

World Wide Wounds

A Review of the Expert Opinion on Latex Allergy

Author(s)

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Key Points

1. It has been demonstrated that a relationship exists between leachable protein levels and allergic reaction.
2. The measurement of total leachable protein is currently a useful method to estimate the allergenic potential of a latex glove.
3. It has not been demonstrated that powdered gloves are more likely to induce sensitisation than powder-free gloves, provided the protein content of the gloves is identical.
4. Chemicals used in glove manufacture can be detected using a range of methods, but determination of the bioavailability is a problem.
5. Synthetic alternatives use the same chemicals as latex products, and may therefore pose a similar risk of contact dermatitis as latex gloves.
6. To avoid latex allergy or latex allergic contact dermatitis, products with low amounts of allergenic proteins and sensitising chemicals should be used.

Abstract

Gloves play an important but sometimes overlooked role in woundcare. Latex allergy has led many woundcare practitioners to question the place of latex gloves in woundcare, and to look for alternative materials. This paper summarises the opinion of a group of European experts on the role of Natural Rubber Latex (NRL) in latex allergy.

Introduction

On the 27th June 2000, a report entitled "Opinion on Natural Rubber Latex Allergy" was

adopted by the Scientific Committee on Medicinal Products and Medical Devices (SCMPMD). [\[1\]](#)

The report had been requested by DG Enterprise (DG III) of the European Commission, who posed a series of 16 questions on latex allergy and related issues to the SCMPMD. The opinion is based mainly on literature related to the use of medical gloves, and the associated risk of developing a latex allergy.

Sensitisation and Elicitation

Distinguishing between latex sensitisation and latex allergic disease is important. Sensitisation, which can be diagnosed *in vivo* by [skin prick tests](#) or *in vitro* through IgE analyses of blood, shows that the individual has been exposed to Natural Rubber Latex (NRL). Latex allergic disease, usually diagnosed through challenge (provocation) tests, means that a person experiences symptoms after contact with latex products. It is possible to exhibit a latex sensitivity and yet be [asymptomatic](#).

The Epidemiology and Diagnosis of Latex Allergy

The experts were asked whether it was possible to identify populations at risk from latex allergy.

They stated that although it is possible to identify certain groups at risk, such as [atopics](#), patients with multiple operations (such as spina bifida), and health professionals, they acknowledged that it was not possible to determine whether any particular person who has a latex sensitivity will experience a serious reaction when undergoing surgery or after close mucosal contact.

They cite publications where patients have experienced a positive skin prick test (SPT), and experience an anaphylactic reaction during surgery, but who have negative IgE to latex.

Whilst noting that the SPT is superior to IgE detection in diagnosing sensitisation, the committee criticise the quality of many of the published papers dealing with sensitisation diagnosis because there is a paucity of information on the methodology used and the quality of the test materials. The committee conclude that they all have limitations, possibly resulting in non specific responses. Essentially, this means that the tests will sometimes indicate sensitivity where none exists, or may not detect a truly sensitive patient.

When it comes to diagnosing latex allergic disease (that is, exhibiting symptoms after contact with latex products), the committee note that the techniques used for challenge testing (either provocation tests, where the patient is exposed to an extract from a latex product, or use tests, where the patient actually uses the product itself) are adequate for the majority of subjects, but have limitations due to the consistency of materials used. With latex gloves in particular, it is becoming increasingly difficult to find gloves with sufficiently high allergenicity, and false negatives may occur.

The role of proteins

Whilst most studies have demonstrated a relationship between leachable proteins and allergic reaction and/or sensitisation, they also draw attention to studies which did not support this relationship. However, the committee have no reservations about implicating leachable proteins in latex gloves with sensitisation and the risk of experiencing an allergic reaction.

The effect of reducing leachable protein levels does not appear to be as clear cut. Whilst the committee agree that reducing protein levels is of benefit to many, they also note that current analytical methods cannot rule out the possibility of a small amount of residual protein remaining in latex products. In particular, leaching may not reduce allergenic proteins in the same proportion as total protein. The implication is that there will always be a small minority who will react to these low levels of [allergens](#).

Despite their reservations, the committee conclude that measurement of total protein is the best method at present to monitor the allergenic properties of latex products, and

that the risk of sensitisation and allergic reaction can be reduced by minimising leachable protein levels.

Methods of measurement and threshold levels.

Because, in the opinion of the committee, there is presently no reliable method of routinely measuring the allergen content of NRL, they concentrate on two methods used to measure leachable protein levels:

- The [modified Lowry assay](#), and
- [Amino acid analyses](#)

The committee chose these methods because they have been shown to correlate well with skin prick testing, although the superiority of the amino acid technique is highlighted because it is less susceptible to interference from chemicals used during glove production.

They conclude that the modified Lowry is useful to distinguish between gloves containing low, moderate and high protein levels, is simple to perform, and can be used as a routine method of monitoring production. However, they believe that because the limit of elicitation/sensitisation is likely to be close to, or below the quantification limit of the assay, they have concerns about whether it can be used to define a safe level.

In contrast, the amino acid method is known to be more sensitive, and probably can measure proteins in the range where exposure limits for sensitisation and allergic reactions are supposed to occur. The method is, however, time consuming and expensive, and therefore not suitable for routine analyses.

Methods for assaying leachable allergen levels were also considered, such as [RAST-inhibition](#) and [IgE ELISA inhibition](#). These methods measure allergens, the proteins which specifically cause the allergic reactions. However, they rely on a solution of pooled sera from patients with a pre-existing latex allergy, and these solutions cannot be easily standardised and availability is limited.

They also rely on solutions of allergenic proteins (thought, or known to be implicated in latex allergy), but these solutions are also not standardised between different manufacturers and laboratories.

The committee therefore conclude that validated assays for determining allergenic content are not yet widely available, and those that are available have not been standardised. They anticipate, however, that [monoclonal antibodies](#) to individual allergens will be available in the near future, which should overcome these problems.

With regards to establishing safe levels of exposure to leachable proteins and/or allergens for sensitisation, the committee state that it would be unethical to perform the studies which would be required (exposing subjects to increasing doses until they developed a [Type I sensitivity](#)). However, because a dose response relationship has been established for gloves, they believe that in the future a threshold level will be established for which less than 5% of the sensitised population will show a positive reaction.

When questioned on the possibility of determining a threshold level of protein which is needed for sensitisation, the committee responded by noting that these levels are not yet known, and that a low level of protein exposure will reduce the risk for sensitisation and elicitation of symptoms.

Powder

Dipped latex is naturally a very 'grippy' material, and powder (hydrolysed cornstarch) has been used in gloves for decades to enable donning. It is also used during the manufacturing process to help remove gloves from the hand-shaped formers on which they are dipped, with the result that even gloves claiming to be 'powder-free' will contain a low level of powder.

Induction of sensitisation by powder

The committee stated that there is little evidence to suggest that powder plays a significant role in the sensitisation to latex proteins.

In studies comparing powdered and non-powdered gloves, levels of latex allergens were higher in the powdered gloves than the non-powdered gloves, therefore the differences observed in the study population may have been due to the differences in latex allergen levels.

The same criticisms were made of studies where an attempt to correlate airborne allergen levels with sensitisation was made - it was not possible to determine whether the airborne powder or the direct skin-contact with the allergens in the glove were responsible for the sensitisation.

The committee conclude that

"No study has been published, in which patients have been exposed to powdered and powder-free gloves respectively, with similar contents of protein. The influence of powder-bound allergens versus direct skin exposure to the same amount of proteins/allergens, on induction of sensitisation, cannot therefore be assessed."

Elicitation of reactivity

The committee again criticised the quality of some of some studies which purport to show elicitation of symptoms in latex-allergic individuals when exposed to powder from latex gloves via their airways. Although vinyl gloves were used as a control, many of the studies didn't report whether the vinyl gloves were powdered, none of these provocation studies were blinded for the patient, nor were any double blind, placebo controlled studies performed.

Interestingly, the committee could not find any studies in which patients had negative skin prick tests but who had allergic asthma, which responded to airborne, powder-bound latex particles, which would have provided good evidence of a role for powder in sensitisation.

Although the committee concluded that exposure to powder from latex gloves can provoke allergic symptoms in sensitised patients, they state that

"The reaction to glove powder is not dependent on the powder but on the protein carried by the powder. In one study, powder from low protein containing gloves did not provoke symptomatic reactivity. It has not been demonstrated that powdered gloves are more likely to induce sensitisation than powder free gloves, provided the protein content of the gloves is identical."

Although it has been postulated that factors such as pH and endotoxin may act to potentiate the sensitising effect of powder from latex gloves, the committee question this, stating that it is not possible to evaluate the effects of these factors because the core role of powder in sensitisation has not itself been established.

The role of other chemicals.

Latex gloves have a range of chemicals added to them during processing. Leaching of the gloves removes most of these additives, but some remain in the final product at low levels. Some of these chemicals cause a [Type 4](#) (delayed) hyper-sensitivity.

Although the committee, perversely, looked at methods of detection before addressing questions on the risks posed by chemicals, it seems logical to initially look for evidence that the chemicals in NRL pose a risk to individuals.

The fact that chemicals used in the manufacture of NRL are well known as contact allergens is not at issue. These chemicals have been documented to cause delayed hyper-sensitivity (Type IV), resulting in allergic contact dermatitis. Many of the chemicals are used by the manufacturers as [antioxidants](#), [vulcanising](#) agents or [accelerators](#), but some of the chemicals detected are not added directly but are the

result of a chemical reaction in the presence of zinc oxide.

The committee conclude that the chemicals are bioavailable, may penetrate into the skin, and can induce delayed type hyper-sensitivity. However, they caution that:

The risk is not confined to NRL, but may also be presented by most synthetic rubber products containing the same or similar chemicals.

The committee drew a distinction between being able to detect and assay residual chemical levels in gloves and whether those chemicals are bioavailable or clinically relevant. Although patch testing the products demonstrates the bioavailability of the chemicals, it is only possible to identify the chemical responsible for the reaction by patch tests using the pure chemical.

When asked whether there were any reliable test methods available to estimate the bioavailable and allergologically relevant chemicals in NRL, the committee agreed that several techniques were available:

- Gas chromatography (GC),
- Gas chromatography-mass spectrometry (GC-MS),
- High performance liquid chromatography (HPLC), and
- High performance thin layer chromatography (HPTLC)

which allow identification of the chemicals present in the glove. However, because they all require extraction with chloroform or other lipophilic media, it is not possible from these tests to determine whether these chemicals are biologically available for the elicitation of an allergic response.

The committee conclude that at present,

There seems to be no agreement on the best applicable method, and this may be dependent on the chemical to be determined.

Finally, with regard to the best way to manage the risk of these chemicals, the committee considered two main techniques: substitution or reduction in exposure.

Although the risk can be managed by substituting sensitisers with non-sensitisers, they state that this is not currently possible for NRL products (although they do not clarify whether this is because no suitable alternatives are presently available).

The committee thought that substituting strong allergens with weaker allergens to be a "reasonable possibility", but report that this is not simple, as it is difficult to determine which chemicals are less potent sensitisers than others *in-vivo*. The problems are compounded by the fact that the chemicals may react to produce different by-products in the final latex product, and the potency and bio-availability of these products may be significantly different from the originals.

Although no *in-vitro* tests are presently available to measure clinically relevant, bioavailable chemical residues in NRL products, the committee agree that it is logical to reduce the level of chemical residues and thereby reduce the sensitising capacity of the products. They also make the point that ingredient information would be useful so that individuals already sensitised can avoid products likely to elicit a reaction.

Chlorination and latex-free alternatives.

Chlorination has become the most common method of producing powder-free gloves. The committee agree that, although it is known that chlorine and hypochlorite can cause adverse or allergic reactions, there is no published data on such reactions to chlorinated gloves.

With regard to the environmental concerns of chlorination, they note that although the chlorination process uses vast quantities of water, processing non-chlorinated gloves to

attain the same low protein levels consumes similar amounts.

The committee state that chlorination may lead to a decrease in the tensile or tear strength of NRL over time, but do not cite any evidence for this.

Many latex-free alternatives are now available, including PVC, neoprene, polyurethane, and various copolymer gloves, which the committee believe to show *"good to moderate performance"*.

However, many of the chemicals used in these gloves are the same ones used in latex glove production, and therefore pose the same types of contact dermatitis risks as latex gloves. The committee conclude that there is only limited data available on the risks associated with these new materials, and note the high price for some of these products.

Glossary

Accelerators

Accelerators are used to increase the rate of the vulcanisation process in latex manufacture.

Allergen

An allergen is an [antigen](#), usually protein, that elicits an allergic reaction.

Amino Acid analyses

A HPLC laboratory assay, which is used to measure total amino acid levels in gloves, and thereby total protein levels. Less susceptible to interfering substances than the modified Lowry assay, but more expensive and time-consuming.

Antigen

A substance that can trigger an immune response, resulting in antibody production. All allergens are antigens, but all antigens are not allergens.

Antibodies

Proteins produced by lymphocytes which neutralize antigens or foreign proteins. Formation of IgE antibodies (immunoglobulin E) may result in asthma, rhinitis or other Type I reactions when the individual is exposed again to the allergen which caused the initial IgE antibody formation.

Antioxidants

Chemicals added to latex to prevent degradation of the latex through contact with air.

Asymptomatic

Asymptomatic individuals do not exhibit symptoms of a disease, even though they may have a positive diagnoses.

Atopic

An Atopic is someone with a pre-disposition, usually genetic to developing IgE mediated responses to common allergens.

IgE ELISA inhibition assay

Enzyme linked immunoabsorbant assay, based on inhibition of the binding of

human latex specific IgE antibodies to allergenic proteins after incubation of the serum with extracts of latex products.

Modified Lowry Assay

A laboratory assay used to measure the total amount of protein in latex products. The method is detailed in European standard EN-455 part 3.

Monoclonal antibodies

[Antibodies](#) which have been cloned from a culture of cells in which all the cells derive from a single cloned cell. They produce antibodies with a single specificity that are, therefore, known as monoclonal antibodies

RAST inhibition test

Radioallergosorbent test, based on inhibition of the binding of human latex specific IgE antibodies to allergenic proteins after incubation of the serum with extracts of latex products.

Skin Prick Test

The Skin Prick Test (SPT) is usually thought of as the gold standard in diagnosing latex allergy. A drop of latex exudate or extract is placed on the skin and a lancet or needle is used to puncture the skin at the site of the exudate. A drop of normal saline is also placed on the skin and similarly the skin is punctured as a control. The reaction from both is compared.

Type I sensitivity

Type 1 sensitivity is an immediate reaction that happens within minutes to 2 hours, depending on route of absorption and dose of allergen. The reaction leads to release of histamine and other chemicals, leading to local and systemic changes, including vasodilatation, smooth muscle contraction (bronchospasm) and increased vascular permeability. In the most serious cases, anaphylaxis may result. It is predominantly caused by protein which occurs naturally in NRL.

Type 4 sensitivity

Type 4 sensitivity is a delayed response. It occurs 6 to 48 hours after contact and includes erythema, itching, oedema, cracking of the skin and red swollen rashes that appear only on skin areas that touched the latex. It is predominantly caused by an allergy to the residues of accelerating agents used during latex manufacture.

Vulcanisation

The process of treating raw latex by subjecting it to heat and sulphur to cross-link the rubber particles, producing a latex film which has excellent elastic properties.

References

1. Scientific Committee on Medicinal Products and Medical Devices. Opinion on natural rubber latex allergy. European Commission, June 2000.