

Latex Protein: A Hidden "Food" Allergen?

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ABSTRACT

Avoidance of latex allergens is the primary method to prevent adverse reactions. Natural rubber latex is found in many different products in both the health care industry and in modern society, and consequently results in unexpected exposures of sensitized individuals. The use of latex gloves by food handlers provides one potential route for inadvertent exposure to latex allergens. In this study we have used two immunological methods to determine whether latex proteins are transferred to foods following contact with latex gloves. Direct transfer of latex protein to cheese was visualized using a modified immunoblot method. Sliced cheese was touched with a gloved finger. A nitrocellulose membrane was applied to lift the potential fingerprints and a rabbit anti-latex antiserum was used to visualize the transfer of any latex fingerprints. After handling lettuce with gloves, transferred protein was recovered by extracting the lettuce and quantified using an inhibition ELISA for latex proteins. Fingerprints of latex protein were readily detectable on cheese after contact with powdered latex gloves, but not with vinyl gloves. Furthermore, powdered latex glove use resulted in measurable amounts of latex protein on lettuce with an exposure-dependent increase in the latex protein levels. Lettuce alone or lettuce handled with vinyl gloves was negative for latex protein. The use of latex gloves by food handlers is the source of an indirect food additive in the form of latex proteins. It is recommended that food handlers avoid the use of

latex gloves to eliminate inadvertent exposure of latex-sensitive individuals. (Allergy and Asthma Proc 21:301-306, 2000)

ImmEDIATE hypersensitivity reactions to natural rubber latex (NRL) have become a serious risk, particularly to health care workers (HCW) and to certain patient groups who undergo frequent medical procedures, such as patients with spina bifida (SB). The prevalence of latex sensitization in HCW is between 5 and 17%¹⁻³ and 50% or greater in SB patients.⁴ Allergic reactions to latex gloves range from delayed-type hypersensitivity reactions² to IgE-mediated type I hypersensitivity reactions.^{1,2} Studies have shown that residual proteins on latex devices cause the IgE-mediated allergic reactions.⁵⁻⁹ Residual protein levels on gloves vary considerably, but in general, powdered gloves have significantly more antigenic protein than powder-free gloves. In addition to the critical requirement for the exclusive use of synthetic gloves, additional protective measures may be necessary for some individuals practicing latex avoidance.

Avoidance is the best method to prevent adverse reactions to latex, but this can be a difficult task. NRL is present in many different products in both the health care industry and the home, resulting in unexpected exposures of sensitized individuals.¹⁰⁻¹⁴ The powder on gloves serves as a vector for latex protein that can be carried in the air and/or on clothing, resulting in the inadvertent exposure of individuals practicing latex avoidance.¹⁵⁻¹⁷ Furthermore, cross-reactivity to certain foods makes avoidance of those foods necessary for clinically reactive patients.¹⁸ The presence of cross-reacting foods is further complicated by the use of latex gloves by food handlers. Anecdotal reports have been made of reactions to foods not suspected of being cross-reacting, but because the foods were handled with latex gloves.¹⁴ Although it is quite conceivable that latex protein could contaminate foods when food handlers wear latex gloves, the contamination of food with latex protein has not been documented. In this study we have used two different laboratory methods to demonstrate that contact of foods by

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Presented at ACAAI 10th International Food Allergy Symposium, Chicago, Illinois, November 11, 1999

Supported by The Guthrie Research Institute

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latex gloves results in contamination of the foods with latex protein. The data demonstrate that the contamination can be considerable. We were able to show contact-dependent increase in the transferred protein levels by inhibition ELISA.

MATERIALS AND METHODS

Gloves and Reagents

Eight brands of gloves were screened for protein levels by ASTM D5712 Lowry assay, and an inhibition ELISA before analysis for protein transfer to foods. The brand of latex gloves chosen for use (E1) was powdered examination gloves containing 258 $\mu\text{g/g}$ of total protein and 22.9 $\mu\text{g/gm}$ of antigenic protein. Two brands of vinyl gloves were used as negative controls. Lettuce and sliced processed cheese were purchased locally.

Experimental Protocol

The experiments were designed to simulate the contact of foods by food handlers' gloves. The hands were thoroughly washed before donning to assure that no latex protein was present on the hands before starting the experiment. Typically, powdered gloves have more protein on their inner surface (average 63% of total, $n = 11$ brands, range 17–97%) than on their outer surfaces. Brand E1 had ~80% of its total protein on the inside surface of the gloves, therefore the gloves were donned inside out to make it easier to detect the protein. Contact with gloved fingers was made with cheese (single fingerprints) and lettuce (multiple contacts) and the foods were processed for the immunological detection of latex protein.

Visualization of Protein Transfer

The transfer of protein by contact of latex gloves with the cheese was visualized using the fingerprint assay,¹⁹ a modified Western blot immunoassay. The assay was performed by gently pressing a gloved finger for 3 seconds to a slice of processed cheese and repeating for a total of four prints. A dry nitrocellulose membrane was carefully placed on the cheese for 30–60 seconds to "lift" the prints from the food. The nitrocellulose was then moistened and separate lanes touched with latex gloves directly as a positive control or synthetic gloves as a negative control. After all prints were made, the membrane was washed with T-PBS, blocked with 10% nonfat dry milk, and incubated overnight with a 1/10,000 dilution of rabbit anti-latex protein antiserum. The membrane was then washed with T-PBS and incubated for 1 hour with a 1/2000 dilution of alkaline phosphatase-labeled goat anti-rabbit antiserum (Promega, Madison, WI). Protein transfer was visualized by development in NBT/BCIP substrate (Promega).

Inhibition ELISA for Latex Protein

The transfer of latex protein to food was quantitated using a competitive inhibition assay (ASTM 6499-00). A small piece of lettuce was manipulated while wearing

gloves and the number of finger contacts recorded. Vinyl gloves served as a negative control. The lettuce was placed in a 50 mL polypropylene tube and extracted with 5 mL of PBS. The extract was then tested for latex protein using an inhibition ELISA.²⁰ The inhibition step was carried out in low-

protein-binding microtiter plates by first blocking the plates with 300 μL of 3% nonfat dry milk/PBS overnight at room temp. Seven twofold dilutions of each extract (100 $\mu\text{L}/\text{well}$) and seven twofold dilutions of an ammoniated latex (AL) reference protein beginning at 2 $\mu\text{g}/\text{mL}$ were made in the blocked low-protein-binding plate. Rabbit anti-latex serum (1/15,000 dilution) was added to each sample dilution (100 μL) before incubating the plates for 2 hours at 37°C. Solid phase antigen was prepared by coating the wells of a 96-well polystyrene ELISA plate (Maxisorb, Nunc) with 0.3 $\mu\text{g}/\text{well}$ of AL protein in carbonate buffer pH 9.6 for 2 hours at 37°C. Solid phase antigen was washed $\times 3$ with phosphate buffered saline containing 0.05% Tween 20 (TPBS), after which the non-reacted sites were blocked for 1 hour with 3% nonfat dry milk/PBS and washed two times with TPBS.

After the 2-hour incubation to allow antibody recognition, samples (100 $\mu\text{L}/\text{well}$) were added to the 96-well plates containing the solid phase antigen and incubated for 2 hours at 37°C. The plates were washed $\times 3$ with TPBS and reacted with a 1/5000 dilution of peroxidase-labeled goat anti-rabbit IgG (Sigma, St. Louis, MO) for 1 hour at 37°C. After washing the plates $\times 3$, a colored reaction was produced by the addition of *o*-phenylenediamine (1 mg/mL) in H_2O containing 0.1% H_2O_2 . The reaction was stopped by the addition of 50 $\mu\text{L}/\text{well}$ of 4 N sulfuric acid. The reaction product was quantified by reading the optical density at 490 nm using an MR 5000 ELISA plate reader (Dynatech, Chantilly, VA). The concentration of latex protein in extracts was determined by comparing the optical density of unknowns to the AL reference standard at three consecutive dilutions using a customized computer spreadsheet and expressed as mass protein per mL of extract. The inhibition assay has a linear working range between 30 and 2000 ng/mL and was recently approved (Dec. 1999) as an ASTM standard assay (D6499-00).

RESULTS

Case Report

A 29-year-old female dental hygienist was diagnosed with latex allergy in 1994 with a positive history and latex skin test. Her symptoms included contact dermatitis, urticaria, occupational rhinoconjunctivitis, and asthma. She has continued to work but wears non-latex gloves and a mask. She had no history of food allergy prior to her latex allergy, but was skin test positive to potato and negative to other foods, including lettuce. She reported no clinical reactivity to foods.

She had an allergic reaction 30 minutes after eating salad from a restaurant salad bar. Symptoms including wheezing, angioedema of eyes, eventually becoming completely swollen shut, tightness in throat, and generalized pruritis; she became lightheaded and blacked out. Latex gloves were used by restaurant employees during food preparation. As a result of this and similar reports from other latex-allergic individuals, we sought to determine whether latex proteins were transferred to foods by contact with gloves.

Protein Levels on Gloves

Eight different gloves were tested for their protein content. Two brands of vinyl gloves served as negative controls. One brand of latex gloves was a powder-free surgical glove, while the others were from two different brands of powdered exam gloves, one lot from one brand and four lots of a second brand. The total protein levels (ASTM D5712-95) and the antigen levels (inhibition ELISA ASTM 6499-00) are reported in Table I. One vinyl glove had detectable protein in the Lowry assay, which presumably represents interference in the assay by manufacturing chemicals, because no protein is used in the manufacture of vinyl gloves.

In order to choose a glove for additional experiments, the transfer of antigen was determined by fingerprint assay. As shown in Fig. 1, the transfer of latex protein from the powdered latex gloves to a nitrocellulose membrane was readily apparent (*lanes 4–8*), but little or no transfer could be observed from the powder-free or vinyl gloves (*lanes 1–3*). The highest levels of extractable and transferable antigen were found on glove E1, which was selected for further experiments.

Transfer to foods

To examine whether latex protein could be transferred to food, a modification of the fingerprint assay was used. Sliced cheese was used because it provides a moist and smooth surface from which potential prints could be lifted. The cheese was gently touched with a gloved finger; a nitrocellulose membrane was then applied to the cheese for

30–60 seconds and removed. For the negative control, a second strip of cheese was touched with a vinyl glove and the same nitrocellulose membrane positioned on the second strip of cheese. The process was repeated for subsequent glove samples.

After the prints were lifted from the cheese, the membrane was wetted and control prints were made by direct contact with the moist membrane. As shown in Fig. 2, lighter but clearly distinct prints appeared where the latex glove contacted the cheese, but not where the vinyl gloves had contact. This experiment was repeated three times with similar results. To rule out the possibility of endogenous alkaline phosphatase activity in the cheese being activated by the fingerprint process, we performed the fingerprint assay with a different reporter system using HRP-labeled anti-rabbit IgG and 4-chloro-1-naphthol as the substrate. A similar pattern of fingerprints was observed for the latex gloves, but not vinyl, indicating that the assay was specific for the latex proteins (data not shown).

To quantitate the amount of protein that was transferred, lettuce leaves were manipulated while wearing gloves, recording the exact number of finger contacts. Next, we extracted the surface of the lettuce with phosphate buffered saline and analyzed the extract by inhibition ELISA for latex protein. The control lettuce (no contact with latex gloves) had no detectable latex antigen, indicating that there was no latex present on the lettuce and there was no recognition of lettuce proteins by the anti-latex antisera. When lettuce was touched with powdered latex gloves, latex protein was readily detectable (Table II). By testing the lettuce after increasing numbers of gloved finger contacts, an exposure-dependent relationship could be demonstrated (Fig. 3). From three separate experiments, we calculated that on average, 0.05 μ g of protein transferred per finger contact with the E1 brand of glove.

DISCUSSION

Latex gloves are commonly worn by individuals in the food service industry. Latex allergic patients report reactions from foods potentially contaminated by latex allergens as a result of contact with food handlers' gloves. At least one report has been documented in the literature of severe reactivity to foods suspected to be contaminated with latex at fast food restaurants.¹⁴ Recently it was reported that allergic symptoms were elicited in a patient after drinking a glass of orange juice stirred with a glove, but not with uncontaminated orange juice.²¹ We provide an additional case report to illustrate the potential severity of these reactions and now demonstrate immunologically that latex proteins are transferred to foods by contact with latex gloves.

Using a visual assay, we show fingerprints of latex protein transferred to sliced cheese at the points of contact with gloves. We have also quantitated the amount of protein that was transferred to lettuce by simulating the type of contact that occurs during food preparation. Taken together, these

TABLE I

Protein Content of Gloves

Glove Sample	Lot # (Exp. date)	Protein μ g/gm	
		Lowry	Inh ELISA
A. Vinyl	803050 (NA)	<28	<0.15
B. Vinyl	484302 (NA)	114	<0.15
C. Powder-free latex	98I0552 (2003)	<28	<0.15
D. Powdered latex	26128 (NA)	549	26.1
E1. Powdered latex	170316 (1993)	258	22.9
E2. Powdered latex	22325 (1997)	168	10.2
E3. Powdered latex	201616B (2001)	90	3.5
E4. Powdered latex	T01456 (2002)	33	0.7

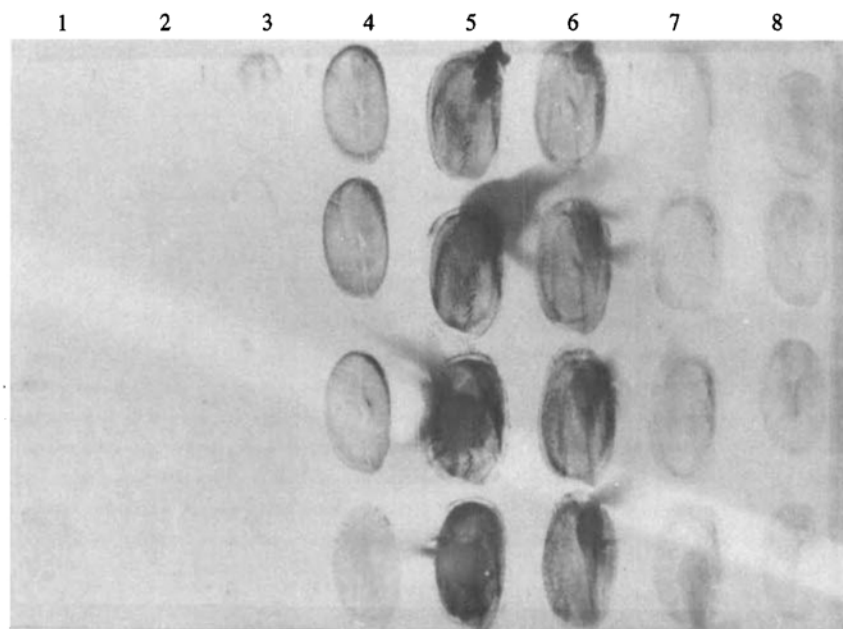


Figure 1. Finger print analysis for latex protein transfer from eight brands of gloves. Lane 1: vinyl glove A; lane 2: vinyl glove B; lane 3: powder-free surgical glove C; lane 4: powdered exam glove D; lane 5: powdered exam glove E1; lane 6: powdered exam glove E2; lane 7: powdered exam glove E3; lane 8: powdered exam glove E4.

data offer direct experimental evidence that latex proteins are easily transferred from gloves to foods.

In this study we chose gloves with a significant amount of protein to enhance our ability to detect the protein. The gloves we used had 258 $\mu\text{g/gm}$ of total protein, which is

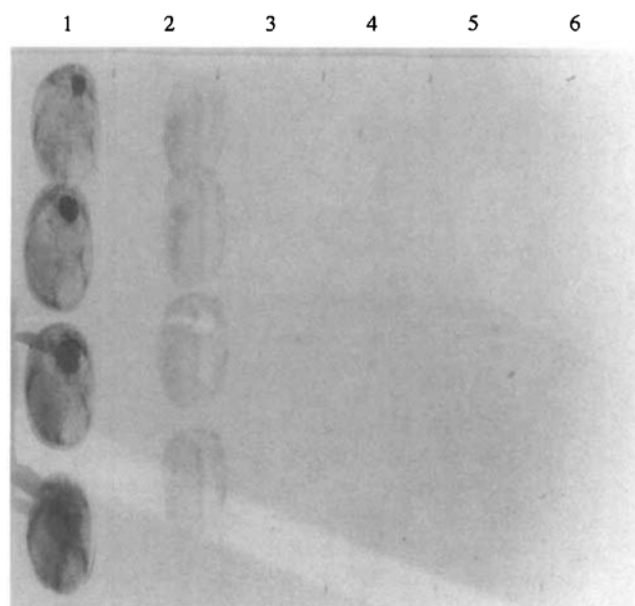


Figure 2. Transfer of latex protein to sliced cheese. Lane 1: glove E1 applied to membrane; lane 2: glove E1 applied to cheese and transferred from cheese to membrane; lane 3: vinyl glove A applied to membrane; lane 4: vinyl glove A applied to cheese and transferred from cheese to membrane; lane 5: vinyl glove B applied to membrane; lane 6: vinyl glove B applied to cheese and transferred from cheese to membrane.

slightly higher than the proposed limit of 200 $\mu\text{g/gm}$ that is under consideration by the FDA as a maximum amount of protein on medical gloves.²² Currently, many powdered gloves exceed this level of protein.²³ Vinyl gloves showed no detectable antigenic protein and no transfer of latex protein to the foods; however, one brand tested did have a protein reading in the Lowry assay indicating these gloves may contain residual chemicals that cause interferences in the Lowry assay. We were unable to determine whether residual chemicals are also transferred to food.

We have used the fingerprint assay to demonstrate protein transfer from both the inside and outside surfaces of gloves and that transfer to the hands could be prevented by an impervious glove liner.^{19,24,25} In this study we used the gloves inside out to enhance the detection of protein. Our previous data indicate that if the glove were donned normally, the primary difference would be in the amount of protein that was transferred. Likewise, we did not perform our experiments with powder-free gloves because the lower amounts of protein on these gloves would make detection difficult.²⁵ However, it is reasonable to assume that lesser amounts of protein are also transferred from these gloves. It is not known how much latex protein is necessary to induce a reaction in a sensitized person, but as little as 70 pg/mL can induce a reaction on skin prick testing.^{26,27} In the present study we found an average of 50 ng transferred to lettuce per single finger contact. Because the level of sensitivity varies from patient to patient, all contact of food with latex gloves should be avoided.

Food handlers' gloves are not regulated by the FDA as medical devices, but fall under the Title 21 CFR 177.2600 regulations. These regulations control materials that are

TABLE II

Amount of Antigenic Latex Protein Transferred		
Glove Brand and Number of Contacts	Total Antigen Detected (μg)	Amount per Contact (μg)
E1, 100	8.76	0.088
E1, 80	6.60	0.083
E1, 60	4.62	0.077
E1, 40	2.94	0.074
None, 0	b.d.	—
A, 100	b.d.	—

Lettuce was handled while wearing gloves, recording the number of finger contacts. The control extracts of lettuce alone (0 contacts) or lettuce with 100 fingerprints from vinyl gloves (Brand A, 100 contacts) were below the detection limit (b.d.) of the inhibition ELISA assay ($0.015 \mu\text{g}/\text{mL}$). Data represent a single experiment.

food contact surfaces that may result in indirect additives to the food. This regulation specifies manufacturing limits on many different rubber polymers and chemical ingredients to rubber materials that may contact food. Components of food processing equipment manufactured from synthetic rubber, such as butyl rubber, do not pose a risk for patients allergic to natural rubber proteins. This regulation does not recognize or propose limits on NRL proteins. Although food processing equipment could have NRL components, much of the latex allergen is presumably removed during routine cleaning of the equipment. The danger with latex glove use by food handlers is that the food is contaminated just before consumption.

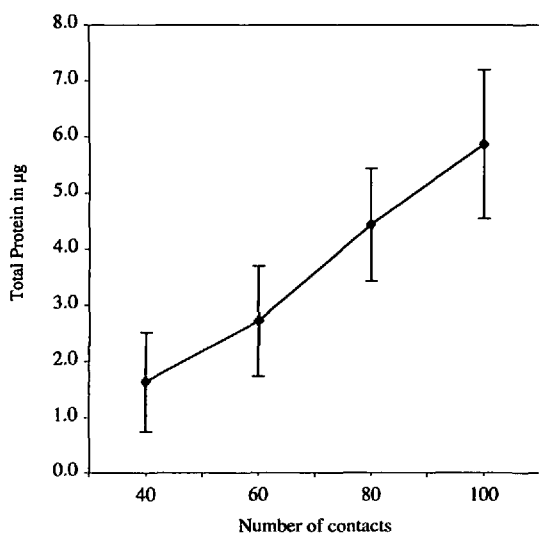


Figure 3. Latex protein level detected after handling a piece of lettuce while wearing latex gloves as described in Table II. The number of times gloved fingers (glove E1) contacted the lettuce was recorded. Lettuce was extracted in 5 mL PBS and the total amount of latex protein determined using the inhibition ELISA. Data represent mean $\pm$ SD from three separate experiments.

In this paper we have demonstrated that latex protein is an indirect food additive as a result of direct contact with food handlers' latex gloves. Although medical gloves are regulated and current proposed changes may limit the amount of protein on gloves, food handlers' gloves are not included in the proposed regulations. Because latex protein can readily be transferred to food, it is recommended that food handlers avoid the use of all types of latex gloves to eliminate inadvertent exposure of latex-sensitive individuals. Gloves should not be a substitute for proper hand washing and, in fact, proper hand washing may be preferable to the use of gloves in the restaurant industry. When food handlers are required to wear gloves, the gloves should be vinyl or polyethylene to avoid food contamination with latex allergens.

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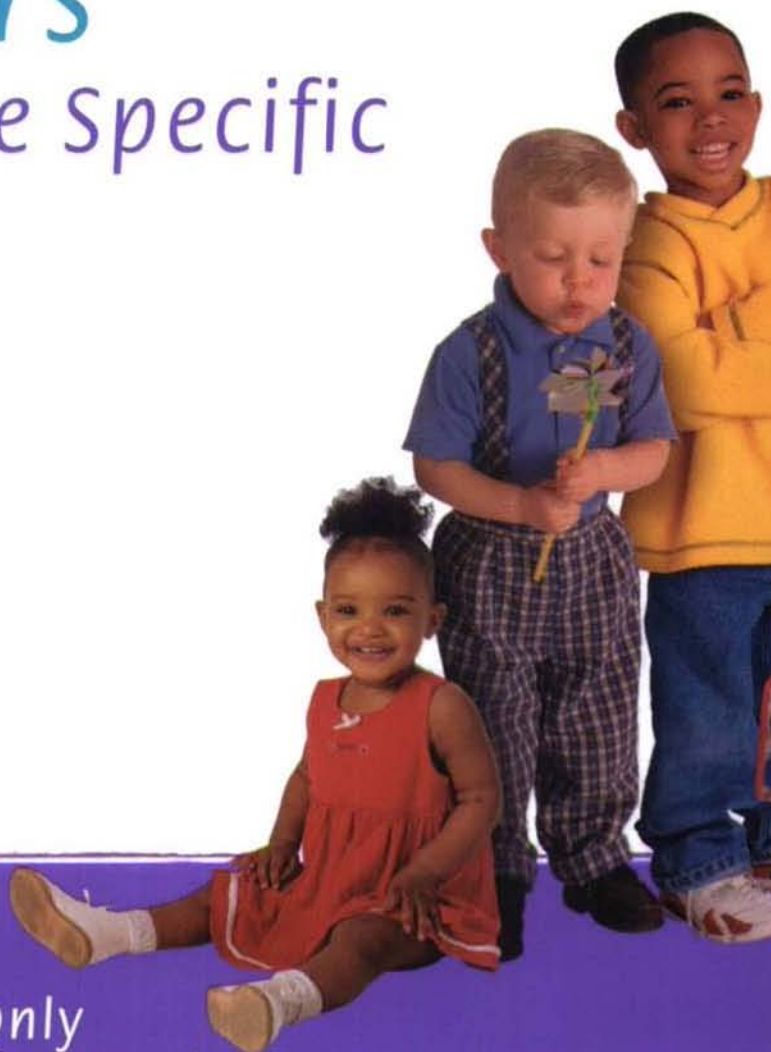


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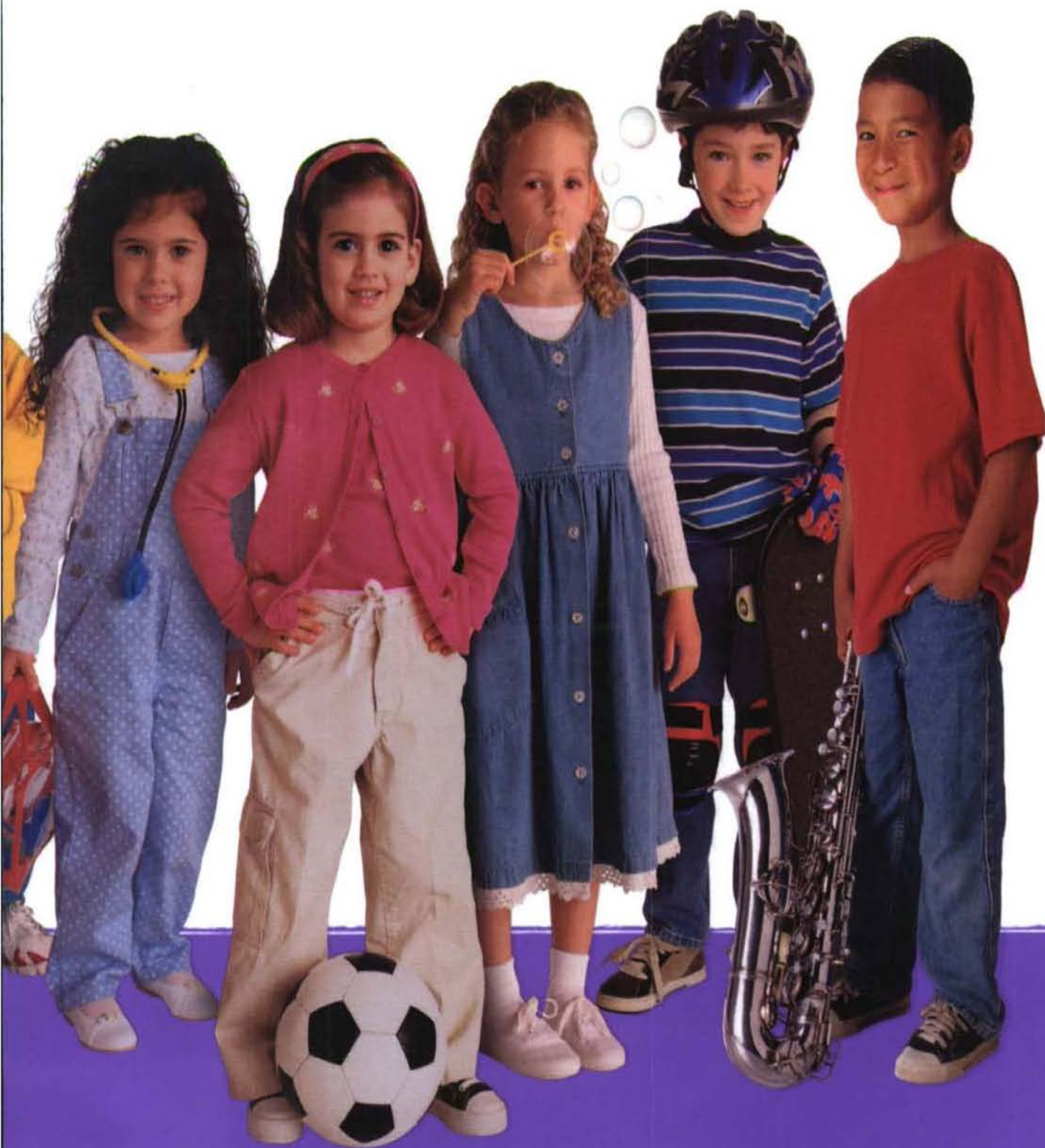


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WARNINGS

Particular care is needed for patients who are transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA-axis function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn.

During this period of HPA-axis suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although PULMICORT RESPULES may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of corticosteroid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instructions. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Transfer of patients from systemic corticosteroid therapy to PULMICORT RESPULES may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, eg, rhinitis, conjunctivitis, eczema (see DOSAGE AND ADMINISTRATION). Patients who are on drugs which suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible pediatric patients or adults on immunosuppressant doses of corticosteroids. In pediatric or adult patients who have not had these diseases, or who have not been properly vaccinated, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package insert for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered. PULMICORT RESPULES is not a bronchodilator and is not indicated for the rapid relief of acute bronchospasm or other acute episodes of asthma. As with other inhaled asthma medications, bronchospasm, with an immediate increase in wheezing, may occur after dosing. If acute bronchospasm occurs following dosing with PULMICORT RESPULES, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with PULMICORT RESPULES should be discontinued and alternate therapy instituted. Patients should be instructed to contact their physician immediately when episodes of asthma not responsive to their usual doses of bronchodilators occur during treatment with PULMICORT RESPULES.

PRECAUTIONS General: Inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see PRECAUTIONS, Pediatric Use). During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, eg, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function. Because budesonide is absorbed into the circulation and may be systemically active, particularly at higher doses, suppression of HPA function may be associated when PULMICORT RESPULES is administered at doses exceeding those recommended (see DOSAGE AND ADMINISTRATION), or when the dose is not titrated to the lowest effective dose. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing PULMICORT RESPULES. Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients post-operatively or during periods of stress for evidence of inadequate adrenal response. It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear in a small number of patients, particularly at higher doses. If such changes occur, PULMICORT RESPULES should be reduced slowly, consistent with accepted procedures for management of asthma symptoms and for tapering of systemic corticosteroids. Although patients in clinical trials have received PULMICORT RESPULES on a continuous basis for periods of up to 1 year, the long-term local and systemic

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effects of PULMICORT RESPULES in human subjects are not completely known. In particular, the effects resulting from chronic use of PULMICORT RESPULES on developmental or immunological processes in the mouth, pharynx, trachea, and lung are unknown. In clinical trials with PULMICORT RESPULES, localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. The incidences of localized infections of *Candida albicans* were similar between the placebo and PULMICORT RESPULES treatment groups. If symptomatic oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (ie, oral) antifungal therapy while still continuing with PULMICORT RESPULES therapy, but at times therapy with PULMICORT RESPULES may need to be interrupted under close medical supervision. Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract, untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular *Herpes simplex*. Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids.

Drug Interactions: In clinical studies, concurrent administration of budesonide and other drugs commonly used in the treatment of asthma has not resulted in an increased frequency of adverse events. Ketoconazole, a potent inhibitor of cytochrome P450 3A, may increase plasma levels of budesonide during concomitant dosing. The clinical significance of concomitant administration of ketoconazole with PULMICORT RESPULES is not known, but caution may be warranted. Omeprazole did not have effects on the pharmacokinetics of oral budesonide, while cimetidine, primarily an inhibitor of cytochrome P450, caused a slight decrease in budesonide clearance and a corresponding increase in its oral bioavailability.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis). In two additional two-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis). However, in the male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings. In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis). Budesonide was not mutagenic or clastogenic in six different test systems: Ames *Salmonella*/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster*, and DNA repair analysis in rat hepatocyte culture. In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m² basis). However, it caused a decrease in prenatal viability and viability in the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg and above (less than the maximum recommended daily inhalation dose in adults on a mcg/m² basis). No such effects were noted at 5 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m² basis).

Pregnancy: **Teratogenic Effects:** Pregnancy Category C—As with other corticosteroids, budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg in rabbits (less than the maximum recommended daily inhalation dose in adults on a mcg/m² basis) and 500mcg/kg in rats (approximately 4 times the maximum recommended daily inhalation dose in adults on a mcg/m² basis). In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 250 mcg/kg (approximately 2 times the maximum recommended daily inhalation dose in adults on a mcg/m² basis). There are no adequate and well-controlled studies in pregnant women. Budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy. **Non-teratogenic Effects:** Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether budesonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised if budesonide is administered to nursing women.

Pediatric Use: Safety and effectiveness of PULMICORT RESPULES in children 12 months to 8 years of age have been established (see ADVERSE REACTIONS). Safety and effectiveness in children less than 12 months of age have not been established. Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately one centimeter per year (range 0.3 to 1.8 cm per year) and appears to be related to dose and duration of exposure. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA)-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth velocity associated with inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with inhaled corticosteroids has not been adequately studied. The growth of pediatric patients receiving inhaled corticosteroids, including PULMICORT RESPULES, should be monitored routinely (eg, via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of inhaled corticosteroids, including PULMICORT RESPULES, each patient should be titrated to his/her lowest effective dose.

Geriatric Use: Of the 215 patients in 3 clinical trials of PULMICORT RESPULES in adult patients, 65 (30%) were 65 years of age or older, while 22 (10%) were 75 years of age or older. No overall differences in safety were observed between these patients and younger patients, and other reported clinical or medical surveillance experience has not identified differences in responses between the elderly and younger patients.

ADVERSE REACTIONS The following adverse reactions were reported in pediatric patients treated with PULMICORT RESPULES. The incidence of common adverse reactions is based on three double-blind, placebo-controlled, U.S. clinical trials in which 945 patients, 12 months to 8 years of age, (98 patients ≥12 months and <2 years of age; 225 patients ≥2 and <4 years of age; and 622 patients ≥4 and ≤8 years of age) were treated with PULMICORT RESPULES (0.25 to 1mg total daily dose for 12 weeks) or vehicle placebo. The incidence and nature of adverse events reported for PULMICORT RESPULES was comparable to that reported for placebo. The following table shows the incidence of adverse events in U.S. controlled clinical trials, regardless of relationship to treatment, in patients previously receiving bronchodilators and/or inhaled corticosteroids. This population included a total of 605 male and 340 female patients.

Adverse Events with ≥3% Incidence Reported by Patients on PULMICORT RESPULES

Adverse Events	Vehicle Placebo (n=227) %	PULMICORT RESPULES Total Daily Dose		
		0.25mg (n=178) %	0.5mg (n=223) %	1mg (n=317) %
Respiratory System Disorder				
Respiratory Infection	36	34	35	38
Rhinitis	9	7	11	12
Coughing	5	5	9	8
Resistance Mechanism Disorders				
Otitis Media	11	12	11	9
Viral Infection	3	4	5	3
Moniliasis	2	4	3	4
Gastrointestinal System Disorders				
Gastroenteritis	4	5	5	5
Vomiting	3	2	4	4
Diarrhea	2	4	4	2
Abdominal Pain	2	3	2	3
Hearing and Vestibular Disorders				
Ear Infection	4	2	4	5
Platelet, Bleeding, and Clotting Disorders				
Epistaxis	1	2	4	3
Vision Disorders				
Conjunctivitis	2	<1	4	2
Skin and Appendages Disorders				
Rash	3	<1	4	2

The table above shows all adverse events with an incidence of 3% or more in at least one active treatment group where the incidence was higher with PULMICORT RESPULES than with placebo. The following adverse events occurred with an incidence of 3% or more in at least one PULMICORT RESPULES group where the incidence was equal to or less than that of the placebo group: fever, sinusitis, pain, pharyngitis, bronchospasm, bronchitis, and headache.

Incidence 1% to <3% (by body system) The information below includes all adverse events with an incidence of 1% to <3%, in at least one PULMICORT RESPULES treatment group where the incidence was higher with PULMICORT RESPULES than with placebo, regardless of relationship to treatment.

Body as a whole: allergic reaction, chest pain, fatigue, flu-like disorder
Respiratory system: stridor
Resistance mechanisms: Herpes simplex, external ear infection, infection
Central & peripheral nervous system: dysphonia, hyperkinesia
Skin & appendages: eczema, pustular rash, pruritus
Hearing & vestibular: earache
Vision: eye infection
Psychiatric: anorexia, emotional lability
Musculo-skeletal system: fracture, myalgia
Application site: contact dermatitis
Platelet, bleeding & clotting: purpura
White cell and resistance: cervical lymphadenopathy

The incidence of reported adverse events was similar between the 447 PULMICORT RESPULES-treated (mean total daily dose 0.5 to 1mg) and 223 conventional therapy-treated pediatric asthma patients followed for one year in three open-label studies. Cases of growth suppression have been reported for inhaled corticosteroids including post-marketing reports for PULMICORT RESPULES (see PRECAUTIONS, Pediatric Use). Less frequent adverse events (<1%) reported in the published literature, long-term, open-label clinical trials, or from marketing experience for inhaled budesonide include: immediate and delayed hypersensitivity reactions including rash, contact dermatitis, angioedema and bronchospasm; symptoms of hypocorticism and hypercorticism; psychiatric symptoms including depression, aggressive reactions, irritability, anxiety and psychosis, and bone disorders including avascular necrosis of the femoral head and osteoporosis.

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Iss. 08/00

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