The business aspects of Vytex™, an ultra low protein natural rubber latex

William Doyle, MBA, Travis Honeycutt, PhD, Matthew Clark, and Russell Culp

Vystar Corporation, 3235 Satellite Boulevard, Building 400, Suite 290, Duluth, GA 30096, USA

Vystar™ Corporation has developed a novel, patented method for the deactivation of the antigenic proteins (AP) in liquid natural rubber latex that involves the denaturing of proteins. Vytex™ natural rubber latex is the result of intensive work as research and development commenced in 1998 and has resulted in the issuance of two patents, with additional patent filings submitted and pending. Initial laboratory and production test data reveal that products made from Vytex™ natural rubber latex have equal or improved chemical and physical properties when compared to natural rubber latex thus allowing a seamless transition for manufacturers using current commercially available product.

Vytex™ natural rubber latex production utilizes existing field latex as the starting feedstock and will be produced commercially using existing local processors in South East Asia. Products made from Vytex™ natural rubber latex in the laboratory and certain production lines achieve low protein levels without the need for extensive washing and post leaching with chlorine. Applications for Vytex™ natural rubber latex include gloves, condoms, catheters, tubing, breather bags, as well as many non-medical products across a wide industry scope. Based on pricing for products currently made from natural rubber latex, or most synthetic materials, Vytex™ natural rubber latex is cost effective and is easily integrated into existing manufacturing schemes.

INTRODUCTION

Natural rubber latex (cis-1,4-polyisoprene) is an irreplaceable strategic raw material used in enormous quantities by industry, transportation, medicine and defense. Worldwide production is currently seven million tons per year, and demand for natural rubber latex (NRL) is expected to continue increasing. Synthetic polymers cannot match the high performance properties and cost effectiveness of NRL, and so natural rubber has not been replaced by synthetics in many applications[1]. The availability and consumption of natural rubber latex (NRL) dates back to the 1800s and today there are over 40,000 commercially available products made from natural rubber latex.

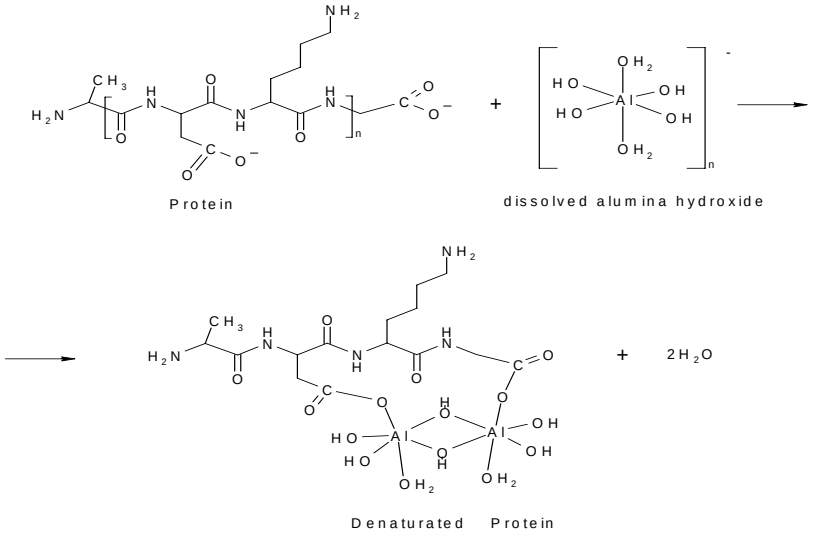
NRL's popularity and longevity can be contributed to several factors. The physical properties of NRL are superior to non-latex synthetic products. Field latex, the feedstock material for NRL products that traditionally came from Malaysia and Thailand, is now being harvested in several new regions around the world such as China, India and Vietnam. Despite the continuing increase in the price of NRL, it is still significantly less expensive than some petroleum based synthetic materials whose costs continue to rise, and constantly fluctuate, with the increasing price of crude oil. Despite advancements in NRL competitive products, consumption of non-tire NRL reached 1.08 million tons in 2004 and continues to increase.[2] Latex prices have been increasing and Malaysia, as well

as other South East Asia countries, has started replanting the *Hevea brasiliensis* tree in an effort to keep up with the growing worldwide demand.

It is well known that liquid natural rubber latex from the *Hevea brasiliensis* tree contains a number of proteins that cause minor to severe allergic reactions. Estimates run as high as 17% of healthcare workers that are affected by latex allergies due to the various targeted proteins within a relatively short range of rubber elongation factors (REF).[3, 4] Many efforts have been made to remove these proteins from NRL by physical and/or chemical methods that affect the complex acid-base behavior or proteins. Most of these methods are complex and offer limited effectiveness resulting in the inadequate removal of allergenic protein and possibly, the reduction of the physical properties of the NRL.

To address the antigenic protein issue in NRL, Vystar has developed and patented several relatively simple processes to deactivate the antigenic proteins. One patented method accomplishes this by treating NRL in the liquid state with $Al(OH)_3$ as an alkali solution prior to vulcanization. Vystar has named and trademarked the resultant natural rubber latex, Vytex™ natural rubber latex.[5, 6] These authors prepared and presented a technical paper in 2005 entitled "A Novel "Protein-Free" Natural Rubber Latex: Properties and Applications" that describes the protein removal process in detail. Additionally, these authors prepared and presented a second technical paper in 2006 entitled "Technological and Physical Properties of a New Low Antigenic Protein Natural Rubber Latex" that investigated the influence of specific patented anti-protein additives on the physical properties of Vytex natural rubber latex. To summarize these two reports, the protein deactivation process used to manufacture Vytex does not compromise the very important physical and chemical properties of natural rubber latex and may improve certain properties especially after aging.

The aim of this current work is to introduce Vytex natural rubber latex to the scientific community and to commercial markets globally. This introduction will include the marketability of Vytex natural rubber latex, the available alternatives to NRL and the economic viability of Vytex natural rubber latex as compared to the synthetic alternatives.



DISCUSSION

Honeycutt, Doyle, Clark, et al began studying the effects of altering the stereochemistry of proteins in natural rubber latex in 1998. This work led to the discovery that altering the stereochemistry of the proteins reduced the allergic content of those proteins as evidenced by ELISA assay. The molecular model shown on the prior page indicates the probable model of the protein after the Vytex manufacturing process[5] (note that while the aluminum has a valence of three, it has a co-ordination number of six).

This new method of treating natural rubber latex deactivates the antigenic proteins in the liquid phase prior to compounding and dipping. Since proteins are principally denatured rather than removed, Vytex natural rubber latex retains the positive characteristics of latex — without the high levels of active antigenic proteins.

NRL as a barrier material has a long history of use dating back to the 1800s. However, the consumption of medical gloves and condoms increased significantly in the 1980s primarily due to the AIDS crisis and epidemic. Due to its low cost and complex chemical and mechanical properties, NRL is considered to have the best broad range of desirable and in most cases, required properties for medical products.[7] Allergic reactions due to contact with natural rubber latex have increased considerably in the previous two decades primarily because of the significant increase in glove and condom usage plus improper preparation, as well as inadequate leaching and washing during their manufacture. The naturally occurring antigenic proteins in raw latex, that have been identified as the cause, migrate from the finished latex product to the skin where the proteins can be absorbed and potentially cause Type I reactions.[8]

The first description of an allergic reaction to latex gloves appeared in the American literature in 1933 when usage was slight, however now more than 22 billion exam gloves from latex are used annually in the United States.[9,10] It has been published that in 2003, that 16.7% of the cases of intra-operative shock were attributed to latex allergies.[11] Similarly, it is estimated that 17% of American healthcare workers and up to 73% or more of frequently exposed patients, such as those with spina bifida, have become sensitized to the antigenic latex proteins.[3,4] Clearly this allergic behavior in healthcare workers is an acquired problem as studies have shown that only 3% of the general population shows any allergic reaction to NRL.

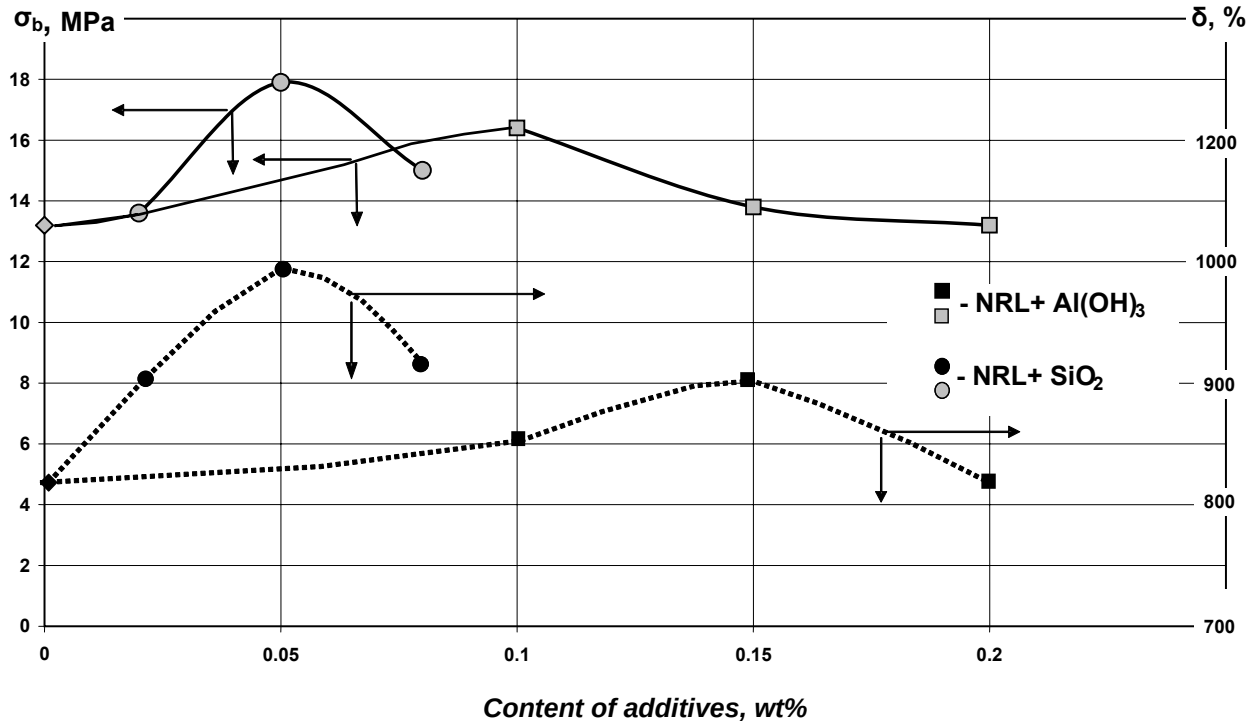
The amount of protein in NRL has remained fairly constant at 1.6-2.0 wt % (16,000-20,000μg/g), but the final concentration varies between 3 to > 600 μg/g depending on the manufacturing technique used.[12] In March 1995, the United States Food and Drug Administration issued interim labeling guidance on permissible levels of protein in medical latex gloves that set the upper limit at 50 μg/g for low protein claims. Most experts argue that the level should be lower since the probability of an allergic reaction decreases with the protein level and should be around 1μg/g as measured by the Elisa assay. [13] Achieving this lower number plus preserving the superior properties of NRL, such as elasticity and tactile sensation, has proven to be elusive. However, Vystar's protein reduction methods have decreased the level of antigenic protein in latex articles

down to ≤0.2μg/g (Elisa assay) while maintaining superior mechanical properties, particularly after aging.

Since there are 240 potentially antigenic proteins in processed latex, and due to the complex nature of the latex extract, accurate protein measurement presented a challenge. Some believe that the optimal estimation of antigenic protein levels are determined by the ELISA Inhibition Assay Method, ASTM D6499-03, while the Modified Lowry Test, ASTM D5712 quantitatively shows the total protein content that includes the potentially allergenic proteins.[14, 15]

Many efforts have been made to remove protein from NRL by physical and /or chemical methods that affect the complex acid-base behavior of proteins. Also, protein content can be decreased to such levels as 200-300μg/g through successive centrifugations of NRL or by enzymatic decomposition, however appearance and physical and chemical properties usually suffer. AP levels were decreased to 20μg/g through the use of proteolytic enzymes and surfactants, but caused loss of elasticity and strength after aging.[16] Ultrasonic leaching or irradiation by cobalt also showed promise to reduce AP levels in the literature, but had issues with effectiveness and cost.[17, 18]

Figure 1. Mechanical Properties of latex films at different amount of anti-protein additives



Most of the above methods are complex and offer limited effectiveness resulting in the inadequate removal of allergenic protein. More promising is the treatment of NRL in the liquid phase by using aluminum hydroxide dissolved in a fixed alkali solution prior to vulcanization. Little research exists in this field and there has not been a blueprint for advancement of the technical method. The solution to lowering the antigenic protein to acceptable levels is complicated due to the complex chemical nature of proteins in NRL and it seems that altering the stereochemistry of the latex proteins is the best approach. The authors believe that the method described in this paper "denatures" the proteins by altering the stereochemistry of their structures thus reducing the proteins ability to generate an immune response. It appears that the deactivation method has no adverse effects on the physical and chemical properties of natural rubber latex as it is used in the manufacture of dipped products (Figure 1).[7]

Of particular interest is that Vytex natural rubber latex appears to have a slightly reduced initial modulus when compared to untreated NRL. Accelerated aging appears to increase or "stiffen" untreated NRL whereas Vytex natural rubber latex maintains its "softness" associated with a low initial modulus. A reduced initial modulus translates into greatly reduced fatigue for items such as surgical and examination gloves. Initial studies of barrier properties of Vytex natural rubber latex indicate that Vytex natural rubber latex is at least equal and slightly superior to conventional NRL for barrier properties while conventional NRL is well known to be superior to synthetics. It is easy to assume that Vytex barrier properties will be significantly higher than synthetic materials. Dipped product manufacturing techniques may be enhanced by greatly reducing the antigenic protein levels prior to production; costs may be positively impacted due to a reduced need for post treatment such as excessive washing and leaching. Processability studies and pilot plant manufacturing runs have been performed for Vytex natural rubber latex at various stages of glove and condom production with favorable test results.

LATEX ALTERNATIVES

Latex gloves have long been the number one choice among surgeons, nurses and healthcare professional because they fit like a second skin as well as provide the comfort and tactile sensitivity required for healthcare procedures. The elasticity of the NRL, unlike synthetics, allows the material to conform to the hand while maintaining comfort over a long period of time. No synthetic material has been able to match the important characteristics of comfort, fit and feel demanded by end-users.

Universal precautions were instituted to provide a barrier against cross contamination and NRL has been the polymer of choice for many applications because of superior physical property performance compared to synthetic alternatives. ASTM standards for barrier properties are more stringent for latex than for synthetic materials. Research has been conducted to compare the in-use barrier properties of both surgical and examination gloves. In surgical gloves, non-latex gloves were found to have a significantly higher failure rate than latex surgical gloves (non-latex 8.4%, latex 6.0%, n=11,118 gloves).[19]

Table 1. Raw Material Characteristic Comparison, Various End Products [19-26]

Material	*Level of Barrier Protection*	*ASTM Strength Requirements (before aging)*	*Strength & Durability*	*Fit & Comfort*	*Elasticity*	*Aller-genicity*	*Environ-mental Impact*	*Supply*	*Cost/ Dry Weight*
Latex	Excellent barrier qualities; tear and puncture resistant	Exam Gloves: Type 1: 18 MPa Type 11: 14 MPa Surgical Gloves: 24 MPa	Excellent tensile strength. Has reseal qualities	Excellent comfort due to low modulus: excellent tactile sensitivity	Natural ability due to elastic quality rubber; keeps shape	Contains protein & chemical accel-erators	Excellent: natural product; incineration: mostly water and carbon dioxide	Excellent: Malaysia adding trees; new growth	$1.40 to $1.60 per lb.
Neo-prene (Chloro-prene)	Good	Surgical gloves: 17 MPa	Strong, has some puncture resistant qualities but once punctured, it easily tears	Provides a good fit, has some elastic ability that enhances fit	Close to latex and allows for flexibility	Contains no latex proteins but has some accelerator chemicals	Landfills: does not decompose Incineration: considerable amounts of hydrochloric acid	Petroleum by-product; supply fluctuates.	$2.50 to $2.70 per lb.
Nitrile	Resistant to punctures and does not develop holes easily Abrasion resistant	Exam Gloves: 14 MPa Surgical Gloves: 17 MPa	Strong, has puncture resistant qualities	Slightly tighter fit than latex due to generally high modulus	Less than latex over time tends to shape to wearer's hand	Contains no latex proteins but has some accelerator chemicals	Landfills: does not decompose Incineration: mainly water, carbon dioxide and NOx.	Petroleum by-product; supply fluctuates.	$1.40 to $1.60 per lb.
Vinyl	Easily breaks during use, Not approved for use in surgical gloves due to poor barrier: not recommended for use in chemotherapy or with glutar-aldehyde. May break down with alcohol.	Exam Gloves: 8 MPa	Weak, breaks easily & punctures easily in use. Exceptionally high in-use failure rates compared to latex	Fit limited baggy	Dexterity compromised	Contains no proteins but chemical accel-erators	Landfills: does not decompose and plasticizers can leach out into the environment. Incineration: considerable amounts of hydrochloric acid	Petroleum by-product; supply fluctuates.	$0.75 to $1.00 per lb
Poly-isoprene	Good barrier	Surgical Gloves: 17 MPa	Puncture resistant but can snag easily	Excellent, similar to latex	Similar to latex	Contains no latex proteins but some chemical accel-erators	Landfills: does not decompose Incineration: mainly water and carbon dioxide	Limited due to inability to increase production	$5.00 to $8.00 per lb.

Failure rates for exam gloves have been studied by several researchers and have noted that vinyl has the highest failure rate (22% to 85%) compared with latex (1% - 21%). One study compared vinyl, latex and nitrile exam gloves and showed vinyl exam gloves failed from 12% to 61%, nitrile 1% to 3%, and latex from 0% to 4%.[27] The NRL polymer continues to be used as the benchmark for synthetic and non-*Hevea* polymer development.

PRICE COMPARISON

Currently, the synthetic segment of the exam glove market has grown to represent 50% of that market (Table 2). However, this segment is made up of both nitrile and vinyl polymers. Although the barrier qualities of nitrile provide a good substitute for natural rubber latex, the comfort, fit, and feel can be compromised. (See chart above). In order to eliminate latex exam gloves, hospitals are in some cases converting 100% to vinyl exam gloves.

Unfortunately, they can be putting their healthcare workers and patients at risk due to vinyl's poor barrier qualities. Vinyl, although a cost effective alternative to latex, provides a poor substitute when barrier is an issue. Switching instead to nitrile exam gloves can provide the required barrier characteristics but they can drastically increase the facility's budget due to their higher acquisition price and also compromise fit and tactile sensation.

Table 2. Exam Glove Cost Comparison and Market Share Data

Exam Gloves	(Cost/Glove)	US Market Share
Latex	$0.03	49%
Nitrile	$0.05	22%
Vinyl	$0.025	29%

Ref: HPIS Q2 2005; data on file.

Surgical gloves have been slow to convert to synthetic alternatives due to their higher price and lack of required attributes. Currently synthetic surgical gloves represent approximately 13% of the total U.S. surgical glove market (Table 3). However, this category has seen a dramatic change with the introduction of polyisoprene surgical gloves, which now make up ~75% of the pairs sold in the synthetic category. The growth of gloves made from this material has been due to how closely polyisoprene mimics the characteristics of natural rubber latex, however at a much higher selling price. This material has been in short supply and thus is limiting the growth of polyisoprene. Neoprene, once the segment leader, now represents approximately 23% of the synthetic segment but still commands a much higher selling price that natural rubber latex.

Table 3. Surgical Glove Cost Comparison and Market Share Data

Surgical Gloves	(Cost/Pair)	US Market Share
Natural Rubber Latex	$0.32-$1.13	87%
Neoprene	$1.71	3%
Nitrile	$2.35	0.1%
Polyisoprene	$1.92	9%
Co-Polymer	$2.06	0.2%

Ref: HPIS Q2 2005; data on file.

As the cost of oil increases, the cost of producing these synthetic materials will also increase which at some point in time will be passed on to the consumer. To obtain a better understanding of the cost differential between natural rubber latex and synthetic materials, Table 1 lists current raw material market costs, while Table 4 compares glove prices.

The cost for non-latex gloves passed along to the healthcare industry can be two to three times that of latex surgical gloves. Current markets prices for these alternatives are listed below.

Table 4. Natural Rubber Latex Compared to Synthetics

Vytex™ Natural Rubber Latex Takes on the Alternatives on All Counts					
	Potential Vytex™ Natural Rubber Latex Gloves	Current Latex Gloves	Current Treated Latex Gloves	Synthetic Gloves *(PVC, nitrile, vinyl, etc.)*	Synthetic Gloves *(neoprene, etc.)*
Allergenicity	★★★★	★ *(powder free)*	★★ *(coated)*	★★★★	★★★★
Liquid Barrier	★★★★	★★★★	★★★	★★	★★★★
Elasticity	★★★★	★★★★	★★	★	★★★
Tactile Sensation	★★★★	★★★★	★★	★	★★★
Exam Glove (each)		$0.025-$0.135	$0.065-$0.17	$0.038-$0.425	
Surgical Glove (pair)		$0.875-$1.05	$0.875-$1.05	$0.975	$1.29-$1.38+

(Data extrapolated from a study by the Maryland School of Nursing)

NRL has been a very cost effective material throughout the years under many different market economies. The primary concern with the use of NRL since the early 1990s, especially in medical applications, has been the sensitization of some individuals to NRL proteins. The protein issue created a demand for alternative materials for use in medical and some consumer products. While some synthetic materials have come close to being able to mimic NRL, relative to certain properties, the total attributes of NRL have been hard to duplicate with synthetic materials and most synthetic latex polymers used in medical applications are not cost competitive.

Although not a new material, Guayule Rubber latex, in development by the USDA since World War II, is now the focus of a start up company called Yulex. Guayule rubber latex is a non-*Hevea* rubber that does not appear to contain the proteins found in *Hevea* rubber that have been the cause of Type I allergic reaction. This material is reported to be higher in cost compared to natural rubber and presently is available in limited quantities. Being

that it is still a natural product and latex, it has its own unique protein set. However, early papers on commercialization published by the company show promise.

Vytex natural rubber latex, with its patented chemical treatment process that lowers antigenic proteins to a level that is less than 0.2µg/g, offers the consumers of finished latex goods the best of both worlds since it maintains all the desirable attributes of NRL with a minimal increase in cost to the end products manufacturer. Consumer demand for products that mimic NRL without the high protein content have been verified in primary market research. This marketability, coupled with the added focus on increasing output in South East Asia, makes Vytex natural rubber latex an excellent alternative to untreated NRL as well as to the synthetics.

References

1) Cornish K. Commercialization of Guayule Latex (Yulex™). Presented at Latex 2006, Frankfurt, Germany.
2) Chen FB. Synthetic Polyisoprene Latex. Presented at the International Latex Conference, 2005; Charlotte, North Carolina.
3) Yassin MS, et al. Latex allergy in hospital employees. Ann. Allergy 1994; 72: 245-9.
4) Kelly KI, and others. A cluster of anaphylactic reactions in spina bifida during general anesthesia. J Allergy Clin. Immunol. 1994; 94: 53-61.
5) Sharivker V, Sharivker S, Blinov V, and Honeycutt T. Decreasing allergenicity of natural latex rubber prior to vulcanization, US Patent Application No 11/096,421 filed October 12, 2005.
6) Honeycutt T, Sharivker V, Sharivker S, Blinov V, and Doyle W. A Novel "Protein-Free" Natural Rubber Latex: Properties and Applications. International Latex Conference Papers, 2005; Charlotte, North Carolina.
7) Honeycutt T, Sharivker V, Sharivker S, Blinov V, Clark M and Doyle W. Technological and Physical Properties of a New Low Antigenic Protein Natural Rubber Latex. Presented at Latex 2006, Frankfurt, Germany.
8) Amdur S. Removing Natural Latex Proteins from Dipped Rubber Goods with Fumed Silica Additives. Presented at the meeting of the Rubber Division, American Chemical Society, Orlando, Florida. Published by SMTL: February, 2000 Version 1.0.
9) Downing J. Dermatitis from rubber gloves. N Engl J Med 1933;208:196-8.
10) Center of Devices and Radiological Health. Medical Glove Powder Report. Rockville, MD, Food and Drug Administration, 1977.
11) Mertes P, Laxenaire M, Alla F. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999-2000. Anesthesiology 2003;99: 549-58.
12) Pailhories G. Reducing proteins in latex gloves. The industrial approach. Clin Rev Allergy 1993; 11:391-402.
13) Meyer K, Beezhold D. Latex allergy: How safe are your gloves? Bulletin from the American College of Surgeons 1997;7,V. 82.

14) Yeang H, Arija S, Yusof F, et al. Allergenic proteins of natural rubber latex. Academic Press, Methods 2002;27:32-45.
15) Beezhold D, Kostyal D, Tomazic-Jeric V. Measurement of latex protein and assessment of latex protein exposure. Academic Press, Methods 2002;27:46-51.
16) Removal of Protein from Natural Rubber Latex. JETRO 1994;10:001-05.
17) Eng A, Kodama S, Kawasaki H. Reduction of Water Extractable Proteins in Natural Rubber Latex Films by Ultrasonic Leaching System. Journal of Rubber Research 1999;2(1):23-6.
18) Kemp DS. Organic Chemistry. Worth Publishers 1980;1422.
19) Korniewicz D. Advantages and Disadvantages of Non-latex Surgical Gloves. Business Briefing: Global Surgery 2004;64-67.
20) An Analysis of Gloving Materials. Ansell Cares. www.ansellhealthcare.com/america/usa/ceu/program7/page8 7/6/2006.
21) FirstHand- Critical Glove Barrier Issues. Kimberly-Clark Health Care Education.
22) Johnson F. Disposable gloves: research finding on use in practice. Nursing Standard. V11;No.16 January 8, 1997.
23) AAMI. Safe use and handling of gluteraldehyde-based products in health care facilities. American National Standard, 1995.
24) Klein R, Party E, Gershey E. Virus Penetration of Examination Gloves. BioTechniques, V9, No2, August 1990.
25) Korniewicz D, Laughon B, Cyr WH, Lytle CD, Larson E. Leakage of Virus through Used Vinyl and Latex Examination Gloves. American Journal of Dentistry V5, No2, April 1990, pp787-788.
26) Korniewicz D, Laughon B, Butz A, Larson E. Integrity of Vinyl and Latex Procedure Gloves. Nursing Research V38, No3, May/June 1989.
27) Rego A, Roley L. In-Use barrier integrity of gloves: Latex and nitrile superior to vinyl. AJIC October 1999;405-410.