

The German experience 10 years after the latex allergy epidemic: need for further preventive measures in healthcare employees with latex allergy

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Abstract

Objectives Powdered latex gloves or latex gloves with high allergen content are forbidden in Germany since 1998. It was the aim of this study to test the hypothesis that nationwide preventive measures enable health care workers with latex allergy to work without health risks about 10 years afterwards.

Methods Ninety-one health care workers who had been reported to the accident insurance between 1996 and 2004 for occupational latex allergy were examined in 2007. The survey included a questionnaire, a physical examination, spirometry, methacholine testing, skin prick testing and serum IgE measurements to latex and environmental allergens.

Results Recent work-related possibly allergic symptoms were reported by 32 subjects (35%), among them 18 subjects (20%) with symptoms of the eyes, nose or airways. Current sensitization to latex was detected in 61 subjects (67%), and 60 subjects (66%) were atopic. Eleven subjects (12%) showed mild airway obstruction, and 27 subjects (30%) were considered hyperresponsive to methacholine. Whereas overall recent symptoms of the eyes, nose or airways were associated with current latex sensitization (OR 4.5; 95% CI

1.3–16.2), this was not the case for objective outcome parameters (spirometry, bronchial hyperresponsiveness).

Conclusions Although most subjects had only mild disease, ongoing work-related symptoms of the eyes, nose or airways in a substantial number of subjects with latex allergy suggest the need for further secondary preventive measures in German healthcare.

Keywords Allergy · Healthcare · Latex · Occupational · Prevention

Introduction

A recent review of eight primary prevention intervention studies on natural rubber latex (NRL) allergy concluded that substitution of powdered NRL gloves with low-protein powder-free NRL gloves or NRL-free gloves greatly reduces NRL aeroallergens, NRL sensitization, and NRL asthma in healthcare workers (HCWs) (LaMontagne et al. 2006). Less information is available about the effect of such interventions on HCWs with sensitization to NRL. An international expert group concluded in 2002 that information about the natural history of NRL allergy is scant (Charous et al. 2002). Since then several follow-up studies of NRL-allergic subjects have been performed after interventions in the US (Bernstein et al. 2003; Hamilton and Brown 2000; Hunt et al. 2002), Europe (Hemery et al. 2004; Nettis et al. 2004; Ruëff et al. 2004; Turjanmaa et al. 2002; Vandenplas et al. 2002) and South Africa (Potter et al. 2001). It is clear from these studies that cessation or reduction of exposure causes a reduction of overall and work-related symptoms, a decrease of the number of sensitized subjects as shown by skin prick tests (SPT) or in vitro testing, and also a decrease of the number of subjects

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with hand eczema or improvement of bronchial hyperresponsiveness. However, most of these studies report a substantial number of subjects with ongoing symptoms after exposure reduction interventions.

Only two studies provided information about work-relatedness of the symptoms after interventions, both with persisting symptoms at work in about 10–20% of the subjects (Bernstein et al. 2003; Potter et al. 2001). It is not clear whether these symptoms are due to incomplete NRL exposure cessation at the workplace. As an alternative hypothesis, subjects with allergy to NRL might be more susceptible to other work-related allergens (mainly skin sensitizers) or irritants (e.g., disinfectants), as many of them are atopic (Nettis et al. 2004; Vandenplas et al. 2002).

In Germany, a nationwide prevention campaign in healthcare was performed in 1997 and 1998 (Latza et al. 2005), and powdered NRL gloves or NRL gloves with high allergen content were no longer allowed after a revised version of the compulsory technical regulations for dangerous substances was edited in December 1997 (Ministry of Labour and Social Affairs 2008). The effectiveness of these measures for primary prevention has been shown (Allmers et al. 2004), but its impact on HCWs with NRL allergy has not been quantified accordingly. This is of considerable importance as it is currently hypothesized that nationwide preventive measures are sufficient also for secondary prevention, i.e., HCWs with NRL allergy may work without health risk in hospitals and other workplaces with previous NRL exposures. It was the aim of this study to test this hypothesis about 10 years after the epidemic.

Methods

Subjects

In 2005/2006, a self-administered questionnaire (Q1) was sent to 772 HCWs who had been reported to the Statutory Accident Insurance in the Health and Welfare Services (BGW) district offices of Bochum and Cologne between 1996 and 2004 for occupational NRL allergy. Simultaneously, an examination with regard to NRL allergy was offered to all persons. Two hundred seventy-seven addresses were unknown. Of the 495 persons who received the invitation, 267 (54%) returned the completed questionnaire Q1 and out of these 127 (26%) agreed to have an examination. In 2007, 91 subjects (18%) were examined and completed a second questionnaire (Q2), the remainders ($n = 36$) were not available until the end of the study period. This survey included a physical examination, skin prick testing (SPT) as well as measurements of IgE antibodies (total and allergen-specific), spirometry, and bronchial responsiveness to methacholine. The study was

approved by the ethics committee of the Ruhr University, Bochum (No. 2620, 2005) and all subjects gave their written informed consent.

Questionnaire

From questionnaire Q1, which is explained in detail elsewhere (Nienhaus et al. 2008), two items are reported in the present manuscript: quantitative NRL-related complaints (1) during the period of the most intensive complaints and (2) during the week before filling the questionnaire, which were rated on a scale from 0 (no complaints) to 10 (severe).

All 91 subjects underwent a (Q2) questionnaire-based interview by the same physician (RM). He collected demographic data (gender, age, smoking status, job category, years of seniority), duration of employment in healthcare with and without work-related symptoms, information about former and current employment, physician's diagnosis of NRL allergy, and current antiallergic or antiasthmatic medication. Latency was defined as the time from beginning work in healthcare to the occurrence of work-related symptoms. Symptomatic exposure time was defined as the time from the beginning of work-related symptoms to the end of work in healthcare. Smoking was defined as current smoking of more than one cigarette a day. Symptoms of conjunctivitis (burning, watering or itchy eyes), rhinitis (runny or blocked nose, sneezing), asthma (variable wheeze or shortness of breath) or skin (any that might be allergic) were assessed for three time periods separately: prior to and during employment in healthcare, and during the last 12 months. If symptoms were reported, they were classified as work-related or not work-related. Information about the kind of gloves used formerly and during recent years was not known by the subjects. HCWs were asked to recall the year of initial work-related symptoms and the year of the physician's diagnosis of NRL allergy. If persons were unable to answer a particular question or to remember a date, this was rated as a missing value.

Physical examination, spirometry, and methacholine testing

All subjects were without medication that could influence the test results on the day of the examination. After auscultation of the lung (RM), inspection of the skin was performed by a dermatologist (MGH). He also recorded several atopic signs, operationalized in the "Erlanger atopy score" according to Diepgen et al. (1996), ranging from 0 to >20. Spirometry was performed as recommended by the American Thoracic Society (1995) with MasterLab (Cardinal Health, Wuerzburg, Germany). Reference values of the European Community for Steel and Coal (ECSC)

were chosen (Quanjer et al. 1993). Methacholine testing was performed by a four-step-one-concentration reservoir test as described earlier (Baur et al. 1998). Bronchial hyperresponsiveness was assumed if a decline of FEV₁ of at least 20% was measured after the highest dose of 243 µg methacholine or earlier.

Skin prick test (SPT)

SPT was performed with identical batches of NRL solutions of Allergopharma (Reinbek, Germany) and Stallergenes (Kamp-Lintfort, Germany) as well as a panel of environmental inhalant allergens, including grass and birch pollen, house dust mite (*Dermatophagoides pteronyssinus*), and cat dander (all Allergopharma). Histamine (10 mg/mL) and saline were used as positive and negative controls, respectively. Tests were performed in duplicate as described recently (van Kampen et al. 2008). A wheal diameter of at least 3 mm in at least one of both tests was defined as positive as it has been shown that small wheal diameters demonstrate the highest test efficiencies (van Kampen et al. 2009).

IgE measurements

Specific IgE antibodies to NRL (k82) as well as to common aeroallergens (sx1, similar to Phadiatop[®], containing timothy, rye, birch, mugwort, *D. pteronyssinus*, *Cladosporium herbarum*, cat and dog) were measured in the sera by ImmunoCAP (Phadia, Uppsala, Sweden) according to the manufacturer's recommendations. CAP values of at least 0.35 kU/L (class 1) were considered positive. Total serum IgE was also measured by ImmunoCAP and reported in kU/L.

Definitions of sensitization

NRL sensitization was defined as either a positive SPT with at least one of the both NRL SPT extracts or a positive CAP result with NRL. Atopy was defined as a positive SPT result to at least one of the common aeroallergens or sx1 of at least class 1. In order to have a more specific definition of atopy we additionally used a more stringent definition of atopy with sx1 of at least class 2.

Data analysis

Characteristics and clinical data of study subjects with and without current NRL sensitization were compared by chi-squared test for categorical variables, *t* test for metric variables, and Mann–Whitney *U* test for ordinal variables. Symptoms recorded in questionnaire Q2 were stratified by work-relatedness (self-reported by each subject) and

compared between groups by chi-squared test. For all analyses, a *p* value of below 5% was considered statistically significant. To evaluate the influence of several variables on skin symptoms during the last 12 months and asthma or rhinitis or conjunctivitis symptoms during the last 12 months multivariate logistic regression models were applied. For the occurrence of skin symptoms during the last 12 months the following variables were considered: age (years), gender (female vs. male), smoking (non- or ex-smokers vs. smokers), skin symptoms prior to exposure (no vs. yes), NRL sensitization (no vs. yes), atopy (no vs. yes), Erlanger atopy score (continuous), and duration of employment in healthcare (years). For asthma, rhinitis or conjunctivitis symptoms during the last 12 months a similar model was used, but additionally bronchial hyperresponsiveness (no vs. yes) was included. These models are estimating prevalence odds ratios (OR) and corresponding 95% confidence intervals (CI). Outcome variables associated with airway obstruction (FEV₁%FVC as absolute values) were evaluated using multivariate linear regression analysis. Data were analyzed using SAS Software 9.2 and SPSS 17.

Results

Selection

The 91 study subjects were somewhat older (43.6 ± 10.6 years) than the 176 non-examined subjects (40.1 ± 7.0 years); however, this difference disappeared if only persons who were still working in the same or a comparable occupation were considered. Also there were no differences in gender, occupation or symptom scores (data from questionnaire Q1; not shown in detail).

Personal data

Overall, female nurses were predominant, current smokers were rare. The mean duration of employment in healthcare was about 10 years before and 10 years after the occurrence of work-related allergic symptoms. Most subjects reported a physician's diagnosis of NRL allergy (Table 1). Personal data of subjects currently sensitized to NRL and of those currently not sensitized to NRL (see below) did not differ, with the exception of a higher proportion of females among those with current NRL sensitization (Table 1). Sixty-two subjects (68%) were still working in the same or a comparable occupation. Ten participants (11%) changed or left their job because of NRL allergy. Forty subjects (44%), most of them currently sensitized to NRL, currently took medication for allergic symptoms (Table 1).

Table 1 Characteristics of 91 health care workers with formerly reported NRL allergy

	Current NRL sensitization ^a (<i>n</i> = 61)	No current NRL sensitization (<i>n</i> = 30)	<i>p</i> value	Total (<i>n</i> = 91)
Female gender, <i>n</i> (%)	59 (96.7)	25 (83.3)	0.024	84 (92.3)
Age, years (mean ± SD)	42.6 ± 9.9	45.6 ± 11.8	0.202	43.6 ± 10.6
Smoking status			0.480	
Smoker, <i>n</i> (%)	9 (14.8)	5 (16.7)		14 (15.4)
Ex-smoker, <i>n</i> (%)	12 (19.7)	9 (30.0)		21 (23.1)
Non-smoker, <i>n</i> (%)	40 (65.6)	16 (53.3)		56 (61.5)
Occupation ^b			0.110	
Medical, <i>n</i> (%)	41 (67.2)	18 (60.0)		59 (64.8)
Dental, <i>n</i> (%)	7 (11.5)	3 (10.0)		10 (11.0)
Geriatric care, <i>n</i> (%)	2 (3.3)	6 (20.0)		8 (8.8)
Laboratory, <i>n</i> (%)	6 (9.8)	2 (6.7)		8 (8.8)
Others, <i>n</i> (%)	5 (8.2)	1 (3.3)		6 (6.6)
Total DEHC ^c , years (mean ± SD)	19.9 ± 9.9	16.8 ± 8.6	0.149	18.8 ± 9.6
Latency, years (mean ± SD)	8.8 ± 8.7	11.6 ± 10.8	0.230	9.6 ± 9.4
Symptomatic exposure time, years (mean ± SD)	10.9 ± 7.1	10.0 ± 5.0	0.572	10.6 ± 6.5
Working in the same or comparable occupation, <i>n</i> (%)	41 (67.2)	21 (70.0)	0.817	62 (68.1)
Changing or leaving job with loss in income because of NRL allergy, <i>n</i> (%)	7 (11.5)	3 (10.0)	0.832	10 (11.0)
Physician's diagnosis of NRL allergy: <i>n</i> (%)	58 (95.1)	28 (93.3)	0.731	86 (94.5)
Medication with bronchodilators, antihistamines or topical steroids within last year, <i>n</i> (%)	29 (47.5)	11 (36.7)	0.326	40 (44.0)

Missing values: latency/symptomatic exposure time (*n* = 10)

^a Either a positive SPT (wheal size ≥ 3 mm with any latex preparation) or NRL-specific IgE ≥ CAP class 1

^b Occupation at the time of work-related symptoms

^c Duration of employment in healthcare (DEHC)

Symptoms

Forty-five subjects (50%) showed allergic symptoms prior to work in healthcare, while 90 subjects (99%) suffered from allergic complaints during the period of work in healthcare (Table 2), among them 87 subjects (96%) with relation to work. Thirty-two subjects (35%) reported work-related symptoms during the last 12 months (Table 2). In both categories of allergic symptoms (all, work-related) frequencies of symptoms of nose, eyes or airways were higher in currently NRL-sensitized than in currently non-sensitized HCWs for the time period of occupational exposure. For the symptoms reported during the last 12 months this difference appeared for all allergic symptoms, but not for work-related symptoms. Work-related nose, eye or airways symptoms during the previous 12 months were present in only four subjects (13%) without current NRL sensitization, whereas these symptoms were reported by 14 subjects (23%) with current NRL sensitization (Table 2). Skin symptoms were not different between both groups, but the proportion of subjects with work-related skin symptoms was somewhat higher in subjects without current NRL sensitization (Table 2).

The intensity of NRL-related symptoms decreased from 8.5 at the time of most intensive complaints to 2.3 at the time of the survey (data from questionnaire Q1; not shown in detail).

NRL-associated symptoms started prior to 1990 in 25% of the subjects, whereas the referred year of most intensive work-related complaints as well as physician's diagnosis of NRL allergy was reported after 1990 in more than 94% of cases (Fig. 1). However, according to all three criteria, the majority of diagnoses/symptoms occurred between 1990 and 2000 (any complaints, 72%; most intensive complaints, 75%; physician's diagnosis, 82%), with a clear maximum in the years 1996–1998. It is noteworthy that few subjects obviously developed NRL allergy after 2000. No obvious differences were apparent between those with and without present NRL sensitization.

Clinical data

Physical examination (auscultation, inspection of the skin) and spirometry showed few abnormalities. Bronchial hyperresponsiveness was present in 27 subjects (30%) (Table 3). Atopy was significantly more frequent in the

Table 2 Symptoms of questionnaire Q2 of 91 health care workers with formerly reported NRL allergy

	Current NRL sensitization ^a (<i>n</i> = 61)			No current NRL sensitization (<i>n</i> = 30)			Total (<i>n</i> = 91)		
	Prior to exposure ^b	During exposure ^c	Last 12 months	Prior to exposure	During exposure	Last 12 months	Prior to exposure	During exposure	Last 12 months
Symptoms, all									
Airways, <i>n</i> (%)	10 (16.4)	40 (65.6)*	28 (45.9) [#]	2 (6.7)	8 (26.7)*	7 (23.3) [#]	12 (13.2)	48 (52.8)	35 (38.5)
Nose or eyes, <i>n</i> (%)	18 (29.5)	59 (96.7)*	42 (68.9)	6 (20.0)	17 (56.7)*	17 (56.7)	24 (26.4)	76 (83.5)	59 (64.8)
Airways or nose or eyes, <i>n</i> (%)	20 (32.8)	59 (96.7)*	49 (80.3) [#]	6 (20.0)	17 (56.7)*	17 (56.7) [#]	26 (28.6)	76 (83.5)	66 (72.5)
Skin, <i>n</i> (%)	24 (39.3)	57 (93.4)	37 (60.7)	10 (33.3)	29 (96.7)	19 (63.3)	34 (37.4)	86 (94.5)	56 (61.5)
Any, <i>n</i> (%)	32 (52.5)	61 (100.0)	55 (90.2)	13 (43.3)	29 (96.7)	25 (83.3)	45 (49.5)	90 (98.9)	80 (87.9)
Symptoms, work-related									
Airways, <i>n</i> (%)	–	34 (55.7)*	9 (14.8)	–	5 (16.7)*	1 (3.3)	–	39 (42.9)	10 (11.0)
Nose or eyes, <i>n</i> (%)	–	47 (77.0)*	11 (18.0)	–	13 (43.3)*	4 (13.3)	–	60 (65.9)	15 (16.5)
Airways or nose or eyes, <i>n</i> (%)	–	48 (78.7)*	14 (23.0)	–	13 (43.3)*	4 (13.3)	–	61 (67.0)	18 (19.8)
Skin, <i>n</i> (%)	–	54 (88.5)	14 (23.0)	–	28 (93.3)	12 (40.0)	–	82 (90.1)	26 (28.6)
Any, <i>n</i> (%)	–	59 (96.7)	20 (32.8)	–	28 (93.3)	12 (40.0)	–	87 (95.6)	32 (35.2)

^a Either a positive SPT (wheal size ≥ 3 mm) with any NRL preparation or NRL-specific IgE $\geq$ CAP class 1

^b Prior to occupation in healthcare

^c At any time during occupation in healthcare

* $p < 0.05$ when comparing currently sensitized with currently not NRL-sensitized subjects during exposure; [#] $p < 0.05$ when comparing currently sensitized with currently not NRL-sensitized subjects in the last 12 months

group of currently NRL-sensitized HCWs than in currently non-sensitized HCWs (Table 3). While 60 subjects (66%) were atopic according to objective parameters, NRL sensitization was still detectable in 61 subjects (67%). Of the 61 subjects with current NRL sensitization 46 subjects (75%) were considered atopic. The concordance of the SPT results using two different NRL solutions was 89% while the concordance of specific IgE and SPT (any NRL SPT solution) was 82%. NRL sensitization was more frequent in atopics (OR 7.4; 95% CI 2.1–25.8). Spirometry and bronchial hyperresponsiveness were not associated with current NRL sensitization or symptomatic exposure time (data not shown in detail).

Multivariate analyses

Multivariate analyses showed that skin symptoms within the last 12 months with or without relation to work were negatively associated with NRL sensitization, but positively with the Erlanger atopy score and the symptomatic exposure time (Table 4). Overall symptoms of nose, eyes or airways were associated with NRL sensitization [also with atopy if the more stringent atopy definition ($\text{sx1} \geq \text{class 2}$) was used, data not shown], but work-related symptoms were associated with the symptomatic exposure time (Table 4).

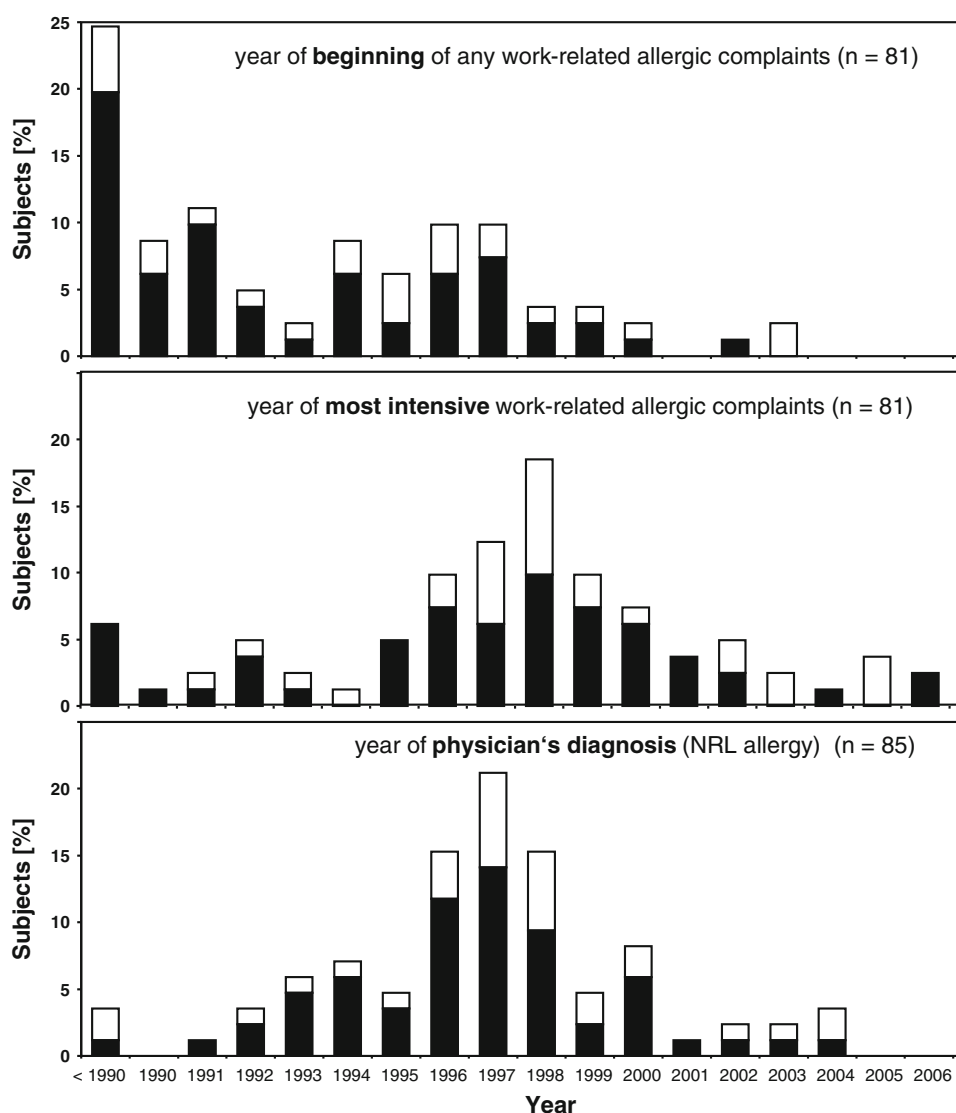
Discussion

This survey comprises a subgroup of 91 out of 772 HCWs with occupational NRL allergy who had been reported to two district offices of the German Accident Insurance for Healthcare between 1996 and 2004. Eighteen percent of those whose addresses were identified underwent the examination. Selection biases may be suspected, the most important being underrepresentation of symptomatic subjects. However, there are no reasons why subjects with ongoing work-related symptoms should be underrepresented in the present study. On the contrary one may expect that subjects with work-related symptoms will consent more frequently to a medical examination which is offered by the accident insurance and may thus result in compensation. Similarly, as health effects were not pronounced, overrepresentation of symptomatic subjects would not change the overall finding of a favorable prognosis.

This study was not primarily designed to assess the prognosis of NRL allergy, and no serial examinations were performed. Instead, we wanted to quantify the need for further preventive measures. Thus, recent symptoms, i.e., symptoms that occurred within the previous year, were chosen as primary outcome.

It is important to realize that reports of NRL allergy did not require a comprehensive diagnostic evaluation.

Fig. 1 Questionnaire answers of the study participants concerning the development of work-related symptoms. *Black bars* represent subjects with current NRL sensitization, *open bars* subjects without current NRL sensitization. Missing values are due to recall inability



However, a physician's diagnosis of NRL allergy was reported by 86 subjects (95%). It is known that sensitization as assessed by SPT or in vitro testing may disappear after cessation of exposure (Nettis et al. 2004; Ruëff et al. 2004). There is little information from longitudinal studies about work-related symptoms or challenge results of those subjects who lost NRL sensitization. A subject with NRL allergy who had lost NRL sensitization was reported to tolerate NRL contact at follow-up, but symptoms at diagnosis were not specified (Ruëff et al. 2004). However, it is known from another allergen (platinum salts) that bronchial challenges with allergen may continue to be positive despite loss of skin sensitization (Merget et al. 1994). Thus preventive measures should be considered for subjects with NRL allergy irrespective of the sensitization status at follow-up.

With the available information, it is impossible to estimate whether there were some earlier false diagnoses of NRL allergy. Although misclassification may have occurred in some cases, this is considered irrelevant for the interpretation of the major results of the present study. About one-third of the subjects had no current NRL sensitization. Subjects without current NRL sensitization were less likely to report ongoing work-related symptoms of the eyes, nose or airways, but were otherwise comparable to those individuals with current NRL sensitization.

Sixty-eight percent of the subjects were still working in healthcare, but only 11% reported NRL allergy as the cause of leaving their job. Low numbers of subjects who changed employment because of NRL allergy were reported also by others (Bernstein et al. 2003; Turjanmaa et al. 2002).

Table 3 Clinical data of 91 health care workers with formerly reported NRL allergy

	Current NRL sensitization ^a (<i>n</i> = 61)	No current NRL sensitization (<i>n</i> = 30)	<i>p</i> value	Total (<i>n</i> = 91)
Physical examination				
Wheeze on auscultation, <i>n</i> (%)	3 (4.9)	2 (6.7)	0.731 ^b	5 (5.5)
Atopic dermatitis, <i>n</i> (%)	8 (13.1)	2 (6.7)	0.355 ^b	10 (11.0)
Erlanger atopy score, median (range)	7.3 (0.5–20.0)	4.0 (1.0–18.5)	0.095 ^c	5.5 (0.5–20.0)
Spirometry				
FEV ₁ %pred, % (mean ± SD)	104 ± 14	102 ± 14	0.435 ^d	103 ± 14
FEV ₁ < 80%pred, <i>n</i> (%)	4 (6.6)	3 (10.0)	0.562 ^b	7 (7.7)
FEV ₁ %FVC, % (mean ± SD)	77 ± 7	78 ± 7	0.597 ^d	77 ± 7
FEV ₁ %FVC < 70%, <i>n</i> (%)	8 (13.1)	3 (10.0)	0.668 ^b	11 (12.1)
Bronchial hyperresponsiveness <i>n</i> (%)	22 (36.7)	5 (16.7)	0.051 ^b	27 (30.0)
Skin prick test ^e				
Any environmental allergen: <i>n</i> (%)	45 (73.8)	12 (40.0)	0.002 ^b	57 (62.6)
NRL				
Stallergenes, <i>n</i> (%)	50 (82.0)	0	–	50 (54.9)
Allergopharma, <i>n</i> (%)	52 (85.2)	0	–	52 (57.1)
Any producer, <i>n</i> (%)	56 (91.8)	0	–	56 (61.5)
In vitro tests				
Total IgE, kU/L (median, range)	99 (9–1835)	76 (5–663)	0.083 ^c	83 (5–1835)
Specific IgE				
Environmental (≥CAP class 1) ^f , <i>n</i> (%)	42 (68.9)	12 (40.0)	0.008 ^b	54 (59.3)
Environmental (≥CAP class 2) ^f , <i>n</i> (%)	37 (60.7)	11 (36.7)	0.031 ^b	48 (52.7)
NRL, <i>n</i> (%)	50 (82.0)	0	–	50 (54.9)

Missing values: skin inspection (*n* = 2), Erlanger atopy score (*n* = 1), bronchial hyperresponsiveness (*n* = 1)

^a Either a positive SPT (wheal size ≥ 3 mm) with any NRL preparation or NRL-specific IgE ≥ CAP class 1; ^b Chi-square test; ^c Mann–Whitney *U* test; ^d *t* test; ^e SPT wheal size ≥ 3 mm; ^f Measured with sx1 (see “Methods”)

The high proportion of subjects with current medication may be explained by the high number of atopics.

Symptoms of NRL allergy were difficult to assess because multiple organs were involved and symptoms were modified by various environmental and occupational factors. Almost all subjects reported previous work-related symptoms. Symptoms of skin and rhinoconjunctivitis/asthma occurred with about equal frequency, and there was a sharp decrease in the intensity of symptoms and the number of subjects with symptoms after exposure cessation, as reported consistently by others (Bernstein et al. 2003; Hamilton and Brown 2000; Hemery et al. 2004; Hunt et al. 2002; Nettis et al. 2004; Potter et al. 2001; Ruëff et al. 2004; Turjanmaa et al. 2002; Vandenplas et al. 2002). The lower number of subjects with recent symptoms of rhinoconjunctivitis/asthma in subjects without current NRL sensitization may be interpreted as a consequence of the loss of NRL allergy. In contrast to symptoms of rhinoconjunctivitis/asthma, recent skin symptoms (with or without relation to work) were equally frequent in subjects with and without current NRL sensitization. We interpret this finding as indicative of further relevant occupational

exposures causing skin symptoms, e.g., irritants or wet work which are dominant causes of skin diseases in healthcare (Mahler 2007). An alternative explanation is misclassification, which may be more likely for skin symptoms than for work-related symptoms of immediate-type allergy. Overall, recent symptoms were mild, but a substantial number of subjects (35%) reported recent work-related symptoms, skin symptoms being somewhat more frequent than rhinoconjunctivitis/asthma symptoms.

Interestingly, symptoms of NRL allergy began often many years before the epidemic, but the most intensive complaints and the numbers of physician's diagnoses of NRL allergy had a clear maximum in the mid 1990s. Few subjects reported first symptoms after the prohibition of powdered NRL gloves in 1997, supporting the view that preventive measures were not implemented in all healthcare settings.

It is one of the strengths of the present study that objective parameters were assessed. Overall, the study subjects did not show severe disease. Considering the high proportion of atopics, a rate of 30% with bronchial hyperresponsiveness or atopic dermatitis (37%) is not conspicuous.

Table 4 Results of logistic regression analysis (OR, 95% CI) of 91 health care workers with formerly reported NRL allergy

	Any symptom	Work-related
<i>Skin symptoms during the last 12 months</i>		
Age (years)	0.95 (0.90–1.00)	0.97 (0.91–1.03)
Gender		
Males versus females (ref.)	1.13 (0.09–13.97)	4.48 (0.25–80.22)
Smoking		
Smokers versus non- or ex-smokers (ref.)	4.54 (0.78–26.51)	4.29 (0.99–18.63)
Skin symptoms prior to exposure		
Yes versus no (ref.)	1.80 (0.51–6.43)	0.71 (0.19–2.61)
NRL sensitization ^a		
Yes versus no (ref.)	0.26 (0.07–0.97)	0.18 (0.05–0.70)
Atopy ^b		
Yes versus no (ref.)	2.31 (0.71–7.56)	0.75 (0.20–2.80)
Erlanger atopy score	1.25 (1.06–1.48)	1.20 (1.04–1.38)
Symptomatic exposure time (years)	1.09 (0.99–1.20)	1.18 (1.06–1.33)
<i>Asthma, rhinitis or conjunctivitis symptoms during the last 12 months</i>		
Age (years)	1.05 (0.99–1.12)	0.99 (0.92–1.06)
Gender		
Male versus female (ref.)	0.58 (0.06–5.27)	3.83 (0.27–54.67)
Smoking		
Smokers versus non- or ex-smokers (ref.)	0.87 (0.17–4.31)	0.71 (0.13–3.82)
Asthma or rhinitis or conjunctivitis symptoms prior to exposure		
Yes versus no (ref.)	#	1.50 (0.31–7.22)
NRL sensitization ^a		
Yes versus no (ref.)	4.54 (1.27–16.22)	1.26 (0.26–6.09)
Atopy ^b		
Yes versus no (ref.)	2.85 (0.88–9.24)	0.27 (0.06–1.23)
Bronchial hyperresponsiveness		
Yes versus no (ref.)	1.55 (0.39–6.23)	4.22 (0.98–18.19)
Symptomatic exposure time (years)	1.03 (0.92–1.16)	1.25 (1.09–1.43)

IgE ≥ CAP class 1

^a Yes = either a positive SPT (wheal size ≥ 3 mm) with any NRL extract or NRL-specific IgE ≥ CAP class 1

^b Yes = either a positive SPT (wheal size ≥ 3 mm) with any environmental allergen or environmental specific IgE ≥ CAP class 1

Not considered due to low numbers of subjects

Logistic regression analysis showed a negative association between recent skin symptoms and NRL sensitization. We interpret this finding as a consequence of efficient NRL avoidance strategies concerning skin contact, but, more important, also as an indication of further non-NRL-related causes of skin symptoms as, e.g., wet work or contact allergens. This interpretation is strengthened by the association between recent skin symptoms and an atopic constitution (Erlanger atopy score), indicating that recent skin symptoms are mainly due to atopic dermatitis. Also the association of recent skin symptoms with the duration of the symptomatic exposure time indicates further occupational exposures to substances or conditions that cause skin symptoms. Possibly, NRL products are causative for recent work-related skin symptoms in rare cases, but other causes are predominant.

Although NRL sensitization and atopy were closely associated, the association between current NRL sensitization and symptoms of eyes, nose or airways was stronger

than the association between atopy and these symptoms, indicating that NRL sensitization per se has an adverse long-lasting impact on airway disease. This is an important finding of the present study as it shows that NRL is among the occupational high molecular weight allergens that may have negative health consequences, as has been shown consistently for many low molecular weight allergens, but only occasionally for high molecular weight substances (Rachiotis et al. 2007).

High NRL allergen contents of German NRL gloves have been described during the NRL epidemic (Baur et al. 1997). A recent investigation showed that allergen contents in many German gloves that are in use, 2008 may still exceed the recommended protein content of 30 µg/g and still contain NRL allergen (von der Gathen et al. 2009). Unfortunately, an environmental survey could not be performed in the present study. Thus it remains unclear, whether exposures to NRL occur by “old” products, or by new brands which still contain too high allergen contents.

Although the present study cannot answer this question, there are two main indicators that there is indeed ongoing relevant NRL exposure at some workplaces. Firstly, subjects with current NRL sensitization had more recent work-related symptoms of immediate-type allergy than subjects without current NRL sensitization. Secondly, few subjects with NRL sensitization reported first symptoms in the new millennium.

The almost normal spirometric values of the study subjects indicate that they had no severe allergic airway disease. The fact that recent work-related symptoms of the eyes, nose or airways at work were reported by only 18 subjects (20%) shows that avoidance of airborne NRL was achieved by the majority of the subjects, but further preventive measures are warranted for a substantial number of HCWs with NRL allergy.

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Conflict of interest statement The authors declare that they have no conflict of interest.

References

- Allmers H, Schmengler J, John SM (2004) Decreasing incidence of occupational contact urticaria caused by natural rubber latex allergy in German health care workers. *J Allergy Clin Immunol* 114:347–351
- American Thoracic Society (1995) Standardization of spirometry (1994 update). *Am J Respir Crit Care Med* 152:1107–1136
- Baur X, Chen Z, Raulf-Heimsoth M, Degens P (1997) Protein and allergen content of various natural latex articles. *Allergy* 52:661–664
- Baur X, Huber H, Degens PO, Allmers H, Ammon J (1998) Relation between occupational asthma case history, bronchial methacholine challenge, and specific challenge test in patients with suspected occupational asthma. *Am J Ind Med* 33:114–122
- Bernstein DI, Karnani R, Biagini RE, Bernstein CK, Murphy K, Berendts B, Bernstein JA, Bernstein L (2003) Clinical and occupational outcomes in health care workers with natural rubber latex allergy. *Ann Allergy Asthma Immunol* 90:209–213
- Charous BL, Blanco C, Tarlo S, Hamilton RG, Baur X, Beezhold D, Sussman G, Yunginger JW (2002) Natural rubber latex allergy after 12 years: recommendations and perspectives. *J Allergy Clin Immunol* 109:31–34
- Diepgen TL, Sauerbrei W, Fartasch M (1996) Development and validation of diagnostic scores for atopic dermatitis incorporating criteria of data quality and practical usefulness. *J Clin Epidemiol* 49:1031–1038
- Hamilton RG, Brown RH (2000) Impact of personal avoidance practices on health care workers sensitized to natural rubber latex. *J Allergy Clin Immunol* 105:839–841
- Hemery ML, Dhiwert-Donnadieu H, Verdier R, Dujols P, Godard P, Demoly P (2004) A clinical and serological follow-up study of health care workers allergic to natural rubber latex who had followed a latex avoidance programme. *Allergy* 59:1013–1014
- Hunt LW, Kelkar P, Reed CE, Yunginger JW (2002) Management of occupational allergy to natural rubber latex in a medical center: the importance of quantitative latex allergen measurement and objective follow-up. *J Allergy Clin Immunol* 110(Suppl):S96–S106
- LaMontagne AD, Radi S, Elder DS, Abramson MJ, Sim M (2006) Primary prevention of latex related sensitisation and occupational asthma: a systematic review. *Occup Environ Med* 63:359–364
- Latza U, Haamann F, Baur X (2005) Effectiveness of a nationwide interdisciplinary preventive programme for latex allergy. *Int Arch Occup Environ Health* 78:394–402
- Mahler V (2007) Skin protection in the healthcare setting. *Curr Probl Dermatol* 34:120–132
- Merget R, Reineke M, Rückmann A, Bergmann E-M, Schultze-Werninghaus G (1994) Nonspecific and specific bronchial responsiveness in occupational asthma due to platinum salts after allergen avoidance. *Am J Respir Crit Care Med* 150:1146–1149
- Ministry of Labour and Social Affairs (last update 2008) TRBA/TRGS 406: airway sensitizing substances. http://www.baua.de/Themen-von-A-Z/Gefahrstoffe/TRGS/TRGS-TRBA-406.html?_nnn=true&_nnn=true
- Nettis E, Colanardi MC, Ferrannini A (2004) Type I latex allergy in health care workers with latex-induced contact urticaria syndrome: a follow-up study. *Allergy* 59:718–723
- Nienhaus A, Kromark K, Raulf-Heimsoth M, van Kampen V, Merget R (2008) Outcome of occupational latex allergy—work ability and quality of life. *PLoS ONE* 3(10):e3459
- Potter PC, Crombie I, Marian A, Kosheva O, Maqula B, Schinkel M (2001) Latex allergy at Groote Schuur Hospital—prevalence, clinical features and outcome. *S Afr Med J* 91:760–765
- Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC (1993) Lung volumes and forced ventilatory flows Report working party standardization of lung function tests. European community for steel and coal. *Eur Respir J* 6(Suppl 16):5–40
- Rachiotis G, Savani R, Brant A, MacNeill SJ, Newman Taylor A, Cullinan P (2007) Outcome of occupational asthma after cessation of exposure: a systematic review. *Thorax* 62:147–152
- Ruëff F, Schöpf P, Putz K, Przybilla B (2004) Effect of reduced exposure on natural rubber latex sensitization in health care workers. *Ann Allergy Asthma Immunol* 92:530–537
- Turjanmaa K, Kanto M, Kautiainen H, Reunala T, Palosuo T (2002) Long-term outcome of 160 adult patients with natural rubber latex allergy. *J Allergy Clin Immunol* 110(Suppl):S70–S74
- van Kampen V, Rabstein S, Sander I, Merget R, Brüning T, Broding HC, Keller C, Müsken H, Overlack A, Schultze-Werninghaus G, Walusiak J, Raulf-Heimsoth M (2008) Prediction of challenge test results by flour-specific IgE and skin prick test in symptomatic bakers. *Allergy* 63:897–902
- van Kampen V, Merget R, Rabstein S, Sander I, Brüning T, Broding HC, Keller C, Muesken H, Overlack A, Schultze-Werninghaus G, Walusiak J, Raulf-Heimsoth M (2009) Comparison of wheat and rye flour solutions for skin prick testing: a multi-centre study (Stad 1). *Clin Exp Allergy* 39:1896–1902
- Vandenplas O, Jamart J, Delwiche JP, Evrard G, Larbanos A (2002) Occupational asthma caused by natural rubber latex: outcome according to cessation or reduction of exposure. *J Allergy Clin Immunol* 109:125–130
- von der Gathen Y, Sander I, Flagge A, Brüning T, Raulf-Heimsoth M (2009) Quantification of protein and allergen content in various latex products (in German). *Allergo J* 18:31 (abstract)