

*Original article***Natural rubber latex allergy among health care workers: A systematic review of the evidence**

Jean Bousquet, MD,^a Antoine Flahault, MD,^b Olivier Vandenplas, MD,^c Jacques Ameille, MD,^d Jean-Jacques Duron, MD,^e Corine Pecquet, MD,^f Karine Chevré, PhD,^g and Isabella Annesi-Maesano, DSc, PhD^g Montpellier and Paris, France, and Yvoir, Belgium

Background: Natural rubber latex is a recognized allergen, but a recent meta-analysis failed to find any association between latex exposure and allergy in health care workers (HCWs).

Objectives: A meta-analysis was carried out under the auspices of the French National Regulatory Authority to assess the allergic risk induced by latex gloves in HCWs.

Methods: The risk of work-related exposure to latex for the development of latex allergy was assessed. Prevalence and incidence rates of latex sensitization or allergy were compared in HCWs and in the general population. Exposure-response relationships were assessed in HCWs.

Results: Latex allergy was found in 4.32% (range, 4.01% to 4.63%) of HCWs and in 1.37% (range, 0.43% to 2.31%) of the general population. Latex-positive skin prick test responses ranged from 2.1% to 3.7% in the general population and from 6.9% to 7.8% for the HCWs. HCWs exposed to latex showed an increased risk of hand dermatitis (odds ratio [OR], 2.46; 95% CI, 2.11-2.86), asthma or wheezing (OR, 1.55; 95% CI, 1.15-2.08), rhinoconjunctivitis (OR, 2.73; 95% CI, 1.97-3.81), and at least one generic symptom (OR, 1.27; 95% CI, 1.09-1.47).

Sensitization to latex was significantly associated with asthma and rhinoconjunctivitis. By contrast, exposure to latex was not associated with a significantly increased risk of positive skin prick test responses to latex (OR, 1.47; 95% CI, 0.94-2.30).

Conclusion: HCWs have an increased risk of sensitization and allergic symptoms to latex.

Clinical implications: Prevention of latex allergy in HCWs is needed. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Latex allergy, health care workers, IgE, skin test, exposure-response relationship, meta-analysis

Natural rubber latex (NRL) is a recognized allergen, and NRL allergy has become an important occupational health problem for health care workers (HCWs).^{1,2} The prevalence of NRL allergy has been estimated at up to 36% in HCWs,¹ and NRL exposure might be one of the leading causes of occupational asthma in this population. Some medical facilities have chosen to convert entirely to NRL-free gloves,³ but others have found this to be a problem logistically.

A recent meta-analysis discovered that HCWs exposed to NRL were at no higher risk of an IgE-mediated sensitization than the general or nonexposed population.⁴ However, this review has been subject to several criticisms.⁵ It was therefore important to perform an independent meta-analysis under the auspices of the French National Regulatory Authority (Agence Française de Sécurité Sanitaire des Produits de Santé) concerning NRL allergy in HCWs.

The Agence Française de Sécurité Sanitaire des Produits de Santé convened a group of experts to assess the allergic risk induced by NRL gloves in HCWs. The aim of the work was to quantify the risk of work-related exposure to NRL for the development of NRL allergy among HCWs by (1) comparing the prevalence and incidence rates of NRL sensitization or allergy in HCWs with those observed in non-HCWs, (2) assessing whether there is a dose-response relationship in HCWs between the intensity of NRL glove exposure and the risk of NRL sensitization or NRL allergy symptoms, and (3) examining the effect of glove-changing policies on NRL sensitization or allergy.

METHODS**Search strategy**

Studies were sought from MEDLINE (1966 to December 31, 2003) and EMBASE (1974 to December 31, 2003). However, some articles published in 2004 relevant to the present analysis were not included because we required assessment of the full year for the meta-analysis.

The following key words were used: latex [AND] glove [AND] (hypersensitivity [OR] sensitization [OR] allergy [OR] asthma [OR] dermatitis [OR] rhinitis [OR] conjunctivitis [OR]

From ^aService des Maladies Respiratoires, Inserm U454, University Hospital, Montpellier; ^bEpidemiology, Information Systems, Modelisation, Inserm U707, University Pierre and Marie Curie, Medical School Saint-Antoine, Paris; ^cService de Pneumologie, Cliniques Universitaires UCL de Mont-Godinne, Yvoir; ^dthe Unit of Occupational Health, Hôpital Raymond Poincaré, Assistance Publique des Hôpitaux de Paris; ^eService de Chirurgie Digestive et Générale, CHU Pitié Salpêtrière, Paris; ^fCentre d'Allergologie, Hôpital Tenon, Paris; and ^gEpidemiology of Allergic and Respiratory Diseases (EPAR), INSERM U707, University Pierre and Marie Curie, Medical School Saint-Antoine, Paris.

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Reprint requests: Jean Bousquet, MD, Clinique des Maladies Respiratoires, Inserm U454, Hôpital Arnaud de Villeneuve, University Hospital, 34295 Montpellier Cedex 5, France. E-mail: jean.bousquet@wanadoo.fr.

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Abbreviations used

HCW: Health care worker
 NRL: Natural rubber latex
 OR: Odds ratio

rhino-conjunctivitis) [AND] (health care worker, [OR] dentist [OR] nurse [OR] surgery).

Selection criteria

The data were extracted in a standardized manner. All studies meeting the search strategy were examined by 2 of the experts, reviewed by the chair of the group, and discussed during plenary sessions of the group.

Exclusion criteria

For more information, see the [reference list](#) in the Online Repository at www.jacionline.org. Exclusion criteria were as follows: studies with methodology making it impossible to assess prevalence or incidence, studies with an insufficient clinical description of the study population, studies in chamber exposure and provocation challenges, letters to the editor, abstracts of meetings, case reports, and review articles.

Assessment of IgE-mediated allergic reactions to NRL

There are discrepancies concerning the more accurate tests that are required to confirm an IgE-mediated allergic reaction to NRL.^{6,7} Moreover, skin tests can be performed with homemade extracts or extracts that can be standardized, but in the present article we did not distinguish between tests, and therefore we considered skin prick tests to latex and serum latex-specific IgE measurement similarly, regardless of the method used.

Studies assessing the prevalence of NRL allergy in HCWs by comparison with non-HCWs

The risk of sensitization and clinical allergy to NRL among HCWs was estimated by comparing the prevalence rates of these outcomes in surveys of HCWs with those found in the general adult population. For this analysis, the following additional inclusion criteria were required:

- The study protocol included the objective assessment of IgE-mediated sensitization to NRL (skin prick testing, serum specific IgE measurement, or both).
- The assessment of NRL sensitization was not restricted to a subset of the target population (eg, symptomatic subjects).
- Surveyed workers did not use low-protein NRL gloves, powder-free NRL gloves, or both.
- Studies in which only symptomatic subjects had an assessment of an IgE-mediated reaction to NRL were not included in the analysis.
- The analysis of NRL sensitization, NRL allergy, or both in the general population was restricted to the survey of adults.
- Studies in which children were tested were excluded.

Exposure-response relationship for NRL allergy in HCWs

In this analysis we examined the effect of NRL exposure on the different symptoms induced by NRL (systemic, skin, nasal, and/or bronchial), on NRL IgE levels and on bronchial hyperreactivity in HCWs.

Effect of interventions on NRL allergy in HCWs

Very few impact studies were carried out, and therefore a meta-analysis could not be performed.

Statistical analysis

A computerized meta-analysis was performed by combining prevalence rates and odds ratios (ORs). It consisted of 4 steps: (1) identifying all relevant studies, (2) assessing study quality, (3) summarizing the results with a standardized form, and (4) studying heterogeneity.⁸ The Quality of Reporting of Meta-analyses statement for meta-analysis was used⁹ because the inclusion of only a subset of all available evidence in a meta-analysis might introduce biases.

Combined prevalence rates of NRL allergy with 95% CIs were obtained from the separate prevalence rates of the considered studies according to whether HCWs were hospital workers without any job specification or had a specific job to perform, as well as for the general adult population. Combined prevalence rates were successively separated according to the presence or absence of information on the participation rate in the studies. Estimates and variances from each study were extracted from publications or calculated if data were available. The combined estimate was then obtained as a (variance based) weighted average of the individual estimates.¹⁰

Relative risk could not be used because it cannot be computed in case-control studies. Combined ORs and CIs were obtained for the ecologic exposure to NRL at work, as well as (1) one or more symptoms (hand dermatitis, wheezing-asthma, or rhinoconjunctivitis) or (2) positive results on NRL skin prick tests. The methods for pooling 2×2 contingency tables used either the Mantel-Haenszel approach or the exact method when a small sample size ($n < 5$) was prevalent in at least 1 cell.

The heterogeneity within the results of the studies was assessed to evaluate the comparability of the single studies. The results were then summarized by using the Breslow-Day heterogeneity test.¹¹

RESULTS

Cross-sectional studies assessing the prevalence of NRL allergy in HCWs by comparison with non-HCWs

The rate of sensitization and clinical allergy to NRL among HCWs and the general population is presented in [Table 1](#).¹²⁻⁶⁷ The data of all of these studies are detailed in [Tables E1](#) and [E2](#) found in the Online Repository at www.jacionline.org.

The mean percentage of NRL-positive skin prick test responses was higher in HCWs than in the general population. Results of skin prick tests carried out with commercial extracts are positive in 2.5% to 13% of HCWs and in 0.5% to 5% of the general population. The results of skin prick tests carried out with homemade extracts are more variable.

The mean percentage of NRL-specific IgE in the serum was higher in HCWs than in the general population. It is difficult to compare the data within the 3 groups for the following reasons: (1) IgE was measured by the use of different methods (CAP, AlaSTAT, and RAST), and (2) there is no effect of time of study and the level of NRL IgE.

IgE-mediated allergy to NRL ranges from 1.4% to 1.65% in the general population and from 4.1% to 5.0% in

TABLE I. Combined prevalence rates according to the meta-analysis of cross-sectional studies

Population	n	Positive SPT response to NRL, % (95% CI)	n	Specific IgE to NRL, % (95% CI)	n	Allergy to NRL, % (95% CI)
HCWs						
Hospital personnel (all jobs)		6.87 (6.40-7.34)		6.95 (6.19-7.73)		4.06 (3.21-4.41)
Known participation rate	5925	7.46 (6.80-8.12)	2965	8.23 (7.26-9.20)	5291	3.93 (3.47-4.39)
Unknown participation rate	4810	6.15 (5.48-6.82)	936	2.88 (1.84-3.92)	5112	4.19 (3.65-4.73)
Specific jobs		7.76 (6.88-8.64)		5.59 (4.75-6.43)		4.97 (4.32-5.62)
Known participation rate	3131	7.19 (6.29-8.09)	2403	6.37 (5.40-7.34)	2795	5.37 (4.63-6.11)
Unknown participation rate	387	12.4 (9.20-15.60)	425	1.18 (0.15-2.21)	672	2.83 (1.59-4.07)
All HCWs		7.09 (6.67-7.51)		6.30 (5.73-6.87)		4.32 (4.01-4.63)
Known participation	9056	7.19 (6.29-8.09)	5368	6.37 (5.40-7.34)	8086	4.79 (4.12-5.46)
Unknown participation	5197	6.62 (5.95-7.29)	1361	1.98 (1.19-2.77)	5784	4.03 (3.53-4.53)
General adult population						
Nonselected populations	1301	2.08 (1.31-2.85)	16,803	10.27 (9.82-10.72)	583	1.37 (0.43-2.31)
Allergic subjects, asthmatic subjects, or both	640	3.73 (3.53-3.93)		NA	424	1.65 (0.45-2.28)

n, Sample size of the pooled sample; SPT, skin prick test; NA, not applicable.

TABLE II. Criteria of the meta-analysis concerning the exposure-response relationship for NRL allergy in HCWs**Primary guides**

Did the study address a focused clinical question? YES, the authors addressed the effect of NRL use on health in HCWs.

Were the criteria used to select articles for inclusion appropriate? YES

Secondary guides

Is it unlikely that important and relevant studies were missed? YES, for the chosen period (1980 to December 31, 2003), the search strategy was extensive (see above).

Was the validity of the included studies appraised? YES, the studies were graded for quality of allocation concealment. No other methodologic criteria were used.

Were the assessments of studies reproducible? YES, the authors report that inclusion criteria were determined *a priori* but they do not report the results or agreements (κ) on the results.

Were the results similar from study to study?

YES, there appears to be no statistical heterogeneity for the prevalence rates.

NO, there was heterogeneity for combined OR, except in the case of asthma and wheezing.

What are the results?

What are the overall results of the overview? Prevalence rates are consistent. Only asthma and wheezing are related to NRL exposure.

How precise are the results? (See above)

Will the results help me in caring for my patients?

Can the results be applied to my patients' care? YES, this is the first valid meta-analysis carried out by an independent group of experts. It is a useful summary of the studies on the effects of NRL in HCWs. Although there might be some controversies because of the poor quality of most data based on ecologic assessment of NRL gloves, the results can be used in practice and lead to improved managed care. However, the study emphasizes the need for appropriately designed prospective trials.

Were all clinically important outcomes considered? YES, appropriate health outcomes were selected. However, standardized definitions of the outcomes are needed. Furthermore, quality of life is important to be considered but has never been studied.

Are the benefits worth the harms and costs? This very important issue has not been addressed by the study but might help an independent group to provide the effectiveness of NRL primary prevention.

the HCW population. However, there are only 3 studies available concerning the general population, and a statistical analysis is therefore not possible. In the HCW population no change in the prevalence of NRL allergy was detected between 1990 and 2003.

Prospective studies assessing the incidence of NRL allergy in HCWs

Very few cohort studies have been carried out to assess the incidence of sensitization and allergic symptoms during exposure.⁶⁸⁻⁷⁰ These studies fail in their attempt

to reach a conclusion because the number of subjects with an NRL allergy was found to be very low.⁶⁸⁻⁷⁰ Also, the protein content of NRL usually decreased during the study.⁶⁸⁻⁷⁰

Exposure-response relationship for NRL allergy in HCWs

For the meta-analysis, several questions were raised (Table II). The analysis assessing the relationship of NRL exposure to health complaints or IgE-mediated allergy in HCWs (epidemiologic evidence) is presented

TABLE III. Risk of NLR exposure for the development of symptoms or an IgE-mediated allergic reaction to NLR**3, A: NLR exposure and hand dermatitis**

Mantel-Haenszel method

Study	n	OR	95% CI
Amin et al, 1998 ⁷¹	83	3.23	1.03-10.11
Holter et al (hand dermatitis), 2002 ⁷²	3104	6.18	4.18-9.16
Kujala and Reijula, 1995 ⁷³	390	1.37	0.90-2.08
Larese Filon et al, 2001 ²⁰	1165	5.47	2.93-10.22
Lonnroth and Shahnnavaz, 1998 ⁷⁴	1172	1.08	0.80-1.46
Mizutani et al, 1995 ⁷⁵	1190	5.09	2.05-12.63
Page et al (hand dermatitis), 2000 ²¹	503	5.90	3.09-11.27
Saary et al, 2002 ⁷⁸	228	0.84	0.50-1.43
Schmid et al, 2002 ⁷⁹	226	2.29	0.77-6.84
Tarlo et al (eczema), 1997 ⁴¹	100	0.60	0.23-1.56
Verna et al, 2003 ²³	197	2.56	1.40-4.68
Meta-analysis	8358	2.46	2.11-2.86

Breslow-Day test of homogeneity of OR between studies: $P < .0001$.**3, B: NLR exposure and asthma or wheezing**Exact method because of small sample size ($n < 5$)

in at least 1 cell of a study

Study	n	OR	95% CI
Galobardes et al (asthma), 2001 ¹⁷	514	1.94	0.73-6.53
Gautrin et al (asthma), 2002 ⁵⁹	769	0.80	0.37-1.59
Holter et al (wheezing), 2002 ⁷²	3104	2.81	1.09-9.22
Page et al (asthma),* 2000 ²¹	506	0.47	0.04-3.31
Saary et al (asthma),* 2002 ⁷⁸	228	1.31	0.32-6.29
Tarlo et al (asthma),† 1997 ⁴¹	100	∞	0.24-∞
Zaza et al (asthma), 1994 ⁸⁰	1489	1.90	1.18-3.00
Meta-analysis	6710	1.55	1.15-2.08

Exact OR homogeneity test: $P < .14$.

*Cell with expected value of less than 5.

†Cell with a 0 value.

3, C: NRL exposure and at least one generic symptomExact method because of small sample size ($n < 5$)

in at least 1 cell of a study

Study	n	OR	95% CI
de Groot et al, 1998 ³⁶	66	0.24	0.07-0.79
Di Lorenzo et al, 2002 ¹⁶	196	1.83	0.99-3.41
Galobardes et al,* 2001 ¹⁷	515	∞	0.12-∞
Garabrant et al, 2001 ¹²	5512	1.11	0.93-1.32
Verna et al, 2003 ²³	197	2.56	1.35-4.92
Zaza et al, 1994 ⁸⁰	1775	5.87	2.19-22.18
Meta-analysis	8261	1.27	1.09-1.47

Exact OR homogeneity test: $P < .0001$.

*Cell with a 0 value.

in Table III.* The results of this meta-analysis indicate that HCWs exposed to NRL show an increased risk of hand dermatitis, asthma or wheezing, rhinoconjunctivitis, and

3, D: NLR exposure and rhinoconjunctivitisExact method because of small sample size ($n < 5$)

in at least 1 cell of a study

Study	n	OR	95% CI
Gautrin et al, 1997 ⁵⁹	769	0.40	0.08-1.31
Holter et al, 2002 ⁷²	3104	7.53	3.53-19.17
Page et al, 2000 ²¹	497	2.27	1.24-4.27
Saary et al,* 2002 ⁷⁸	132	∞	2.36-∞
Tarlo et al, 1997 ⁴¹	100	2.02	0.58-9.02
Meta-analysis	4602	2.73	1.97-3.81

Exact OR homogeneity test: $P < .0001$.

*Cell with a 0 value.

3, E: NLR exposure and positive skin prick test responses

Mantel-Haenszel method

Study	n	OR	95% CI
Di Lorenzo et al, 2002 ¹⁶	176	0.90	0.34-2.36
Galobardes et al, 2001 ¹⁷	514	1.89	0.82-4.31
Gautrin et al,* 1997 ⁵⁹	758	1.31	0.14-11.78
Saary et al, 2002 ⁷⁸	228	2.59	0.69-9.67
Schmid et al, 2002 ⁷⁹	226	0.42	0.11-1.56
Sussman et al,* 1998 ⁶⁸	433	1.06	0.15-7.61
Tarlo et al,† 1997 ⁴¹	95	11.37	0.65-198.1
Meta-analysis	2430	1.47	0.94-2.30

Breslow-Day OR homogeneity test: $P < .14$.

*One cell with an expected value of less than 5.

†One cell with a 0 value, Logit estimation.

at least one generic symptom. Sensitization to NLR was significantly associated with asthma and rhinoconjunctivitis. Although an OR of greater than 1 was observed also between exposure to NRL and positive skin prick test responses to NRL, this did not reach statistical significance (95% CI, 0.94-2.30; Table IV).

Effect of interventions on NRL allergy in HCWs

Two retrospective studies of incident cases among HCWs have assessed the effect of NRL prevention programs in hospitals.^{81,82} They showed a reduction in new cases of NLR allergy after the substitution of powdered gloves for nonpowdered gloves. However, the observed decrease in NRL allergy might have been an artifact of a rising number of identified cases before glove changes in relation to an increased awareness of the risk in the medical community since the early 1990s.

Similar findings have been reported in population-based studies derived from compensation agencies. A temporal association between decreasing numbers of claims for suspected NRL allergy and the implementation of prevention programs that involved the substitution of powdered NRL gloves with powder-free NRL gloves has been documented in Canada⁸³ and Germany.⁸⁴

Two studies have reported the findings of repeated cross-sectional surveys conducted before and after glove changes.^{78,79} The change in glove policy was accompanied

*References 12, 16, 17, 20, 21, 23, 36, 41, 51, 68-80.

TABLE IV. NRL sensitization and symptoms**4, A: Asthma or bronchial hyperreactivity**Exact method because of small sample size ($n < 5$)
in at least 1 cell of a study

Study	n	OR	95% CI
Archambault et al (asthma),* 2001 ⁷⁰	110	9.84	1.21-72.40
Mace et al, 1998 ⁵¹	147	5.32	1.65-18.97
Nettis et al,* 2002 ⁷⁶	295	40.56	11.56-167.3
Page et al,* 2000 ²¹	510	0.48	0.04-3.37
Potter et al, 2001 ⁷⁷	717	2.91	1.89-4.49
Meta-analysis		3.95	2.74-5.70

Exact OR homogeneity test: $P < .0001$.

*One cell with an expected value of less than 5.

4, B: RhinoconjunctivitisExact method because of small sample size ($n < 5$)
in at least 1 cell of a study

Study	n	OR	95% CI
Archambault et al,* 2001 ⁷⁰	110	2.73	0.24-18.99
Mace et al, 1998 ⁵¹	224	6.83	2.60-18.12
Nettis et al,* 2002 ⁷⁶	295	5.83	2.38-14.62
Meta-analysis		5.70	3.13-10.39

Exact OR homogeneity test: $P < .7$.

*One cell with an expected value of less than 5.

by a significant decrease in the proportion of students reporting glove-related symptoms (pruritus, urticaria, and rhinoconjunctivitis). However, the number of subjects and the participation of the target population to the study were low in one study.⁷⁸

The tertiary prevention of patients with suspected or diagnosed NRL allergy was found in 2 studies in which patients with NRL allergy were placed in NRL-free environments.^{14,85}

DISCUSSION

The general impression is that in the United States and many European countries, the “epidemic” of latex allergy has passed, and therefore this present study might not be of great interest. However, latex-free hospitals are still rare in these countries, and in most countries throughout the world, there lack preventative measures. The present study is therefore important in terms of practical changes in policies and behaviors that might be carried out at health care facilities.

Prevalence of sensitization and allergy to NRL in HCWs by comparison with non-HCWs

The systematic review of prevalence studies indicates that “pooled” prevalence rates of positive skin prick test responses and clinical allergy to NRL are 3 to 3.5 times higher among HCWs than in unselected samples of the

general adult population. However, other factors must be taken into consideration:

- The rate of specific IgE antibodies against NRL was surprisingly low in HCWs.
- These results should be viewed with caution because the methods used (skin tests or IgE measurements) vary and the results of studies with skin tests to NRL and NRL IgE measurement are not consistent.
- Moreover, only 3 studies have examined NRL allergy in unselected samples of the general population.
- The “healthy worker effect”⁸⁶ cannot be studied in this population because this effect would have led to the underestimation of the prevalence of NRL allergy-sensitization in HCWs.

Overall, it can be concluded that there is epidemiologic evidence that HCWs have an increased risk of NRL sensitization and allergy.

Prospective studies assessing the incidence of NRL allergy

Data are insufficient, and although they suggest that exposure to NRL gloves is associated with an increased risk of NRL sensitization, more data are required to make a valid conclusion.

Exposure-response relationship for NRL allergy in HCWs

A meta-analysis was used to assess the risk factors for the development of NRL allergy in HCWs because individual studies had insufficient power to come to any firm conclusions.⁸⁷ However, meta-analyses might generate misleading results by ignoring meaningful heterogeneity among studies,⁸⁸ entrenching the biases in individual studies, and introducing further biases through the process of finding studies and selecting results to be pooled. We presented both heterogeneity and homogeneity but strengthened the validity of results for which data pooling was homogeneous. Moreover, it is known that the existence of publication bias can influence the conclusions of a meta-analysis because of the heterogeneity of the studies. Epidemiologic (observational) surveys assessing the risk factors for NRL allergy might be less affected by publication bias in comparison with randomized trials. Therefore it seems that the data can be used in a reasonable manner to elicit public views on the provision of health care.⁸⁹

Assessment of the exposure-response relationship in prevalence studies shows that HCWs exposed to NRL have an increased risk of hand dermatitis (OR, 2.46), asthma or wheezing (OR, 1.55), rhinoconjunctivitis (OR, 2.73), and at least one generic symptom (OR, 1.27) by comparison with nonexposed HCWs. Sensitization was significantly associated with asthma and rhinoconjunctivitis. By contrast, exposure to NRL was not associated with a significantly increased risk of positive skin prick test responses to NRL. Although the data represent more than 2000 individuals, more than 4000 individuals would

need to be analyzed to achieve a statistical power. This is the first meta-analysis showing a relationship between NRL exposure in HCWs and allergy. However, these results do not accord with those published by Garabrant and Schweitzer,⁴ possibly because (1) Garabrant and Schweitzer did not exclude some of the articles because of methodologic problems, (2) they did not perform a quantitative meta-analysis, (3) they did not estimate the risks by pooling the indicators, and (4) more articles were analyzed in the present study, which was performed some years later.

Although some studies have examined the relative risk of disease (in particular asthma) in subjects exposed to certain occupational agents (eg, flour) by comparison to a reference population, there is no other meta-analysis that has assessed the exposure-response relationships in prevalence studies.

Effect of interventions on NRL allergy in HCWs

The effect of interventions cannot be assessed because of the restriction of data derived from retrospective studies.

The effect of powder-free gloves was examined in only one prospective cohort study,⁶⁸ which failed to show the protective effect of powder-free NRL gloves. Although powder-free gloves allow a reduction in the level of airborne NRL allergens and glove-related symptoms, the lack of appropriate study does not allow any conclusions to be reached on powder-free gloves.

Conclusion

This systematic review carried out by an independent group of experts suggests that HCWs have an increased risk of sensitization and allergic symptoms to NRL, whereas there is only weak evidence that switching to low-powdered NRL gloves results in a decrease in the incidence of sensitization because of methodologic limitations of available data. However, the NRL allergen content of gloves currently manufactured might decrease the risk of sensitization of HCWs. The possibility that using low-powdered NRL gloves might reduce sensitization and diseases has thus been insufficiently examined and needs to be studied extensively in the future if low-powdered NRL continues to be used in preference to standard latex gloves.

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