

Latex Gloves with a Lower Protein Content Reduce Bronchial Reactions in Subjects with Occupational Asthma Caused by Latex

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Latex gloves have been documented as causing rhinitis and asthma. Using inhalation challenges, we evaluated the bronchial response to hypoallergenic gloves in eight health care workers with latex-induced asthma. The subjects were exposed to the powdered latex gloves causing asthma at work and various brands of gloves with a lower protein content, either low-powdered, nonpowdered, or powdered. Exposure to hypoallergenic gloves resulted in the absence (in six subjects) or a significant reduction (in two subjects) of bronchial response. The effects of repeated exposure to hypoallergenic gloves was assessed in two subjects who did not demonstrate changes in peak expiratory flow rates and nonspecific bronchial responsiveness to histamine. This study on a limited number of patients suggests that the use of hypoallergenic gloves could be an effective means of reducing the risk of asthmatic reactions in health care workers with latex-induced asthma when complete avoidance cannot be achieved. The long-term effect of exposure as well as the widespread use of hypoallergenic gloves warrant further investigation on larger cohorts of subjects. **Vandenplas O, Delwiche J-P, Depelchin S, Sibille Y, Vande Weyer R, Delaunoy 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.**

Materials containing latex have been documented as causing IgE-mediated hypersensitivity reactions ranging from mild urticaria to life-threatening anaphylaxis after cutaneous, mucosal, or visceral exposure (1). Recently, it has been demonstrated that water-soluble protein allergens from latex gloves are transferred to cornstarch powder (2) and that they may act as aeroallergens causing rhinitis and asthma (3, 4).

Although removal from exposure should be strongly recommended to health care workers with occupational asthma caused by latex gloves (5), procedures aimed at reducing the level of airborne latex allergens in the working environment should be considered if complete avoidance is not possible for professional reasons. Such procedures include all staff members since exposure may result from inhalation of latex-contaminated cornstarch powder particles disseminated in the air by colleagues using latex gloves (6). The widespread use of latex-free gloves is so far precluded by the fact that vinyl gloves provide unsatisfactory mechanical properties, and other synthetic elastomer gloves are considerably more expensive. The protein and allergen content of latex gloves can be lowered by washing the gloves during the

manufacturing process (7, 8). Furthermore, reducing the amount of cornstarch powder used would reduce airborne latex allergens. Latex gloves with a lower protein content are sold as "hypoallergenic" gloves although this product labeling is not precisely defined and regulated (9, 10).

The aim of this study was to determine whether commercial brands of latex gloves with a lower protein content and various amounts of cornstarch powder, hereafter referred to as "hypoallergenic" gloves (10), could be effective in preventing asthmatic reactions in subjects with latex-induced asthma. We used inhalation challenges and workplace exposure in order to assess the bronchial response to these hypoallergenic gloves as compared with the gloves causing asthma at work.

Eight health care workers with a history of latex-glove-related asthma were used in this study. They were informed of the aims, risks, and procedures of the study and they signed a statement of informed consent. The study protocol was approved by the local ethics committee. The subjects underwent inhalation challenges with the gloves causing asthma at work as well as with hypoallergenic gloves. They were also skin-tested with extracts of the various brands of gloves used during inhalation challenges.

The gloves causing asthma at work were powdered Triflex® gloves (Baxter Healthcare Corp., Valencia, CA) (Gloves A). The hypoallergenic gloves were low-powdered Triflex® gloves (Baxter Healthcare) (Gloves B), non-powdered Nutex® gloves (Ansell Medical) (Gloves C), and powdered Sensi-Touch® gloves (Ansell GmbH, München, Germany) (Gloves D).

Spirometry was assessed before each challenge exposure and thereafter at regular intervals for at least 6 h (11). Peak expiratory flow rates

(Received in original form June 20, 1994)

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(PEFR) were monitored hourly until bedtime and on the next morning. Each participant underwent the following sequence of inhalation challenges. On the first day (control day), the subjects were asked to handle vinyl gloves for 1 h in a 5-m³ challenge room. At the end of the control day, the baseline level of nonspecific bronchial responsiveness to doubling concentrations of histamine (from 0.03 to 16 mg/ml) was determined. The concentration of histamine causing a 20% fall in FEV₁ (PC₂₀) was interpolated on individual dose-response curves. Significant bronchial hyperresponsiveness was defined as a PC₂₀ value < 16 mg/ml (12). On separate days, the subjects were challenged with the latex gloves that caused asthma at work (Gloves A) and with at least two of the three brands of hypoallergenic latex gloves (Gloves B, C, and D). The subjects wore vinyl gloves in order to prevent any direct cutaneous contact with latex gloves. They were asked to open the glove bags and to shake each pair of gloves continuously for 3 min. The duration of exposure was progressively increased (5, 10, 15, 30, 60 min) on the same day until FEV₁ fell by more than 20% or until a cumulative exposure of 4 h was completed. Exposure to latex gloves could not be blinded since the trade names were printed on the gloves and/or on the paper bags. Inhalation challenges with hypoallergenic gloves were performed in a random order at 4-wk intervals. The eight subjects remained occupationally exposed to latex during the study. The interval of time between workplace exposure and inhalation challenges was kept constant. Workplace exposure and treatment remained unchanged throughout the study. When hypoallergenic gloves did not induce significant changes in FEV₁, histamine PC₂₀ was reassessed 6 h postexposure in order to detect an increase in nonspecific bronchial responsiveness (13). Changes in histamine PC₂₀ more than 3-fold from one assessment to the next were considered significant according to the reproducibility of the test in our laboratory. Postchallenge histamine PC₂₀ was not measured in Subjects 2 and 7 whose baseline PC₂₀ values were < 0.03 mg/ml. Two subjects (Subjects 1 and 2) were exposed for 2 h to native cornstarch powder (Fluidamid R444P; Roquette Frères, Lestrem, France) by tipping the powder from one tray to another (14). These challenges confirmed that asthmatic reactions elicited by powdered latex gloves were not related to the cornstarch powder.

Considering that some hypoallergenic gloves did not cause asthma during the laboratory challenge tests, we tried to assess the effect of repeated exposure to these gloves. PEFR were recorded in Subject 3 who worked in an operating room where Gloves D were exclusively used and in Subject 4 who was exposed to Gloves D (40 pairs of gloves for 1 h) on 7 consecutive days. Histamine PC₂₀ was measured before and after these exposures.

The subjects were skin-prick-tested using eight common inhalant allergens, negative (diluent) and positive (histamine chlorhydrate, 1 mg/ml) controls. Cutaneous reactions were read after 15 min and considered posi-

tive when ≥ 3 mm as compared with negative control values. Atopy was defined by a positive test for at least one of the common allergens. Skin prick tests were also performed with the following extracts: (1) sterile powdered vinyl glove (Baxter Healthcare) extract as a negative control, (2) commercial extract of ammoniated natural latex at 1:100 wt/vol (Stallergènes SA, Brussels, Belgium), and (3) extracts from the four brands of latex gloves used in the inhalation challenge protocol. The glove extracts were prepared by cutting pieces (about 3 × 3 cm) of gloves incubated overnight at 37° C in PBS solution (1 mg glove/1 ml PBS). The eluate was centrifuged at 4,000 × *g* for 10 min, and the supernatant was filtered through a 0.22-μm Millipore filter (Millipore Corp., Bedford, MA). The protein concentration of the final extracts was determined in duplicate on three samples of each brand of gloves using the bicinchoninic acid method (Pierce, Rockford, IL) with bovine serum albumin as the standard. The mean content in protein of the extracts was: Gloves A, 102 μg/ml; Gloves B, 55 μg/ml; Gloves C, 56 μg/ml; Gloves D, 54 μg/ml. Based on the protein concentration of the glove eluate, the estimated content in extractable protein of the various brands of gloves was 51, 27.5, 28, and 27 μg/g of glove, respectively. Skin tests with undiluted latex and glove extracts were performed in duplicate and read blindly except for Subject 1.

The baseline clinical and functional features of the subjects are summarized in Table 1. The subjects had been exposed to latex gloves for 1 to 10 yr before onset of asthma. Five of the eight subjects were atopic; Subject 2 had evidence of airway obstruction, and all subjects showed bronchial hyperresponsiveness to histamine.

The results of inhalation challenges with the different brands of gloves are detailed in Table 2. Inhalation challenges with the powdered gloves used at work (Gloves A) elicited an immediate asthmatic reaction in five subjects (Subjects 1, 3, 5, 6, and 8) and a dual reaction in three subjects (Subjects 2, 4, and 7). Asthma was preceded by symptoms of rhinoconjunctivitis.

The hypoallergenic gloves with a lower content in protein whether low-powdered (Gloves B, 27.5 mg/g of glove), nonpowdered (Gloves C, 28 mg/g), or powdered (Gloves D, 27 mg/g) did not induce significant changes in FEV₁ or in histamine PC₂₀ in six subjects. Low-powdered Gloves B induced a dual asthmatic reaction in Subject 2 after 180 min of exposure (Figure 1) and an isolated late reaction in Subject 7 after 240 min of exposure (Figure 2). The duration of exposure required to induce an asthmatic reaction with Gloves B was, however, substantially longer than the exposure causing asthma with Gloves A (20 min for Subject 2 and

TABLE 1
BASELINE CLINICAL AND FUNCTIONAL FEATURES OF THE SUBJECTS

Subject No.	Sex	Age (yr)	Atopy*	Smokers	Occupation	Glove-related Symptoms	Duration of Exposure before Asthma (yr)	Treatment	FEV ₁		FEV ₁ /FVC (%)	Baseline Histamine PC ₂₀ (mg/ml)
									(L)	(% pred)		
1	F	27	+	No	Nurse (Pulmonary unit)	A, R, C, U	3	C, HA	3.3	101	77	0.70
2	F	29	+	No	Nurse (Surgery unit)	A, R, C, U	1	S, B	2.2	85	64	< 0.03
3	M	35	+	No	Surgeon	A, R, U	5	C, B	4.1	100	72	1.38
4	F	33	-	No	Nurse (Intensive care unit)	A, R, C, U	8	S, B, HA	2.8	93	80	0.35
5	F	35	+	Ex	Nurse (Internal medicine)	A, R, C, U	5	-	2.9	104	75	4.00
6	F	34	-	No	Nurse (Internal medicine)	A, R, C	10	B, HA	3.1	96	77	0.28
7	F	26	-	No	Nurse (Operating room)	A, R, C, U	1	S, B, HA	2.9	91	75	< 0.03
8	F	29	+	No	Nurse (Intensive care unit)	A, R, C, U	9	HA	3.6	119	85	0.40

Definition of abbreviations: A = asthma; R = rhinitis; C = conjunctivitis; U = urticaria; C = inhaled cromoglycate; HA = oral H₁-antagonist; S = inhaled steroid; B = inhaled bronchodilators.

* Defined as the presence of one or more positive skin reactions to common inhalant allergens.

TABLE 2
RESULTS OF INHALATION CHALLENGES

Subject No.	Type of Glove*	Duration of Exposure (min)	Maximal Fall in FEV ₁ †		Pattern of Reaction	Nonasthmatic Symptoms‡	Postchallenge Histamine PC ₂₀ § (mg/ml)
			Early	Late			
1	A (powdered)	120	27 (0)	10 (300)	Immediate	R, C	ND
	B (low-powdered)	240	—	—	—	—	0.46
	C (non-powdered)	240	—	—	—	—	0.35
2	A (powdered)	20	29 (0)	29 (480)	Dual	R, C	ND
	B (low-powdered)	180	24 (15)	35 (360)	Dual	R	ND
	C (non-powdered)	240	—	—	—	—	ND
	D (powdered)	240	—	—	—	R (mild)	ND
3	A (powdered)	120	23 (15)	—	Immediate	R (mild)	ND
	C (non-powdered)	240	—	—	—	—	0.74
	D (powdered)	240	—	—	—	—	1.32
4	A (powdered)	90	33 (15)	26 (300)	Dual	R, C	ND
	B (low-powdered)	240	—	—	—	—	0.29
	D (powdered)	240	—	—	—	—	0.18
5	A (powdered)	120	26 (0)	—	Immediate	R, C	ND
	B (low-powdered)	240	—	—	—	—	3.70
	D (non-powdered)	240	—	—	—	—	2.40
6	A (powdered)	120	32 (15)	—	Immediate	R, C	ND
	B (low-powdered)	240	—	—	—	—	0.21
	D (powdered)	240	—	—	—	—	0.16
7	A (powdered)	70	28 (0)	29 (360)	Dual	R, C	ND
	B (low-powdered)	240	—	23 (360)	Late	R (mild)	ND
	C (non-powdered)	240	—	—	—	—	ND
	D (powdered)	240	—	—	—	R (mild)	ND
8	A (powdered)	120	24 (15)	—	Immediate	R, C	ND
	B (low-powdered)	240	—	—	—	—	0.47
	D (powdered)	240	—	—	—	—	0.32

Definition of abbreviations: R = rhinitis; C = conjunctivitis.

* The gloves used during inhalation challenges are those causing asthma at work (Gloves A) and hypoallergenic gloves (Gloves B, C, and D); see text for trade names.

† Expressed as the percent change from preexposure value and presented in detail when $\geq 10\%$. The interval of time (minutes) between the end of challenge exposure and the lowest FEV₁ value is shown in parentheses.

‡ Symptoms experienced by the subjects during inhalation challenges.

§ Nonspecific bronchial hyperresponsiveness was assessed 6 h after the end of exposure to hypoallergenic gloves in the absence of significant changes in FEV₁. Post-challenge histamine PC₂₀ was not assessed in Subjects 2 and 7 whose baseline values were < 0.03 mg/ml.

70 min for Subject 7). Subjects 2 and 7 also experienced mild rhinitis during exposure to powdered Gloves D, although prolonged exposure to this brand of gloves (4 h on 2 consecutive days for Subject 2) did not cause significant bronchial response. Repeated exposure to Gloves D did not result in significant changes in PEF_R or in histamine PC₂₀ in Subjects 3 and 4. No systemic adverse reaction was observed during inhalation challenges.

Results of skin tests are presented in Table 3. None of the subjects showed a positive reaction to the vinyl glove extract. Extracts of hypoallergenic gloves induced a significantly smaller skin reaction than did powdered Gloves A causing asthma at work. There was no strict relationship between the size of the cutaneous reaction and the protein content of the extracts. Latex gloves causing asthma at work (Gloves A, 102 μ g/ml) produced a stronger reaction than did the commercial latex extract even though the latter had a markedly higher protein content (2,400 μ g/ml). Although the extracts of hypoallergenic gloves B, C, and D had similar contents in protein, Gloves B elicited a larger skin reaction than did Gloves C and D. Skin reactivity to the extracts of hypoallergenic gloves did not appear to predict whether a bronchial response occurred. All subjects had positive skin test reactions to Gloves B, whereas only two developed an asthmatic reaction. A significant skin reaction was elicited by Gloves C in three of eight subjects and by Gloves D in six of eight subjects, although none of these subjects developed an asthmatic reaction.

* * *

The results of inhalation challenges show that hypoallergenic latex gloves with a lower protein content significantly reduced the risk of developing an asthmatic reaction in subjects with occupational asthma caused by latex. Exposure to hypoallergenic gloves, either powdered or not, did not elicit bronchial response in six of eight subjects. In the remaining two subjects (Subjects 2 and 7), hypoallergenic gloves resulted in a reduction in bronchial response since the duration of exposure causing an asthmatic reaction with low-powdered Gloves B (180 and 240 min, respectively) was significantly longer than that of Gloves A used at work (20 and 70 min, respectively). Interestingly, Subject 7 showed an isolated late reaction after exposure to Gloves B, whereas she developed a dual reaction after exposure to Gloves A. This observation confirms that isolated late reactions can result from exposure to low doses of airborne latex as previously demonstrated for common inhalant allergens (15).

At present, there is no standardized method for determining the allergenic potential of latex materials, mainly because relevant latex allergens are not precisely identified (2, 4, 16, 17). *In vitro* methods for quantitative assessment of latex allergens offer promise (10), but it remains uncertain whether their results correlate with the *in vivo* effects of latex materials. Therefore, we used inhalation challenges in order to evaluate *in vivo* the effects of exposure to hypoallergenic gloves at the level of the respiratory target organ. We assessed both the changes in FEV₁ and in histamine PC₂₀ in order to detect bronchial reaction to hypoallergenic

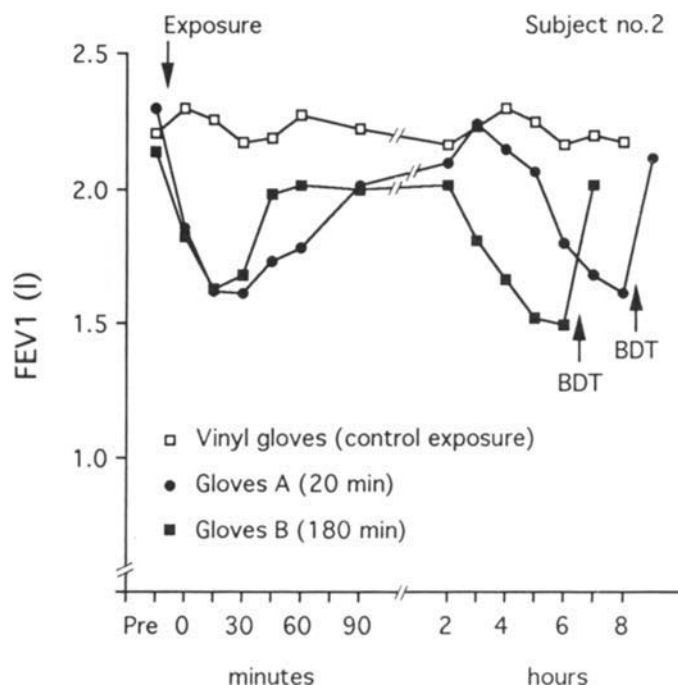


Figure 1. The results of inhalation challenges in Subject 2 are illustrated. The changes in FEV₁ after exposure to vinyl gloves (Control) (open squares), to the powdered gloves causing asthma at work (Gloves A) (closed circles), and to nonpowdered hypoallergenic gloves (Gloves B) (closed squares) are shown. A dual asthmatic reaction was observed after exposure to Gloves A for 20 min and after exposure to Gloves B for 180 min. Challenges with hypoallergenic Gloves C and D did not induce significant changes in FEV₁ and are not presented. See text for trade names of gloves. BDT = inhaled bronchodilator (salbutamol, 200 µg).

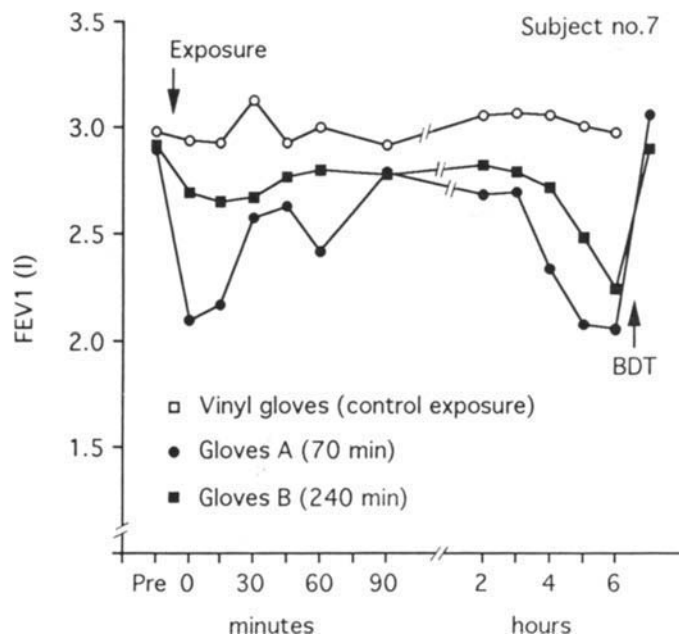


Figure 2. The results of inhalation challenges in Subject 7 are illustrated. The changes in FEV₁ after exposure to vinyl gloves (Control) (open squares), to the powdered gloves causing asthma at work (Gloves A) (closed circles), and to nonpowdered hypoallergenic gloves (Gloves B) (closed squares) are shown. A dual asthmatic reaction was observed after exposure to Gloves A for 70 min. Exposure to Gloves B for 240 min elicited an isolated late asthmatic reaction. Challenges with hypoallergenic Gloves C and D did not induce significant changes in FEV₁ and are not presented. See text for trade names of gloves. BDT = inhaled bronchodilator (salbutamol, 200 µg).

TABLE 3
RESULTS OF SKIN PRICK TESTS

Subject No.	Histamine (1 mg/ml)	Skin Reaction (mean diameter, mm)				
		Latex* (2,400 µg/ml)	Glove A† (102 µg/ml)	Glove B (55 µg/ml)	Glove C (56 µg/ml)	Glove D (54 µg/ml)
1	4	3	8	4	3	4
2	3	4	11	6	4	4
3	4	4	8	4	—	3
4	4	4	6	4	—	3
5	3	4	6	3	—	—
6	3	4	7	5	4	—
7	3	4	7	5	—	3
8	5	4	6	3	—	3
Mean	3.6	3.8	7.3	4.2	1.4	2.5
SD	0.7	0.1	1.6	1.0	1.9	1.6

* Commercial extract (Stallergènes SA, Brussels, Belgium); the protein content of undiluted extracts is presented between parentheses.

† Including those causing asthma at work (Gloves A) and hypoallergenic gloves (Gloves B, C, and D); the extract of vinyl gloves (negative control) elicited < 1 mm reactions in all subjects; see text for trade names of gloves.

gloves since an increase in nonspecific bronchial hyperresponsiveness may represent an early marker of bronchial response to sensitizing occupational agents in the absence of changes in airways caliber (13). We also investigated the effect of repeated exposure to hypoallergenic gloves in two subjects who did not demonstrate significant changes in PEFR or in histamine PC₂₀. Nevertheless, the effects of long-term exposure to hypoallergenic warrants further investigation.

The subjects were challenged by handling latex gloves (3) because this method is more likely to reproduce the mode of exposure at the workplace than the inhalation of nebulized glove extracts proposed by some investigators (18, 19). Challenge tests were standardized only by specifying the number of gloves handled per minute. However, the subjects served as their own controls, which may be expected to minimize possible differences in glove handling. It is likely that this exposure protocol created more intense levels of exposure than did hospital work. This is supported by the fact that Subject 2 developed an asthmatic reaction after a 20-min challenge with Gloves A, whereas monitoring of PEFR demonstrated that she had to be exposed for several hours at work in order to experience asthma. Quantitative assessment of airborne allergens would be useful in order to compare the level of exposure during challenge tests to that found at the workplace (6).

Comparison of our results for protein assay with previously published data is difficult because most studies do not provide the protein concentration in glove eluates. Furthermore, differences in the methods used to obtain glove extracts are likely to influence the resulting amount of protein. The figures found in this study are in the range of reported protein contents, which ranged from 25 to 410 µg/g of glove (20, 21), and they confirmed that hypoallergenic gloves have a lower protein content (7, 8). However, the content in total protein does not reflect accurately the allergenic content of gloves (7, 20). Skin testing confirmed that hypoallergenic gloves elicited weaker skin reactions than did regular gloves (7, 8). However, we cannot draw definitive conclusions with regard to the correlation between skin tests and inhalation tests because we did not titrate skin reactivity using serial dilutions of glove extracts. Furthermore, the discrepancy between skin testing and inhalation challenges could be explained at least in part by differences in the level of nonspecific bronchial responsiveness of the subjects. Thus, Cockcroft and colleagues (22) demonstrated that the factors that can influence the bronchial response to allergens include the dose of allergen, the degree of immunologic sensi-

zation of the subject, and the level of nonspecific bronchial responsiveness. Subjects 2 and 7, who developed an asthmatic reaction after exposure to hypoallergenic Gloves B, showed the highest level of bronchial hyperresponsiveness to histamine (Table 1). Although each subject could not be tested with the three brands of hypoallergenic gloves, the amount of cornstarch powder that may enhance the generation of airborne latex allergens did not appear to play a crucial role since low-powdered Gloves B induced asthma in two subjects, whereas powdered Gloves D did not. Further studies are needed to determine whether the absence of bronchial response to hypoallergenic gloves is due to a lower content in all allergens, to qualitative differences in allergen composition, to individual differences in the pattern of IgE response against latex allergens, or to the combination of several factors.

Although obtained in a limited number of patients, our results indicate that hypoallergenic gloves with a lower protein content could be useful in reducing the risk of asthmatic reactions in subjects with latex-induced asthma. Because asthmatic reactions can result from indirect exposure to airborne latex allergens, hypoallergenic gloves should be used by all staff members working in the environment of affected subjects when complete avoidance cannot be implemented. However, the safety of hypoallergenic gloves should be properly evaluated for each individual worker because highly sensitive subjects may still develop asthma after prolonged exposure. The proportion of those subjects with high bronchial reactivity to latex is unknown. Although the results of inhalation challenges in the laboratory represent a useful initial guide, the effects of long-term exposure remain to be investigated. Moreover, before the benefits of widespread use of hypoallergenic gloves can be evaluated, studies on larger cohorts of subjects are required. This study outlines the need for further characterization and quantification of relevant latex allergens, which could help manufacturers in reducing the allergen content of gloves below the level that elicits reactions in already sensitized subjects and hopefully below the level that initiates sensitization.

Acknowledgment: The writers wish to thank Mrs. Geneviève Evrard for her excellent technical assistance in performing inhalation challenges.

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