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**SCIENTIFIC COMMITTEE ON MEDICINAL  
PRODUCTS AND MEDICAL DEVICES**

**Opinion  
On  
Natural rubber latex allergy**

**Adopted by  
The Scientific Committee on Medicinal Products and Medical Devices  
On 27 June 2000**

# Natural Rubber Latex Allergy

## *The Opinion of the Scientific Committee on Medicinal Products and Medical Devices*

*Adopted on 27 June 2000*

### **Questions**

DG Enterprise (DG III) has asked the SCMPMD to express its opinion on risks associated with the use of medical devices manufactured from natural rubber latex. A total of 16 questions dealing with various aspects of allergy to natural rubber products were presented to the SCMPMD.

### **Background**

Description of the problem

Medical devices made from Natural Rubber (NR) may cause allergic reactions to patients and users because of allergy to proteinaceous components or chemical constituents of the material. Allergic reactions to proteinaceous allergens in NR products have the potential to provoke life threatening (anaphylactic) reactions in sensitised individuals (type I allergy). This risk is present in health care settings, and in the general public, following contact with NR products or possibly due to cross reactions to different fruits. Allergic contact dermatitis (type IV allergy) caused by chemicals present in NR products is a well known, and frequent, cause for workers compensation claims.

Groups of Medical Devices containing natural latex

The following common groups of medical devices produced in the natural rubber latex (NRL) process and the dry natural rubber (DNR) process have been identified.

NRL: medical gloves (examination/surgical gloves), condoms, catheters, tracheostomy tubes, wound drains, and dental rubber dam (Kofferdam).

DNR: adhesive tapes, elastic bandages, anaesthesia masks, syringe plungers, intravenous injection ports, pads and contraceptive diaphragms.

### **Answers**

The answers to the various questions were based on information available in the scientific literature and various public reports. The results of this inventory are presented below in detail for each separate question followed by a conclusion.

## Executive Summary

In this document the view of the Scientific Committee on Medicinal Products and Medical Devices (SCMPMD) is presented regarding the risks for the development of allergy during the use of natural rubber latex products. The opinion is mainly based on literature focused on the allergy risk during the use of medical gloves. Indeed besides atopics risk groups identified for the development of latex allergy are the medical profession, and patients needing multiple surgery such as children with congenital malformations, two groups frequently exposed to latex medical gloves.

It is important to make a distinction between latex sensitisation and latex allergic disease. The diagnosis of latex sensitisation can be made both by *in vivo* skin prick test (SPT) with soluble antigens and/or *in vitro* determination of specific IgE in blood samples. For the diagnosis of latex allergic disease challenge (provocation) tests can be used. Both for the demonstration of latex sensitisation and latex allergic disease the lack of standardised materials hampers the diagnosis which makes comparison of the various published results difficult.

For latex medical gloves a relationship between leachable protein levels and the risk of allergic reaction or sensitisation has been demonstrated in several studies, either directly or indirectly. So, the risk for latex sensitisation and/or allergic reactions can be reduced by minimising the amount of leachable proteins. For the determination of the amount of extractable proteins of medical gloves two methods are available, the modified Lowry method and the amino acid analysis method. Both methods have their advantages and disadvantages. Both methods detect all proteins present and not just the allergenic proteins. Some chemicals can interfere with the results in the modified Lowry assay. The assay gives the possibility to distinguish between low, moderate and high protein values, which is relevant in prevention. The method is relatively simple to perform and can be used in production control. However, since the limit of elicitation/sensitisation is likely to be close or below the quantification limit of the assay, it can not be used to define a safe protein level. Amino acid analysis can technically be used for all rubber products, but has not yet been clinically validated for other products besides gloves. It is a rather sensitive method and can probably measure proteins in the range where exposure-limits for sensitisation and elicitation are supposed to occur. The amino acid analysis method seems a good candidate as reference method but is in contrast to the modified Lowry method, not suited for current production control.

For the determination of the allergen content of medical gloves two assays are available both based on the same (inhibition) principle, the RAST- inhibition and ELISA-inhibition (RAST, radioallergosorbent test, ELISA enzyme linked immunosorbent assay). However, until now it has not been possible to standardise these assays, because of a lack of standardised human antibodies and/or standardised allergens. Assays using pooled rabbit antiserum do not provide an accurate assessment for allergenic activity in humans as the antigens recognised may differ. The possibility remains that assays measuring concentrations of selected allergens by immunological methods will not cover all eventualities. Yet, such methods are likely to offer higher specificity and precision than total leachable protein assays. The measurement of total leachable protein is currently a useful method to estimate the allergenic potential of a

latex glove. However, this need not be the case for all natural rubber latex products. At present, a practical approach might be to determine total leachable proteins by amino acid analysis in the finished products during process validation, and use these data as part of the technical documentation of the production process. A method for process control may be the modified Lowry assay as described in the standards of CEN and ASTM if it is validated against the amino acid analysis for the particular latex formulation in the manufacturing process.

The lowest dose (or threshold level) of proteins for inducing sensitisation and/or elicitation of an allergic response has not been established. For some rubber products, especially gloves, a dose response relationship has been demonstrated. For the elicitation of an allergic (anaphylactic) reaction in symptomatic allergic patients, provocation studies may be performed to determine the lowest dose eliciting a response. So, it is possible that in the future a threshold level can be determined for which less than 5% of the sensitised population will show a positive reaction. A low level of protein exposure will obviously reduce the risk for sensitisation and elicitation of symptoms.

With regard to the presence of glove powder it has been established that latex proteins bind to powder particles present on cornstarch powdered gloves. 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. Provocation studies show that exposure to powder from latex-gloves can provoke allergic symptoms (asthma, rhinoconjunctivitis, urticaria, anaphylaxis) in latex-sensitised patients. As the influence of powder on sensitisation has not been demonstrated, powder characteristics that may be relevant for sensitisation cannot be established.

The presence of biologically relevant chemicals, e.g. chemicals known to induce sensitisation, in latex medical gloves can be demonstrated by various methods including gas chromatography (GC), gas chromatography-mass spectrometry (GC-MS), high pressure liquid chromatography (HPLC) and high performance thin layer chromatography (HPTLC). Quantification of chemicals present in medical devices such as medical gloves and determination of bioavailability is still a problem. There seems to be no agreement on the best applicable method, and this may be dependent on the chemical to be determined.

The induction of allergic contact dermatitis by chemicals present in natural rubber latex is well demonstrated. The risk for allergic contact dermatitis, however, is not confined to natural rubber latex products but may also be presented by the currently available synthetic alternatives to natural rubber latex products. These alternatives may pose a similar risk for contact dermatitis as latex gloves depending on the chemicals used during the production process. The risk can theoretically be reduced by substitution of the most potent sensitisers with less sensitising chemicals, but systematic dose-response-studies ranking these sensitisers are not (yet) available in the scientific literature.

In conclusion, risk groups for latex allergy are atopics, and subjects frequently in contact with latex medical gloves, such as the medical profession and patients needing

multiple surgery. In order to avoid latex allergy or latex allergic contact dermatitis, products with low amount of residuals of allergenic proteins and sensitising chemicals should be used. Latex-sensitised subjects must avoid direct contact with natural rubber latex products. Information on the package of medical devices on the presence of natural rubber latex is therefore essential. Medical gloves and condoms of alternative materials are available. In general, ingredient information on rubber products may prevent allergic responses in those subjects allergic to latex proteins and/or chemicals.

## Full Opinion

### **Preamble**

In general, a latex is a watery suspension (or dispersion) of small polymeric particles (0.02 to 2  $\mu\text{m}$ ), but from the botanical point of view the term latex is used for liquids derived from various plants. In the following the term latex is used as synonym for natural rubber latex (NRL) from the *Hevea brasiliensis* tree. The latex fluid from the *Hevea brasiliensis* tree consists of about 34% rubber polymer (poly-isoprene), 2% proteins, 1.6% resins, 1.4% sugar, 0.6% ash, 0.4% fatty acids and 60% water (Mellstrom, 1994). The latex undergoes several complex manufacturing processes in which chemicals are added to act as preservatives, anticoagulants, accelerators for vulcanisation and antioxidants. The latex proteins contribute to the characteristic properties of latex products such as elasticity, tensile strength and barrier function. Although the manufacturing process of dipped products (medical gloves, condoms, catheters, balloons) includes leaching phases for the removal of excess chemicals and proteins, residues of chemicals and/or proteins remain.

It is not known why latex products and especially latex gloves are such potent sensitisers for allergies. It seems likely that the frequent and/or prolonged use of latex gloves contributes to the allergy induction. In addition, it is possible that some proteins are changed during the manufacturing process such that they become allergenic or that their allergenicity increases.

The condition now known as "Latex allergy" is caused by the proteins of the *Hevea brasiliensis* tree present in the products manufactured from latex. However, allergy to rubber products not only is caused by the proteins but also by the chemicals and/or residues thereof.

Generally the chemicals induce a delayed type hypersensitivity (DTH), and the proteins an immediate type hypersensitivity ranging from mild local wheal and flare reactions to anaphylaxis. The former is mediated by immune (T) cells and generally occurs hours to days after contact with the allergen, while the latter is mediated by antibodies (IgE) and in sensitised persons symptoms occur within minutes to hours. The most common adverse reaction among glove users is irritant contact dermatitis, which is a non allergic response and should not be misdiagnosed as allergy. This irritant contact dermatitis may predispose for sensitisation to allergens in the gloves used.

Although allergy by its nature is a disease entity the immune reactions involved belong to the basic repertoire of the immune system of an individual. It is the extent of the immune reaction and its detrimental effects that makes it a disease entity i.e. symptomatic allergy. For immune responses in general and therefore also with respect to allergy there is a marked difference between becoming sensitised (the induction phase) and antigen/allergen contact after being sensitised (the challenge phase). Generally for the challenge phase lower amounts of antigen/allergen are needed than for the induction phase. One can become immunised/sensitised after one or a few contacts with a relatively high dose of an antigen/allergen, but frequent contacts with low doses over a prolonged period of time may also result in sensitisation, such as probably occurs in the case of latex allergy. Each subsequent contact then may result in a more or less severe allergic reaction.

Most of the literature dealing with allergy from rubber products is based on studies with medical gloves manufactured from natural rubber latex (NRL), while literature on other NRL products like condoms is limited and literature on dry natural rubber, such as used in car tyres, is scarce.

The opinions expressed below are provided on the basis of a series of questions posed to the Scientific Committee on Medicinal Products and Medical Devices

***Question 1. Are the available epidemiological data adequate to identify a risk in patients or users? Can populations at particular risk be identified?***

***Opinion***

Risk groups for immediate type sensitisation to natural rubber latex (NRL) proteins, when using rubber products, are atopic persons (personal history of atopic eczema, hay fever or asthma) and those with hand dermatitis. Among different occupations health care workers show the highest prevalence of latex allergy, up to 17 % depending on methods used for diagnosis and the allergenicity of the latex gloves used. (Turjanmaa 1987, 1995b, 1996, Vandenplas 1995b). Latex allergy has been described in several other occupations where protective gloves are used, e.g. in housekeeping personnel, hairdressers, greenhouse workers, workers in textile factories (Carrillo 1995, Pisati 1998, Sussman 1995, Van Der Walle 1995). Dental students show a low prevalence of latex allergy at the beginning of their studies but increased numbers of them become sensitised during the years of studying suggesting that the use of gloves is an important cause of sensitisation (Heese 1995, Levy 1999). Atopic children, especially those with food allergy, also belong to risk groups for latex-allergy, pacifiers and balloons being probably the most important sensitisers in this group (Niggeman 1998, Novembre 1997, Porri 1997, Ylitalo 1997).

Among patients, the most severe reactions have occurred with barium enema examinations in the USA, where 15 patients died because of the mucosal contact to the latex balloon used (Fezcko 1989). Spina bifida patients are the largest single risk

group with latex sensitisation up to 60 % (Kelly 1994). However, children with other congenital malformations also belong to risk groups because of the frequent contact to latex materials during repeated operations (Ylitalo 2000).

Latex allergy seems to be less frequent in the general population, clearly < 1% (Turjanmaa 1996). Workers in rubber estates and latex glove factories in South East Asia show low sensitisation rates of < 2% (Sri-akajunt 1997). Higher prevalences have been reported but the differences in the findings based on serological assays may relate to the non specificity of these assays and need to be further investigated (Liss 1999). Incidence studies are only few, one giving no clear increase in Canada, and another showing an increase in Finland (Jolanki 1999, Liss 1997).

There is no knowledge of who among the latex sensitised persons will experience serious reactions when undergoing surgery or having close mucosal contact with latex products. There are publications describing patients with a positive skin prick test (SPT) but negative specific IgE to latex and who are still experiencing an anaphylactic reaction during operation (Leynadier 1989).

In conclusion, it is possible to identify risk groups for latex allergy such as atopics, the medical profession, and patients with multiple operations like spina bifida children. However, the quality of most epidemiological studies on latex allergy is generally poor. Groups studied with adequate methods are too small for epidemiological analysis and large population studies are often performed with methods not allowing correct diagnosis.

## ***Question 2. How adequate are the techniques for diagnosing sensitisation to natural rubber?***

### ***Opinion***

Sensitisation means that a person has developed after contact with a latex product IgE to latex proteins and/or has a positive SPT reaction. When symptoms are present after secondary contact the condition is called allergy.

IgE reacting with latex proteins can be determined with common immunological techniques. For latex proteins specificity and sensitivity may vary depending on the assay used (Turjanmaa 1996). For the SPT there is at least one standardized allergen on the market in Europe (Turjanmaa 1997). In addition there are several non standardized SPT allergens on European market, where sensitivity and specificity are not defined (Turjanmaa 1995a). Eluates made from latex gloves have been used for the diagnosis of latex allergy for a long time,, but the decreasing and often unknown allergenicity of latex gloves makes the method difficult to use generally (Turjanmaa 1997, National Agency for Medicines 1999).

The European Academy of Allergy and Clinical Immunology has published guidelines for performing skin prick tests (Dreborg 1989). Unfortunately in many published papers there is information neither on the methodology of testing nor on the quality of the test material, which makes comparison of different results difficult.

In conclusion, both SPT and/or determination of specific IgE can be used for diagnosis of latex sensitisation. However, these techniques each have their limitations, possibly resulting in non specific responses. The sensitivity of the SPT is superior to that of the detection of specific IgE to latex. However, there are very few publications dealing adequately with the problem. Sensitivity and specificity can only be determined when the test results are compared to the test results of a challenge to latex (see below) (Brockow 2000, Turjanmaa 1988).

### ***Question 3. How adequate are the techniques for diagnosing allergic disease to natural rubber?***

#### ***Opinion***

Allergy to NRL means that a person has symptoms from contact to latex products and in addition the immunologic pathomechanism is verified either with a positive SPT or specific IgE antibodies to latex.

Challenge (provocation or use test) can be performed either on skin, nose or lungs. So far, the methods are not standardised. There are publications on skin provocation in a relatively well described manner, but the problem is that the allergenic glove material used is not commonly available (Turjanmaa 1996, Kurtz 1999). If provocation tests are performed with a low-allergenic glove, false negative results may occur (National Agency for Medicines 1999). Some gloves contain a milk protein, casein, which may give positive results when challenging persons who are allergic to milk but not to latex (Ylitalo 1999). Sensitivity of skin provocation tests may be increased by performing the test on damaged skin (Hamilton 1997). Lung challenges are published from a few centers where the problems are the same as with the skin. Both tests need experienced doctors and equipment for treating anaphylactic reactions which may occur (Jaeger 1992, Vandenplas 1995b).

If the patient has experienced an intraoperative anaphylaxis and SPT and/or specific latex IgE antibodies are positive and no other cause could be verified for the reaction, a diagnosis of latex allergy may be considered established and the challenge test should not be done because of risk of an anaphylactic reaction (Turjanmaa 1996).

It is important to make a difference between sensitisation and allergy to latex. There are many papers dealing with sensitised persons with no anamnestic symptoms but once the challenge is performed the reaction often turns out to be positive giving the patients useful information what may happen when they touch latex products (Kim 1999, Ylitalo 2000). In addition, cross reactions to various fruits and vegetables are common in latex allergic subjects and may interfere with the diagnosis (Ylitalo 2000).

In conclusion, the techniques for diagnosing latex allergy are adequate for the majority of subjects. However, there are some limitations with regard to the materials available for diagnostic testing and the occurrence of cross-reactions which influence the diagnosis in a minority of subjects.



***Question 4. Is there a direct relationship between leachable protein levels and risk of latex allergy and/or sensitisation?***

***Opinion***

For many allergens it is well known that there is a direct relationship between allergen concentration during exposure and the risk of sensitisation. This is shown in retrospective studies for example for mite and cockroach allergens (Sporik 1999) or  $\alpha$ -Amylase (Nieuwenhuijsen 1999). In addition for latex the prevalence of sensitisation was significantly higher in groups using powdered gloves with high protein content than in those using powder-free gloves with low protein content (Allmers 1998, Levy 1999). However, generally it is rather difficult if not impossible to quantify exactly the current or historical exposure to leachable latex proteins in any subject.

The level of exposure to proteins is quantified by measuring leachable protein levels per product or per surface area or weight of the products. Exposure is a prerequisite for the risk of sensitisation, but the actual sensitising risk depends on many factors, including exposure site, amount of allergen, frequency and duration of contact, and genetic background (in particular atopy) of the individual. Other difficulties for determining exposure of certain populations are:

- natural rubber products are rather ubiquitous, so exposure may occur in occupational and non-occupational environments.
- the capability of proteins to penetrate through skin and mucous membranes varies with the condition of the surface.
- measurements of protein levels depend on the methods used for extraction and protein determination, and conditions may vary for the different types of latex products.

The methods used for quantification may not always reflect the biological availability of the proteins during product use, but merely indicate the potential release of the proteins present. A possible direct relationship between exposure to leachable protein levels and risk of latex allergy and/or sensitisation can only be documented on experimental animals, where exposure to latex proteins can be controlled. This is not achievable with humans due to ethical restrictions.

Frequent exposures to latex products are statistically significantly correlated with a higher prevalence of latex allergy in healthcare workers (Liss 1997, Wrangsjö 1994a, Yassin 1994, Lagier 1992), children with multiple operations (Kelly 1994, Konz 1995), and other subjects with a high, but not exactly quantified exposure to latex products (Sri-akajunt 1997, Amin 1998, Tarlo 1997, Levy 1999). Statistically significant correlations between leachable protein levels from latex products, and allergen content/activity, as assessed by allergen specific IgE ELISA-inhibition, RAST-inhibition and skin prick testing were demonstrated (Beezhold 1996, Palosuo 1998). In studies of dental students (Heese 1995, Tarlo 1997, Amin 1998, Levy 1999) an increase in the prevalence of latex allergy was observed with each year of dental school. Studies involving spina bifida children indicate a clear relationship of sensitisation with the number of surgical procedures performed (Mazon 1997).

Elicitation of allergic reactions by skin prick testing or by airway provocation have been demonstrated in several studies to be associated with the protein content (European Commission 1998, Bauer 1998a, Brehler 1997, Palosuo 1998, Vandenplas 1995a). However, although many studies have demonstrated a relationship between leachable protein levels and the risk of latex allergy and/or sensitisation, studies have also been presented which did not support such a relationship (Bauer 1997).

It is known that only a limited number of proteins from latex source material are recognised by IgE antibodies from sensitised subjects (Alenius 1994). In this respect little is known about extracts from latex products.

Most studies have focussed on the water-leachable protein moiety as being the sensitising agent. Many of the proteins have been characterised (Czuppon 1993, Kurup 1993, Alenius 1995, 1996, Akasawa 1996, Slater 1996, Breiteneder 1998, Posh 1998), but there seems to be little information about other possible antigenic or allergenic substances in the latex, e.g. the carbohydrate or lipid moiety of the proteins. The leaching process during production is performed with aqueous solutions and any lipophilic or hydrophobic substances will remain in the latex products, so in theory these substances may contribute to the subsequent clinical exposure to antigenic/allergenic substances.

In conclusion, for latex gloves a relationship between leachable protein levels and the risk of allergic reaction or sensitisation has been demonstrated in several studies, either directly or indirectly.

### ***Question 5. Can the risk be managed by controlling leachable protein levels?***

#### ***Opinion***

Since increased exposure to latex proteins leads to a higher prevalence of sensitisation, the logical conclusion is that less protein reduces the incidence of sensitisation (Boyer 1995, Vandenplas 1995a, Laoprasert 1998). Indeed low protein/allergen gloves seem to have reduced the prevalence of (Turjanmaa 1999).

However, the risk of allergy cannot be completely controlled by reducing the amount of leachable protein, even though the reduction will be of benefit to many. There are major and minor allergens among the leachable proteins and the analytical methods available today cannot totally rule out the possibility of any residual allergen in latex products. At the moment measurement of total protein is the best available way to monitor the allergenic properties of latex products, but it may not be sufficient. The total protein content is not necessarily equivalent to allergen content. The leaching process during production reduces the amount of proteins, but the reduction in specific or total allergenic protein is not necessarily in the same proportion as the reduction in proteins.

In conclusion the risk for latex sensitisation and/or allergic reactions can be reduced by minimising the amount of leachable proteins.

***Question 6. If so, are the currently available test methods adequate for this purpose in view of their quantification limit?***

***Opinion***

The measurement of leachable proteins is a substitute for direct determination of allergens. However, at present there is no method routinely available that can reliably evaluate the allergen content of NRL products. The method used for protein determination should avoid interference from non-allergenic compounds. Several methods have been considered. Few of these have been correlated to biological activity. Two methods, the modified Lowry and an amino acid analysis have been described and standardised for some types of products, making comparison of different alternative brands of these products possible. Only these standardised methods are considered here.

Modified Lowry assay measures total extractable protein. It is a colorimetric method, and uses a reference protein standard for comparison. It is strongly influenced by the tyrosine and tryptophan content of the proteins, which may vary in the products tested. The values obtained are relative to the reference protein (albumin or other defined purified protein). There is no standard reference latex protein available.

The method is technically suitable for most of the currently available gloves. The main disadvantage is the interference with some chemicals; e.g. Diphenylguanidin (Chen 1997) may give false high values especially when analysing foam rubber or other products in which these chemicals are present. Turbidity of extracts caused by saponins can occasionally disturb the whole measurement (European Commission 1998).

Standardised methods for extraction procedures and protein measurements are described in the standards EN-455-3 for gloves, and ASTM D 5712-99 for latex products in general (CEN 1999, ASTM 1999). The limit of quantitation was reported as 10 µg/g (extraction and detection, European Commission 1998), and 14.1 µg/ml (extraction and detection, ASTM 1999). The modified Lowry method is validated for gloves and condoms. In foams for example it is not possible to measure reproducibly latex proteins by the modified Lowry method (Havinga 1999). The modified Lowry method does not distinguish between sensitising and non-sensitising proteins. Added proteins, such as casein, can not be distinguished from latex proteins.

Amino acid analysis can also be used to quantitate protein amounts (EN 455-3, CEN 1999). It measures the amino acid content of proteins after hydrolysis in hydrochloric acid (6N). It is independent of amino acid composition, structural differences and the size of proteins. There are no interferences in the assay itself. The method requires expensive advanced instruments and experienced staff. It is not suitable for process control. Similar to the modified Lowry method amino acid analysis does not distinguish between sensitising and non-sensitising proteins and/or latex and other proteins.

The modified Lowry and the amino acid analysis methods were validated clinically by skin prick testing using a selection of gloves. A good correlation was found for both methods (European Commission 1998). The amino acid analysis method, however, was superior as it could be used for all gloves tested independent of the chemicals present in the gloves.

The amount of protein present in extracts of gloves, and their reactivity in a panel of positive reacting patients needs to be established. However, so far the number of clinical studies where the amount of protein has been measured is very limited. In one study the proportion of sensitised patients reacting to a skin prick test decreased considerably when the protein amount was below 70 µg per gram glove (Yip 1994). Differences in sensitising capacity is described between “low protein gloves” with a protein content below 25 µg/g glove, compared to “high protein gloves” with a protein content of 300-600 µg/g glove (Levy 1999). In general measurements of the protein content of gloves was found to vary from 0 to more than 1000 µg/g glove (Bauer 1997).

Conclusion: Both detection methods (Modified Lowry and amino acid analysis) have some advantages and disadvantages. The modified Lowry method can only be used for some rubber products, due to interferences with different chemicals. The method can be reproducible under ideal conditions, but differences between laboratories may be expected. The modified Lowry method gives a possibility to distinguish low, moderate and high protein values, which is relevant in prevention. Furthermore the method is relatively simple to perform and can be used in production control. However, since the limit of elicitation/sensitisation is likely to be close or below the quantification limit of the assay, it can not be used to define a safe protein level.

Amino acid analysis can technically be used for all rubber products, but has not yet been clinically validated for other products besides gloves. It is a rather sensitive method and can probably measure proteins in the range where exposure-limits for sensitisation and elicitation are supposed to occur. The amino acid analysis method seems a good candidate as reference method but is in contrast to the modified Lowry method, not suited for current production control.

***Question 7. Is there a reliable assay for the allergens leachable from natural rubber products?***

***Opinion***

There are two assays available for detection of allergenic proteins present in natural latex products. These assays are based on the same principle and detect proteins, which are recognised as allergens in man e.g., RAST-inhibition and IgE ELISA-inhibition. (Yunginger 1994, Bauer 1997, Palosuo 1998). (RAST, radioallergosorbent test, ELISA, enzyme-linked immunoabsorbant assay). The principle of these assays is 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. The reduction in reaction of the antisera with the allergenic control proteins immobilised on a solid phase, is a measure for the presence of allergenic proteins in the extract.

The assays are performed as follows:

Step 1: The standard/reference control allergens are fixed on a solid phase (cellulose sponge in RAST-inhibition or polystyrene in ELISA-inhibition). This may be done by the manufacturer (RAST) or by the laboratory (ELISA-inhibition).

Step 2: The IgE-antibodies in the serum of a patient binds to the fixed allergens.

Step 3: The now fixed IgE-antibodies are determined by a conjugated anti IgE antibody.

For RAST- or ELISA-inhibition testing of extracts of latex products, the IgE-antibodies in a well defined pool of patients sera are pre-incubated with the extract prior to step two. Depending, on the presence of allergenic protein in the extract part of the IgE-antibodies are bound to the soluble allergenic proteins, and thus not further available for binding to the control solid phase allergens in the RAST or ELISA (step two and three). The concentration of allergens is determined by comparison of the results to those of standard allergen solutions.

However, there are limitations to the use of these assays.

1. The fixed allergens are not standardised, they vary between different manufacturers and different laboratories. Most of the recent investigations were not performed on the extract of gloves or other latex products, but on proteins isolated from latex fluids. A lot is known about proteins in the latex serum (the fraction of latex fluid, that is not present in the latex product) and the reaction of patients IgE to those proteins, little is known about the leachable proteins from latex products. Many of the proteins are modified and are break-down products following alkaline hydrolysis during the manufacturing process.
2. The IgE-antibody pool of patient sera is not standardised and cannot be prepared reproducibly. In addition the availability of these kind of serum pools is limited. Monoclonal antibodies against similar epitopes are an option that probably will become available within the near future.
- 2 There is no standard reference allergen solution available.

Antibodies for the detection of antigens in the latex fluid can be raised in animals by active immunisation. The profile of the antibodies reflects the antigens present in the materials used for immunisation. Not all antigens present in the latex fluid are present in the latex products and may be allergenic in humans. One such assay is described in a recently published ASTM standard D 6499-00 (ASTM 2000). This ASTM standard uses polyclonal rabbit antisera specific for natural rubber latex proteins.

However, the standard clearly states: "Although this method detects antigenic proteins, it should not be considered as a measure of allergenic proteins. Correlation of proteins/antigens levels with the level of allergenic proteins has not been fully established".

In conclusion validated assays for determining the amount of leachable allergens are not yet widely available. In some centres assays for the quantitative determination of leachable allergens are operational. However, until now it has not been possible to standardise such assays, because of a lack of the availability of standardised human

antibodies and standardised allergens. Assays using pooled rabbit antiserum do not provide an accurate assessment for allergenic activity in humans. Probably monoclonal antibodies to individual latex allergens will be available in the near future and overcome the problem of limited availability of specific antisera.

***Question 8. If not, can such an assay be developed? Is an assay for total leachable protein a satisfactory substitute?***

### ***Opinion***

For reasons discussed in the chapter mentioned above the possibility remains that assays measuring concentrations of selected allergens by immunological methods will not cover all eventualities. Yet, such methods are likely to offer much higher specificity and precision than total leachable protein assays.

The measurement of total leachable protein is currently a useful method to estimate the allergenic potential of a latex glove (European Commission 1998). However, this need not be the case for all NRL products. When specific assays designed for measuring actual allergens become available, it is likely that they will replace the measurement of total leachable proteins.

At present, a practical approach might be to determine total leachable proteins by amino acid analysis in the finished products during process validation, and use these data as part of the technical documentation of the production process. A method for process control may be the modified Lowry assay as described in EN 455-3 if it is validated against the amino acid analysis for the particular latex formulation in the manufacturing process.

***Question 9 Is there a means of estimating levels of exposure to leachable protein and/ or leachable allergens that:***

***Induce sensitisation?***

***Elicit symptoms in sensitised individuals?***

### ***Opinion***

For an estimation of the doses of latex exposure inducing sensitisation, induction studies in humans would be needed. However, induction studies in humans cannot be performed, as it is unethical to sensitise healthy subjects. Skin or airway exposure studies from which a lowest sensitising dose could be deducted are lacking. Induction studies in animals have not been carried out so estimates of a lowest sensitising dose cannot be obtained. When performing such a study both single dose and repeated dose over a time period has to be taken into account.

Elicitation studies in previously sensitised individuals have been performed both after skin and airway provocations (Vandenplas 1995ab, Valentino 1994, Allmers 1997, Jaeger 1992, Brugnami 1995, Ho 1996, Pisati 1994, Orfan 1994). In few of these studies the exposure has been measured and then mainly as arbitrary units. As already mentioned, the results from different immunological assays may not be comparable.

With skin prick tests limits for elicitation of positive reactions might be established (European Commission 1998). In other studies it has been found that the number of positive reacting individuals decreased with a decreasing amount of allergens (Yip 1994, Beezhold 1996, Heese 1997, Palosuo 1998), while a definitive limit for elicitation could not be established as the values obtained for the amount of allergens neared the detection limit. In addition, in sensitised individuals the size of the skin prick test reaction correlated with the protein content of glove extracts (Beezhold 1996, Palosuo 1998).

Airway provocation tests indicated that symptomatic responses were absent when the allergen content in the air was less than 0.6 ng/ cubic meter, which was the detection limit of the assay (Baur 1998ab). Also gloves with a protein content below approximately 30 µg/g did not provoke asthmatic symptoms during airway challenge (Vandenplas 1995a). When the air exposure was reduced below the detection limit during a period of one year a reduction in the latex specific IgE was noted in sensitised patients (Allmers 1998)

In conclusion, a limit for protein and/or allergen exposure cannot be established even when sensitive immunological methods are available. Also the uncertainty about biological availability of the allergenic proteins in different rubber products limits the use of the detection methods, including the extraction method. For some rubber products, especially gloves, a dose response relationship has been demonstrated, and it is possible that in the future a threshold level can be determined for which less than 5% of the sensitised population will show a positive reaction.

***Question 10 Can threshold levels for these biological responses be established that could form a scientifically valid basis for risk management?***

### ***Opinion***

Threshold levels of proteins for the induction of natural latex allergy can not be determined as the dosages needed for sensitisation are not known. For the elicitation of an allergic (anaphylactic) reaction in symptomatic allergic patients, provocation studies may be performed to determine the lowest dose eliciting a response. (European Commission 1998, Yip 1994, Beezhold 1996, Palosuo 1998, Bauer 1998ab, Vandenplas 1995a). A low level of protein exposure will obviously reduce the risk for sensitisation and elicitation of symptoms.

***Question 11 Significance of glove powder for induction of sensitisation and elicitation of symptoms:***

## *Opinion*

Powder is used as lubricant to ease donning of the gloves, but small amounts of powder are also used during manufacturing to facilitate stripping of the newly made glove. This explains why even powder-free gloves may contain minute amounts of powder. Latex-allergens have been demonstrated to adhere to the cornstarch glove-powder (Beezhold 1992, Tomazic 1994). The glove powder acts as protein carrier resulting in airborne allergens.

### Induction of sensitisation

Experimental induction of sensitisation via upper and lower airways has been demonstrated in animals with solutions of latex-allergens, but not with powder as a carrier (Reijula 1994, Kurup 1994, Xia 1999). No human experimental sensitisation studies have been published. Sensitisation due to inhalation of airborne latex allergens has been suggested in a few case reports where no direct latex-contact to skin seemed to have taken place. The sensitisation route is difficult to prove, however, since latex-contact from domestic use or contact during surgery and dental treatment is difficult to rule out (Vandenplas 1996).

The influence of powder on the sensitisation rate in exposed populations was determined in some cross-sectional studies and one incidence study (Levy 1998, 1999, Brehler 1997, Sussman 1998). In the incidence study the study-population was selected, as persons already sensitised were excluded. The possibility to find statistically significant differences in this study seems poor but was not calculated. The levels of latex-allergens in the powdered and powder-free gloves were not comparable in any of these studies. Thus, the differences observed may as well be due to differences in direct skin exposure to latex-allergens rather than the influence by powder, or due to the airborne exposure. The level of IgE in sensitised patients seems to be correlated to the level of latex-allergens in the air, but the IgE level is also correlated to the amount of latex-allergens in the gloves (Allmers 1998). The use of powder-free latex-gloves/synthetic gloves or low-allergen, powdered gloves is reported to reduce the amount of latex-allergens in the air (Bauer 1993, Allmers 1998, Tarlo 1994, Heilman 1996). In addition, air ventilation and the number of gloves handled also has a significant influence on the amount of latex-allergens in the air (Allmers 1998, Tarlo 1994, Heilman 1994, Swanson 1994).

Powder may also contribute to skin irritation, and thereby facilitate penetration of latex-allergens via the skin (Brehler 1998).

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

Several papers describe provocation of asthmatic symptoms and rhino-conjunctivitis in latex-sensitised individuals when exposed via airways to powder from latex-gloves (Vandenplas 1995a, Valentino 1994, Allmers 1997, Jaeger 1992). Most of the provocations have been carried out by handling a number of powdered gloves in front of the patients. In most of these reports vinyl gloves have been used as a control. It is



not stated in all cases, whether these gloves were powdered. In most studies the forced expiratory volume per second (FEV1) has been used as parameter. Occasionally the clinical symptoms or blood content/flow changes by pletysmography have been registered.

Inhalation-provocation studies conducted with extracts instead of powder have also been carried out, including comparison of extracts from powdered gloves, powder-free gloves and native powder (Brugnami 1995, Ho 1996). Other study designs have included workplace challenge, where the patient has been tested during conditions similar to workplace conditions (Pisati 1994, Orfan 1994). Inhalation provocation studies seem to indicate a dose response and dose effect relationship.

The reaction to glove powder is not dependent on the powder but on the proteins carried by the powder. In one study powder from low protein containing gloves did not provoke symptomatic reactivity (Vandenplas 1995a).

None of the provocation studies are described as being blinded for the patient, nor have traditional double-blind placebo controlled experiments been carried out. Initial tests with vinyl gloves have, however, generally been carried out. Provocation studies with airborne powder-bound latex-particles in atopic patients with allergic asthma but negative skin prick test to latex have not been reported.

In conclusion, powder particles from natural rubber latex gloves can carry latex allergens and such contaminated powder particles can cause reactions in patients after inhalation. 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. The role of powder by itself for the sensitisation process has not been studied in adequately designed studies.

The results from the provocation studies give sufficient evidence to conclude that exposure to powder from latex-gloves can provoke allergic symptoms (asthma, rhinoconjunctivitis, urticaria, anaphylaxis) in latex-sensitised patients.

***Question 12 If so, does this depend on factors such as the characteristics and quantity of the powder used?***

### ***Opinion***

Latex proteins have been shown to adhere to cornstarch in larger amounts than to talc (magnesiumsilicate). Also the biological availability of latex proteins seems to be greater with cornstarch than with talc (Lundberg 1997). There are differences in pH, partly due to a difference in magnesium oxide content (FDA CDRH 1997). In addition particle size and additives may differ as well. The significance of these parameters for irritancy and/or sensitising activity is not known. Irritation appears to facilitate penetration of latex allergens via the skin (Brehler 1998).

One study (Williams 1997) has demonstrated that high amounts of endotoxin may be present at the inside of latex gloves. The endotoxin was released as very small respirable particles but was not physically associated with the powder in the gloves.

Endotoxin can act as adjuvant for IgE production against latex proteins (Mizoguchi 1986, Slater 1998). So, the hypothesis was raised that also for latex sensitisation endotoxin has adjuvant activity. Experimentally the adjuvant activity of endotoxin for intranasal exposition was demonstrated (Slater 1998). Endotoxins are probably also acting as skin irritants (Shmumes 1984).

In conclusion, as the influence of powder on sensitisation has not been demonstrated, factors that may be relevant cannot be established. The influence of factors as pH, particle size and shape and endotoxins have been postulated but not proven. Cornstarch may bind and release greater amounts of protein than talc, which has been abandoned for other reasons.

***Question13 Are there reliable methods for the estimation of bio-available and allergologically relevant chemicals in natural rubber products?***

***Opinion***

Several techniques are available for the detection of the chemicals present in latex products such as medical gloves, including gas chromatography (GC), gas chromatography – mass spectrometry (GC-MS), high pressure (performance) liquid chromatography (HPLC) and high performance thin layer chromatography (HPTLC). These techniques require extraction of the rubber with a technically suited medium such as chloroform or other lipophilic media (Kaniwa 1987, Knudsen 1993, European Commission 1998, Knudsen 2000a). Although these methods allow the identification of the chemicals present in natural rubber products, this does not by itself mean that these chemicals are also bioavailable for the induction of allergic responses. Bioavailability can be demonstrated by a positive patch test to the glove material in a patient with a positive patch test to the pure chemical substance as well. Studies have demonstrated that sensitising rubber chemicals can leach to aqueous solutions similar to human sweat, in amounts sufficient to provoke delayed type allergic reactions in sensitised individuals (Hansson 1997, Emmet 1994, Kaniwa 1994a, Knudsen 1993). The presence of chemicals causing positive patch test reactions in rubber footwear was confirmed by GC and HPLC (Kaniwa 1994b), and in rubber gloves by GC-MS or HPTLC (Kaniwa 1994c, Knudsen 1993, Knudsen 2000a).

Very few studies have dealt with quantitative determinations of rubber chemicals from rubber products (Knudsen 1993, Emmet 1994, Hansson 1997, Kaniwa 1994a). A method, describing an extraction procedure and a quantitative analysis for the most common rubber chemicals in rubber gloves has been described (Knudsen 2000a). In this study no direct correlation was found between the total amount of chemicals determined in the extracts and the number of positive patch test reactions in a population of patients already sensitised to rubber chemicals. There was a tendency for gloves with a low total amount of chemicals to give few reactions while gloves with a high total amount of chemicals gave many reactions.(Knudsen 2000b).

Quantification in terms of presence of the chemicals per gram glove or square centimetre of glove material for establishing limits which would prevent either an

allergic response in sensitised patients or induction in non sensitised people has not been demonstrated yet. If a limit could be established, the question remains whether a limit should be based on total content or extracted amount, and in case of the latter what should be the extraction vehicle. Quantitative determination of chemical residues is strongly influenced by the extraction procedure used (European Commission 1998). The biologically relevant extraction procedure may vary with the chemical composition of the rubber material. The determination of the chemicals may also be directly influenced by the chemical composition of the material due to interference's etc (European Commission 1998).

In addition, cross reactivity can occur between various chemicals (i.e. thiurams and carbamates (Knudsen 1996, Knudsen 2000b), and mixtures of chemicals can be present in the gloves. The qualitative detection of chemicals in some product is no proof that the chemicals are either bioavailable or clinically relevant, but indicate that the potential for induction of allergic contact dermatitis is present, however. Patch testing with the products can demonstrate bioavailability, although identification of the provoking chemicals still needs to be achieved by assessment of patch test responses to the pure chemical.

In conclusion, the methods mentioned could be used for the identification of biologically relevant chemicals. Quantification of chemicals present in medical devices such as medical gloves and determination of bioavailability is still a problem. There seems to be no agreement on the best applicable method, and this may be dependent on the chemical to be determined.

***Question 14 Is there reliable scientific evidence that risks are presented by chemicals present in natural rubber products?***

***Opinion***

In this answer only the risk for sensitisation taken is into account. Other possible risks are not dealt with. It should be emphasised that the risk for sensitisation in principle is related to the chemicals and not to the materials in which these chemicals are being used. The risk is thus not confined to natural rubber latex but also to many synthetic rubbers containing the same or other chemicals.

Rubber chemicals have been well documented as contact allergens (Cronin 1980, Scheper 1991, Taylor 1995) for decades. Several experimental studies have demonstrated the sensitising capacity of these chemicals in both animals (Magnussen 1969, Maurer 1979) and man (Kligmann 1966). In addition, clinical studies have well established the sensitising effect of rubber products in man (Estlander 1986, 1994, Conde-Salazar 1993, Kaniwa 1994a, Wrangsjö 1994b, Duarte 1998). In most cases the sensitisation is related to the use of natural rubber latex gloves (Conde-Salazar 1993), but sensitisation from rubber shoes has been reported, especially in Japan (Kaniwa 1994b). Causality is demonstrated by the presence of a positive patch test to the rubber material concomittantly with a positive patch test to the pure chemical, and demonstration of the particular chemical in the rubber material (Fregert 1969, Rycroft

1992). The frequency of sensitisation in populations of eczema-patients to e.g. thiuram-mix varies in different studies from 2.3 % (Cronin 1980) to 12.2 % (Conde-Salazar 1993). It should be stressed, that these frequencies do not reflect the prevalence of sensitisation in random populations, where figures less than 0.5% to thiuram are more likely found (Nielsen 1992). The number of individuals sensitised to rubber chemicals compared to individuals sensitised to latex-allergens varies in different studies, but seems to be rather similar (De Groot 1998).

The chemicals most often reported as contact allergens belong to the thiuram-carbamate- and mercaptobenzothiazole groups, guanidines and several antioxidants have occasionally been reported as sensitisers (Estlander 1994). Presently a change in use of chemicals in single use medical gloves seems to have taken place with zinc diethyldithiocarbamate (ZDEC), zinc dibutyldithiocarbamate (ZDBC), zinc mercaptobenzothiazole (ZMBT), and zinc dipentamethylene-dithiocarbamate (ZPC) as some of the most frequently used chemicals (Knudsen 2000a). Some of these chemicals are added directly at harvesting as preservatives, others are added as vulcanizers, accelerators, retarders, antioxidants etc. During manufacturing, chemical reactions may occur in the presence of zinc oxide such as conversion of thiurams to zinc dithiocarbamates. So, although not used by the manufacturers of the gloves and thus not on the label, some “unknown” chemicals or residues thereof may be present in the gloves.

In conclusion, there is reliable scientific evidence that chemicals present in natural rubber latex pose a risk for sensitisation against these chemicals. The rubber chemicals are bioavailable, may penetrate into the skin, and can induce delayed type hypersensitivity resulting in allergic contact dermatitis. This risk is not only confined to natural rubber latex but may also be presented by most synthetic rubber products containing the same or similar chemicals.

***Question15 Can the risk be managed by controlling the levels of bio-available and allergologically relevant chemicals in natural rubber products?***

***Opinion***

Substitution

The risk can theoretically be eliminated by a complete substitution of sensitisers with non-sensitiser and/or a reduction in exposure (Rycroft 1992, Cardin 1986). This is not compatible with the use of natural rubber products, although the use of new technologies such as irradiation instead of the traditional vulcanisation process may decrease the demand for accelerators (Wan Manshol, 1998).

Relative risk of different chemicals

Substitution of strong allergens with weaker allergens is a reasonable possibility. Rating of sensitisers has been performed using experimental models in guinea pigs (Wang 1988, Ikarashi 1994) and mice (Ikarashi 1994, Basketter 1999a, Van Och 2000). However, experiments systematically investigating chemicals used in natural rubber latex products have not been reported. For tetramethylthiuramdisulfide

(TMTD), zinc dimethyldithiocarbamate (ZDMC), mercaptobenzothiazole (MBT) and diethylamine (DEA) a decrease in sensitising potency has been reported (Van Och 2000) and also for N-isopropyl-N'-phenyl-p-phenylenediamine (IPPD), TMTD, MBT and ZDEC (Ikarashi 1993). Analysis of 134 chemicals tested in the local lymph node assay (LLNA), guinea pig maximisation assay (GPMT) and/or with clear clinical evidence for human skin sensitisation potential, revealed that an EC3 (effective dose causing a stimulation index of 3 compared to vehicle control) in the LLNA is an acceptable threshold value for hazard identification (Basketter 1999b). However, it should be kept in mind that the LLNA does not discriminate absolutely between detection of irritant and sensitising activity (Montelius 1994). In addition rubber products may contain reactive/conversion products and these may be different in bioavailability with regard to leaching compared with the original chemicals.

Experimental models using rubber material for both induction and elicitation can in general only distinguish between high and low sensitising material (Kligman 1966, Magnussen 1969, Maurer 1979, Marzuli 1982). As in the local lymph node assay quantitative data are obtained on the induction phase of the immune response, although a more accurate comparison of sensitising potency might be possible (Basketter 1999b, Van Och 2000).

In humans the relative frequency of sensitisation to different rubber chemicals varies with the population studied (domestic exposure, industrial exposure), geographical location and time. These parameters express more variability in exposure than the variation in sensitising capacity of the chemicals (Fregert 1969, Van Ketel 1976, Lammintausta 1985). Almost all patients reacting to carbamates also react to thiurams (Knudsen 1996).

Very rarely reactions exclusively to carbamates are diagnosed (Knudsen 1996, Heese 1997), despite the fact, that several rubber products apparently are produced using carbamates and not thiurams as accelerators. The reason for this is not clear, but some degree of cross-reactivity may be relevant. It is also remarkable that an increase in the frequency of sensitisation to thiuram mix recently has been reported from Germany (Schnuch 1998). One study has demonstrated a co-variation between the degree of sensitisation to thiuram and reactivity to carbamates (Knudsen 1996). Van Ketel 1984 reports that after continued exposure patients sensitised to thiurams also will react to rubber containing carbamates, despite a negative skin test reaction to carbamates.

Butylated compounds are believed by many to be weaker sensitisers than methyl, ethyl and penta-methylene-derivatives, but experimental data are not available.

#### Reduction of exposure

Sensitisation and elicitation thresholds for the rubber chemicals are not known. In principle these thresholds can be determined using *in vivo* models:

- 1) By using different concentrations of pure chemicals in animal models or humans for induction of sensitisation.
- 2) Elicitation studies with dilutions of pure chemicals in previously sensitised humans (or animal models).
- 3) Models for sensitisation in animals or humans, where the rubber product itself is used for both induction and elicitation

- 4) Elicitation studies with rubber material in individuals previously sensitised to rubber chemicals.

*In vitro* models comprise quantitative determination of rubber chemicals in extracts of rubber products.

From the studies in animal models a ranking may be obtained of the relative strength, but extrapolation of these data to concentrations/dosages needed for sensitisation in man is rather difficult. A parallelogram approach based on experimental data, and species comparison of animal and man in a mechanistically relevant *in vitro* system is a good basis for such extrapolation (Van Loveren 1998). Data on *in vitro* effects of chemicals on skin components e.g. Langerhans cells and keratinocytes, in animals and man may prove valuable. However, to date no such exercises have been performed.

Studies of elicitation thresholds in previously sensitised patients using the rubber material itself are difficult to interpret because of the possibility for synergism (Johansen 1998) in patients with concomitant sensitivity to more than one of the rubber chemicals and the presence of different mixtures of rubber chemicals in the rubber materials. (Knudsen 2000b). Repeated tests of the same panel will tend to alter the sensitivity of the test panel. Concomitant sensitivity (and/or cross-reactivity) to several of the rubber chemicals is frequent (Cronin 1980, Taylor 1995, Estlander 1994).

All *in vivo* systems have the disadvantage that they cannot be used for production control. As the surplus of chemicals is usually leached out by washing, great variations in content of leachable chemicals can be anticipated during the production.

The influence of powder on the sensitisation for delayed type hypersensitivity reactions by rubber gloves has not been systematically studied. One study shows that powder may affect skin roughness (Brehler 1998). This may increase the risk for induction of sensitisation. The study cannot directly be transferred to all brands of gloves and powder.

In conclusion, rubber accelerators such as thiurams, carbamates and mercaptobenzothiazoles are contact sensitisers which pose a risk for development of allergic contact dermatitis. The risk can theoretically be reduced by substitution of the most potent sensitisers with less sensitising chemicals, but systematic dose-response-studies are not available in the scientific literature ranking these sensitisers. Studies in animal models, preferably as dose-response models, might contribute to increase the current knowledge of the relative sensitising capacity of well known as well as new chemicals. For evaluation of the relative potency for sensitisation of the various chemicals used during natural rubber latex production the LLNA in mice seems an appropriate assay. Extrapolation of data performed with pure chemicals to sensitising capacity of chemicals in latex rubber products is complicated, however.

*In vitro* tests, measuring clinically relevant, bioavailable residues of rubber chemicals in the products are not available at the moment. However, reduction in the amount of chemical residues in the rubber products also seems to result in a reduction in the bioavailable amounts, and thereby also in a reduction of the sensitising capacity.

To avoid elicitation in sensitised individuals ingredient information will be helpful.

***Question 16. Is there scientific evidence that chlorinated latex products or substitute non-latex materials may have adverse effects to users or patients or to the environment or have safety-related disadvantages to usability?***

### ***Opinion***

Today chlorination is the most widely used method in manufacturing powder-free latex medical gloves. In addition to chlorinated latex gloves several non-latex alternatives showing good to reasonable performance are available (Anonymus 2000). These comprise a range of synthetic materials with characteristics similar to natural rubber latex. The synthetic gloves are produced from various polymers such as polyvinylchloride (PVC), polychloroprene (neoprene), polyurethane, styrene-butadiene-styrene/styrene-isoprene-styrene copolymer, polyisoprene, styrene-ethylene-butylene-styrene copolymer, and acrylonitrile

#### Adverse effects to users or patients

No published data are available on adverse reactions to gloves due to chlorination. Although it is known, that hypochlorite or chlorine may cause adverse or allergic reactions (Kaufman 1989), no data are available on residual hypochlorite or chlorine in powder-free gloves.

For synthetic gloves the same accelerators and antioxidants may be used in the production as for latex production and thus may cause the same allergic contact dermatitis problems as latex gloves.

#### Environment

Environmental problems are:

##### *Chlorine or hypochlorite itself*

The use of chlorine or hypochlorite is common in various industrial processes and its environmental impact is dependent on the safety measures used.

##### *Chlorination as water consuming process*

Chlorination needs a lot of water. One manufacturer estimated about one-half litre per glove. This intensive washing procedure is the main reason for the low protein content in powder-free chlorinated gloves. Reducing the protein content of non chlorinated gloves needs at least the same amount of water.

##### *Polyvinylchloride (PVC)*

Use of PVC may pose a risk because of the phthalates present in the products.

#### Safety-related disadvantages.

Chlorinated and synthetic gloves have to fulfil the same quality requirements with regard to barrier effectiveness leakage as latex gloves as published in EN 455-1 and EN 455-2 (CEN 1998). Moreover, the chlorination process may result in a change of

properties of the material, particularly a risk of a decrease in tensile or tear strength over time, possibly resulting in a greater tendency towards tearing during use.

A major disadvantage may be the consumer price for some of these alternatives.

In conclusion, there are alternatives available to natural rubber latex gloves which have similar characteristics as latex gloves. These alternatives may pose a similar risk for contact dermatitis as latex gloves depending on the chemicals used during the production process. In general data on the risk associated with the substitute non-latex materials is very limited.



## **REFERENCES**

- Akasawa A, Hsieh L-S, Martin BM et al. A novel acidic allergen, Hev b5, in latex. *J Biol Chem* 271:25389-25393, 1996
- Alenius H, Kalkkinen N, Lukka M, Reunala T, Turjanmaa K, Yip E, Palosuo T. Prohevein from rubber tree (*Hevea brasiliensis*) is a major latex allergen. *Clin Exp Allergy* 25:659-665, 1995
- Alenius H, Kalkkinen N, Reunala T, Turjanmaa K, Palosuo T. The main IgE-binding epitope of a major latex allergen, prohevein, is present in its N-terminal 43 amino acid fragment, hevein. *J Immunol* 156: 1618-1625, 1996
- Alenius H, Kurup V, Kelly K, Palosuo T, Turjanmaa K, Fink J. Latex allergy: Frequent occurrence of IgE antibodies to a cluster of 11 latex proteins in patients with spina bifida and histories of anaphylaxis. *J Lab Clin Med* 123: 712-720, 1994
- Allmers H, Huber H, Wirtz C, Kirchner B, Raulf-Heimsoth M, Baur X. Expositionstestungen mit gepuderten Handschuhen bei 60 Latexallergikern aus dem Gesundheitswesen. *Dtsch med Wschr* 122:1308-1312, 1997
- Allmers H; Brehler R; Chen Z; Raulf-Heimsoth M; Fels H; Baur X  
Reduction of latex aeroallergens and latex-specific IgE antibodies in sensitized workers after removal of powdered natural rubber latex gloves in a hospital. *J Allergy Clin Immunol* 102:841-846, 1998
- Amin A, Palenik CJ, Cheung SW, Burke FJ. Latex exposure and allergy: a survey of general dental practitioners and dental students. *Int Dent J.* 48:77-83, 1998
- Anonymus. Synthetic surgical gloves. *Health Devices* 29: 37-66, 2000.
- ASTM Standard test method for the analysis of aqueous extractable protein in natural rubber and its products using the modified Lowry method. ASTM Designation 5712-99, West Conshohocken, PA, USA, 1999
- ASTM. Standard test method for the immunological measurement of antigenic protein in natural rubber and its products. ASTM Designation D 6499-00, West Conshohocken, PA, USA, 2000
- Basketter DA, Lea LJ, Dickens A, Briggs D, Pate I, Dearman RJ, Kimber I. A comparison of statistical approaches to the derivation of EC3 values from local lymph node assay dose responses. *J. Appl Toxicol* 19: 261-266, 1999a
- Basketter DA, Lea LJ, Cooper K, Stocks J, Dickens A, Pate I, Dearman RJ, Kimber I. Threshold for classification as a skin sensitizer in the local lymph node assay: a statistical evaluation. *Food and Chemical Toxicology* 37, 1167-1174, 1999b.

Baur X, Ammon J, Chen Z, Beckmann U, Czuppon AB. Health risk in hospitals through airborne allergens for patients pre-sensitised to latex. *The Lancet*. 342:1148-1149, 1993

Baur X, Chen Z, Liebers V. Exposure-response relationships of occupational inhalative allergens. *Clin exp Allergy* 28: 537-544, 1998a

Bauer X, Chen Z, Allmers H. Can a threshold limit value for natural rubber latex airborne allergens be defined? *J Allergy Clin Immunol* 101:24-27, 1998b

Baur X, Chen Z, Raulf-Heimsoth M, Degens P. Protein and allergen content of various natural latex articles *Allergy* 52: 661-664, 1997

Beezhold D, Pugh B, Liss G, Sussman G. Correlation of protein levels with skin prick test reactions in patients allergic to latex. *J Allergy Clin Immunol* 98: 1097-1102, 1996

Beezhold D, Beck W.C. Surgical powder bind latex antigens. *Arch Surg* 127:1354-1357, 1992

Boyer EM. The effectiveness of a low-chemical, low-protein medical glove to prevent or reduce dermatological problems *J. Dent Hygiene* 69:67-73, 1995

Breiteneder H. Scheiner O. Molecular and immunological characteristics of latex allergens. *Int Arch Allergy Immunol* 116:83-92, 1998

Brehler, Leynadier, Beezhold D, Pugh B, Liss G, Sussman G. Correlation of protein levels with skin prick test reactions in patients allergic to latex. *JACI* 98: 1097-1102, 1996

Brehler R, Kolling R, Webb M, Wastell C. Glove powder - A risk factor for the development of latex allergy? *Eur. J Surg* 579 (Suppl):23-25, 1997

Brehler R, Voss W, Müller S. Glove powder affects skin roughness, one parameter of skin irritation. *Contact Dermatitis* 39: 227-230, 1998

Brockow K, Weber T, Rakoski J, Ring J. Skin test reactivity in patients with latex allergy. *J Allergy Clin Immunol* 104 :237, 2000

Brugnami G, Marabini A, Siracusa A, Abbritti G. Work related late asthmatic response induced by latex allergy. *J Allergy Clin Immunol* 96:457-464, 1995

Cardin CW, Weaver JE, Bailey PT. Dose-response assessments of Kathon biocide. *Contact Dermatitis* 15:10-16, 1986

Carrillo T, Blanco C, Quiralte J, et al. Prevalence of latex allergy among greenhouse workers. *J Allergy Clin Immunol* 96:699-701, 1995.

CEN. Medical gloves for single use. Part 1: Requirements and testing for freedom of holes. EN 455-1, Centre Européen de Normalisation (European Committee for Standardisation), Brussels, Belgium 1998

CEN. Medical gloves for single use. Part 2: Requirements and testing for physical properties. EN 455-2, Centre Européen de Normalisation (European Committee for Standardisation), Brussels, Belgium 1998

CEN. Medical gloves for single use. Part 3: Test methods for biocompatibility and requirements for biocompatibility labeling. EN 455-3, Centre Européen de Normalisation (European Committee for Standardisation), Brussels, Belgium 1999

Chen CF, Teoh SC, Porter M. False positive results with the american society for testing and materials D5712-95 test method for protein given by a common vulcanisation accelerator. *J Allergy Clin Immunol* 100: 713-714, 1997

Conde-Salazar L, del Rio E, Guimaraens D et al: Type IV allergy to rubber additives: a 10-year study of 686 cases. *J Am Acad Derm* 29:176-80, 1993

Cronin E. Rubber. In: Cronin E (ed) *Contact Dermatitis*, Churchill Livingstone, NY, pp 714-40, 1980

Czuppon AB, Chen Z, Rennert S et al . The rubber elongation factor of rubber trees (*Hevea brasiliensis*) is the major allergen in latex, *J Allergy Clin Immunol* 92:690-697, 1993

De Groot H, De Jong NW, Duijster E et al. Prevalence of natural rubber latex allergy (Type I and TypeIV) in laboratory workers in the Netherlands. *Contact Dermatitis* 38: 159-163, 1998

Dreborg S. Skin tests used in type I allergy testing. Position paper. Sub-Committee on Skin Tests of the European Academy of Allergology and Clinical Immunology. *Allergy* 44 Suppl 10: 1-59, 1989

Duarte I, Nakano JT, Lazzarini R. Hand Eczema. Evaluation of 250 patients. *Am J Cont Derm* 9: 216-223, 1998

Emmet EA, Risby TH, Taylor J, Chen CL, Jiang L, Feinman SE. Skin elicitation thresholds of ethylbutyl thiurea and mercaptobenzothiazole with relative leaching from sensitising products. *Contact Dermatitis* 30: 85-90, 1994

Estlander, T., Jolanki, R., and Kanerva, L., *Dermatitis and urticaria from rubber and plastic gloves*. *Contact Dermatitis* 14: 20, 1986.

Estlander T, Jolanki R, Kanerva L. Allergic contact dermatitis to rubber and plastic gloves. In: Mellström GA, Wahlberg J, Maibach HI (eds) *Protective gloves for occupational use*. CRC Boca Raton, USA pp 221-239, 1994

European Commission. Determination of allergological relevant compounds in disposable gloves. Correlation of chemical, allergological and immunological data. Final report MAT1 – CT 940060. European Commission, Directorate General XII Science, Research and Development. Brussels, Belgium 1998

Food and Drug Administration, Center for Devices and Radiological Health. Medical glove powder report Washington, DC, USA 1997, ([www.fda.gov/cdrh/glvpwd/html](http://www.fda.gov/cdrh/glvpwd/html))

Fezcko PJ, Simms SM, Bakirci N. Fatal hypersensitivity during a barium enema. *Am J Roentgenol* 153:276-277, 1989

Fregert S, Hjorth N, Magnusson B et al. Epidemiology of contact dermatitis. *Transactions of Sct John's Hospital Dermatological Society* 55: 17-35, 1969

Hamilton RG, Adkinson NF. Validation of the latex glove provocation procedure in latex allergic subjects. *Ann Allergy Asthma Immunol* 79: 266-272, 1997

Hansson C, Bergendorff O, Ezzelarab M, Sterner O. Extraction of mercaptobenzothiazole compounds from rubber products. *Contact Dermatitis* 36: 195-200, 1997

Havinga JS. Latex protein allergy, evaluation of the modified Lowry method. TNO report BU4.99/030882-1/JH. Delft, The Netherlands. 1999

Heese A: Allergien gegen latexhandschuhe. Ecomed, Landsberg, FRG, p 143, 1997

Heese A, Peters K-P, Stahl J, et al. Häufigkeit und Zunahme von Typ-I-Allergien gegen Gummihandschuhen bei Zahnmedizinstudenten. *Hautarzt* 46:15-21,1995

Heilman DK, Jones RT, Swanson MC, Yunginger JW. A prospective controlled study showing that rubber gloves are the major contributor to latex aeroallergen levels in the operating room. *J Allergy and Clin Immunol* 98:325-330, 1996

Ho A, Chan H, Tse KS, Chan-Yeung M. Occupational asthma due to latex in health care workers. *Thorax* 51:1280-1282, 1996

Ikarashi Y, Tsuchiya T, Nakamura A. Evaluation of contact sensitivity of rubber chemicals using the murine local lymph node assay. *Contact Dermatitis* 28: 77-80, 1993

Ikarashi Y, Ohno K, Momma J, Tsuchiya T, Nakamura A. Assessment of contact sensitivity of four thiourea rubber accelerators: comparison of two mouse lymph node assays with the guinea pig maximisation test. *Fd Chem Toxic* 32: 1067-1072, 1994

Jaeger D, Czuppon AB, Baur X. Latex-specific proteins causing immediate-type cutaneous, nasal, bronchial, and systemic reactions. *J Allergy Clin Immunol* 89:759-767, 1992

Johansen JD, Skov L, Volund A, Andersen K, Menné T. Allergens in combination have a synergistic effect on the elicitation response: a study of fragrance-sensitized individuals. *Br. J Dermatol* 139: 264-270, 1998

Jolanki R, Estlander T, Alanko K, et al. Incidence rates of occupational contact urticaria caused by natural rubber latex. *Contact Dermatitis* 40:329-331, 1999

Kaniwa M-A High performance liquid chromatography identification and determination of dithiocarbamates in vulcanised rubber products. *J. Chromatogr.* 405:263 – 271, 1987

Kaniwa M-A, Isama K, Nakamura A et al. Identification of causative chemicals of allergic contact dermatitis using a combination of patch testing in patients and chemical analysis. *Contact Dermatitis* 30: 20-25, 1994a

Kaniwa M-A, Isama K, Nakamura A, Kantoh H, Itoh M, Miyoshi K, Saito S, Shono M. Identification of causative chemicals of allergic contact dermatitis using a combination of patch testing in patients and chemical analysis. Application to cases from rubber footwear. *Contact Dermatitis* 30: 26-34, 1994b.

Kaniwa M-A, Isama K, Nakamura A, Kantoh H, Hosono K, Itoh M, Shibata K, Usuda T, Asahi K, Osada T, Matsunaga K, Ueda H. Identification of causative chemicals of allergic contact dermatitis using a combination of patch testing in patients and chemical analysis. Application to cases from rubber gloves. *Contact Dermatitis* 31: 65-71, 1994c

Kaufman AY, Keila S. Hypersensitivity to sodium hypochlorite *J. Endodontics* 15: 224-226, 1989

Kelly KJ, Pearson M, Kurup V, et al. A cluster of anaphylactic reactions in childrens with spina bifida during general anaesthesia: epidemiological features, risk factors, and latex hypersensitivity. *J Allergy Clin Immunol* 94:53-61, 1994

Kim KT, Safadi GS. Relation of latex-specific IgE titer and symptoms in patients allergic to latex. *J Allergy Clin Immunol* 103:671-677, 1999

Kligmann A. The identification of contact allergens by human assay. *J Invest Dermatol* 47: 393-408, 1966.

Knudsen BB, Larsen E, Egsgård H, Menné T. Release of thiurams and carbamates from rubber gloves. *Contact Dermatitis* 28: 63-69, 1993

Knudsen BB, Menné T. Contact allergy and exposure patterns to thiurams and carbamates in consecutive patients. *Contact Dermatitis* 35: 97-99, 1996

Knudsen BB, Hametmer C, Seycek O, Heese A, Koch H-U, Peters K-P. Allergologically relevant rubber accelerators in single use medical gloves. *Contact Dermatitis* 2000a, In press.

- Knudsen BB, Hametmer C, Seycek O, Heese A, Koch H-U, Peters K-P. Bioavailability of rubber accelerators in rubber gloves and patch test reactivity. *Dermatosen in beruf und umwelt*, 2000b, in press.
- Konz KR, Chia JK, Kurup VP, Resnick A, Kelly KJ, Fink JN. Comparison of latex hypersensitivity among patients with neurologic defects, *J. Allergy Clin. Immunol.* 95: 950, 1995
- Kurtz KM, Hamilton RG, Adkinson NF. Role of application of provocation in the diagnosis of occupational latex allergy. *Annals of Allergy, Asthma, & Immunology* 83:634-639, 1999
- Kurup, V.P., Kelly, K.J., Turjanmaa, K., Alenius, H., Reunala, T., Palosuo, T., Fink, J.N., Immunoglobulin E reactivity to latex antigens in the sera of patients from Finland and the United States, *J. Allergy Clin. Immunol.* 91: 1128, 1993.
- Kurup VP, Kumar A, Choi H et al. Latex Antigens Induce IgE and Eosinophils in Mice. *Int Arch Allergy Immunol* 103:370-377, 1994
- Lagier, F., Vervloet, D., Lhermet, I., Poyen, D., Charpin, D. Prevalence of latex allergy in operating room nurses, *J. Allergy Clin. Immunol.* 90: 319, 1992.
- Lammintausta K, Kalimo K. Sensitivity to rubber. Study with rubbermixes and individual rubber chemicals. *Dermatosen* 33: 204-208, 1985
- Laoprasert N, Swanson MC, Jones RT, Schroeder DR, Yunginger JW. Inhalation challenge testing of latex-sensitive health care workers and the effectiveness of laminar flow HEPA-filtered helmets in reducing rhinoconjunctival and asthmatic reactions. *J Allergy Clin Immunol* 102: 988-1004, 1998
- Leynadier F, Pecquet C, Dry J. anaphylaxis to latex during surgery. *Anaesthesia* 44:547-550, 1989
- Levy DA, Allouache S, Chabane MH, Leynadier F. Powder-free protein-poor natural rubber latex gloves and latex sensitisation. *JAMA* 281:988-989, 1999
- Levy DA, Allouache S, Brion M et al: Effect of powdered vs non-powdered latex gloves on the prevalence of latex allergy in dental students. *J Allergy Clin Immunol* 101:1 S160 (abstract), 1998
- Liss GM, Sussman GL. Latex sensitization: occupational versus general population prevalence rates. *Am J Ind Med* 35:196-200, 1999
- Liss GM, Sussman GL, Deal K, et al. Latex allergy: epidemiological study of 1351 hospital workers. *Occupational and Environmental Medicine* 54:335-342, 1997
- Lundberg M, Wrangsjø K, Johansson SGO. Latex allergy from glove powder – an unintended risk with the switch from talc to cornstarch? *Allergy* 52:1222-1228, 1997.

- Magnusson B, Kligmann AM. The Identification of Contact Allergens by animal assay. The Guinea Pig Maximization Test. *J Invest Dermatol* 52: 268-276, 1969
- Marzulli, F.N., Maibach, H.I., Human predictive tests for allergic contact dermatitis. In: Maibach, H.I., Gellin, G.A.,(eds.).*Occupational and industrial dermatology, Yearbook medical publishers* pp187-189, 1982
- Maurer TH, Thomann P, Weirich EG, Hess R. Predictive evaluation in animals of the contact allergenic potential of medically important substances. II. Comparison of different methods of cutaneous sensitization with "weak" allergens *Contact Dermatitis* 5: 1-10, 1979
- Mazon A, Nieto A, Estornell F, Nieto A ,Reig C, Garcia-Ibarra F. Factors that influence the presence of symptoms caused by latex allergy in children with spina bifida. *JACI* 99: 600-604, 1997
- Mellström GA, Boman AS. *Gloves: Types, Materials, and Manufacturing*. In: Mellström GA, Wahlberg JE, Maibach HL. *Protective gloves for occupational use*, CRC Press, Boca Raton, FL, USA, 1994.
- Mizoguchi K, Nakashima Y, Hasegawa K. Augmentation of antibody responses of mice to inhaled pretein aand simultaneously inhaled bacterial polysaccharide. *Immunobiology* 34: 355-365, 1986
- Montelius J, Wahlkvist H, Boman A, Fernström P, grabergs L, Wahlberg JE. Experience with the murine local lymph node assay: inability to discriminate between allergens and irritants. *Acta Derm Venereol (Stockh)* 74: 22-27, 1994
- National Agency for Medicines. Natural rubber allergen content of latex gloves. A market surveillance study. National Agency for Medicines, Helsinki, Finland. *TLT-INFO* 1/1999, 1999
- National Agency for Medicines. Allergen content of latex gloves. A market surveillance study of medical gloves used in Finland in 1999. Publications by the National Agency for Medicines, Helsinki, Finland. 1999
- Nielsen NH. Allergic contact sensitization in an unselected danish population. *Acta Derm Venereol* 72: 456-460, 1992
- Nieuwenhuijsen MJ; Heederik D; Doekes G; Venables KM; Newman Taylor AJ Exposure-response relations of alpha-amylase sensitisation in British bakeries and flour mills. *Occup Environ Med* 56:197-201, 1999
- Niggemann B, Kulig M, Bergmann R, et al. Development of latex allergy in children up to 5 years of age - a retrospective analysis of risk factors. *Pediatr Allergy Immunol* 9:36-39, 1998
- Novembre E, Bernardini R, Brizzi I, et al. The prevalence of latex allergy in children seen in a university hospital allergy clinic. *Allergy* 52:101-105, 1997

- Orfan NA, Reed R, Dykewicz MS, Ganz M, Kolski GB. Occupational asthma in a latex doll factory *J Allergy Clin Immunol* 94:826-830, 1994
- Palosuo T, Mäkinen-Kiljunen S, Alenius H, Reunala T, Yip E, Turjanmaa K. Measurement of natural rubber latex allergen levels in medical gloves by allergen-specific IgE-ELISA inhibition, RAST-inhibition and skin prick test. *Allergy* 53: 59-67, 1998
- Pisati G, Baruffini A, Bernabeo F, Stanizzi R. Bronchial provocation testing in the diagnosis of occupational asthma due to latex surgical gloves. *Eur Respir J* 7:332-336, 1994
- Pisati G, Baruffini A, Bernabeo F, et al. Environmental and clinical study of latex allergy in textile factory. *J Allergy Clin Immunol* 101:327-329, 1998
- Posh, A., Chen, Z., Raulf-Heimsoth, M., Baur, X. Latex allergens, Clinical and experimental *Allergy* 28: 134, 1998.
- Porri F, Pradal M, Lemièrre C, et al. Association between latex sensitization and repeated latex exposure in children. *Anesthesiology* 86:599-602, 1997
- Reijula K E, Kelly K J Kurup VP et al. Latex-induced dermal and pulmonary hypersensitivity in rabbits. *J Allergy Clin Immunol* 94:891-902, 1994
- Rycroft R.J.G., Menné T, Frosch P.J, Benezra C. Textbook of contact dermatitis. Springer-Verlag, Berlin 1992
- Scheper R J, Von Blomberg BM. Cellular mechanisms in allergic contact dermatitis. In Rycroft RJG, Menné T, Frosch PJ, Benezra C (eds). Textbook of contact dermatitis. Springer-verlag Berlin pp11-27, 1991
- Shmunès E, Darby T. Contact dermatitis due to endotoxin in irradiated latex gloves. *Contact Dermatitis* 10: 240-244, 1984
- Schnuch A, Uter W, Geier J, Frosch PJ, Rustemeyer T. Contact allergies in healthcare workers. Results from the IVDK. *Acta Derm Venereol* 78: 358-363, 1998
- Slater JE, Paupore EJ, Elwell MR, Truscott W. Lipopolysaccharide augments IgG and IgE responses of mice to the latex allergen Hev b 5. *J Allergy Clin Immunol* 102: 977-983, 1998
- Slater JE, Vedvick T, Arthur-Smith A et al. Identification, cloning and sequence of a major allergen (Hev b5) from natural rubber latex (*Hevea brasiliensis*) *J Biol Chem* 271:25394-25399, 1996
- Sporik R; Squillace SP; Ingram JM; Rakes G; Honsinger RW; Platts-Mills TA. Mite, cat, and cockroach exposure, allergen sensitisation, and asthma in children: a case-control study of three schools. *Thorax* 54:675-680, 1999



Sri-akajunt N, Sadhra S, Burge PS, et al. Latex sensitization amongst workers in Thai rubber estates and latex glove factories. *Revue francaise d'Allergologie et d'Immunologie* 37:1217, 1997 (poster).

Swanson MC, Bubak ME, Hunt et al: Quantification of occupational latex aeroallergens in a medical center. *J Allergy Clin Immunol* 94:445-451, 1994

Sussman GL, Lem D, Liss G, et al. Latex allergy in housekeeping personnel. *Annals of Allergy, Asthma, & Immunology* 74:415-418, 1995

Sussman GL, Liss GM, Deal K et al: Incidence of latex-sensitisation among latex glove users. *J Allergy Clin Immunol* 101:171-178,1998

Tarlo SM, Sussman G, Contala A, Swanson MC. Control of airborne latex by use of powder-free latex gloves. *J Allergy Clin Immunol* 93:985-989, 1994

Tarlo SM, Sussman GL, Holness L. Latex sensitivity in dental students and staff: A cross sectional study. *JACI* 99 396-401, 1997

Taylor JS. Allergy to rubber In: Fisher's Contact Dermatitis 4th ed. Baltimore Williams and Wilkins. pp 697-752, 1995

Tomazic V.J. Shampaine E.L. Lamanna A, Withrow T.R. Adkinson N.F. Hamilton R.G. Cornstarch powder on latex products is an allergen carrier. *J. Allergy Clin Immunol* 93: 751-758, 1994

Turjanmaa K, Alenius H, Mäkinen-Kiljunen S, et al. Commercial skin prick test preparations in the diagnosis of rubber latex allergy (abstract). *J Allergy Clin Immunol* 93:299, 1995a

Turjanmaa K, Alenius H, Mäkinen-Kiljunen S, et al. Natural rubber allergy. Review. *Allergy* 51: 593-602, 1996

Turjanmaa K, Mäkinen-Kiljunen S, Reunala T, et al. Natural rubber latex allergy - the European experience. In: Fink J (ed) *Latex allergy. Immunology and allergy clinics of North America*, vol 15. WB Saunders, Philadelphia, pp 71-88, 1995b

Turjanmaa K, Palosuo T, Alenius H, et al. Latex allergy diagnosis: in vivo and in vitro standardization of a natural rubber latex extract. *Allergy* 52:41-50, 1997

Turjanmaa K, Reinikka-Railo H, Reunala T, Palosuo T. Continued decrease in Natural Rubber Latex (NRL) allergen levels of medical gloves in nationwide market surveys in Finland and co-occurring decrease in NRL allergy prevalence in a large university hospital. *J Allergy Clin Immunol* 104: Abstracts S373 Abstract#1094, 1999

Turjanmaa, K., Incidence of immediate allergy to latex gloves in hospital personnel, *Contact Dermatitis*, 17, 270, 1987.

- Turjanmaa K, Reunala T, Räsänen L. Comparison of diagnostic methods in latex surgical glove contact urticaria. *Contact Dermatitis* 19:241-247, 1988
- Valentino M, Pizzichini A, Monaco F, Governa M. Latex-induced asthma in four healthcare workers in a regional hospital. *Occup Med* 44: 161-164, 1994
- Vandenplas O, Delwiche J-P, Depelchin S, Sibille Y, Weyer Rv, Delaunois L. Latex gloves with a lower protein content reduce bronchial reactions in subjects with occupational asthma caused by latex. *Am J Respir Crit Care Med* 151: 887-891. 1995a
- Vandenplas O, Delwiche J-P, Evrard G, et al Prevalence of occupational asthma due to latex among hospital personnel. *Am J Respir Crit Care Med* 151:54-60, 1995b
- Vandenplas O, Delwiche J-P, Sibille Y. Occupational asthma due to latex in a hospital administrative employee. *Thorax* 51:452-454, 1996
- Van Der Walle H, Brunsveld V, Latex allergy among hairdressers. *Contact Dermatitis* 11:381-384, 1995
- Van Ketel WG. Thiuram-mix. *Contact Dermatitis* 2: 232-236, 1976
- Van Ketel WG, van den Bergh WHHW. The problem of sensitisation to dithiocarbamates in thiuram-allergic patients. *Dermatologica* 169: 70-75, 1984
- Van Loveren H, De Jong WH, Vandebriel RJ, Vos JG, Garssen J. Risk assessment in immunotoxicology. *Toxicology Letters* 102-103: 261-265, 1998
- Van Och FMM, Slob W, De Jong WH, Vandebriel RJ Van Loveren H. A quantitative method for assessing the sensitising potency of low molecular weight chemicals using a local lymph node assay: employment of a regression method that includes determination of the uncertainty margins. *Toxicology*, 146: 49-59, 2000
- Wan Manshol bin W. Zin. Radiation vulcanised natural rubber latex (RVNRL), Malaysian Rubber Seminar. pp 28 –31, 1998
- Wang X, Suskind RR. Comparative studies of the sensitization potential of morpholine, 2 mercaptobenzothiazole and 2 of their derivatives in guinea pigs. *Contact Dermatitis* 19:11-15, 1988
- Williams BF, Halsey JF. Endotoxin as a factor in adverse reactions to latex-gloves. *Ann Allergy Asthma Immunol* 79: 303-310, 1997
- Wrangsjö, K., Osterman, K., vanHage-Hamsten, M., Glove related skin symptoms among operating theatre and dental care unit personnel, *Contact Dermatitis* 30: 139, 1994a.
- Wrangsjö K, Meding B. Occupational contact allergy to rubber chemicals. *Dermatosen* 42: 184-189, 1994b

Xia J-Q, Rickaby DA, Kelly KJ, Choi H, Dawson CA, Kurup VP. Immune response and airway reactivity in wild and IL-4 knockout mice exposed to latex antigens. *Int Arch Allergy Immunol* 118:23-29, 1999

Yassin, M., Liers, M., Fisher, T., O'Brien, K., Cross, J., Steinmetz, C. Latex allergy in hospital employees. *Ann. Allergy* 72: 245, 1994.

Yip E, Turjanmaa K, Ng KP Mok, KL. Allergic responses and levels of extractable proteins in NR latex gloves and dry rubber products. *J Nat Rubber Res.* 9:79-86, 1994

Ylitalo L, Mäkinen-Kiljunen S, Turjanmaa K et al. Cow's milk casein, a hidden allergen in natural rubber latex gloves. *J Allergy Clin Immunol* 104:177-180, 1999

Ylitalo L, Turjanmaa K, Palosuo T, et al. Natural rubber latex allergy in children who had not undergone surgery and children who had undergone multiple operations. *J Allergy Clin Immunol* 100:606-612, 1997

Ylitalo L. Natural rubber latex allergy in children, PhD Thesis, *Acta Universitatis Tamperensis* 719, University of Tampere, Tampere, Finland, 2000

Yunginger JW, Jones RT, Fransway AF, Kelso JM, Hunt LW Extractable latex allergens and proteins in disposable medical gloves and other rubber products. *J Allergy Clin Immunol* 93, 836-842, 1994