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Allergic contact dermatitis to two antioxidants in latex gloves: 4,4′-thio*bis*(6-*tert*-butyl-*meta*-cresol) (Lowinox 44S36) and butylhydroxyanisole

Allergen alternatives for glove-allergic patients

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Allergic contact dermatitis developed on the hands and/or face of two patients after exposure to latex examination gloves. Both patients were patch test negative to the usual rubber allergens, but both had a positive patch test reaction to 4,4′-thio*bis*(6-*tert*-butyl-*m*-cresol) (Lowinox 44S36). Patient 2 was also patch test positive to butylhydroxyanisole. The patients were tested with other gloves, to find gloves that they could safely use. Glove manufacturers were queried to ascertain the occurrence of Lowinox 44S36 and butylhydroxyanisole in different brands of latex and vinyl examination gloves. A list of gloves and their associated allergens was generated and is provided to assist dermatologists in helping patients choose gloves free of specific allergens. (J AM ACAD DERMATOL 1991;24:37-43.)

Seven to eight billion gloves are used annually in the United States. Gloves can be allergenic.[1,2] Antioxidants and accelerators added to rubber in the manufacturing process are the major allergens.[3]

We describe two patients with allergic contact dermatitis to 4,4′-thio*bis*(6-*tert*-butyl-*m*-cresol) (Lowinox 44S36), the antioxidant in Perry latex examination gloves. The second patient was coincidentally allergic to butylhydroxyanisole (BHA), an antioxidant that is used in the manufacture of some brands of latex gloves.

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Dermatologists are often asked to recommend gloves for patients with glove allergies. Many brands of latex examination gloves are available, and it is useful to know the allergens present in specific brands so that patients can be advised.

CASE REPORTS

Case 1

A pruritic dermatitis developed in a 48-year-old nurse's aide on the back of the hands and on the forearms, cheeks, and neck. The reaction first occurred on a hot sunny day, and the patient believed the dermatitis was light-related. The eruption cleared when she was away from work and recurred when she returned to her job. She was not atopic.*

*In this article an atopic person is defined as one who has a personal history of or a first-degree relative with asthma, allergic rhinitis, and/or eczema.

Table I. Significant allergens to which patients 1 and 2 were tested

Allergens tested	Concentration	Patch test reaction	
		Patient 1	Patient 2
Lowinox 44S36	1% pet.	+	+
BHA	2% pet.	−	+
BHT	2% pet.	−	+
Gloves			
Perry	As is	+	+
Puritee	As is	−	+
Pristine	As is	−	−
Elastyren	As is	−	−
Travenol Ultraderm	As is	−	+
Dermaprene	As is	−	−
Perry vinyl	As is	−	−
Neutralon	As is	−	−
Allerderm vinyl	As is	−	NT
Ebonette neoprene	As is	NT	−
Sterile Disposa	As is	NT	−
Tradition talc-free	As is	NT	−
Bithionol (photopatch)	2% pet.	+	−
Fentichlor (photopatch)	2% pet.	+	NT
Colophony	20% pet.	−	+
Neomycin sulfate	20% pet.	−	+
Cinnamic alcohol	5% pet.	+	+
Rubber dam	As is	NT	−
Standard malaysian rubber (supplied by Johnson & Johnson, New Brunswick, N.J.)	As is	NT	−
Mercaptobenzothiazole	1% pet	−	−
Thiuram mix	1% pet.	−	−
Carba mix	3% pet.	−	−

+, Positive patch test reaction at 2 and 7 days; −, negative patch test reaction at 2 and 7 days; *NT*, not tested; *pet.*, petrolatum.

Patch testing was performed with the North American Contact Dermatitis Group (NACDG) standard screening allergens, vehicle and preservatives, photoallergens, and many contactants from the patient's workplace, including the gloves she used. She had a positive patch test reaction to Perry latex examination gloves (Smith & Nephew, Massillon, Ohio) and to cinnamic alcohol at 2 days and at 7 days. The patient had a positive reaction to the photoallergens bithionol and fenticlor on the illuminated side but not on the covered side at 2 days and 7 days. She was patch test negative to the rubber chemicals on the NACDG screening tray and to 10 additional brands of latex gloves and vinyl gloves (Table I).

The components of the Perry gloves were obtained with full cooperation of the manufacturer, Smith & Nephew. A positive patch test reaction was obtained from Lowinox 44S36 (1% in petrolatum), the antioxidant used in the Perry glove manufacturing process. The patient's dermatitis resolved when she changed to a vinyl glove.

Case 2

An erythematous, pruritic, vesicular dermatitis developed in a 53-year-old female baker on the left cheek and lips 2 days after a dental appointment. The dermatitis resolved during the next 5 days. Dental contactants were Perry latex examination gloves, lidocaine, methyl methacrylate temporary crowns, benzocaine, zinc oxide–eugenol cement, and a rubber dam. A similar facial dermatitis developed after three subsequent dental appointments during which only the latex gloves touched the face. She was not atopic.

Patch tests were applied to routine allergens, 10 brands of disposable latex and vinyl gloves, BHA, butylhydroxytoluene (BHT), and other dental allergens. She was patch test positive at 2 days and at 7 days to Perry latex examination gloves, Puritee gloves (Orox Corp., Cincinnati, Ohio), Travenol gloves (Baxter Healthcare Corp., Valencia, Calif.), colophony, neomycin, cinnamic alcohol, and Lowinox 44S36. She was patch test negative to the rubber dam, natural rubber, tetramethylthiuram, and 2-mercaptobenzothiazole, and photopatch test negative to bithionol. A list of ingredients from the manufacturer of Puritee gloves, Orox Corp., revealed that the gloves contain BHA. This patient had a positive patch test to the BHA (2% in petrolatum). Perry gloves contain no BHA.

METHODS

Patch tests were performed on four occasions with the Finn Chamber method with Scanpor tape (Epitest Ltd., Oslo, Norway). Reactions were read at 2 days and at 7 days according to the methods of the NACDG.* Photoreactions were illuminated at 24 hours with 8 joules from the UV Blak-Ray long-wave lamp (UVP Inc., San Gabriel, Calif.) and read at 2 days and at 7 days. There was no reaction on the unilluminated side. Positive patch test reactions persisted for 7 days. The glove samples were moistened in tap water for 20 minutes before application. The sites were evaluated approximately ½ hour after removal with the use of the routine NACDG scoring system.[4] The allergens, vehicles, and concentrations of the agents to which the patients were patch test positive are shown in Table I.

Sixty-five patients, 37 women and 28 men, were examined between 1986 and 1987 to Lowinox 44S36, 2% in petrolatum, as controls, and none had a positive allergic

*Details of the methods used by the NACDG are described in the booklet distributed with the allergens sold by Dermatology Services, Inc., a subsidiary of the American Academy of Dermatology.

reaction. Between May 1988 and December 1989, 125 patients underwent patch testing with BHA (in 2% petrolatum) and none had a positive reaction.

DISCUSSION

In the United States, approximately 10 to 12 billion gloves were used in 1988. Of those, 7 to 8 billion were latex examination gloves, 1 to 2 billion were latex surgeon's gloves, and 3 to 4 billion were vinyl gloves (see Table II for data on latex gloves).

Latex gloves are manufactured by dipping a mold into natural rubber latex. A number of additives are added to latex during the manufacturing process, the most important of which are sulfur for vulcanization, antioxidants, and surfactants.[5] The antioxidants in rubber prevent deterioration of rubber by atmospheric oxygen and ozone. It is probable that small amounts of antioxidants and accelerators are released from rubber even when it is completely cured.[6,7]

Lowinox 44S36 is an alkylated, sterically hindered bisphenol that contains a thioether group. (Fig. 1, item *A*). Because of its low volatility, it is an excellent nondiscoloring and nonstaining, long-term stabilizer for polyolefins, polyester and acrylic resins, ethyl cellulose, and synthetic rubber. Lowinox 44S36 is effective as a free radical trap and as a peroxide splitter. It is widely used as an antioxidant in tennis shoes, primarily in piping around the outside of the soles, in latex used to produce examination gloves and condoms, and in neoprene latex and polyethylene. Given its wide use, its allergenic potential must be low.

Curiously, patient 1 was phototest positive to bithionol. Bithionol is a potent photosensitizer that was withdrawn from the market in 1968 for uses in which there may be contact with the skin.[8] To determine whether the patient had encountered bithionol in her workplace or home, we requested a list of compounds that contain bithionol. A computer printout generated by the U.S. Environmental Protection Agency listed two products containing bithionol. Bithionol (Bitin) is also used as an antiparasitic drug in human beings. Our patient had no known contact with any of these products.

In theory, Lowinox 44S36 and bithionol could cross-react. There is some structural similarity between Lowinox 44S36 and bithionol (see Fig. 1). In an attempt to determine whether Lowinox 44S36

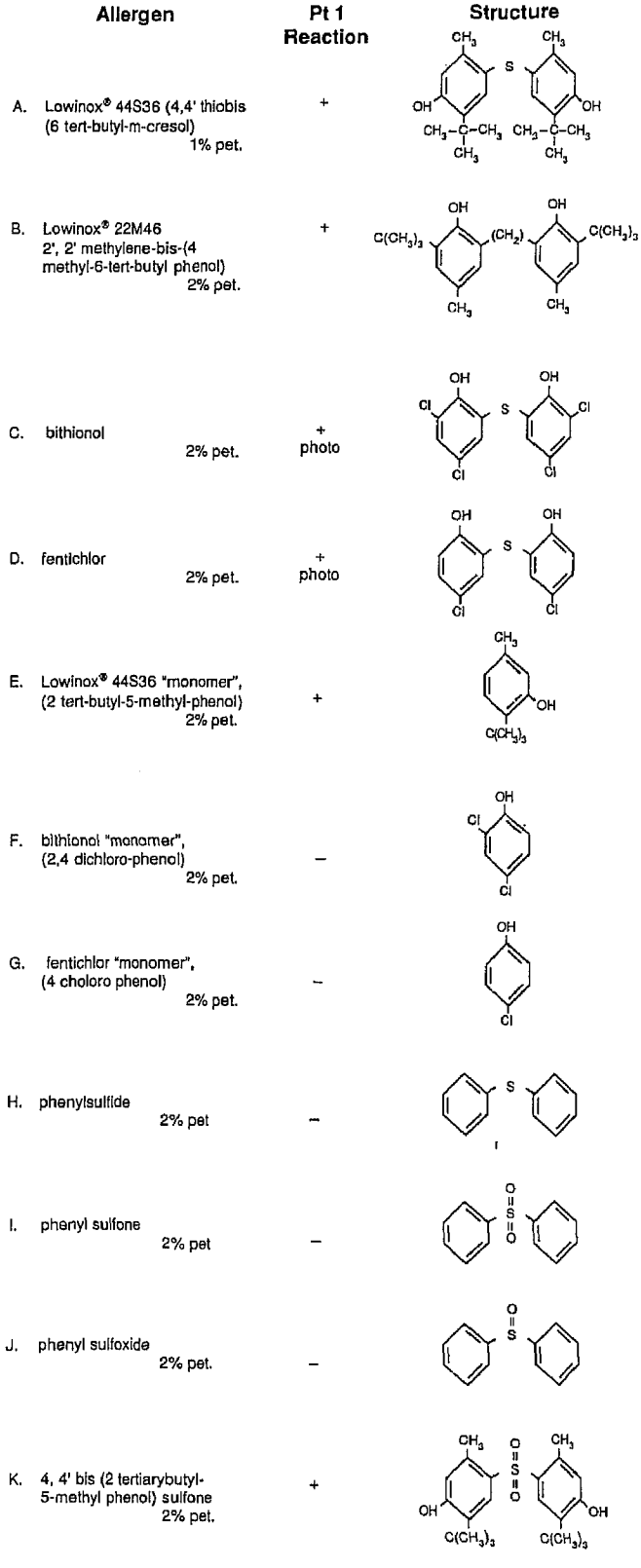


Fig. 1. Patient 1. Allergen structures and patch test reactions.

Table II. Common latex examination gloves and their associated antigens*

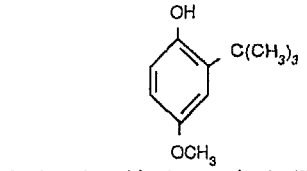
Gloves	Manufacturer	Antigen							Comments
		MBT	TH	CAR	LOW	BHA	ST	GI	
Surgeon's latex gloves									
Bio Gel D	Reagent Hospital Products, Mamoroneck, NY	−	−	+	−	−	−	+	Powder-free, low in CAR
Eudermic	Becton Dickinson, Franklin Lakes, N.J.	−	−	+	NA	NA	+	+	Latex
Micro-Touch	Surgikos, Arlington, Tex.	+	−	+	−	−	+	+	White or brown latex
Neutralon	Surgikos	+	−	+	−	−	+	+	Polyurethane elastomer; patented; inner coating brown glove
Perry Derma-Guard	Smith & Nephew Medical, Massillon, Ohio	+	−	+	+	−	+	+	Brown glove
Perry Standard	Smith & Nephew Medical	+	+	+	+	−	+	+	White or brown latex
Pristine	World Medical Supply, San Jose, Calif.	−	+	−	−	−	−	+	Powder-free; dipentamethylenethiuram tetrasulfide
Puritée	Orox, Cincinnati, Ohio	−	−	−	−	+	+	+	Pure rubber; powder is optional; packet is included
Travenol	Baxter Pharmaseal, Valencia, Calif.	+	−	+	−	−	+	+	
Ultraderm	Baxter Pharmaseal	−	−	+	−	−	+	+	Low CAR
Surgeon's synthetic gloves									
Dermaprene	Ansell, Dothan, Ala.	+	−	−	−	−	+	+	Neoprene; accelerator isodiphenylthiourea; green
Elastyren	Allerderm Labs, Mill Valley, Calif.	−	−	+	−	−	+	+	Styrene butadiene block polymer; available in sterile and nonsterile
Neolon	Becton Dickinson	−	−	+	−	−	−	+	Neoprene glove; low in CAR lactose powder; brown glove
Vinyl examining gloves									
TriFlex	Baxter Pharmaseal	−	−	−	−	−	+	−	Available in sterile and nonsterile; sterilized with ethylene oxide

CAR, Carbamates; *GI*, gamma irradiation sterilization; *LOW*, Lowinox 44S36; *MBT*, mercaptobenzothiazole; *NA*, information not available; *ST*, starch powder; *TH*, tetramethylthiuram.

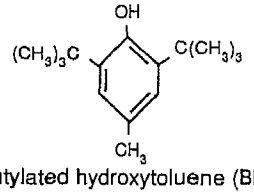
*This table was prepared by Mary Lou Belozer and Frances J. Storrs, MD (Oregon Health Sciences University) with the help of members of the glove industry. It is accurate only as of 1989.

Table II. Cont'd

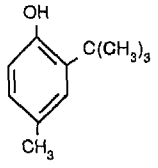
Gloves	Manufacturer	Antigens							Comments
		MBT	TH	CAR	LOW	BHA	ST	GI	
TruTouch	Becton Dickinson	–	–	–	–	–	+	–	Available in sterile and nonsterile; sterilized with ethylene oxide
Surgikos	Surgikos	–	–	–	–	–	+	+	Available sterile or nonsterile
Latex examining gloves									
Flexam Exam	Baxter Pharmaseal	–	–	+	–	–	+	+	Produced in Malaysia; both sterile and nonsterile available
Flexam Exam	Baxter Pharmaseal	+	+	+	–	–	+	+	Domestically produced; both sterile and nonsterile available
Medigrip	Ansell, Inc.	+	–	+	+	–	+	–	
Perry orthopedic	Smith & Nephew Medical	+	+	+	+	–	+	+	Thicker than Perry examination glove
Perry sterile examination	Smith & Nephew Medical	+	+	+	+	–	+	+	Available in both sterile and nonsterile
Sensi-Touch	Ansell	+	+	–	+	–	+	–	Nonsterile examination glove
Travenol	Baxter Pharmaseal	+	–	+	–	–	+	+	
Travenol procedure	Baxter Pharmaseal	+	–	+	–	–	+	+	Available in right- and left-handed gloves
Household weight gloves									
Allerderm cotton	Allerderm Lab	–	–	–	–	–	–	–	Cotton; can be used as glove liner; can order directly from company
Allerderm vinyl	Allerderm Lab	–	–	–	–	–	–	–	Vinyl glove that contains mica powder; can be ordered direct from company
Bluette and Benchmarks	Pioneer Consumer Glove Willard, Ohio	–	–	–	–	–	–	–	Neoprene lined with knitted cotton; talc used in manufacturing
Nimble-fingers	Pioneer Consumer Glove	–	–	–	–	–	–	–	Vinyl pylox (light weight); contains mica powder; no accelerators used
Task Handlers	Pioneer Consumer Glove	+	–	+	–	–	–	–	Neoprene; *does* contain $CaCO_3$ powder
4H	Academ, Menlo Park, Calif.	NA	NA	NA	NA	NA	–	–	Patented; plastic laminate



A. butylated hydroxyanisole (BHA)



B. butylated hydroxytoluene (BHT)



C. Lowinox® 44S36 "monomer", 2 tert-butyl 5 methyl phenol

Fig. 2. Structural formulas of BHA *(A)*, BHT *(B)*, and Lowinox 44S36 monomer 2-*tert*-butyl-5-methylphenol *(C)*.

and bithionol have a common antigenic determinant, we altered the chemical structures of Lowinox 44S36 by purchasing or synthesizing the chemicals shown in Fig. 1 (see items *H* to *K*).* Patient 1 was patch test and photopatch test negative to all the structures except the sulfone of Lowinox (4,4-*bis*[2-*tert*-butyl-5-methylphenol] sulfone; Fig. 1, item *K*).

As a further step, we purchased chemicals equivalent to the monomers of Lowinox 44S36, bithionol, and fentichlor; 2-*tert*-butyl-5-methylphenol, 2,4-dichlorophenol, and 4-chlorophenol, respectively (see Fig. 1, items *E* to *G*). The monomer of Lowinox 44S36, 2-*tert*-butyl-5-methylphenol, gave a positive reaction on patch testing; however, the monomers of bithionol and fentichlor were patch test and phototest negative (in patient 1).

In this patient the reactive portion of the Lowinox molecule appears to be the monomer, which is equivalent to half the molecule minus the sulfur constituent. In contrast, bithionol and fenticlor require the entire molecule for reactivity. The structural similarity of these molecules is therefore misleading.

*Chemical consultation, synthesis, and analysis was performed by Dr. Jack Fellman, Oregon Health Sciences University.

Patient 2 was patch test positive to Perry gloves, Puritée gloves, and Travenol Ultraderm gloves. She was patch test negative to Micro X-am, Pristine, Ansell Dermaprene, Spectra surgical, Perry vinyl, and Elastyren gloves. She was also patch test negative to natural rubber, the rubber dam, and to photopatch tests with bithionol. Lowinox 44S36, the antioxidant in Perry gloves, resulted in a positive patch test reaction. The relevant allergen in Puritée and in Travenol Ultraderm gloves is the antioxidant BHA, to which patient 2 was patch test positive.

BHA and BHT are antioxidants that are widely used in foods, rubber, cosmetics, and plastics.[12] White et al.[9] described seven patients with facial eczema who were allergic to BHT (1% in petrolatum) in their cosmetics. Meneghini et al.[10] reported that one of 360 patients tested with BHA (5% in petrolatum) had a positive patch test reaction.

In a series of 112 patients, Roed-Peterson and Hjörth[11] found two patients allergic to both BHA (2% in petrolatum) and BHT (2% in petrolatum) and one patient allergic to each alone.

BHA and BHT are two of several antioxidants used in food to prevent undesirable flavor and color deterioration.[12] Patient 2 was a baker and may have become sensitized to these antioxidants by her occupational exposure to BHA and BHT. In Roed-Peterson and Hjörth's series[11] two patients reproduced the vesicular dermatitis on their hands after experimental ingestion of BHA and BHT. We found no other reports that linked BHA allergy to rubber glove allergic contact dermatitis.

The structures of BHA and BHT are shown in Fig. 2 for comparison to the structure of Lowinox 44S36 monomer. The similarity of BHA, BHT, and Lowinox monomer resides in the presence of the hydroxyl group in the *ortho* position to the tertiary butyl group. It is possible that this combination of substituents is the allergenic determinant in these compounds.

An important point in dealing with allergens is that trade names may be ambiguous and misleading. We discovered that Puritee gloves contain the antioxidant 2,2-methylene-*bis*(4-methyl-6-*tert*-butylphenol), which is designated Lowinox 22M46. Lowinox 22M46 has a chemical structure different from Lowinox 44S36 in Perry gloves. Both patients were patch test negative to Lowinox 22M46. The similarity of the trade names can lead to confusion if the chemical names and structures are not recognized and compared.

After an extensive 3-month survey of the cooperative and helpful glove industry, a list of some of the common latex examination gloves available with their associated antigens, including the usual rubber allergens and some antioxidants, was generated (Table II). This list may prove helpful in assisting patients with glove allergy to choose gloves that are free of a particular allergen. As glove use becomes more common, it may be useful to keep in mind rarer allergens such as the antioxidants, Lowinox 44S36 and BHA, as possible relevant allergens in patients with allergic contact dermatitis to gloves.

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