

Quantified environmental challenge with absorbable dusting powder aerosol from natural rubber latex gloves

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Background: There are few data that link quantified natural rubber latex (NRL) absorbable dusting powder aerosol to biologic responses in NRL-sensitized subjects. **Methods:** We conducted a study on 30 health care workers with possible occupational asthma. All the subjects but 2 had a positive skin prick test result with NRL extract. Quantified environmental challenge (QEC) with powdered NRL gloves was performed in a 7-m³ chamber. The patients would don and discard a pair of gloves every 3 minutes up to a maximum of 60 minutes. The concentrations of NRL aeroallergen were measured by a competitive IgE immunoassay. Ocular and respiratory symptoms and pulmonary function were monitored. **Results:** Twenty-six patients (87%) had rhinoconjunctivitis, 19 (63%) had an asthmatic response (responders), and 1 patient developed eosinophilic bronchitis on QEC. The asthmatic responses were of the early type in 15 patients, dual in 3, and isolated late in 1 patient. The duration of exposures sufficient to elicit asthmatic responses varied from 3 to 114 cumulative minutes. Time-weighted average NRL aeroallergen concentrations during QEC with responders ranged between 199 and 1107 ng/m³. NRL concentrations measured at various time points during exposure were reproducible. Measured concentrations of NRL aeroallergen between responders (677 ± 281 ng/m³) and nonresponders (611 ± 351 ng/m³) were not statistically different. The cumulative inhaled NRL aeroallergen dose required for an asthmatic response ranged between 25 to 515 ng. **Conclusion:** The total dose of latex aeroallergen eliciting an asthmatic response during QEC was mostly affected by the duration of exposure and varied widely from person to person. (J Allergy Clin Immunol 2003;111:788-94)

Key words: Aeroallergen, immunochemical assay, natural rubber latex, occupational asthma, specific inhalation challenge

Over the last few years, natural rubber latex (NRL) has emerged as a significant sensitizer contributing to asthma, particularly among health care workers.¹⁻³ Specific inhalation challenge (SIC) to NRL aerosols has been proposed as the gold standard for establishing a diagnosis of

Abbreviations used

ADP:	Absorbable dusting powder
BH:	Bronchial hyperresponsiveness
FEIA:	Fluoroenzyme immunoassay
NRL:	Natural rubber latex
OA:	Occupational asthma
PC ₂₀ :	Provocative concentration of methacholine causing a 20% fall in FEV ₁
QEC:	Quantified environmental challenge
SIC:	Specific inhalation challenge
SPT:	Skin prick test

NRL-induced asthma.^{4,5} Several methods have been used for SIC with NRL, including SIC with in-house aqueous NRL glove extract^{6,7} or commercially available NRL extract.⁸ These methods, however, do not simulate natural exposure. It has been demonstrated that latex proteins bind to cornstarch particles and that NRL allergens can be extracted from glove powder.⁹ Absorbable dusting powder (ADP) aerosols that carry NRL allergenic proteins become airborne when powdered latex gloves are used, with resulting latex allergen exposure to the conjunctiva and upper and lower airways.⁹ Therefore, SIC with an ADP aerosol from NRL gloves can be considered a more natural form of exposure to latex aeroallergen from powdered NRL gloves.¹⁰⁻¹³ Recently, a hooded exposure chamber has been described, which allows a semiquantitative evaluation of respiratory allergy to latex.¹⁴

Standardization of SIC with NRL would require measurements of NRL allergens generated during SIC that mimics workplace exposure. The aim of this study was to quantify NRL bio-aerosol concentrations in a challenge chamber and measure biologic outcomes (respiratory symptoms and lung function) after exposure to latex aeroallergens carried on ADP from NRL gloves.

METHODS

Subjects

The study included 30 health care workers who were referred for investigation of possible occupational asthma (OA) between 1999 and 2001. All subjects were still working at the time of the study, and they were continually exposed at work to airborne latex allergens from NRL gloves. Four subjects, however, worked in hospital rooms, namely the intensive care unit and the renal dialysis unit, in which only powder-free NRL gloves and vinyl gloves had been used for the last 4 months before the quantified environmental challenge (QEC).

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All patients underwent a standardized diagnostic assessment that included a medical and occupational questionnaire, skin prick tests (SPTs) with NRL, measurements of NRL-specific IgE antibodies, assessment of bronchial hyperresponsiveness (BH) to methacholine, and QEC with NRL gloves powdered with ADP.

These subjects had developed work-related symptoms of cough, chest tightness, shortness of breath, or wheezing. They had been exposed to NRL for between 28 and 300 months. The mean duration of asthma symptoms in these patients was 32.3 months (range, 1 to 120 months). Sneezing, itching, and runny nose preceded the development of asthma symptoms in most subjects. Twenty-three subjects were taking inhaled corticosteroids on a regular basis and short-acting or long-acting inhaled β -agonists at the time of the study. The subjects were told to refrain from taking inhaled bronchodilators for at least 12 hours before inhalation testing, and the dose of inhaled corticosteroids was taken at least 24 hours before QEC.

Clinical history

The clinical history was collected by 1 allergist (S.Q.) by using an open questionnaire, which included the following items: nature and frequency of respiratory (shortness of breath, wheezing, cough, and chest tightness), nasal (blocked nose, rhinorrhea, and sneezing), and ocular (itching, watery eyes, and redness) symptoms; characterization of exposure at work; association of symptoms with exposure to a specific agent or task; smoking habits; and history of atopic disease.¹⁵ Additional questions were asked regarding the presence of work-related cutaneous symptoms (itching, redness, and urticaria), anaphylactic reactions, and allergy to fruits and nuts (kiwi, avocado, banana, and chestnut).

Skin prick tests

NRL extract was prepared from fresh nonammoniated latex obtained from *Hevea brasiliensis* trees. After successive steps of washing and concentration by ultrafiltration, the extract was sterilized and glycerinated. It yielded a protein and allergen profile similar to Food and Drug Administration reference extract E8 as determined by electrophoretic methods and IgE immunoblotting. The total protein content of this extract was 400 μ g/mL. SPTs were performed with this characterized nonammoniated NRL extract, negative (normal saline) and positive (histamine chlorhydrate 10 mg/mL) controls, and 21 common inhalant allergens (ALK-Abelló, Madrid, Spain). A wheal diameter 3 mm or greater with erythema, compared with the saline control, was defined as a positive reaction. Atopy was defined as the presence of a positive skin reaction to at least 1 of the common allergens.

Total and specific IgE determination

Total serum IgE level was measured by Pharmacia CAP System IgE fluoroenzyme immunoassay (FEIA) according to the manufacturer's instructions (Pharmacia, Uppsala, Sweden). Nonammoniated NRL-specific IgE concentrations were determined by Pharmacia CAP System FEIA. A result higher than 0.35 kU/L was regarded as positive.

Lung function tests

A spirometer (Datospir 100; Sibelmed, Barcelona, Spain) was used for pulmonary function measurements. Spirometry was performed according to recommended standards.¹⁶ Bronchial hyperresponsiveness to methacholine was assessed by using the procedure described by Cockcroft et al¹⁷ with some modifications.¹⁸ Provocative concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀) values of less than 16 mg/mL were considered to reflect significant BH.⁵ For subjects who did not react to a concentration of methacholine of 16 mg/mL, a PC₂₀ of 32 mg/mL was assigned for statistical analysis of results.

QEC

QEC with NRL gloves was performed in a 7-m³ challenge chamber according to a previously described protocol.¹³ Monitored parameters included conjunctival and respiratory symptoms, pulmonary function, exposure duration, and asthmatic reaction type (ie, immediate, late, or dual). This challenge chamber was equipped with vacuum exhaust and high-efficiency particle arrest filtration, which removed residual particles after each challenge. Spirometry was performed just before QEC and thereafter every 10 minutes for the first hour and then hourly for a total of at least 9 hours after the end of exposure. On a control day, the subjects were asked to handle vinyl gloves up to 15 minutes to ensure that fluctuations of FEV₁ were less than 10%. On the next day, the subjects were challenged by handling powdered NRL gloves. ADP aerosols that carry NRL allergenic proteins were generated by donning, doffing, and shaking a pair of inside-out powdered NRL gloves every 3 minutes up to a maximum of a 60-minute exposure interval. Patients wore vinyl gloves to prevent direct skin contact with NRL. QECs were performed with the same batch (2V9J003) of nonsterile medical examination gloves commonly used in our hospital (Flexam powdered; Allegiance Healthcare Corporation, McGaw Park, Ill). Exposure times were progressively increased (ie, 3, 6, 15, 30, and 60 minutes) until FEV₁ fell by 20% or more or until a cumulative exposure of 114 minutes was completed. Methacholine PC₂₀ was assessed again 24 hours after NRL exposure to detect changes in BH.¹⁹ A greater than 3-fold reduction in postchallenge PC₂₀ value compared with the control value was considered a significant change.¹⁹ During QEC, bronchial (cough, wheezing, and shortness of breath), ocular (swelling, itching and watery eyes), and nasal (itching, sneezing, congestion, and rhinorrhea) symptoms were registered.

Measurement of total dust

The concentrations of total dust particles during QEC were measured with an aerosol monitor (DustTrack model 8520; TSI, St Paul, Minn), and the results were expressed in mg/m³.

Quantitation of latex aeroallergen

NRL aeroallergens were captured with a volumetric air sampler and polytetrafluoroethylene filters (Quan-Tec-Air, Inc, Rochester, Minn). The sampling flow rate was 2.5 L/s through a 0.3- μ m filter rated 99.9% efficient. The NRL aeroallergens were quantified (ng/m³) as a time-weighted average by a competitive IgE immunoassay by using sera from latex sensitive individuals.²⁰ Briefly, latex allergens were extracted from the filters in 1 mL of 0.1 mol/L phosphate buffer containing 0.2% bovine serum albumin and 0.01% sodium azide and assayed immunochemically by an inhibition technique. Extracts of the filters or a laboratory reference standard from latex gloves (Bodyguards; TK Glove Products Co, Ltd, Huntington Beach, Calif) competed with solid-phase reference latex glove allergens for specific IgE antibodies obtained from 3 sensitized health care workers. Radioiodinated affinity-purified rabbit anti-IgE was used for detection.²¹ The results were calculated with logistic regression and expressed as mass protein per cubic meter of air, based on a glove extract that contained 7 mg of protein per milliliter, as determined by the bicinchoninic acid protein assay and calculated by linear regression, compared with a standard of bovine serum albumin. The limit of detection of the assay was 50 ng/sample, allowing detection of approximately 5 ng in 1 m³ of air. The gloves used for the QEC were tested to check that they had a high allergen content (more than 100 μ g of latex allergen per g of rubber).

Statistical analysis

Subjects with a positive or with a negative QEC result were compared by using the Wilcoxon rank sum test for numeric variables

TABLE I. Demographic, clinical, and occupational data of the study patients (n = 30)

Gender (female %)	27 (90%)
Age (y)*	36.1 ± 8.62
Atopy	25 (83.3%)
Nonsmokers	28 (93.3%)
Total serum IgE (kU/L)*	240.3 ± 332.08
Occupation	
Nurses	15 (50.0%)
Nurse aides	7 (23.3%)
Physicians	1 (3.3%)
Laboratory staff	2 (6.7%)
Paramedics	5 (16.7%)
Duration of exposure (mo)*	125.6 ± 83.78
Duration of asthma symptoms (mo)*	32.3 ± 33.44
FEV ₁ (% predicted)	95.5 ± 8.41
BH (PC ₂₀ methacholine)	
< 1 mg/mL	10 (33.3%)
1 - <4 mg/mL	10 (33.3%)
4 - 16 mg/mL	6 (20.0%)
> 16 mg/mL	4 (13.3%)
Positive SPT to aeroallergens	
NRL	28 (93%)
Grass pollen	21 (70%)
House dust mites	11 (37%)
Cat or dog dander	6 (20%)
Molds	5 (17%)
Positive SPT to fruits/nuts	
Kiwi	18 (60%)
Avocado	18 (60%)
Banana	12 (40%)
Chestnut	11 (37%)

*Results expressed as mean ± SD.

TABLE II. Work-related symptoms (n = 30)

Contact urticaria	28 (93.3%)
Rhinitis	29 (96.7%)
Conjunctivitis	20 (66.7%)
Anaphylaxis	2 (6.7%)
Asthma	
Shortness of breath	25 (83.3%)
Wheezing	23 (76.7%)
Cough	19 (63.3%)
Chest tightness	14 (46.7%)
Medication	
Short-acting inhaled β_2 -agonist	26 (86.7%)
Long-acting inhaled β_2 -agonist	9 (30.0%)
Inhaled corticosteroids	23 (76.7%)
Clinical allergy to fruits/nuts	13 (43.3%)

and the chi-square or Fisher exact tests for categoric variables. The sensitivity of the clinical history, SPT and specific IgE against NRL latex, and assessment of BH to methacholine was estimated as the proportion of subjects showing a positive test result among those with a positive QEC result. Specificity was calculated as the proportion of subjects with a negative test result among those with a negative QEC result. The positive predictive value of diagnostic

tests was defined as the proportion of subjects with a positive QEC among those with a positive test result, and the negative predictive value was the proportion of subjects with a negative QEC result among those with a negative test result. Correlation between total dust and NRL aeroallergen concentrations during QEC was done by using Spearman correlation. All statistical tests were 2-tailed. A *P* value of .05 or less was considered significant.

RESULTS

The baseline demographic and clinical characteristics of the subjects are shown in Table I. The nature of the work-related symptoms are shown in Table II. Twenty-six (87%) subjects experienced rhinoconjunctivitis on QEC, and 19 subjects (63%) had an asthmatic response. The asthmatic responses were immediate in 15 individuals, immediate and late (dual) in 3, and 1 isolated late response was observed in 1 subject. The QEC was repeated in this subject, and again an isolated late asthmatic response was observed. One individual developed cough due to eosinophilic bronchitis on QEC with NRL gloves²² (this patient was not included in the analysis of asthmatic responses). The duration of exposures sufficient to elicit asthmatic responses was 3, 6, 15, 30, and 60 minutes in 2, 5, 7, 2, and 3 individuals, respectively. The maximum fall in FEV₁ during asthmatic responses ranged between 20% and 43% (median, 23%).

There were no differences between subjects showing an asthmatic response (positive QEC) or no asthmatic response (negative QEC) with regard to age, duration of exposure to NRL at work, nature and duration of work-related symptoms, use of asthma medications, atopy, and frequency of positive SPT to fruits/nuts. Awareness of a relationship between exposure to NRL and asthma symptoms was more common in subjects with a positive QEC result (68%) than in patients with a negative QEC result (20%, *P* < .05).

Assessment of BH to methacholine at the time of the study did not discriminate between subjects with a negative or positive QEC result. BH was absent in 1 (10%) of 10 subjects with a negative QEC and in 2 of 19 (10%) subjects with a positive QEC result. In these 2 subjects, however, BH to methacholine was demonstrated 24 hours after QEC with NRL gloves (PC₂₀ values of 6.5 and 1 mg/mL, respectively). Noticeably, both subjects worked in hospital rooms in which powdered NRL gloves had been removed 4 months ago.

Baseline PC₂₀ methacholine values were significantly lower (*P* < .05) in subjects with a positive QEC result (4.7 ± 9.80 mg/mL; range, 0.08 to 32 mg/mL) than in those with a negative QEC result (8.4 ± 10.03 mg/mL; range, 0.25 to 32 mg/mL). After QEC, PC₂₀ methacholine values in subjects with a positive QEC result (1.2 ± 1.84 mg/mL; range, 0.21 to 6.5 mg/mL) were again lower (*P* < .05) than in those with a negative QEC result (10.5 ± 14.40 mg/mL; range, 1.8 to 32 mg/mL). Thus, an average 3.9-fold reduction (*P* = .005) in PC₂₀ methacholine from baseline values was observed after positive QEC, whereas no significant changes were observed in subjects who showed no response to QEC.

A positive SPT result to NRL was found in all subjects with NRL-induced asthma but also in 8 (80%) of the 10 subjects without NRL-induced OA. These 8 subjects, however, had rhinitis and contact urticaria caused by NRL. A positive NRL-specific IgE (CAP) result was detected in 18 (95%) of the subjects with NRL-induced asthma and in 6 (60%) of subjects without NRL-induced asthma ($P < .05$). Nevertheless, the concentrations of NRL-specific IgE antibodies were not significantly different in subjects with positive QEC results (6.7 ± 12.31 kU/L; range, 0 to 54.5 kU/L) or negative QEC results (4.1 ± 8.39 kU/L; range, 0 to 27.5 kU/L). For a specific IgE concentration cutoff of 0.35 kU/L the sensitivity and specificity of the CAP assay were 95% and 40%, respectively. For the diagnosis of NRL-induced asthma, a cutoff of 0.75 kU/L could be more appropriate, showing a slight reduction in sensitivity (84%) but a greater specificity (50%).

The sensitivity, specificity, and positive and negative predictive values of these diagnostic tests as compared to QECs with NRL gloves are presented in Table III. When the postchallenge assessment of BH to methacholine was taken into account, the sensitivity of BH increased from 90% to 100% and the negative predictive value from 33% to 100%. The best diagnostic performance was attained by combining the SPT response to NRL and a PC₂₀ methacholine value less than 4 mg/mL at baseline (sensitivity, 84% and specificity, 70%).

The powdered NRL gloves used throughout the challenges demonstrated high allergen content (208 μ g per g of rubber), providing steady state NRL aeroallergen concentrations shortly after initiating the challenge. A steady state concentration of total dust was reached after 3 minutes of exposure and was sustained over the challenge protocol. The average total dust concentration during asthmogenic QEC was 0.086 ± 0.043 mg/m³ (range, 0.024 to 0.168 mg/m³). Airborne NRL concentrations measured at various time points were reproducible. The cumulative dose of NRL aeroallergen associated with asthma genesis was therefore predominantly determined by the duration of exposure. A significant correlation was found between total dust concentrations and NRL aeroallergen concentrations during QEC ($r = 0.7$, $P < .01$). Time-weighted average NRL aeroallergen concentrations were not statistically different between individuals demonstrating asthmatic responses (677 ± 281 ng/m³; range, 199 to 1107 ng/m³) or nonresponse (611 ± 351 ng/m³; range, 312 to 1351 ng/m³) to the inhalation challenge.

More than 70% of the responders were sufficiently dosed at 15 minutes. Given the time-weighted average concentration range and minutes of exposure, cumulative dose indexes can be calculated as nanograms per unit of exposure ($0.5 \text{ L/breath} \times 15 \text{ breaths/minute} \times \text{duration of exposure minute} \times 10^{-3} \text{ m}^3/\text{L} \times \text{NRL aeroallergen concentration ng/m}^3 = \text{dose of NRL aeroallergen in ng}$).²³ The cumulative inhaled latex dose indexes for patients demonstrating asthmatic responses on QEC ranged between 25 and 515 ng (mean, 196.8 ± 166.83 ng) and

TABLE III. Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values of diagnostic tests for NRL-induced asthma compared with QEC (n = 29 subjects)

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Clinical history	89	50	77	71
SPT to NRL	100	20	70	100
NRL-IgE (CAP)	95	40	75	80
BH to methacholine	90	10	65	33
SPT to NRL plus BH to methacholine*	84	70	84	70

*Considering PC₂₀ less than 4 mg/mL.

for those with negative QEC ranged between 198 and 1155 ng (mean, 465 ± 340.02 ng).

DISCUSSION

OA caused by IgE-mediated allergy to airborne NRL has been described in health care workers,^{1,4-13} workers in glove manufacturing²⁴ and doll manufacturing plants,²⁵ and among employees in the textile industry.^{26,27} The prevalence of NRL-induced OA among these work forces varies from 2.5% to 10%.^{1,24-26} The need to confirm the diagnosis of OA by objective methods has been stressed.²⁸ The diagnosis of NRL-induced OA among health care workers may be particularly cumbersome because the variability of NRL exposure in different areas and depending on specific job tasks, the possibility of indirect exposure to NRL,²⁹ and exposure to other asthmogenic agents present in the workplace³⁰ may complicate the establishment of the work-relatedness.

In the assessment of health care workers with suspected NRL-induced asthma, the clinical history performed by a standardized questionnaire combined with an interview by an experienced physician⁴ or by consensus judgment provided by 4 physicians⁵ has been found to have a high sensitivity (87% and 92%) but a low specificity (32% and 14%), respectively, as compared to SIC. Our results confirm that the clinical history provides a high sensitivity (89%) but a low specificity (50%). In our study, the positive (77%) and the negative predictive values (71%) of the clinical history were similar to those reported by Vandeplass et al⁵ (75% and 50%, respectively), possibly because the prevalence of OA in our study (63%) was very similar to that in the aforementioned study (69%).

We found that SPT with a characterized extract of NRL has a high sensitivity (100%) but a low specificity (20%). SPT is very useful to detect IgE-mediated sensitization to NRL, but it is not as useful in confirming the diagnosis of NRL-induced OA, because 30% of the subjects with positive SPT results had negative QEC results. However, a negative SPT result with NRL is very useful to rule out NRL-induced OA (negative predictive value, 100%). The usefulness of the determination of NRL-spe-

cific IgE has not been previously investigated in the diagnosis of NRL-induced asthma. Baur et al³¹ found symptoms of the upper and lower respiratory tract and NRL-specific IgE antibodies only in health care workers employed in rooms with detectable latex aeroallergen levels. In addition, a significant decrease of NRL-specific IgE concentrations was observed in sensitized subjects after removal of powdered latex gloves.³² Nevertheless, as reported with other occupational allergens, some individuals can react positively on skin or serologic IgE tests and not demonstrate allergen-induced asthma.

Despite the fact that all the subjects included in this study had 1 or more symptoms suggestive of work-related asthma, 4 of them showed no BH to methacholine at baseline and were not taking any asthma medication. Two of these subjects developed BH to methacholine after QEC with NRL. In another subject, eosinophilic bronchitis without asthma was diagnosed, and, in the remaining subject, BH to methacholine was absent even after QEC, indicating that this patient did not have asthma. It has been documented that an absence of significant changes in airway caliber during SIC but with an increase in BH to pharmacologic agents after the allergen challenge may precede the development of an asthmatic reaction to a second SIC.^{19,30} As corroborated in our study, the sensitivity of SIC may be improved with the assessment of BH to pharmacologic agents on the day before and after SIC. Moreover, we observed an average 3.9-fold reduction in PC₂₀ methacholine from baseline in subjects with a positive QEC, which is considered to be clinically significant.¹⁹

Only 68% of the subjects with NRL-induced asthma who were evaluated in this study suspected NRL as the cause of their asthma. In addition, our study and previous investigations^{4,5} point out that the clinical history, assessment of BH, and immunologic tests are not as reliable as SIC in diagnosing NRL-induced OA. Thus, SICs should be recommended to demonstrate the causal relationship between asthma and exposure to airborne NRL. When it is not possible to carry out SIC with NRL, the combination of SPT to NRL and BH to methacholine (PC₂₀ less than 4 mg/mL) appears to have the best diagnostic performance.

The most suitable way to perform SIC with NRL allergens is a matter of debate. SIC with soluble NRL extracts is problematic because the allergenic composition of naturally occurring NRL bio-aerosols and aqueous extracts of NRL may be different.²⁰ Moreover, water-soluble extract of allergens can elicit asthmatic responses in sensitized subjects who have never experienced spontaneous symptoms of asthma.³³ SIC is an experimental test in which the respiratory effect of an agent present in the workplace is assessed under controlled conditions, including the generation of low and stable concentrations of this agent.³⁴ A natural form of aerosol generation and delivery during a deliberate inhalation challenge is desirable but usually not always feasible. Thus, SIC with ADP released from handling NRL gloves should be the preferred way to assess the airway response to NRL allergens because it reflects workplace conditions. Airborne NRL allergen is relatively unique in that its generation

and delivery via ADP are hand-held and user controlled.³⁵ This feature allows a precise, reproducible, natural aerosol generation to be coupled with an accurate method for bio-aerosol quantification. Ideally, the NRL aeroallergen concentration should be measured during the challenge. In our study, a good correlation was found between total dust and NRL aeroallergen concentrations during QEC, indicating that, once the SIC procedure has been standardized, the total dust concentration might be used as a surrogate for NRL aeroallergen concentration. A similar correlation between total dust and NRL aeroallergen concentration has been found by Kujala et al,³⁶ but not by Baur et al,³¹ possibly because in the latter study total dust was not measured in a challenge chamber but in hospital rooms, where different sources of inhalable dust are present.

Studies quantifying NRL aeroallergens have included medical, dental, and manufacturing environments.^{20,29,31,32,37-40} Only one study to date attempts combining lung function measurements during deliberate inhalation challenge and quantitative NRL bio-aerosol measurements.¹³ This study involved the use of a laminar flow helmet during NRL aerosol challenges with and without high-efficiency particle arrest filtration. The cumulative inhaled latex doses that caused asthmatic responses in 4 volunteers ranged from 110 to 1500 ng.¹³ However, the conclusions of that study were limited because simply wearing the helmet without a filter provided a protective effect, making these environmental concentrations less meaningful when linking clinical observations. Very recently, methods have been developed to quantify isolated airborne latex allergens (Hev b 1 and Hev b 6.02) from powdered NRL gloves.^{36,41} This approach might serve to improve the SIC procedure but, on the other hand, can make it very complicated, if not unpractical, because of the number of allergens in NRL.

Although the NRL aeroallergen concentrations achieved during QEC in our study (range, 199 to 1107 ng/m³) can be considered high, they are within or close to the upper limit of NRL aeroallergen concentrations detected in areas of some medical centers in which powdered NRL gloves were frequently used.^{20,37} In fact, NRL aeroallergen concentrations greater than 200 ng/m³ have been occasionally detected in medical centers.^{20,31,37} Moreover, a sufficiently high NRL aeroallergen concentration is necessary to avoid false-negative results on SIC. In other controlled occupational challenges it is not uncommon to find the need to produce exposure levels that are higher than those apparently producing workplace effects to elicit a positive response, which is likely to be due to the shorter duration of exposure during SIC and perhaps to the absence of other contributing factors such as exercise or irritant factors in the controlled exposures.³⁴

Our data from QEC show that exposure to a concentration of 199 ng/m³ or higher during a relatively short period of time will provoke asthma in a significant number of sensitized asthmatic patients. These data also suggest that 0.6 ng/m³ as a time-weighted average threshold that is

critical for allergic symptom onset or clinical features of NRL sensitivity may be too conservative.³¹ For example, if a work environment had a measured time-weighted average NRL concentration of 50 ng/m³, it would take almost 6 hours of exposure to inhale a dose of 125 ng. Probably of most importance and interest was that none of the reactions in this study were life-threatening. Even though these data bring us no closer to defining sensitizing doses or understanding exposures and circumstances that cause systemic reactions, they do help provide some rationale, reason, and support for the recommended product and environmental guidelines, and perhaps they may help frame permissible exposure limits to NRL allergen.

Based almost entirely on data without linkage to biologic responses, the NRL allergen content in latex gloves, dust, or the air people may breathe has been quantified and categorized as low, moderate, or high.^{20,29,39,40} The guidelines are as follows: for glove/bulk samples (ng/g): less than 10,000 low; 10,000 to 100,000 moderate; greater than 100,000 high; for air samples (ng/m³): less than 10 low; 10 to 50 moderate; greater than 50 high. In both cases "low" indicates an acceptable product or air sample, "moderate" merits some concern, and "high" warrants immediate action including source identification and control measures.

These studies provide important, objective data for recommended permissible exposure limits and support of environmental assessment guidelines.

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