Allergic and latex-specific sensitization: Route, frequency, and amount of exposure that are required to initiate IgE production

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Quantitative data that documents human exposure-response relationships for IgE sensitization to allergens are limited. Although seemingly straightforward, documentation of exposure-response relationships can be difficult. Issues that are related to study design, allergen standardization, exposure assessment, and evaluation for sensitization can impact greatly on study results. Despite these issues, exposure-response relationships for sensitization to protein allergens have been documented in several occupational groups, which include enzyme-detergent workers, bakers, and laboratory animal workers. In general, atopy acts as an effect modifier in these settings, steepening the exposure-response relationship. Several studies suggest that the greatest risk for sensitization is within the first several years of exposure. For 1 allergen, the protease subtilisin, a short-term exposure limit of 60 ng/m^3 has been recommended by the American Council of Governmental Industrial Hygienists.

With regard to natural rubber latex, exposure-related factors such as number of operations have been shown to be risk factors for sensitization of children with spina bifida. By contrast, fewer studies show exposure-response relationships for IgE sensitization of health care workers to natural rubber latex, and the area remains controversial. However, a recent cohort study that evaluated incident sensitization in dental hygiene students suggests strongly that, with sufficient exposure, employment in health care can lead to an increased risk of IgE sensitization to natural rubber latex. (J Allergy Clin Immunol 2002;110:S57-63.)

Key words: *Latex, IgE, sensitization, exposure-response*

Natural rubber latex (NRL) exposure can cause or exacerbate a number of IgE-mediated clinical diseases, including asthma, allergic rhinitis, urticaria, and anaphylaxis.[1-3] The induction of an allergen-specific IgE response, or IgE sensitization, is a key precursor to the development of clinically apparent allergic disease. Although exposure to allergen is clearly important for the development of specific IgE sensitization, quantitative data that documents human exposure-response relationships for IgE sensitization to occupational allergens are limited.[4,5] Thus, in most cases, it has not been possible to establish exposure limits for allergens for the primary prevention of occupationally related allergic diseases.

Abbreviations used
HCW: Health care worker
NRL: Natural rubber latex

Many factors account for difficulties that have been encountered in the establishment of exposure-response relationships for sensitization to occupational allergens. Measurement of exposure often is not straightforward. For example, often it is unclear how best to quantify complex, incompletely characterized allergens, which can contain numerous individual allergenic constituents. Even when methods for allergen measurement are available, the best strategies for the assessment of the level of exposure may be unclear. Multiple routes of exposure may cause sensitization, which can complicate exposure assessment.

Documentation of sensitization is also complex, especially when the tests that are used are optimized for use in clinical settings rather than in general populations. Finally, issues that are related to study design can markedly affect a study's ability to document exposure-response relationships for sensitization to occupational allergens.

This brief review will address some of the important difficulties in the establishment of exposure-response relationships for sensitization to NRL and occupationally related allergens in general. Despite these problems, examples of occupational allergens in which exposure-response relationships for IgE sensitization have been reported will be discussed. Finally, current knowledge that is relative to exposure-response relationships for sensitization to NRL will be reviewed.

CONSIDERATIONS FOR ASSESSMENT OF EXPOSURE TO ALLERGENS

Measurement of allergen levels

Measurement of allergen levels can often be problematic. This is particularly true for NRL. Crude NRL contains more than 150 polypeptides, of which 56 polypeptides have been reported to act as allergens.[6,7]

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Furthermore, there are varying patterns of IgE response to individual NRL proteins in different exposure groups; patients with spina bifida are particularly likely to be sensitized to Hev b 1 and Hev b 3, and health care workers (HCWs) are likely to be sensitized to a range of allergens, which includes Hev b 2, Hev b 5, Hev b 6, and Hev b 7.[8,9] Despite these complexities, the state of the art for the measurement of NRL allergen in environmental samples is to perform inhibition assays that use crude NRL extracts and patient sera as assay reagents.[10,11] Given the potential for variability in both NRL extracts and patient sera, these assays are difficult to standardize across laboratories. Recombinant NRL allergens show considerable promise for the standardization of NRL extracts.[8,9] However, it remains to be determined which of these NRL allergens will be the most appropriate to measure in environmental samples.

Route of exposure

Allergens potentially gain access to lymphoid organs with the ability to serve as sites for the induction of a specific IgE response through multiple routes. For example, in the case of NRL, direct external contact (such as, with gloves) can result in skin exposure. Aerosols of lubricating glove powder that is contaminated with NRL allergen can impact on mucous membranes of the eyes, nose, trachea and large airways, oropharynx, and small airways. Particles impacting in the nasopharynx or oropharynx subsequently can be swallowed and enter the gastrointestinal tract. Mucous membranes of the gastrointestinal tract and urogenital tracts can be exposed to NRL allergen by direct contact with indwelling NRL devices, such as catheters. Internal exposure can occur with the use of NRL gloves during surgical procedures and the use of internally placed NRL devices, such as wound drains. Despite these numerous potential routes of exposure, most studies that evaluate exposure to occupational allergens in general, and NRL in particular, directly measure only inhalation exposure and thus may fail to measure other exposures that are relevant for the development of IgE sensitization.

Skin exposure is an exposure route of particular potential importance that is rarely measured in exposure-response studies of allergen sensitization. In animal models, allergen exposure through the skin induces specific IgE responses. Furthermore, subsequent aerosol exposure can result in airway hyperreactivity, which suggests that IgE sensitization through the skin can predispose to the development of allergen-induced asthma.[12,13] Although seldom measured directly, skin exposure most likely plays an important role in sensitization to NRL. There is a clinical perception that hand dermatitis predisposes to the development of NRL allergy, perhaps caused by decreased skin barrier function.[14] Animal data support the concept that skin exposure alone is sufficient to induce immune responses to NRL, because the topical application of NRL has been reported to induce IgG_1 responses in hairless guinea pigs.[15] The same investigators demonstrated that NRL proteins were capable of penetrating both abraded and intact human surgical skin specimens.

The nose is another potentially important route of exposure for IgE sensitization. Human studies have demonstrated that the instillation of antigen into the human nose can induce a primary IgE response.[16] Nasal exposure in individuals who are sensitized already can also induce secondary IgE responses.[17] Thus, aerosolized particles of large size that deliver allergen to the nose and smaller aerosolized particles in the respirable range are both likely to be important in the induction of IgE sensitization, and both should be considered in the establishment of the exposure-sensitization relationship.

Use of appropriate exposure metrics

It is unclear what is the best way to the express level of exposure in the evaluation for allergen exposure-sensitization relationships. Most epidemiologic studies of occupational groups extrapolate data from a relatively small number of measurements to generate estimates of exposure across job categories and over time. This strategy has limitations. Levels of exposure that are measured at 1 point in time may not be reflective of exposures at other points in time. For example, in a recent study of NRL allergy, it was found that extractable protein levels in NRL gloves (and thus NRL allergen levels) decreased markedly over the course of the study.[18] Thus, the level of exposure was not constant over the course of the study and, by implication, at other times previous to the study. It is also unclear whether cumulative, peak, or current exposures are the most important determinants of IgE sensitization. However, in the case of NRL, it appears that current exposures have an important effect on specific IgE levels. Two papers have documented that removal from exposure leads to decreased levels of serum-specific IgE in individuals who are sensitized to NRL.[19,20] Therefore, equivalent cumulative lifetime exposures that are achieved with differing recent exposures might not result in similar current sensitization status.

CONSIDERATIONS FOR THE ASSESSMENT OF SENSITIZATION TO ALLERGENS

Documentation of IgE sensitization

The specific approach that was used to document IgE sensitization clearly has the ability to impact on the documentation of an exposure-response relationship for induction of IgE sensitization by an allergen. This is especially a problem for a complex allergen such as NRL. In 1 study, NRL was reported to contain 56 allergens that could bind IgE from the sera of individuals who are NRL allergic.[7] Furthermore, different populations of individuals who are NRL allergic (HCWs and patients with spina bifida) exhibit differing patterns of IgE sensitization to these individual allergenic proteins.[8,9] Therefore, the content of specific allergenic proteins that were used as antigens in tests for sensitization to NRL, which has not yet been standardized fully, has the potential to affect test performance markedly, particularly in individuals with lower levels of detectable serum-specific IgE.

A related problem with documentation of IgE sensitization in epidemiologic studies is the application of tests and test thresholds that are intended for clinical use for screening of populations. Clinical tests are performed in patient populations in which there is a relatively higher pretest probability for the condition of interest than in the general population. The higher the true prevalence of a condition, the better a test will perform according to the following equations[21]: (TP · Sens)/100 derives true positives identified by a test; (100 – TP) · (100 – Spec)/100 derives false positives identified by a test; True Positives + False Positives derives apparent prevalence, where TP is the true prevalence of the condition, Sens is the test sensitivity, and Spec is the test specificity.

It can be appreciated from these equations that, for any given test sensitivity or specificity, increased true prevalence of a condition will result in an increased percentage identification of true positives by the test, a decreased rate in identification of false positives, and a more accurate apparent prevalence rate.

In the case of NRL, a range of sensitivities and specificities have been reported for the identification of NRL sensitization and allergy by the various available in vitro tests. For example, a recent study evaluated the ability of 3 serologic tests that had been cleared by the US Food and Drug Administration to predict whether subjects were positive to NRL on the skin prick test.[22] Serologic tests that were studied were the Pharmacia-Upjohn CAP assay, the Diagnostic Products Corporation microplate AlaSTAT, and the Hycor HY-TEC EIA. The specificities of these tests were 97%, 97%, and 73%, respectively, with the use of the tests' recommended threshold values.[22] With the use of the previously cited equations, even if the true prevalence of NRL sensitization in a population was zero, screening with these 3 tests would yield apparent prevalences of 3%, 3%, and 27%, respectively. Another study that evaluated performance of the CAP and AlaSTAT assays in the identification of individuals with both a positive NRL skin test and history consistent with NRL allergy documented specificities of 90% and 92%, respectively.[23] Even with a true prevalence of NRL sensitization in a population of zero, these specificities would yield apparent prevalences of 10% and 8%, respectively, of NRL sensitization, if the tests were applied for the screening of the general population. Thus, tests and test thresholds for the identification of specific IgE sensitization that are acceptable for clinical practice may result in considerable misclassification when applied to epidemiologic screening of low-prevalence populations.

CONSIDERATIONS IN STUDY DESIGN

Study design can markedly impact on the ability of a study to detect relationships between exposure and response. Cross-sectional study design (that is, a design that evaluates a population at a single point in time) has the problem of failing to evaluate individuals who have already had adverse effects from an exposure and have left the population. As a result, those individuals who are least susceptible to the health effects of an exposure may be over-represented in the study. This "healthy worker effect" can prevent a study from finding relationships between exposure and response and, in the most extreme case, result in the artifactual finding that exposures protect against the health effect of interest.

The statistical power of a study is also crucial in the determination of its ability to demonstrate relationships between exposure and response. With IgE sensitization to NRL as an example, several studies have used serologic tests to document an apparent prevalence of sensitization in the general population of approximately 6%.[24,25] To have a power of 80% to show a 50% increase in apparent prevalence rate to 9% in an exposed population at a significance level of probability of <.05, a study would need to enroll 1275 subjects per group (Sigmastat; SPSS Inc, Chicago, Ill).

A final issue in study design is to take into account the great variability of humans in their responses to allergen exposure. This lack of uniformity in exposure-response relationships can be partially accounted for by various effect modifiers that modify susceptibility to IgE sensitization (such as atopy), other genetic factors (such as polymorphisms), and smoking. Therefore, exposure-response relationships for IgE sensitization of a susceptible group (such as atopic individuals) to an allergen would likely be different from exposure-response relationships for other study participants.

EXPOSURE-RESPONSE RELATIONSHIPS FOR SENSITIZATION TO OCCUPATIONAL ALLERGENS OTHER THAN NRL

Despite the difficulties in the documentation of exposure-response relationships for IgE sensitization to high molecular weight allergens, these relationships have been documented in some occupational settings. It is likely that the general lessons that are learned from these settings apply to NRL allergy. Such settings include IgE sensitization in baking, laboratory animal facilities, and enzyme-detergent manufacturing plants.

Occupational allergy in bakers has long been recognized, with the first description of Baker's asthma given by Ramazzini in 1700.[26,27] Houba et al[28,29] have reported 2 cross-sectional studies that documented IgE sensitization to α-amylase and wheat flour in bakers. Both studies included quantitative measurement of allergen exposure. These studies show an exposure-response relationship for IgE sensitization of bakers. Atopy is an effect modifier that steepens the exposure-response relationship.

Laboratory animal workers are at high risk of the development of IgE sensitization to animal-derived proteins and associated allergic diseases.[30] A large cohort study documented epidemiologic correlates of exposure and atopy to be risk factors for IgE sensitization of apprentices in animal health technology.[30,31] The incidence of occupationally related sensitization was greatest in the first 2 years of exposure and declined to incidence levels similar to those for common allergens after 4

years.[32] A large cross-sectional study that included quantitative measurement of allergen exposure documented exposure-response relationships for IgE sensitization to rat urinary allergen. Atopy was a strong effect modifier, markedly steepening the exposure-response relationship.[33] Finally, a large cohort study of newly employed workers that included quantitative assessment of allergen exposure documented that an exposure-response relationship existed for sensitization to rat urinary allergen. Atopy was also a risk factor. The highest incidence of sensitization was in the first 12 months of employment and 80% of conversions occurred within 2 years.[34]

Occupational allergy in enzyme-detergent workers was first reported in the 1960s. At that time, it became common practice to add proteolytic exoenzymes that derived from strains of the *Bacillus* genus (such as *B subtilis*) to detergent products. Exposure to these enzymes was associated with outbreaks of occupational allergic disease in manufacturing plants. By the early 1970s, strict controls on exposure had been instituted, which resulted in decreased sensitization and allergic disease. Based on these experiences, the enzyme subtilisin is the only protein allergen for which the American Council of Governmental Industrial Hygienists has established exposure guidelines, in this case a short-term exposure limit of 60 ng/m^3.[35-37] A review of 1 factory's experience of following 1642 workers over the period from 1968 until 1975 was reported in 1977.[35] Increased exposure (based on dustiness of job) and atopy were associated with an increased incidence of sensitization. The greatest proportion of sensitization occurred within the first 2 years of observation.

Several general lessons emerge from studies of IgE sensitization in bakeries, animal care facilities, and enzyme-detergent manufacturing plants. It is likely that these are relevant to the problem of NRL allergy. First, allergen exposure is a risk factor for IgE sensitization. Furthermore, an exposure-response relationship exists, with an increasing risk of sensitization that is associated with increasing exposure. Second, atopy is an important effect modifier, steepening the exposure-response relationship. Finally, sensitization usually occurs within the first several years after the initiation of exposure.

EXPOSURE-RESPONSE RELATIONSHIPS FOR SENSITIZATION TO NRL

NRL sensitization in children

Since the early 1990s, it has been apparent that children with spina bifida are at increased risk for both NRL IgE sensitization and anaphylactic reactions to NRL during surgical procedures.[38,39] NRL sensitization rates that range between 34% and 65% have been reported in patients with spina bifida.[39-42] Direct internal or mucosal contact with NRL medical devices appears to be an important route of sensitization in this population. With regard to exposure-response relationships, exposure-related factors (such as the number of operations or the use of devices such as bladder catheters or ventriculoperitoneal shunts) has been associated with an increased risk of NRL sensitization and allergy. Atopy is also an important risk factor.[40-42]

Two European studies have documented the prevalence of NRL IgE sensitization in all children seen at allergy clinics to be evaluated for allergic disorders. In 1 study, 2.2% of 453 children had positive skin prick test results to a NRL extract. One half of the sensitized children reported symptoms that were related to NRL exposure, mostly triggered by contact with balloons and gloves. Atopy and a history of surgical procedures were risk factors for NRL sensitization. NRL sensitization was associated with sensitization to foods (such as apple, kiwi, and chestnut).[43] In a similarly designed study, 1.7% of 3269 children had positive NRL skin prick tests, which were confirmed by re-examination in 1.1% of the children. Contact urticaria was the most common symptom, with balloons and gloves being reported as important triggers. Atopy was an important risk factor for NRL IgE sensitization. Sensitization was identified both in children with a history of multiple surgical procedures and children with no history of surgical procedures.[44] Thus, 1% to 2% of children who are examined at allergy clinics demonstrate IgE sensitization to NRL by skin prick test, often without a history of unusual exposure to NRL allergen.

NRL sensitization in HCWs

Over the past decade, clinical NRL allergy has been a significant problem for HCWs.[1] Exposure of IgE-sensitized HCWs to NRL can lead to a range of allergic symptoms that include contact urticaria, rhinoconjunctivitis, asthma, or even anaphylaxis. Atopic HCWs have consistently been found to be at increased risk for both sensitization and clinical disease.[10,14,18,45-47]

Despite the clear clinical impression that employment in the health care industry is associated with symptomatic NRL allergy, there has been much controversy about whether exposures that are related to such employment increase the risk of IgE sensitization to NRL.[48,49] Evidence exists both to support and to refute this idea. On the affirmative side, Baur et al[10,50] in 2 cross-sectional studies have shown relationships between objective measurements of airborne NRL allergen levels and the risk of sensitization in HCWs and have suggested that exposures in excess of 0.6 ng/m^3 are associated with an increased risk of NRL sensitization and related symptoms. Levy et al[51] reported in 1999 that dental students who worked with powdered NRL gloves were more likely to experience NRL IgE sensitization than dental students who worked with nonpowdered NRL gloves. In 1999, Liss and Sussman[49] reviewed the current studies and found that, if assessed by skin prick test, the prevalence of NRL sensitization in the general population was approximately 1%, although reported prevalence of NRL IgE sensitization in HCWs ranged from 2.9% to 12.1%. If assessed by serologic assays, prevalence in general populations ranged from 4.1% to 18%. This serologic assay–based prevalence rate is similar to those documented by serologic factors in a number of HCW populations, in which

prevalence rates ranged from 5.5% to 8.9%.[52-55] Liss and Sussman[49] suggested that the suboptimal specificity of serologic assays would increase the apparent prevalence of NRL sensitization, potentially obscuring differences between HCWs and the general population. This is consistent with the analysis of Yeang,[21] which suggests that serologic tests of suboptimal specificity could markedly overestimate the prevalence of NRL IgE sensitization in the general population.

The most direct evidence for a linkage between occupational exposure to NRL and specific IgE sensitization in HCW is provided by a recently reported study that examined the incidence of specific IgE sensitization in a cohort of 769 apprentices, including 417 apprentices in animal health technology, 230 apprentices in pastry-making, and 122 apprentices in dental-hygiene technology.[31] Subjects were entered into the study within 3 months of the start of exposure to relevant occupational allergens. The dental hygiene students were at 2 schools and were followed for up to 32 months after the start of the exposure to NRL. Median time of exposure to NRL gloves over this period was 517.5 hours. The geometric mean airborne latex allergen concentration at 1 of the schools during usual clinical work measured by personal air sampling was 54.7 ng/m^3. NRL IgE sensitization was assessed by skin prick test. The cumulative incidence rate of skin prick test positivity to NRL over the course of the study was significantly greater in dental hygiene apprentices (7/110 apprentices) than in pastry makers (3/185 apprentices (incidence rate ratio, 3.92; 95% CI, 1.04 to 14.86) or animal health technicians (4/391 apprentices; incidence rate ratio, 6.22; 95% CI, 1.85 to 20.86).[56] Among the dental hygiene students, baseline history of physician-diagnosed asthma or respiratory symptoms on exposure to cold air and atopy that was defined by skin prick test with common aeroallergens were significant risk factors for subsequent incident sensitization to NRL. Sensitized dental hygiene students were significantly more likely to experience incident cutaneous, rhinoconjunctival, and respiratory symptoms (dyspnea and/or wheezing). Cumulative incidence of probable occupational asthma to latex was 4.5%.[57]

In contrast, several studies have failed to show relationships between being a HCW, or a HCW with NRL exposure, and NRL IgE sensitization. In 1 cross-sectional study, self-reported daily glove use and years of use were not different in operating room nurses who were NRL skin prick test–positive (n = 17 nurses) and –negative (n = 230 nurses).[58] In another study, 227 individuals who were skin prick test–negative were assigned to work in units that used powder-free gloves and 208 individuals were assigned to work in units that used powdered gloves. Marked differences in exposure to airborne NRL allergen were documented by objective measurement. Over the next year, 2 individuals in each group became skin prick test–positive (although only those individuals who worked in the units that used powdered gloves had symptoms).[18] In a large cross-sectional study, 532 of 640 eligible employees of a Denver hospital were evaluated for NRL allergy by questionnaire and serologic testing for NRL-IgE (CAP; Pharmacia). Of the participants, 6.2% demonstrated IgE antibodies to NRL, with no association between self-reported glove use or departmental NRL environmental allergen levels and sensitization.[55] Finally, an analysis of NRL sensitization in the National Health and Nutrition Examination Survey III, which was conducted between 1988 and 1991, has recently been reported.[48] This is a large population-based, cross-sectional survey that was intended to assess health status of the US population. The 5512 adults who were assessed for NRL allergy in the study completed questionnaires that indicated their occupations and underwent serologic testing for serum IgE to NRL with the use of a previous version of the AlaSTAT test (Diagnostic Products). This study showed that self-reported employment in the health care industry was associated with an odds ratio for NRL sensitization of 1.52, but this did not attain statistical significance (95% C, 0.93 to 2.47). Male sex, physician-diagnosed asthma or hay fever, and race designated as "black non-Hispanic" or "black Hispanic and other" were all risk factors for sensitization.[48]

CONCLUSION

Demonstration of exposure-response relationships for IgE sensitization to occupationally related high molecular weight allergens can be difficult. Issues that are related to study design, strategies for exposure assessment, and approach to evaluation for IgE sensitization can all affect study results markedly. Despite these issues, exposure-response relationships for IgE sensitization to occupational allergens have been demonstrated in several settings, including bakeries, laboratory animal facilities, and enzyme-detergent manufacturing plants. General themes from these studies include the roles of exposure, atopy, and duration of exposure in the development of specific IgE sensitization. In these settings, allergen exposure is a risk factor for IgE sensitization; atopy is an important effect modifier that steepens the exposure-response curve for the induction of sensitization; and sensitization to an occupational allergen usually occurs within the first several years after the initiation of the exposure.

With regard to NRL, exposure-related factors (such as number of operations) have been shown to be risk factors for sensitization of children with spina bifida to NRL. By contrast, fewer studies show exposure-response relationships for IgE sensitization of HCWs to NRL, and the area remains controversial. However, a recent cohort study that evaluated the incident NRL sensitization in dental hygiene students strongly suggests that, with sufficient exposure, employment in the health care field can lead to an increased risk of IgE sensitization to NRL.

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