

Extractable Protein Levels in Latex Products, and their Associated Risks, Emphasizing American Dentistry

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Abstract

Background: Over 8% of the US population have detectable Type I hevea latex IgE antibodies and, upon exposure to natural latex and rubber products, are at risk for potentially dangerous reactions, especially in dental settings where these products meet mucosal membranes.

Methods: Extractable antigenic protein levels were quantified in dental dams, examination gloves, and various other dental and rubber products. ASTM standards D6499 (antigenic protein) and D5712 (total protein) were used to quantify protein content.

Results: In dental dams, extractable protein content ranged from low/non-sensitizing levels (<3 µg/dm²) to high/sensitizing levels (130-200 µg/dm²). Also, while examination gloves from Malaysian glove manufacturers consistently exhibited a lower extractable protein content (<9 µg/dm²), than gloves from Thai manufacturers (16-23 µg/dm²) these levels should both still be non-sensitizing. There was no correlation between extractable protein content and the price or thickness of dental dams or examination gloves. Most of the other assorted dental products tested displayed low extractable protein content (<2.5 µg/dm²). Nearly all dental products made from natural rubber contained detectable antigenic Hevea proteins, subjecting previously sensitized patients and providers to risk of severe allergic reaction. A case study describes a female patient, with no previous history of Type I latex allergy, who reacted severely to a dental dam mouth exposure, necessitating her admission to the intensive care unit (ICU) of a local hospital for management of respiratory failure, with discharge after 4 days.

Conclusions: Some dental products may pose a significant risk of Type I latex protein allergy sensitization, due to repeated contact, and that a single exposure can induce a severe reaction in a previously sensitized person, even when no prior latex allergy history is known.

Keywords: Latex allergy; Extractable protein; Product safety; Case report

Introduction

Many commercial medical products are made with natural rubber harvested from the Brazilian rubber tree (*Hevea brasiliensis*, Müll, Arg.). Utilized for its combination of strength, flexibility, and hydrophobicity, natural rubber provides both patient comfort and protection against the transmission of blood-borne pathogens [1]. Unfortunately, natural rubber and latex products made from *Hevea* possess allergenic proteins in varying combinations and amounts. High protein levels in products not leached during their manufacture have led to the sensitization of a significant proportion of the population with life-threatening Type I latex allergy [2-9]. The instigators of this sensitization, soluble *Hevea* proteins, are found in *Hevea* natural rubber latex, a cytoplasm (lacking nuclei and mitochondrion) containing many constituents, most notably rubber

particles and three general categories of proteins: hydrophilic (water-soluble) proteins (~50% of total protein content); rubber particle bound proteins (~25%); and other hydrophobic proteins (~25%) [11]. Liquid latex (a rubber particle emulsion) is used to manufacture dipped products like medical gloves and dental dams, while other products, such as stoppers and tires, are made from solid rubber (made by coagulating and drying liquid latex). Products from each method of manufacture contain all three groups of proteins.

Type I latex allergy, caused by exposure to *Hevea* latex proteins, remains a major public health problem in the United States and throughout the world. *Hevea*-specific IgE antibodies are detectable in over 8% of the general U.S. population (~30 million Americans), although many of these people do not yet present clinical symptoms of latex allergy [4]. Few, if any, Americans exhibited Type I latex allergy before the 1980's AIDS epidemic, when the CDC required glove use for any direct patient contact. This had the effect of an immediate thirty-fold increase in latex glove demand, with ever increasing demand

following [9]. To meet this exponential increase in demand, new and existing manufacturers truncated the fabrication process, eliminating the in-line washing/leaching steps, thereby producing products with far higher protein levels than previously seen. Exposure to these highly allergenic items resulted in an unprecedented and massive surge in the number of health care workers and patients with Type I latex allergy [8]. Inhalation of aerosolized, protein-bearing cornstarch glove powder, as well as direct contact with mucosal membranes and body fluids of patients with latex products during medical and dental procedures, were major contributors to worker and patient sensitization [10].

Various methods to reduce allergenic protein levels in latex have been used, including multiple types of deproteinization, and double centrifugation [13,14]. However, while protein precipitation and double centrifugation methods reduce the total protein load in *Hevea* latex products, making them less sensitizing, it is impossible to eradicate all proteins from natural rubber products. So called “deproteinized natural rubber (DPNR)” latices, have been treated with proteases and peptidases – enzyme which partially break up the latex proteins, but have more protein than the untreated latices; and nearly all the protein has become the soluble type like that which caused Type I latex allergy, originally.

Today, most manufacturers use effective, inline leaching during latex product fabrication, and the Food and Drug Administration recently (January 18, 2017) banned powdered medical gloves which

eliminates the issue of exposure from aerosolization. In this final rule, FDA banned: (1) Powdered surgeon’s gloves (21 CFR 878.4460), (2) powdered patient examination gloves (21 CFR 880.6250), and (3) absorbable powder for lubricating a surgeon’s glove (21 CFR 878.4480). Properly leached products pose a low risk of sensitization, but it is impossible to determine protein content by physical appearance of a product [15,16]. Of course, even well leached, low protein, latex products still pose a risk of triggering a serious reaction to any patient who has already been sensitized with Type I latex allergy: the protein dose to sensitize a person is often far greater than the dose required to trigger a systemic, or even an anaphylactic reaction, in a sensitized individual [1].

Dental patients are particularly at risk due to the frequency of procedures utilizing latex products, the unfortunate suitability of saliva as a protein extraction medium, and the inability to predict when a sensitization threshold is crossed resulting in a Type I, possibly life-threatening, allergic reaction to the next latex protein exposure [1].

Previous researchers quantified extractable protein in certain products and have found that toy balloons and dental dams are a significant source of latex allergen exposure [10,17-21]. The following research focuses on products typically used in dentistry to determine product extractable protein levels, and the relationship of extractable latex protein content, to product type, cost, and manufacturing location.

Manufacturer	Color/Weight	Scent	Price (\$/dam)	Protein (µg/dm ²)	Protein (µg/g)	Thickness (mm)
Coltene/Whaledent	Fiesta/heavy	Natural	0.58	49	42	0.25
Coltene/Whaledent	Fiesta/thin	Natural	0.48	86.8	119.8	0.15
Coltene/Whaledent	Dark	Natural	0.36	153.1	143.5	0.18
Crosstex	Blue	Natural	0.19	2.57	3.56	0.16
Henry Schein	Green	Natural	0.24	2.03	2.03	0.21
Hygenic	Natural	Natural	0.33	131.9	205.8	0.14
Ivory	Green	Natural	0.28	0.64	0.69	0.21
Ivory	Green	Mint	0.28	7.22	8.57	0.17
Patterson Dental	Dark/medium	Natural	0.36	155.7	173.4	0.19
Patterson Dental	Natural/medium	Natural	0.36	166.1	195.3	0.2
Patterson Dental	Thin green	Natural	0.34	170	214.3	0.16
Patterson Dental	Medium green	Natural	0.36	188.6	216.3	0.18
Patterson Dental	Green/heavy	Natural	0.36	198.5	215.9	0.25
Safetouch	Blue	Natural	0.25	1.37	2.01	0.13
Safetouch	Thin green	Mint	0.25	1.71	2.71	0.13
SS White	Green	Mint	0.19	2.63	3.69	0.16
Guayule	Natural	Natural	-	0.066*	0.075*	0.4

Table 1: Extractable protein in unframed, powdered, natural rubber latex dental dams determined by immunochemical ELISA. All unframed dams were manufactured in Malaysia (except Ivory natural scent; Sweden). Prices are as of July 2009. The guayule natural rubber is not currently

commercially available. Extractable proteins from *Hevea* dams were quantified by ASTM D 6499, whereas guayule dams proteins were quantified using a guayule-specific immunochemical ELISA (Kostyal et al, LLC, 2011). ASTM D6499 does not detect guayule proteins.

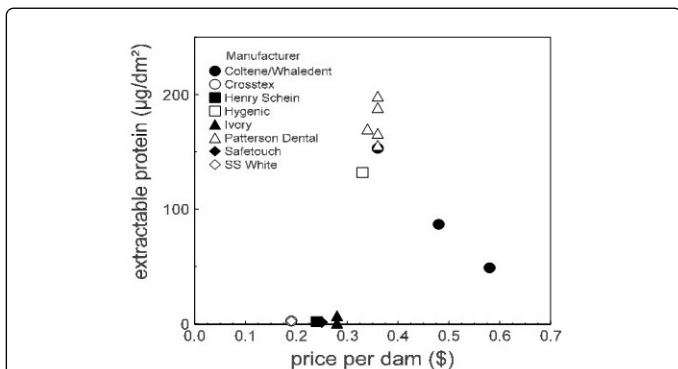


Figure 1: Relationship between unit price and extractable protein content of powdered natural rubber latex dental dams.

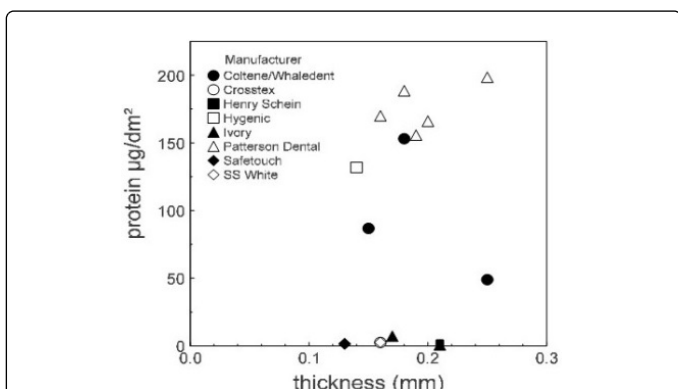


Figure 2: Relationship between thickness of dental dams and extractable protein content in dental dams.

Materials and Methods

An assortment of rubber materials and products used in dental practices were procured in 2009 and 2011. Extractable protein was quantified using the immunochemical ELISA testing method described in ASTM standard D 6499-03 (Standard test method for the immunological measurement of antigenic protein in natural rubber and its products). ASTM standard D 6499-03 was modified to more accurately quantify low protein content by diluting the standard curve down from 2 mg/ml to 0.2 mg/ml. This method is referred to as the trace protein method in this paper. *Hevea* latex was established as a positive control, while nitrile (a synthetic latex) and guayule latex (an alternative natural rubber) were utilized as negative controls. Furthermore, once dental dams from Patterson Dental were proven to

contain high amounts of soluble protein, this brand was included as a positive control in subsequent assays. For all data reported in this paper, carefully matched background optical densities were subtracted from raw spectrometric data.

For particular samples, extractable protein, presented as total protein, was quantified using the test method prescribed by ASTM D5712 (Standard test method for analysis of aqueous extractable protein in natural rubber and its products using the modified Lowry method). Total protein in liquid latex samples was quantified using the method described in ASTM D1076-06, Category 4 (Standard specification for rubber-concentrated, ammonia-preserved, creamed, and centrifuged natural latex).

Results

Dental Dams

Extractable protein content was quantified in 17 different samples of unframed, powdered dental dams (Table 1), Malaysia being the predominant country of manufacture, excepting one each from Sweden and the USA. Using the threshold values of 50 µg/g and 200 µg/dm² established as non-sensitizing protein dose levels, seven dental dam samples, from three companies, had significantly high extractable protein contents [22]. An additional seven dental dam samples, from five companies, contained low extractable protein levels. Unexpectedly, there was no correlation between extractable protein content and the price of a dental dam (Figure 1, $r^2=0.215$).

Additionally, thickness of the dam was not correlated to extractable protein content (Figure 2; $r^2=0.065$). With the exception of one powdered dental dam manufactured in Germany, with relatively high extractable protein content, framed dental dams consistently had low extractable protein levels (<3 µg/dm²; Table 2). Framed dental dams are devices in which the dam is prefitted to a skeleton that fits close to the patient's face and allows the dental dam film to be positioned to isolate the targeted dental area, while also permitting access to the mouth for suction, or other devices, without having to remove and replace the dam during the procedure.

Dental Examination Gloves

Extractable protein levels in 26 examination glove samples (from ten brands), including vinyl, nitrile, and guayule gloves as controls, were examined (Table 3). Examination gloves manufactured in Malaysia presented low extractable protein contents (<9 µg/dm² and <11.6 µg/g). Thai manufactured gloves (Plak Smacker brand) contained higher extractable protein levels (16-23 µg/dm²) but were well below the sensitization threshold levels of 200 µg/dm² and 50 µg/g. Consistent with results from dental dam testing, extractable protein content was not correlated with the cost of gloves.

Manufacturer	Material	Country of Manufacturer	Color	Powder	Price (\$/dam)	Protein (µg/dm ²)	Protein (µg/g)	Thickness (mm)
Aseptico/Advena	NR latex	Unknown	Blue	Y	1.3	2.57	2.75	0.21

Ivoclar Vivadent	NR latex	Malaysia	Blue	Y	1.45	2.74	2.51	0.28
Loser and Co./Zirc Co.	NR latex	Germany	Natural	Y	1.9	64.25	54.87	0.27
Aseptico/Advena	Synthetic rubber	Unknown	Mauve	N	2.6	0.27*	0.25*	0.23
Hygenic	Synthetic rubber	USA	Purple	N	2.23	2.27/0.17*	1.51/0.09*	0.45
Hygenic	Nitrile	USA	Purple	N	1	0.35*	0.17*	0.52
Loser and Co./Zirc Co.	Synthetic rubber	USA	Blue	N	2.1	0.25*	0.3*	0.25

Table 2: Extractable protein in framed dental dams. Protein values were determined by immunochemical testing using the trace protein method instead of the standard method in ASTM D6499. The Aseptico/Advena natural rubber dam claims to be made from a special process that minimizes allergens (NR latex, vanilla scented). Both natural and synthetic framed dams by Loser and Co/Zirc Co are antimicrobial. Prices determined July 2009.

Miscellaneous Dental Products

A variety of non-glove or dental dam rubber products were tested. Cure light barriers, dam clamp cushions, dental tape, finger cots, multi-use latex barriers, prophylaxis angles and wedjets had very low extractable protein levels (<7.90 µg/dm² and <7.95 µg/g, Table 4). Isolator and protective devices and t-bar light barriers had somewhat higher extractable protein levels but only one product, the Magic

Clamp isolator and protector had a protein content over the 50 µg/g threshold. The children's toys examined, both the balloons and the finger puppets, had low levels of extractable protein, (7.09 µg/dm² and 1.44 µg/dm², respectively; Table 4). However, previous research has shown that, similar to dental dams (Figure 1, Table 1), latex balloon extractable protein content is highly dependent on manufacturer [10].

Mfr	Material	Country of Mfr	Color	Scent	Powder	Size	Price (\$/100)	Protein (µg/dm ²)	Protein (µg/g)
Adenna	Latex	Unknown	Black	Natural	N	XL	7.74	1.33	1.83
AmerCare Inc.	Latex	Malaysia	Black	Natural	N	M	5.99	1.24	1.86
AmerCare Inc.	Latex	Malaysia	Blue	Natural	N	M	15.98	3.13	2.31
AmerCare Inc.	Latex	Malaysia	Natural	Natural	N	M	4.59	1.75	3.27
AmerCare Inc.	Latex	Malaysia	Natural	Natural	Y	M	3.79	5.34	8.28
Cypress	Latex	Unknown	Natural	Natural	N	XL	6	1.21	2.08
Evolution One	Latex	Malaysia	Natural	Natural	N	M	11.9	4.41	6.14
Glove Nation	Latex	Malaysia	Black	Natural	Y	M	5.99	0.59	0.85
Glove Nation	Latex	Malaysia	Natural	Natural	N	M	4.59	0.41	0.61
Glove Nation	Latex	Malaysia	Natural	Natural	Y	M	3.79	6.9	8.48
Glove Nation	Latex	Malaysia	Blue	Natural	N	M	15.98	0.85	0.5
High Five	Latex	China	Natural	Natural	N	M	8.26	0.08	0.4
High Five	Latex	Malaysia	Blue	Natural	N	M	7.5	0.14	0.68
Plak Smacker	Latex	Malaysia	Natural	Natural	Y	M	3.99	8.6	11.54
Plak Smacker	Latex	Thailand	Natural	Bubblegum	N	M	7.65	16.53	26.34
Plak Smacker	Latex	Thailand	Natural	Natural	N	M	4.99	22.97	37.33
Plak Smacker Blossom	Latex	Unknown	Blue	Natural	N	S	8.5	4.24	6.09
Superior	Latex	Malaysia	Natural	Natural	Y	M	nd	0.72	1.01

Tillotson	Latex	Malaysia	Natural	Natural	N, polymer-lined	L/XL	9.81	0.18	0.87
Tillotson	Latex	Malaysia	Natural	Natural	N, polytex-lined	L	14.03	0.05/3.02*	0.24/4.37*
Dynarex	Nitrile	Malaysia	Blue	Natural	N	M	8.64	0.69*	1.76*
Dynarex	Vinyl	China	Natural	Natural	N	M	5.61	0.68*	1.34*
High Five	Nitrile	China	Blue	Natural	N	M	nd	4.36*	7.99*
King Seal	Synthetic	Malaysia/Indonesia	Natural	Natural	N	M	nd	0.57*	0.8*
Plak Smacker Blossom	Nitrile	Unknown	Green	Natural	N	M	nd	0.21*	0.34*
Guayule	Guayule	USA	Natural	Natural	N	-	-	1.12*	0.8*

Table 3: Extractable protein in examination gloves. Protein values* determined by immunochemical testing using trace protein method instead of standard method in ASTM D6499.

Alternative Product Materials

Alternative elastomeric materials have been developed to circumvent the risk of Type I latex allergy in patients, including guayule latex, and protease-treated latex (deproteinized natural rubber or DPNR) [12-14]. Examples of DPNR gloves are the sample tested from Tillotson (Table 3). Using both the D5712 (total extractable protein) and the D6499 (antigenic extractable protein) quantification methods, Tillotson gloves were compared to latex film samples with high (Patterson Dental) and low protein content (Ivory) dental dams. However, Tillotson glove samples gave different results for the two methods (Figure 3). Tillotson gloves displayed significantly high levels of total extractable protein, which makes the marketing term “deproteinized” misleading. Although the protease treatment did not remove the protein, and actually increased total extractable protein, it did disrupt most of the pre-existing epitopes associated with the current form of Type I latex allergy.

Case Report

A 62-year-old woman presented to a local dentist office in need of an uncomplicated restoration. The patient had a limited medical history and self-reported no prior reaction to latex. In preparation for her procedure, a dam was placed in the mouth to check for fit, then promptly removed. Within 10 minutes of dam exposure, the patient started to complain of a tingling sensation around her lips. She was reexamined by a dentist within 5 minutes of the initial complaint of lip tingling. Substantial swelling of the lips and tongue were noted, and emergency services (EMS) were contacted.

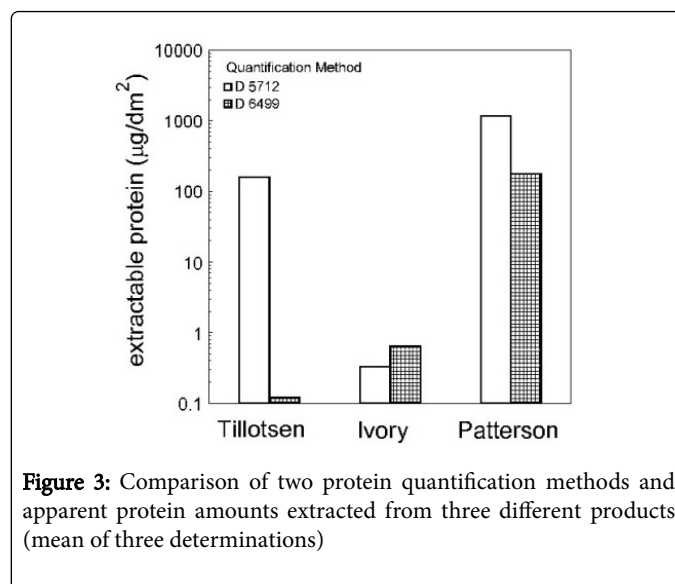


Figure 3: Comparison of two protein quantification methods and apparent protein amounts extracted from three different products (mean of three determinations)

Upon EMS arrival (20 minutes after initial symptoms developed) the patient was given 50 mg intravenous diphenhydramine, 0.3 mg intramuscular epinephrine, and 20 mg intravenous famotidine. She was subsequently intubated in the emergency room and admitted to the intensive care unit (ICU) for management of respiratory failure.

Manufacturer	Product	Material	Country of Manufacturer	Color	Protein (µg/dm ²)	Protein (µg/g)
Hygenic	Wedjets	Latex	USA	Yellow	1.39	0.4
Grafco	Finger cot	Latex	China	Natural	2.13	1.71
Magic Clamp	Isolator and protector	Latex	Unknown	Green	62.39	78.98
Steri-shield	Multi-use latex barrier	Latex	Malaysia	Blue	7.9	7.95
Steri-shield	Cure light barrier	Latex	Malaysia	Natural	2.26	2.04

Steri-shield	T-bar light barrier	Latex	Malaysia	Blue	20.48	21.34
Cushee	Dam clamp cushion	Rubber	Canada	Blue/yellow	1.03*	0.16*
Danville	Dental tape		Unknown	White w print	0.17*	0.52*
Dental Resources	Prophy angle	Synthetic	USA	Grey	11.34*	0.23*
Hygenic	Wedjets	Synthetic	USA	Green	0.21	0.09
Magic Clamp	Isolator and protector	Synthetic	Unknown	Blue	10.18*	2.14*
Pioneer	Balloon	Latex	USA	White w print	7.09	4.6
Unknown	Finger puppet	Unknown	Unknown	Black, white	1.44*	0.29*

Table 4: Extractable protein in miscellaneous dental products (non-powdered). Protein values* determined by immunochemical testing using trace protein method instead of standard method in ASTM D6499.

The patient required mechanical ventilation and was given dexamethasone 10 mg every 6 hours, diphenhydramine 50 mg every 6 hours, and famotidine 20 mg every 12 hours. A substantial reduction in airway edema was noted at 72 hours, as evinced by physical exam and endotracheal tube cuff leak. At this time, the patient was extubated and transferred to a standard care medical floor. She was discharged 24 hours later on hospital day four.

Serum *Hevea* specific IgE antibodies were collected upon ICU admission. Analysis was conducted via ImmunoCAP autoanalyzer and revealed a negative result (lower limit of detection=0.24 mg/mL). The ImmunoCAP has an approximate sensitivity and specificity of 70 and 95 percent, respectively [23]. Considering the limited sensitivity of IgE analysis it is reasonable to assume the patient reacted to *Hevea* proteins in the dental dam based on the clinical presentation. The patient was counseled on using extreme caution in situations where a repeat latex exposure is likely, and referred to an allergy specialist on discharge. Ultimately, the patient did not seek any further care and was lost to follow up.

Discussion

Most of the latex products that we tested, used in American dental practice, do not have extractable protein levels greater than the 200 µg/dm² and 50 µg/g protein thresholds set by FDA. These products are not likely to present a dose sufficient to sensitize most people [1]. Of all the products tested, only a subset of dental dams have sufficiently high levels of extractable latex proteins to pose a significant risk of patient sensitization to *Hevea* latex proteins [1]. Such exposure may lead to new cases of Type I latex allergy. While, it was logical to assume that inexpensive dental dams would exhibit the highest extractable protein content, there was no correlation between cost of dam and protein content (Figure 1) and the lowest cost dental dams actually had the lowest extractable protein contents. Malaysian dental dam manufacturing plants broadly either produced low protein or high protein dental dams, and so we investigated if the high protein dams retained more protein than low protein dams due to product thickness. Our research demonstrated that film thickness was not correlated with extractable protein content. Unfortunately, apart from the data set provided by this study, there is no way to reliably determine whether a dental dam has a high extractable protein content from brand name, appearance, price, or country of manufacture. However, dental dams purchased two years apart were found to have consistent protein levels.

For example, Patterson Dental and Hygenic brand dental dams remained at high protein levels (>140 µg/dm²) while CrossTex dental dams retained low levels (5.15µg/dm²). The current protein testing methods (ASTM methods D5712-03, D6499-07 and D7247-08) are designed specifically to evaluate natural rubber products made from *Hevea* latex. Identifying high protein materials and promoting safer products is greatly enhanced through the vigorous utilization of these testing procedures [10,22,24]. Yet, these methods are intended for manufacturers, and are technologically and resource dependent, providing a barrier for most users. Therefore, without product protein content data, the only safe course of action for dental providers is to assume all natural rubber dental dams pose a significant sensitization and reaction risk to patients. Rinsing high protein dams in water does not significantly decrease extractable protein content (data not shown) and special extraction media must be used (Cornish, unpublished data). That dental dams, especially high protein ones, pose a significant risk to dental patients is very clear from the case study reported in this paper, even though the brand of dental dam was not ascertained.

Other dental products contained lower protein levels than the highest protein dental dams, with cost, again, not being a correlating factor. Among the examination gloves studied, the two highest extractable protein content brands were on the lower end of costs per pair, but other similarly low-priced gloves had low protein levels.

When it comes to Deproteinized Natural Rubber (DPNR) materials, these materials display antigen content below the sensitization threshold [1]. This would not protect previously sensitized patients from allergic reactions, but it would mean that patients would be afforded some protection due to delayed sensitivity. However, the sensitization potential of these new epitopes has yet to be evaluated in humans, and the soluble protein levels are greater than those that caused Type I latex allergy. Thus, products made from DPNR latices should always be thoroughly leached (washed) during their manufacture to reduce the protein exposure to as low as can be achieved.

Conclusion

The majority of commercial dental products contain very little extractable protein, but a subset of dental dams have sufficiently high levels of soluble latex protein to pose a significant risk of Type I latex allergy reaction and sensitization. There is currently no method developed to determine which products do or do not contain high

levels of protein through rapid visual, physical or chemical testing. Therefore, all dental dams, unless specifically labeled otherwise, must be treated as though they have high extractable protein content. Furthermore, nearly all natural rubber dental products contain detectable *Hevea* antigenic proteins, and have the potential to induce dangerous Type I allergic reactions in patients previously sensitized to latex proteins. For this group of patients, dental providers can only safely use products made from guayule natural rubber latex or synthetic elastomers, none of which harbor *Hevea* antigenic latex proteins.

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