinical assessment and management of occupational asthma. In: Bernstein IL, Chang-Yeung M, Malo J-L, et al, editors. *Asthma in the workplace*. New York: Marcel Dekker Inc; 1994. p. 103-19.
70. Crapo R, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing-1999. *Am J Respir Crit Care Med* 2000;61:309-29.
71. O'Brien IM, Newman-Taylor AJ, Burge PS, Harries MG, Fawcett IW, Pepys J. Toluene diisocyanate-induced asthma. II. Inhalation challenge tests and bronchial reactivity studies. *Clin Allergy* 1979;9:7-15.
72. DeZotti R, Gubian F, Larese F. Challenge test with latex gloves and allergic symptoms in hospital workers. *Eur J Allergy Clin Immunol* 1996;31:47-8.
73. Baur MB, Chen Z, Liebers V. Exposure-response relationships of occupational inhalative allergens. *Clin Exp Allergy* 1998;28:537-44.
74. Lagier F, Badier M, Martigny J, Charpin D, Vervloet D. Latex as aeroallergen. *Lancet* 1990;336:516-7.
75. Laoprasert N, Swanson MC, Jones RT, Hunt LW, Reed CE, Schroeder DR, et al. How much latex aeroallergen is required to induce symptoms in latex-sensitive health care workers? [abstract]. *J Allergy Clin Immunol* 1998;101:S166.
76. Vandenplas O, Delwichee J-P, Depelchin S, Sibille Y, Vande Weyer R, Delaunois L. Latex gloves with a lower protein content reduce bronchial reactions in subjects with occupational asthma caused by latex. *Am J Respir Crit Care Med* 1995;151:887-91.
77. Ho A, Chan H, Tse KS, Chan-Yeung M. Occupational asthma due to latex in health care workers. *Thorax* 1996;51:1280-2.
78. Moneret-Vautrin DA, Debra JC, Kohler C, Stringini R, Kanny G, Guillaumot A, et al. Occupational rhinitis and asthma to latex. *Rhinology* 1994;32:198-202.
79. Pisati G, Baruffini A, Bernabeo F, Stanizzi R. Bronchial provocation testing in the diagnosis of occupational asthma due to latex surgical gloves. *Eur Respir J* 1994;7:332-6.
80. Pisati G, Baruffini A, Bernabeo F, Falagiana P. Environmental and clinical study of latex allergy in a textile factory. *J Allergy Clin Immunol* 1998;101:327-9.
81. Fish JE, Ankin MG, Kelly JF, Peterman VI. Comparison of responses to pollen extract in subjects with allergic asthma and non-asthmatic subjects with allergic rhinitis. *J Allergy Clin Immunol* 1980;65:154-61.
82. Ahmed T, Fernandez RJ, Wanner A. Airway responses to antigen challenge in allergic rhinitis and allergic asthma. *J Allergy Clin Immunol* 1981;67:135-45.
83. Baur X, Huber H, Degens PO, Allmers H, Ammon J. Relation between occupational asthma case history, bronchial methacholine challenge, and specific challenge test in patients with suspected occupational asthma. *Am J Ind Med* 1998;33:114-22.
84. Chang-Yeung M, Lam S, Koerner S. Clinical features and natural history of occupational asthma due to western red cedar (*Thuja plicata*). *Am J Med* 1982;72:411-5.
85. Paggiaro P, Bacci E, Paoletti P, Bernard P, Dente FL, Marchetti G, et al. Bronchoalveolar lavage and morphology of the airways after cessation of exposure in asthmatic subjects sensitized to toluene diisocyanate. *Chest* 1990;98:536-42.
86. Brugnami G, Marabini A, Siracusa A, Abbritti G. Work-related late asthmatic response induced by latex allergy. *J Allergy Clin Immunol* 1995;96:457-64.