

Starch and natural rubber allergen interaction in the production of latex gloves: A hand-held aerosol

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Starch powders continue to be used as donning agents on natural rubber (NR) gloves. NR aeroallergens are an important aspect of human sensitivity to latex. Asthma, upper airway, and ocular symptoms are associated with these airborne proteins. These bioaerosols feature starch as the carrier. The association of NR allergen and starch is demonstrated in NR glove manufacturing, in laboratory simulation, and as occupational aeroallergens in health care environments. Four aspects of latex allergen affinity for starch powders were examined by using a competitive IgE immunoassay for NR latex. Allergen content was assessed in finished gloves before and after powder process points and related to the allergen content of the raw latex source material. In another manufacturing process, allergen uptake by two different starch powders was quantified. NR allergen affinity for the starches was also determined under laboratory conditions. Finally, NR aeroallergens carried by starch powder in production facilities were measured. This article outlines the sources, mechanisms, and conditions for NR allergens to interact with two different starches. The quantitative airborne allergen data are used to compare and contrast various occupational indices of NR allergen exposure. Powdered NR gloves continue to cause concern; however, the technology used for contemporary glove powder applications may be advanced and improved enough to consistently produce powdered gloves with a low allergen content. (*J Allergy Clin Immunol* 2002;110:S15-20.)

Key words: Starch, natural rubber allergen, latex, gloves

Starch is an organic chemical produced and stored by all green plants. It is a white, granular, odorless, and tasteless powder that is insoluble in cold water, alcohol, or other solvents. Starches are polysaccharides comprised of glucose monomers joined in linear α 1,4 linkages (amylose) and α 1,4 linkages branched at α 1,6 link-

Abbreviations used

ADP: Absorbable dusting powder
ASTM: American Society for Testing and Materials
FDA: Food and Drug Administration
NR: Natural rubber
OS: Oat starch

ages (amylopectin). Amylose molecules form helical structures that entrap molecules of the appropriate size. These complexes are nonstoichiometric and are referred to as *inclusion compounds*. The starch-protein interaction is known to be essential for many food products (baked goods), but the exact nature of the interaction between starch and protein remains unclear. In their native state, starch granules do not have membranes. Their surfaces consist of tightly bundled chain ends resembling the bottom of a broom. When starch is hydrated, some of the starch molecules near the granule periphery are drawn tangentially along the surface and form a membrane or packet.¹ In the natural rubber (NR) glove industry, two varieties of starch are used for the production of latex gloves. Cornstarch, or absorbable dusting powder (ADP), was the first starch introduced (1947) and continues to dominate as the glove-donning lubricant. The first rubber gloves manufactured with oat starch (OS) as a donning product were produced in 1995. These starches, like all starches, have similarities; however, their differences make them interesting to compare in the production of powdered NR latex gloves.

Chemical structure is the most obvious difference between ADP and OS in that ADP is cross-linked and OS is not. If non-cross-linked starch is autoclaved, it will gelatinize, rendering a useless glove. Gloves of the past were routinely autoclaved for sterilization, and cross-linking cornstarch was a necessary modification in the development of ADP. Contemporary gloves are sterilized by ethylene oxide or gamma irradiation.

Certainly, there are physical differences of shape, size, and gelatinization temperature ranges caused by amylose and amylopectin ratios (Table I).

The last area of contrast is in the manufacturing process in which these starches are used as glove-donning lubricants. ADP, according to the product monograph, may contain up to 2% magnesium oxide.² The OS used in these studies does not include magnesium oxide. This fact, in combination with cross-linking of ADP, may have

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TABLE I. Physical and chemical characteristics of oat and corn starch

Starch source	Shape	Average size (μm)	Amylose/amylopectin	Gelatinization temperature range ($^{\circ}\text{C}$)
Oat	Polygonal	8	24/75	53-59
Corn	Round/polygonal	14	28/72	62-72

bearing on the alkalinity of its slurry mixture. The average pH of OS and ADP slurry mixtures is 6.9 and 10.2, respectively, under laboratory conditions. Their alkalinities are more similar during actual manufacturing. Further, manufacturing protocols for OS and ADP slurries are of different suspension percentages. The ranges of total solids content of the OS and ADP slurries are 3% to 5% and 7% to 12%, respectively. The finished gloves from these studies reflect this difference in residual OS or ADP powder (~75 mg vs ≥ 150 mg, respectively).

Manufacturers converted from talc to the use of ADP for surgical gloves in the 1970s. The use of ADP as the donning agent in most examination gloves began in the 1980s.³ Before the late 1980s, dry powder application was a popular method for placing donning lubricant on NR gloves. The American Society and Materials (ASTM) standard, 3578 (1991), for examination gloves requires the absence of talc for compliance claims. To this end, a change was made to wet slurry application in the late 1980s to reduce the nuisance dust in the production facilities created by some dry powder application protocols and to meet ASTM voluntary standards. Very soon after the change to the wet slurry powder application, "a new problem became apparent."³ The Food and Drug Administration (FDA) began to receive reports of allergic reactions to gloves and the glove powder. Together, these observations formed a solid temporal, cause-and-effect relationship deserving very careful study.

METHODS

The competitive IgE immunoassay for NR latex of Swanson et al⁴ was used for all analyses. Briefly, the assay is designed to use a pool of 7 NR latex-sensitive human serum samples with an ammoniated NR latex allergen extract standard made from gloves with high allergen content. Glove and starch samples were extracted 1:5 wt/vol, and the allergen content was expressed as mass units (in nanograms or micrograms) per kilogram of material. Air samples were collected and quantified by the methods of Reed et al⁵ with an Air Sentinel (Quan-Tec-Air, Inc, Rochester, Minn). Allergen content in finished gloves at production points before and after the powder application was related to the allergen content of the raw ammoniated latex source material. Also, the effect of leaching or washing the glove rubber before wet slurry powder application was demonstrated during September and February production runs in Malaysia.

In another manufacturing process study, allergen uptake by ADP and OS on powdered NR gloves was compared. Powder-to-powder and powder-to-glove allergen contents were examined. Starch slurries were collected directly from the slurry tanks, vacuum-filtered, and allowed to dry for extraction (1:5 wt/vol) and determination of allergen content per gram of starch. Aided by these results, NR allergen affinity for ADP and OS were determined under laboratory conditions. Simulated starch slurry water was created when ammoniated NR source material was centrifuged at 20,000g and the liquid fraction was diluted at several concentrations with water. The undiluted preparation had a concentration of 3000 $\mu\text{g/mL}$. Various

amounts of ADP (5 to 25 mg) or OS (10 to 1000 mg) were put into tubes containing known quantities of available (free) NR allergen (114, 163, or 306 μg). After incubation at room temperature overnight, the slurries were spun down and the supernatants were assayed for NR allergen content.

Finally, NR latex aeroallergens carried by starch powder in production facilities and in health care facilities were quantified and compared. The health risk of using or manufacturing these products is not examined in this article; however, it is discussed.

RESULTS

NR allergens before and after powder process points

The allergenicity of NR gloves on 3 production lines (A, B, and C) before and after ADP application is presented in Table II. Unlike line C, production lines A and B did not use dry film leaching. The allergen content of the ammoniated latex, or source material, had no bearing on the allergen content of the final glove product. Also, it was evident that dry film leaching the gloves from line C significantly reduced the allergen content of the powdered gloves compared with that of powdered gloves from lines A and B. Because of subsequent washings, dry film leaching makes no difference in the allergen content of powder-free gloves, with the exception of polymer-coated gloves. Glove data from other studies, in which samples were collected over much longer manufacturing runs that used dry film leaching, showed a more meager decrease in allergen content. This may have been due to the unabated increase of allergenic proteins in the ADP slurry tank over time. The allergenicity of raw ammoniated latex source material ranged from 452 ng/L to 4022 ng/L. The powdered gloves demonstrated wide variability in allergen content, regardless of the allergenicity of the source material, ranging from 27.6 ng/kg to 4,618 ng/kg. The allergen content of chlorinated, powder-free gloves ranged from undetectable (<0.5 ng/kg) to 13.5 ng/kg.⁶

NR allergens on ADP and OS glove production lines

Two glove manufacturing lines of similar construction, age, and design (both using post-vulcanization leaching) were operated to study ammoniated NR allergen association with ADP and OS. Ten different process points were sampled and analyzed for ammoniated NR allergen. Only the slurry tanks containing the respective starches (ADP and OS) demonstrated divergent values. The ADP slurry water allergen content over time was inversely related to the slurry powder allergen content (Fig 1). ADP consistently bound more allergen than OS. Quantitation of extractable allergen from the starches conservatively demonstrated 2 to 4 times more allergen association with ADP than with OS. Furthermore, the

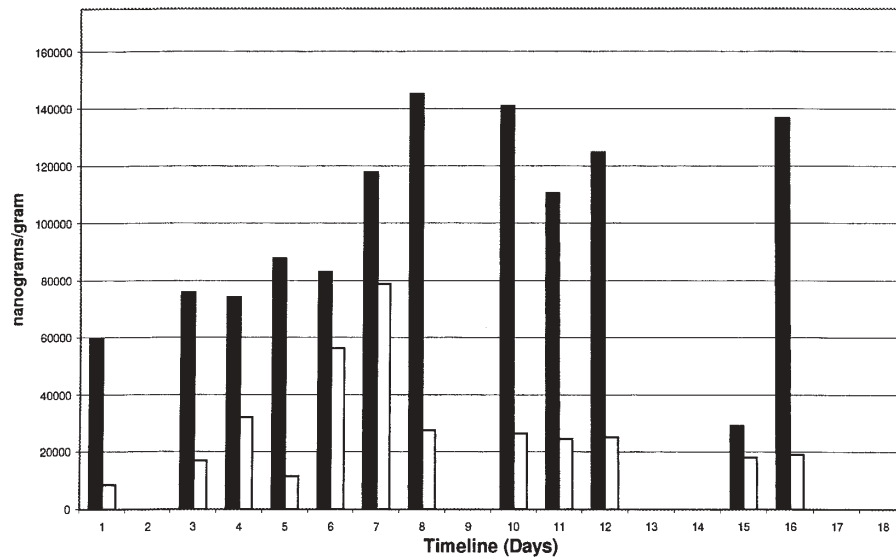


FIG 1. Comparison of slurry starch allergen content (in nanograms per gram). Filled bars, ADP; open bars, OS.

TABLE II. Allergen content in raw ammoniated latex and corresponding gloves

	Line A powdered glove	Line A powder-free glove	Line B powdered glove	Line B powder-free glove	Line C powdered glove	Line C powder-free glove
Sept 1999						
AL (ng/mL)	1,956,900	451,800	809,007			
Sample 1	4,311,280	567	670,160	1,125	27,647	8,146
Sample 2	2,237,200	ND	815,980	1,033	29,336	7,230
Sample 3	1,970,090	515	793,990	1,704	30,587	4,039
Sample 4	2,810,470	2,136	430,840	1,108	32,502	3,955
Sample 5	4,543,450	2,915	620,040	1,813	33,566	4,897
Sample 6	4,618,260	2,196	669,780	1,263	32,107	4,067
Sample 7	3,355,580	2,188	739,610	949	28,822	3,203
Sample 8	2,313,660	1,553	941,280	922	29,058	4,589
Sample 9	4,248,880	2,942	406,060	1,294	28,883	3,943
Sample 10	4,109,290	2,552	522,240	786	27,708	3,788
Mean	3,451,816	1,756	660,998	1,200	30,022	4,786
Feb 2000						
AL (ng/mL)	4,022,295	806,791	2,313,441			
Sample 1	1,371,079	12,538	317,964	7,568	87,865	6,745
Sample 2	1,048,101	9,422	316,431	6,122	117,309	6,629
Sample 3	1,320,012	10,966	230,593	6,188	74,573	6,311
Sample 4	789,230	13,525	221,340	5,672	75,287	6,832
Sample 5	1,477,686	11,044	243,397	5,176	90,511	7,198
Sample 6	1,484,308	9,857	252,845	4,932	63,859	7,650
Sample 7	1,840,197	9,851	292,631	4,723	79,294	8,277
Sample 8	1,568,907	12,428	209,354	3,587	93,947	7,001
Sample 9	290,064	12,200	327,553	6,564	81,783	7,238
Sample 10	2,283,410	9,980	217,355	5,149	102,681	5,128
Mean	1,347,299	11,181	262,946	5,568	86,711	6,901

All glove values are expressed as nanograms per gram of rubber.
ND, Not detectable.

allergen content per gram of the finished glove exceeded that of the OS powder (Fig 2). Exactly the opposite occurred with ADP (Fig 3). Thus, on a mass basis, the ADP powder may contain more allergen than the finished glove.⁷

NR glove powder affinities for NR allergens

Determination of NR allergen affinity for ADP and OS glove powder under laboratory conditions was aided and guided by the results of the manufacturing process stud-

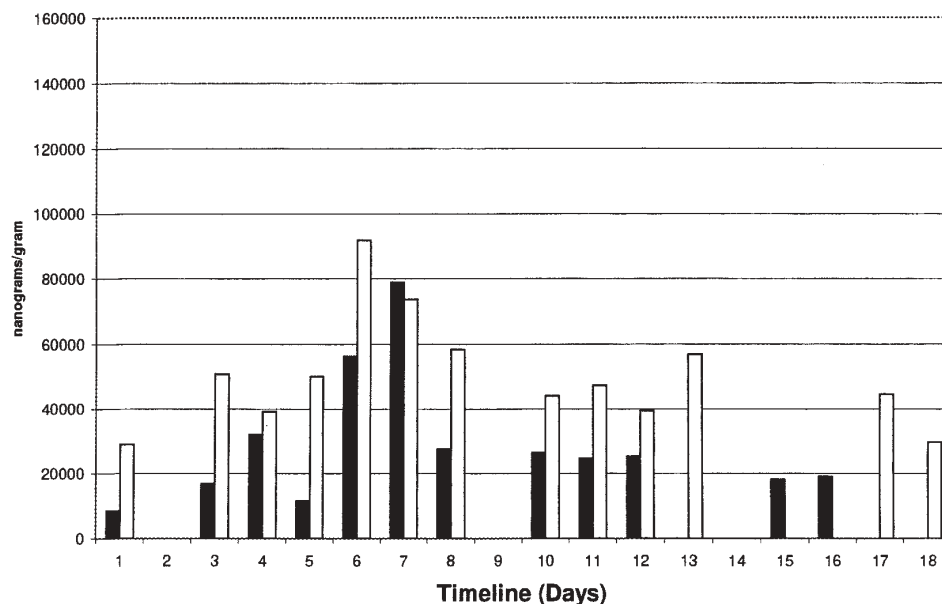


FIG 2. Allergen content of OS slurry powder and finished glove (in nanograms per gram). *Filled bars*, OS slurry powder; *open bars*, OS glove.

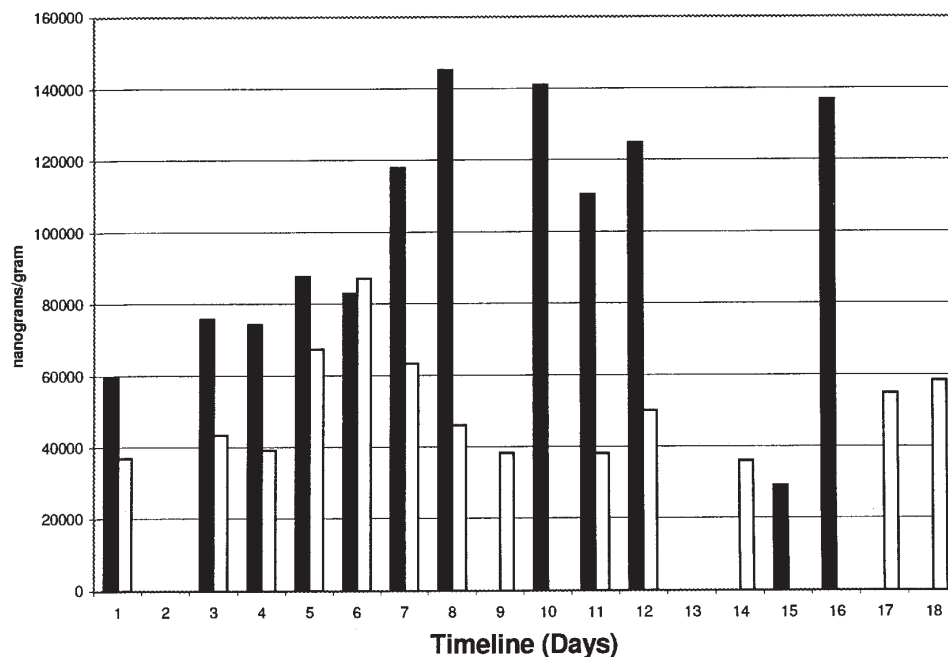


FIG 3. Allergen content of ADP slurry powder and finished glove (in nanograms per gram). *Filled bars*, ADP slurry powder; *open bars*, ADP glove.

ies. During manufacture, the slurry water concentration of NR allergen rises as the gloves pass through it for application of the glove-donning powder. Simulation of actual changes in the concentration of allergen present in the slurry water was accomplished by combining several different concentrations of ammoniated NR allergen source material with varied amounts of respective starches (Table III).

The NR allergen bound to the starch was calculated by subtracting the measured aqueous allergen (free) from the total available allergen in the sample. Both starches demonstrate an affinity for NR allergens; however, ADP exhibits a much higher affinity for allergen than does OS. The total allergen uptake per milligram of ADP is dramatically greater than that of OS.

TABLE III. Natural rubber latex allergen binding affinity for glove powders

Starch (mg)	Available allergen per sample 306 µg		Available allergen per sample 163 µg		Available allergen per sample 114 µg	
	Free (µg/sample)	Bound (µg/sample)	Free (µg/sample)	Bound (µg/sample)	Free (µg/sample)	Bound (µg/sample)
ADP						
5	248	58	102	61	85	29
10	250	56	109	54	91	23
15	225	81	67	96	74	40
20	189	117	42	121	5	109
25	216	90	5	158	2	112
OS						
10	326	0	118	45	81	33
50	254	52	107	56	68	46
100	228	78	112	51	115	0
500	223	83	118	45	99	15
1000	200	106	98	65	81	33

Free allergen is actual measurement; starch-bound allergen is calculated as (Available – Free = Bound).

Occupational NR aeroallergens

It is a rare occurrence to find quantifiable NR aeroallergen outside health care or glove production facilities. Almost without exception, it is not found in homes, offices, or schools or outdoors.

Airborne NR allergens are commonly found in medical and dental office buildings.⁸⁻¹⁰ Recently, glove production facilities have been surveyed for airborne NR allergen.¹¹ Results from two separate Malaysian glove manufacturing facilities are presented in Table IV.

The first factory was producing chlorinated, powder-free gloves without post-vulcanization washing (post-cure leaching). Keep in mind that almost all NR gloves (including powder-free) are powdered at some point in their production, and only a very few gloves are made by a totally powder-free process. The airborne concentrations spanned yet another order of magnitude beyond maximum health care facility concentrations, reaching 10⁴ ng/m³ in this factory.

The second factory was producing gloves powdered with ADP or OS. These processes included a post-vulcanization wash that greatly reduced the rate of allergen buildup in the slurry waters, and hence, reduced the amount of allergen associated with the starch. This reduction is reflected in the lower airborne concentrations of NR allergen at the beading station and especially at the hand stripping and autostripping stations. More dispersion, more glove volume, or a combination of both factors might explain the generally higher concentrations at other locations in the second factory.

DISCUSSION

Starch powder is the vehicle that carries the NR aeroallergen.¹² NR allergen association with starch powders during manufacture has not been previously studied. The FDA proposes a recommendation of 120 mg of powder per glove. Given the manufacturer's specification for total solids content in slurry suspensions, ADP powder residues on contemporary gloves average 260 mg per glove.¹³

TABLE IV. Airborne concentrations of natural rubber latex within latex glove production facilities

Location	Average concentrations (ng/m ³)	
	Factory 1* (1998)	Factory 2 (2000)
Autostripping	23,679	4,162
Hand stripping	17,674	3,140
Dry tumblers	4,947	5,947
Beading	536	278
Compounding	232	858
Vertical dryer	81	886
Quality control packing	27	52
Protein lab	13	NT
Office area	14	26

NT, Not tested.

*No leaching after vulcanization (chlorinated gloves).

The studies of allergen uptake on ADP and OS glove production lines clearly point to the slurry tank and the wet powder application as the primary source and mechanism for allergen association with donning powders of NR gloves. The allergen content of the glove powder is related to the allergen concentration of the slurry tank water at the time of powder application; it is not related to the allergen content of the glove on which the powder is applied. The chemical and physical differences (likely related to charge and hydroxyl groups)¹⁴ between starches require further study.

The allergenicity of the raw ammoniated NR source material has no impact on the final allergen content of powder-free gloves, despite speculation that genetic variation among trees or overlapping or wounding trees may influence the finished product. The potency of the source material can have an impact on powdered gloves (as shown in Table II) if the slurry tank conditions are neglected or overlooked.

Manufacturers must focus attention on the powdering process of NR gloves. Collectively, these results can be used to formulate a solution to the powder-protein problem, which can be tested. Simply stated, one starch may serve to make the other even more acceptable in the scheme of powdered glove production.

The FDA did not choose to eliminate the use of powdered gloves, preferring to limit the protein content of the glove rubber and the powder mass. Its proposed guidelines for powder and protein limits in medical gloves may fall short in reducing the allergen content of the glove powder. By deductive reasoning and inference, the allergen content of the ADP slurry glove powder on NR gloves during the 1980s and thereafter was a key factor in the abrupt widespread sensitization in the workplace. As stated in "The Industry Perspective on Latex,"³ manufacturers converted to ADP for surgical gloves in the 1970s, and although it was not required by FDA regulation, use of ADP for examination gloves began in the 1980s. "At that time a new problem became apparent, as hot, latex-covered formers warmed slurries of ADP..."³ This indirectly states that those ADP slurry applications to NR latex gloves did not take place before the 1980s. These asthmagenic, hand-held bioaerosols were unwittingly propelled into the working atmosphere of thousands of health care professionals. This was undoubtedly the underlying reason for the explosion of NR sensitivity in the 1990s. If exposure to rubber itself were sufficient to cause sensitization, the epidemic would have occurred much earlier.

If starch powders continue to be used, it is the degree of protein association with the powder, not the amount of powder, that is of primary concern. Given the current state of the manufacturing process, regulatory decisions, and these objective data, the use of OS as a glove-donning powder is a rational choice over ADP. Ultimately, the use of both starch powders in tandem may be a reasonable approach to the satisfactory reduction of NR protein (allergen) association with starch, thereby advancing and improving powdered NR latex glove production technology.

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