

Allergic Contact Dermatitis from Mercapto Compounds

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Despite being well-known allergens, mercaptobenzothiazole and its derivatives continue to be widely used in natural and synthetic rubber, in the mining industry, and in a variety of nonrubber products. The purpose of this article is to review the epidemiology and the clinical characteristics of allergic contact dermatitis from mercapto compounds.

ALLERGIC CONTACT DERMATITIS FROM MERCAPTOBENZOTHAZOLE and its derivatives has been recognized since the mid-1900s, when synthetic rubber compounds became widely produced and used.^{1,2} The literature now contains many reports of allergic contact dermatitis from mercaptobenzothiazole (MBT) and its derivatives, morpholinyl mercaptobenzothiazole (MOR), N-cyclohexyl-2-benzothiazyl sulfenamide (CBS), and dibenzothiazyl disulfide (MBTS). Mercapto compounds are used in the manufacture of natural and synthetic rubber, in mining processes, and in a wide variety of nonrubber products.^{3,4} The purpose of this article is to review the epidemiology and the clinical characteristics of allergic contact dermatitis from mercapto compounds. In situations in which authors of other publications did not report statistical tests for association, we performed chi-square analysis with SAS (*Statistical Analysis System*) software (SAS Institute Inc., Cary, NC). In situations in which patient numbers were not reported, they were calculated from reported percentages; when percentages were not reported, percentages were calculated from reported patient numbers. We also calculated pooled weighted averages for prevalence data.

Epidemiology

Although mercapto compounds (MBT and mercapto mix) are commonly found on antigen screening trays, allergy to

mercapto compounds is relatively uncommon; it failed to make a list of the 22 most frequent allergens detected by the Information Network of Departments of Dermatology (IVDK) group in central Europe between 1992 and 1996.⁵ There has been an overall decline in the prevalence of MBT allergy in the past 30 years. A study conducted by Rudner and colleagues in the early 1970s found MBT (2% in petrolatum [pet]) sensitivity in 58 (5%) of 1,200 patch-tested patients.⁶ The most recent preliminary results of patch-test surveillance from the North American Contact Dermatitis Group (NACDG), from 2003 to 2004, indicate that only 1.2% of 3,490 people who were patch-tested with MBT 1% pet had positive reactions, 90.5% of which were considered relevant (definite, probable, and possible relevance combined).⁷ Prevalence data prior to 2003 from this group are as follows: 0.9% (2001–2002),⁸ 2% (1998–2000),⁹ 1.8% (1996–1998),¹⁰ and 2.1% (1994–1996)¹¹; relevance ranged from 75.8 to 80.5%. A meta-analysis of TRUE Test (Allerderm Laboratories, Phoenix, AZ) data from 14 studies compiled by Krob and colleagues found a prevalence estimate of 0.9%, ranking MBT nineteenth among allergens included in the TRUE Test.¹² Considering the wide use of MBT in industry, this relatively low prevalence of allergy is surprising, and it has been suggested that MBT may have a low sensitizing potential or is more highly bound than other rubber accelerators.¹³

The prevalence of reactions to MBT derivatives found in mercapto mix also appears to be decreasing. The mercapto mix in the NACDG standard series currently consists of 0.25% each of MBT, MOR, CBS, and MBTS. Between 2003 and 2004, 1% of 3,491 patients who were patch-tested with a mercapto mix reacted; of these reactions, 88.2% were considered relevant.⁷ Prevalence data prior to 2003 from the NACDG are as follows: 0.7% (2001–2002),⁸ 1.3% (1998–2000),⁹ 1.8% (1996–1998),¹⁰ and 2.2% (1994–1996).¹¹ Relevance ranged from 77.1 to 86.8%. Data

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from the TRUE Test meta-analysis indicated an estimated prevalence of 1.1%, ranking mercapto mix eighteenth among allergens in the TRUE Test.¹² It is not surprising that sensitization from compounds in mercapto mix occurs with a similar frequency to that from MBT, as these compounds are known to act as a group allergy.^{14,15}

There do not appear to be significant differences in sensitization rates to MBT and its derivatives between different age groups. When Nethercott and colleagues examined data from 4,055 patients who were patch-tested by the NACDG between 1985 and 1989, they found that 2.1% and 2.5% of patients respectively were sensitized to MBT 1% pet and a mercapto mix 1% pet that consisted of 0.33% each of MOR, MBTS, and CBS.¹⁶ When these data were analyzed by age groups (those aged > 40 years and those aged < 40 years), individuals older than 40 years were slightly more likely to have allergic contact dermatitis (50.1% vs 46.9%, $p < .05$).¹⁷ However, the prevalence of MBT allergy in those older than 40 years (2.2% [55 of 2,513]) was not significantly different from that of those younger than 40 years (1.6% [38 of 2,367]). The difference in mercapto mix sensitization between people older than 40 years and those younger was also not statistically significant (2.7% [68 of 2,512] and 1.7% [40 of 2,361], respectively).¹⁷

Children are also susceptible to allergic contact dermatitis from MBT and its derivatives. In general, very young children infrequently develop contact allergies,¹⁸ but as Levy and colleagues point out, growing children become mobile and are more exposed to objects (which may contain mercapto compounds, such as rubber toys or clothing).¹⁹ Romaguera and Vilaplana performed a retrospective analysis of 141 Spanish children (age ≤ 14 years) who were patch-tested with the TRUE Test, which includes both MBT and a mercapto mix. Four (2.8%) patients had positive reactions to MBT, and 4 children (2.8%) reacted positively to the mercapto mix.²⁰ A recent retrospective analysis of patch-test patients in Vienna showed that MBT and its derivatives are not among the top ten most common allergens for children between the ages of 1 and 10 years.²¹ However, the prevalence may be higher than it was 30 years ago. Upon review of the records of 87 children with patch-test reactions between 1970 and 1973 in a clinic in Lille, France, it was found that only 1 child (1.1%) reacted positively to MBT.¹⁹ In a prospective study of 270 atopic children in Italy between 1970 and 1975, 25 children (9.3%) had positive allergic contact reactions to at least one antigen, but no children (0%) reacted to MBT 2% pet or mercapto mix 2% pet.¹⁸ Because these studies were conducted in differing locales, it is possible that the prevalence of allergic contact dermatitis varied because of differing amounts of exposure. Also, these studies are rela-

tively small in size, which prevents definitive conclusions from being drawn. However, they do suggest that for children, the prevalence of contact allergy to MBT and its derivatives may be similar to the prevalence of mercapto allergy in adults.

Gender may affect the prevalence of allergy to MBT and its derivatives. When analyzed by gender, the NACDG data from patients patch-tested between 1985 and 1989 suggested that men were more likely than women to be sensitized to MBT 1% pet (3.2% males vs 1.3% of females sensitized, $p < .05$) and mercapto mix 1% pet (2.8% males vs 1.5% females sensitized, $p < .05$). The authors theorized that this might be due to increased exposure of one sex to certain articles of clothing containing rubber additives.²² Also, in an epidemiologic study of 999 rubber tire factory workers who were patch-tested with various allergens, including MBT 1% pet and a mercapto mix, Varigos and Dunt found that women working in the rubber tire factory were more likely to have occupational contact dermatitis than men were ($p < .001$).²³ However, they did not report data separately for MBT or its derivatives.

Other studies have found no difference in sensitization to mercapto compounds in regard to gender. In a small study in New Delhi, India, 75 patients with suspected contact allergy were patch-tested with the Indian standard series and indigenous antigens. Of these 75 patients, 4 of 38 men (10.5%) and 1 of 37 women (2.7%) had positive reactions on patch tests with MBT 2% pet (calculated by Fisher exact test, $p > .05$) whereas equal numbers of men and women (1 in each group) reacted to a mercapto mix 2% pet.²⁴ An analysis of 15 years of patch-testing data collected in Taiwan studied 2,235 patch-tested patients. A total of 99 patients were found to react to one or more rubber chemicals; 23.8% (10 of 42) of the men had positive patch-test reactions to a mercapto mix, as did 26.3% (15 of 57) of the women (calculated by Fisher exact test, $p > .05$).²⁵ An examination of occupation-related hand eczema in one city in Sweden revealed similar numbers of reactions to a mercapto mix 2% pet among patch-tested men and women (1.1% [4 of 355] of the men and 0.6% [4 of 726] of the women; calculated by Fisher exact test, $p > .05$).²⁶ Recent data compiled from 2,766 patch-tested children and adults in an allergy clinic in Vienna indicated no significant difference in the prevalence of positive reactions to MBT 2% pet between males and females.²¹ It is likely that differences in sensitization among genders are due to variations in exposure to MBT and its derivatives rather than to a specific gender's propensity toward sensitization.

Race has not frequently been examined in relation to differences in prevalence of allergy to MBT and its derivatives.

In North America, the general respective prevalences of contact dermatitis among black and white individuals appear to be similar²⁷ although in the past it was noted that black persons “readily” acquired contact dermatitis from MBT.²⁸ DeLeo and colleagues examined patch-test data collected by the NACDG from 9,624 individuals between 1992 and 1998. They found that there was no statistically significant difference between white persons and black persons in prevalence of contact allergy to MBT 1% pet or a mercapto mix 1% pet.²⁹ Likewise, Dickel and colleagues, retrospectively evaluating 991 patch-tested patients who presented to the Cleveland Clinic between 1988 and 1991, found no significant difference in sensitivity to MBT 1% pet or a mercapto mix 1% pet between black persons and white persons.³⁰ These results support the hypothesis that rates of contact dermatitis from MBT and mercapto mix are similar for both black and white people.

Internationally, prevalence of allergy to mercapto compounds varies, as individual populations’ exposure to mercapto compounds varies with differences in culture and industry. As shown in Table 1, the global pooled weighted average of allergy to MBT among patch-test clinic patients is 1.7%. The pooled weighted average prevalence of allergy to mercapto mix compounds among patch-tested patients is 1.5%.

Structure

MBT and the other ingredients in a mercapto mix (MOR, CBS, and MBTS) are closely related, and allergy to MBT may be considered a group allergy.^{15,31} Cross-reactions between MBT and its derivatives were recognized prior to the mid-1950s.¹⁴ In fact, MBT and MBTS are interconvertible via oxidation-reduction reactions; the reaction favors one or the other, depending on the chemical environment (Fig 1).³² It is believed that 2-MBT predominates in the skin because of the presence of the reducing sulfhydryl compound glutathione, found in living cells.^{32,33} The reduced form of glutathione is also present and is believed to function in reductive reactions in the immediate extracellular environment.^{34,35} In the presence of excess glutathione, the main product of CBS, MOR, and MBTS is MBT.³² If glutathione is not present, MOR and CBS slowly convert to MBTS. Since the lowest common denominator of these reactions is MBT, it is likely, as Hansson and Agrup stated, that MBT is the “true hapten of all the mercapto compounds.”³²

The structures of MBT and its derivatives are ideal for inducing sensitization. First, the MBT portion of mercapto compounds is of a low molecular weight, which contrib-

utes to its ability to permeate the skin.^{36,37} Second, MBT has a thiol group, which is likely capable of several reactions with amino acids³⁸; it may form a thioester bond with the carboxylic acid group of an amino acid. MBT’s thiol group is also capable of forming bonds with the amino group of lysine. Disulfide bond formation may be possible with cysteine’s thiol group.³⁸ These reactive groups of amino acids act as potential docking sites for MBT and mercapto compounds to attach themselves to proteins. New compounds have been formed when MBT and MOR react in vitro with amino acids.³⁸ New bond formation may be the manner in which the hapten, MBT, becomes large enough to cause allergenicity.³⁸

Furthermore, thiazole and benzene rings are believed to be an essential component of sensitization, as Fregert described in 1969. He tested patients with several compounds that are structurally similar to MBT but that lack either the thiazole ring combined with the benzene ring, or the thiol group in the 2 position. There was no cross-sensitization in the molecules that lacked these features. This suggests that the thiol group, the benzene ring, and the thiazole ring are important for sensitization (Fig 2).³⁹

Function

MBT is most commonly used as a rubber accelerator during the process of vulcanization. Vulcanization was discovered in 1839 by Charles Goodyear, who found that heating rubber in the presence of sulfur resulted in a superior form of rubber.⁴⁰ Vulcanization results in the polymerization of rubber, which improves the durability and strength of the material and eliminates the flaws of cracking and stickiness found in natural rubber. Accelerators such as MBT are used to catalyze vulcanization and lower the temperature necessary for vulcanization, making this process efficient enough for mass production.⁴⁰ Synthetic nonlatex rubber products also require accelerators, and MBT may be found in these substances, including some spandex and neoprene products.^{41,42} MBT is also unique in that it can work both as an accelerator and as an antioxidant.¹⁵ According to *Fisher’s Contact Dermatitis*, an estimated 4 to 5 pounds of additives (90% of which are accelerators and antidegradants) go into every 100 pounds of finished rubber.⁴³ These additives are required to produce durable and cost-effective products.⁴⁴ Today, MBT and its related compounds are believed to be among the most common accelerators used in the manufacture of natural and synthetic rubber.³

MBT is found in many different types of rubber products. It is a common cause of shoe dermatitis due to the rubber soles and adhesives found in many shoes.^{45,46}

Table 1. Prevalence of Allergic Contact Dermatitis to Mercapto Compounds

Location	Year Published	Total No. Patients Tested	% of patients positive (n)*	
			MBT	Mercapto Mix
North America ⁷	unpublished	3490	1.2% (42)*	1% (35)* [†]
North America ⁸	2004	4907	0.9% (44)*	0.7% (34)* [‡]
Taiwan ²⁵	2004	2235	—	1.1% (25)* ^{****}
New Delhi, India ¹³⁵	2004	220	5% (11)**	5% (11)**
North America ⁹	2003	5834	2.0% (117)*	1.3% (76)*
Vienna, Austria ²¹	2003	2766	0.6% (17)**	—
New Delhi, India ²⁴	2000	75	6.66% (5)**	2.66% (2)**
North America ¹⁰	2000	3440	1.8% (62)*	1.8% (62)* [§]
North America ¹¹	1998	3115	2.1% (65)*	2.2% (69)*
Chandigarh, India ¹³⁶	1998	200	4% (8)**	5% (10)**
Central Europe ¹³⁷	1997	5058	—	0.9% (46)*
Riyadh, Saudi Arabia ¹³⁸	1996	271	0.7% (2)* ^{****}	—
North America ¹³⁹	1995	3525	1.8% (63)*	2.6% (91)* [#]
Shanghai, China ¹⁴⁰	1994	88	—	3% (3)* ^{***}
Singapore ¹⁴¹	1992	5557	—	0.5% (29)*
North America ¹⁶	1991	3968	2.1% (83)*	2.5% (99)* ^{***}
Nanjing, China ¹⁴²	1990	204	—	2.9% (6)* ^{****}
Saskatoon, Canada ^{143*}	1988	468	—	1.6% (7)* ^{****}
Finland ¹⁴⁴	1985	3332	—	0.6% (19)**
Japan ¹⁴⁵	1982	178	0.6% (1)*	0% (0)*
Denmark ¹⁴⁶	1980	3225	—	1.2% (3)* ^{††}
Melbourne, Australia ¹⁰¹	1979	486	2.1% (10)*	0.9% (30)* ^{****}
Spain ¹⁴⁷	1979	2806	—	2.3% (11)* ^{****}
Belgium ¹⁴⁸	1979	810	—	5.1% (143)**
North America ⁶	1973	1200	5% (58)**	1.2% (10)*
Weighted Average	—	—	1.7% (588/33675)	1.5% (821/53461)

*In instances where patient numbers were not reported they were calculated from the percentages, and in instances where percentages were not reported, percentages were calculated from patient numbers.

MBT = mercaptobenzothiazole; n = number of patients in sample population; pet = petrolatum.

* = 1% pet., ** = 2% pet., *** = pet., **** = concentration not reported.

[†]3491 patients were tested to the mercapto mix 1% pet.

[‡]4908 patients were tested to the mercapto mix 1% pet.

[§]3439 patients were tested to the mercapto mix 1% pet.

^{||} The crude rate of sensitization was used.

[#]3497 patients were tested to the mercapto mix 1% pet.

**3979 patients were tested to the mercapto mix 1% pet.

^{††}178 patients were tested to mercapto mix (1%) and none reacted, while 256 patients were tested to mercapto mix 2% pet, with 3 reactions.

Medical exposure to mercapto compounds has caused allergic contact dermatitis from gloves, catheters, stomal equipment, and rubber straps used to attach electrocardiograph electrodes.^{13,47–51} MBT is known to leach into medications via rubber stoppers in bottles used to contain medicines.^{52,53} In fact, the list of rubber products that contain MBT is extensive. Table 2 presents a partial list of some products that may contain MBT or its derivatives.

MBT is widely used outside of rubber manufacturing. For example, MBT is used as a fungicide and as an anti-corrosive in cutting fluids used in the metalworking industry.⁵⁴ In the mining industry, gold, silver, and zinc are collected with the help of MBT.⁴ Paper mills may use MBT as a slimeicide.⁵⁵ Because of the broad spectrum of products in which MBT functions, the most common source of MBT in the environment seems to be water, a result of runoff

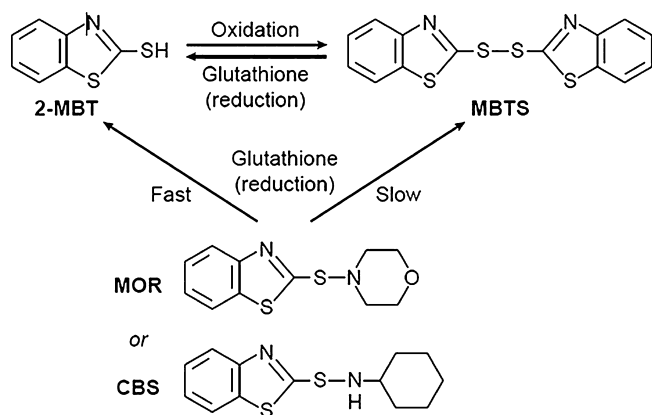


Figure 1. Interconversion pattern between compounds of mercaptobenzothiazole (MBT) mix in a phosphate buffer (pH, 6.5). (CBS = N-cyclohexyl-2-benzothiazyl sulfenamide; MBTS = dibenzothiazyl disulphide; MOR = morpholinyl mercaptobenzothiazole; N = nitrogen; NH = amino group; S = sulfur; SH = thiol group) (Adapted from Hansson and Agrup.³²)

from the manufacture of MBT-containing products and from the leaching of MBT out of such products.⁵⁶ Examples of other nonrubber sources are listed in Table 3.

Systemic Toxicity

Due to the reactivity and wide use of mercapto compounds, the toxic potential of mercapto compounds has been scrutinized. Rubber accelerators, in general, are highly reactive chemicals that theoretically have the potential to cause harmful biologic reactions.⁵⁷ MBT fed to rats (0.5 g/kg/d) is known to cause liver damage and can cause death.⁵⁸ Results are mixed in regard to the mutagenic potential of MBT in animals and humans. A study of the teratogenic potential of MBTS fed to pregnant rats found no adverse effects on the pre- or postnatal development of the offspring.⁵⁹

Table 2. Rubber Products That May Contain Mercaptobenzothiazole and Related Compounds

Earplugs ¹⁴⁹
Sponges ^{74,150}
Rubber bands ^{151,152}
Rubber fingerstalls ¹⁵³
Condoms ^{51,133,154,155}
Gloves ^{13,44,64,89,156}
Shoes ^{14,46,77,78,96,100–102,104,106,107,109,111–113,119,121,122,157}
Catheters ^{49,50}
Electrocardiograph electrode straps ⁴⁷
Hot water bottles ³¹
Swimwear ³
Toys ³
Tires and tubes ³
Renal dialysis equipment ³
Diaphragms ³
Medical devices ³
Rubber pillows and sheets ³
Bathing caps ¹⁰³
Suspenders ³¹
Handles ³¹
Underwear, bras ^{1,157}
Rubber bank note counters ¹⁵⁸
Neoprene splints ⁴²
Urinals ⁵¹

Adapted from Marks J, DeLeo V.³

Hinderer and colleagues found MBTS to have some mutagenic characteristics in a battery of in vitro mutagenic assays.⁶⁰ Other animal studies provided some evidence of carcinogenicity of MBT in rats but produced equivocal evidence of carcinogenicity in mice.⁶¹ Human studies have also produced results that are difficult to interpret. Collins and colleagues followed a cohort of 1,059 full-time employees of a rubber chemical plant from 1955 to 1996; 600 (57%) of

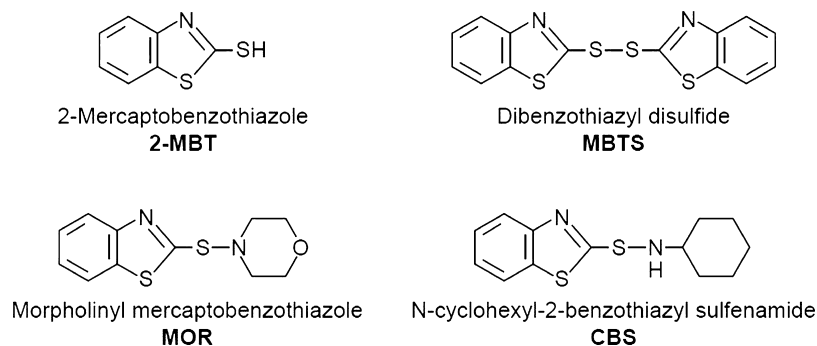


Figure 2. Structures of mercaptobenzothiazole (MBT), morpholinyl mercaptobenzothiazole (MOR), N-cyclohexyl-2-benzothiazyl sulfenamide (CBS), and dibenzothiazyl disulphide (MBTS).

Table 3. Nonrubber Products That May Contain Mercapto-benzothiazole and Related Compounds

Antifreezes ^{159,160}
Adhesives ¹⁵⁹
Cements ¹⁵⁹
Detergents ¹⁵⁹
Tree sprays ¹⁵⁹
Veterinary topical medications ^{159,161,162}
Paints ¹⁵⁹
Photographic film emulsions ^{159,163}
Cleaners for automobile cooling systems ¹⁵⁹
Greases ¹⁵⁹
Pottery molds ¹⁵⁹
Cutting fluids ^{54,132,164}
Slimicides ⁵⁵
Fungicides ¹⁵⁹
Anticorrosives ¹⁵⁹
Pottery releasing fluids ¹⁶⁵

Adapted from Fisher AA.¹⁵⁹

these employees were known to have been exposed to MBT. At the conclusion of the observation period, only the standardized mortality ratio of bladder cancer (8.9) was greater than expected for the 600 MBT-exposed workers (95% confidence interval [CI], 4.7–15.2; 13.0 observed vs. 1.5 expected). The increased rate of bladder cancer found in this study was confounded by the fact that the workers exposed to the greatest amount of MBT were also exposed to 4-aminobiphenyl (a known bladder carcinogen) during the same period. Eighty-nine MBT-exposed workers with known exposure to 4-aminobiphenyl had a standardized mortality ratio (SMR) of 27.1 (95% CI, 11.7–53.4; 8.0 observed vs 0.3 expected). When data from 270 workers with known MBT exposure but no known exposure to 4-aminobiphenyl were analyzed, no cases of bladder cancer were observed, resulting in a standardized mortality ratio of 0 (95% CI, 0.0–24.7; 0.0 observed vs 0.2 expected). However, in a group of workers with no known exposure to 4-aminobiphenyl, those who had known MBT exposure did tend to have an increased risk of bladder cancer with cumulative MBT exposure ($p = .04$). It should be noted that while MBT-exposed workers without known exposure to 4-aminobiphenyl appeared to have better outcomes, they may have had unknown exposures to 4-aminobiphenyl within the plant.⁶²

A similar cohort study in Wales followed 2,160 rubber chemical factory employees with exposure to MBT, aniline, *o*-toluidine, and phenyl- β -naphthylamine from 1955 to 1996. The MBT-exposed workers were found to have greater-than-expected rates of (1) cancer of the large in-

testine, with a standardized mortality ratio of 257 (7.00 observed, 2.73 expected; $p < .05$), and (2) bladder cancer, with a standardized mortality ratio of 408 (7.00 observed, 1.72 expected; $p < .01$). However, there was no significant trend found with Poisson regression between cumulative MBT exposure and bladder cancer in this study (p values for trend: $p = .24$, $p = .06$). Many employees were exposed not only to MBT but also to other chemicals that are also potential carcinogens. Because of these confounding exposures and the small numbers of observed cancers in this study, the carcinogenic potential of MBT is still unclear.⁶³

Type I Reactions to Mercapto Compounds

There are several reports of contact urticaria to MBT and its derivatives. In 1996, Brehler described a woman who developed contact urticaria after wearing latex gloves. She switched to latex-free nitrile gloves; after a year without problems, she began to react to the nitrile gloves as well. The patient was scratch-tested and showed strong positive reactions to the nitrile gloves she had been using, as well as to MOR. Patch tests with a standard series, rubber chemicals, and gloves yielded negative results. The nitrile gloves she had been wearing were known to contain a high amount of benzothiazoles.⁶⁴

In 1992, Fuchs and Wahl studied 31 patients with contact urticaria and/or systemic reactions to latex products. They found two patients with relevant immediate urticarial reactions on scratch-testing with a mercapto mix, tetramethylthiuram disulfide, and para-phenylenediamine.⁶⁵ In 1990, Belsito described the case of a gynecologist who had a 5-year history of recurrent hand and foot dermatitis. The frequency and severity of the attacks had increased and included rhinoconjunctivitis and an urticarial eruption of the hands. He had positive reactions on scratch-chamber tests with rubber products, positive closed patch-test reactions to MBT 1% pet, and positive open scratch-test reactions to MBT 1% pet and to a mercapto mix 1% pet. The result of a radioallergosorbent test (RAST) was negative. It was determined that this patient had both contact urticaria from MBT and contact hypersensitivity to MBT.⁶⁶

In 1988, Turjanmaa and Reunala examined the prevalence of contact urticarial reactions coincident with contact hypersensitivity reactions.⁶⁷ They evaluated 53 glove-allergic patients with patch tests or scratch-chamber tests, RASTs, latex prick tests, and use tests with gloves. Three patients had scratch-chamber reactions to either a mercapto mix ($n = 1$) or MBT ($n = 2$), suggesting that they may have had contact urticarial reactions to these compounds.

However, in all three patients, the reactions were smaller than the size of histamine scratch-chamber tests. One of the patients who had a positive scratch-chamber test reaction to MBT also had positive patch-test reactions to MBT and its derivatives.⁶⁷ The relative scarcity of these reports suggests that type I allergies to mercapto compounds are an infrequent and only recently recognized problem, especially considering how long MBT and mercapto mix compounds have been used in manufacturing.

Type IV Reactions to Mercapto Compounds

Reports of delayed-type hypersensitivity to organic rubber accelerators appeared in the literature in the early 1900s.⁶⁸ Reactions specific to MBT were first mentioned by Bonnevie and other authors in 1938.^{1,2} Prior to then, some authors considered MBT to be nonallergenic.⁶⁹ According to Fossereau and colleagues, allergy to MBTS was recognized in 1934 by Rabeau.¹⁵ In 1952, Blank and Miller also reported allergic reactions to several other mercapto group compounds.¹⁴ Since that time, the literature has been filled with reports of contact hypersensitivity to mercapto compounds.

The potential of MBT and its derivatives to induce sensitivity has been examined in many animal studies. In some animal tests, MBT appears to be a strong sensitizer. For example, Maurer and colleagues found that 19 of 20 guinea pigs that were sensitized to MBT had positive reactions to MBT (0.1% in 30% propylene glycol, concentration 15% pet) on epidermal challenge.⁷⁰ Using the Buehler method, Wang and Susskind successfully sensitized 7 of 10 guinea pigs to MBT 2% pet whereas 10 of 10 animals were sensitized to MOR 2% pet. Also, 5 of the 10 MOR-sensitized animals reacted to 0.5% MOR, and 2 of 7 of the MBT-sensitized animals reacted to 0.5% MBT on challenge testing.⁷¹ A local lymph node assay showed MBT to produce a moderate proliferation response.⁷² Recently, however, local lymph node assays of mice, performed by De Jong and colleagues, showed MBT to cause sensitization inconsistently, and it was considered to be a weakly responding sensitizer.⁷³ These more recent results are consistent with the epidemiologic data on mercapto compound allergy in that MBT and its derivatives are capable of producing an allergic response but are “hypoallergenic” enough that the prevalence of allergy to mercapto compounds is relatively low.

It is unclear how much exposure is required to elicit sensitization to mercapto compounds. One case report described a woman who suffered an acute severe facial dermatitis that was traced to the rubber sponge she used to apply

cosmetics. She was patch-tested with the standard series and found to have a strong positive reaction only to MBT. To identify the individual components in the rubber of the sponge she used to apply her make-up, high-performance liquid chromatography was performed. MBT was found in small amounts (2 to 4 parts per million). The authors postulated that MBT was the most likely cause of her eruption and that this small amount was able to elicit a delayed-type hypersensitivity response in this patient.⁷⁴ Emmett and colleagues examined 12 MBT-sensitive volunteers and found that MBT was able to elicit sensitization at concentrations as low as 0.01% pet. Another patient had a mild (+) reaction to MBT 1% pet, a doubtful reaction to MBT 0.316% pet, and negative reactions to lower concentrations.⁷⁵ These studies suggest that elicitation thresholds vary among patients.

The manner of exposure to mercapto compounds does appear to affect sensitization. Researchers have postulated that rubber additives are more likely to be liberated in the warm, humid environment created by shoes and gloves.^{76–78} For example, in a 10-year retrospective study of 686 patients with type IV allergy to rubber additives, rubber gloves and boots were thought to be a common source of dermatitis.⁷⁶ Similarly, in a prospective analysis of 43 student athletes with suspected allergic contact dermatitis, 9 (20.9%) had positive patch-test reactions to mercapto compounds. Most of these athletes were found to be participating in sports that involved a wet environment and intimate contact with rubber-containing products.⁷⁹ Sports participation, in particular, exposes the skin to trauma and environmental insults as well as large volumes of perspiration that may create conditions that allow skin to be easily sensitized.⁸⁰ Because wearable rubber products are often not “breathable,” they may also foster environments that release MBT and its derivatives.

Occupational Dermatitis from Mercapto Compounds

When patients develop allergy to MBT or mercapto mix, it is more likely to be in the context of occupational dermatitis. In fact, in the 10-year study by Conde-Salazar and colleagues, 111 of 686 (16%) rubber-sensitive patients were sensitive to mercapto mix (ie, MOR, CBS, and MBTS, each in concentrations of 0.5% pet). Occupation was a significant factor ($p < .001$) for rubber sensitization in construction workers in this study (336 of 715 [47%] construction workers reacted), but correlations between occupation and the specific mixes, including the mercapto mix, were not analyzed.⁷⁶ The NACDG study from 1987 to 1989,

involving 1,579 patients, found that patients with occupational dermatitis were more likely to react to MBT and a mercapto mix. Positive patch-test reactions to MBT 1% pet were seen in 5.1% (14 of 274) of patients with occupational dermatitis, compared with 1.7% (20 of 1,259) of patients with non-occupational dermatitis (odds ratio [OR], 3.3; $p < .01$). Similarly, 4.6% (13 of 282) of occupational dermatitis patients reacted to a mercapto mix 1% pet whereas only 1.6% (20 of 1,259) of non-occupational dermatitis patients had allergic reactions (OR, 3.1; $p < .01$).⁸¹

Data that are more recent confirm the likelihood of an occupational relevance of allergy to mercapto compounds. When Rietschel and colleagues examined NACDG data on 5,839 patients seen for suspected contact dermatitis between 1998 and 2000, they found that of 101 patients allergic to MBT, 30 (29.7%) had occupationally relevant reactions. Also, of 65 patients with allergy to a mercapto mix, the reactions of 20 (30.8%) were occupationally relevant.⁸² Another study evaluated data recorded in the Register of Occupational Skin Diseases in Northern Bavaria between 1990 and 1999. Of 4,112 patients evaluated for occupational dermatitis, 0.8% (31) reacted to a mercapto mix 1% pet and/or MBT 2% pet. The authors found that 11 (35%) of the 31 workers who had positive test reactions to mercapto mix and/or MBT had an occupationally relevant source for this compound, placing it among the most frequent occupationally relevant sensitizers.⁸³ However, in a smaller study of 230 patch-tested patients with suspected occupational dermatitis in Italy, only 2 (0.9%) of patients had occupationally relevant allergy to a mercapto mix 1% pet.⁸⁴

An occupation-related erythema multiforme eruption was reported in one factory worker who was exposed to rubber chemicals in a gel he contacted while extracting rubber piping. After 3 weeks of work, he was hospitalized for a widespread eruption that had developed over 1 week. He was found to have patch-test sensitivity to MBT and several other rubber compounds. Several other workers in the factory were found to have similar eruptions.⁸⁵ Despite the relatively low prevalence of mercapto allergy, consideration of occupational exposure in patients who have positive patch-test reactions to MBT and related compounds is important.

The prognosis of patients with occupational contact dermatitis from mercapto compounds is unclear but may be extrapolated from general studies. Fregert observed 555 patients with occupational dermatitis seen during a 10-year period. He reported that 20% of the women (6 of 29) and 20% of the men (9 of 44) who had occupational allergies to rubber had completely cleared while 42% of the women (12 of 29)

and 50% of the men (22 of 44) had only partial clearing.⁸⁶ Specific rubber additives were not analyzed individually.

Glove Allergy Caused by Mercapto Compounds

Accelerators account for most allergic contact dermatitis reactions to gloves.⁸⁷ Allergic contact dermatitis from gloves usually presents with dermatitis of the dorsa of the hands and involvement of the wrists, but it may also present as patchiness and involve the palms.⁸⁸ In the 1970s, Fisher described a series of 11 surgeons with contact hypersensitivity to gloves, 7 (64%) of whom were allergic to MBT.⁸⁹ When von Hintzenstern and colleagues reviewed 67 cases of occupationally relevant glove allergy between 1985 and 1990, they found 2 (3%) positive patch-test reactions to a mercapto mix 2% pet.⁹⁰ Between 1995 and 2001, the IVDK registered 2,047 patients who were patch-tested because of a suspected glove allergy associated with their occupation. Of these, 1,984 were tested with MBT 2% pet and/or one of its derivatives, and 2.9% (58) of these people had positive patch-test reactions to at least one mercapto compound.¹³

The higher incidence of mercapto allergy associated with gloves in this population when compared to the rest of the patch-tested population is likely due to the increased use of mercapto compounds in gloves. A recent chemical analysis of the accelerators in 19 different brands of gloves found that zinc-MBT was present in 47.4% (9 of 19) of the gloves analyzed.⁹¹ MBT derivatives, along with dithiocarbamates, are according to Geier et al, "now the most frequently mentioned ones (vulcanization agents) in rubber glove ingredients lists."¹³ People suffering from contact hypersensitivity due to gloves may find relief with accelerator-free gloves.^{87,88,92} A helpful source of information that physicians can use to identify glove ingredients for patients is the "Helpful Resources" section of the American Contact Dermatitis Society Web site, under "Exam Gloves" and "Surgical Gloves."⁹³ Another option is to use glove liners, which may block or diminish type IV reactions to some rubber accelerators.⁹⁴ Barrier creams, occasionally used to prevent skin contact with allergens, may interact with rubber⁹⁵ and are generally not recommended as a defense against allergens found in gloves.

Shoe Allergy Caused by Mercapto Compounds

As mentioned previously, it is likely that conditions of humidity and occlusion often found in the environment of feet in shoes, create ideal circumstances for sensitization to mercapto compounds. It is thought that the moisture and

humidity found in shoes (along with the fact that footwear is often worn without socks during the warmer months) increase skin contact with allergens.^{78,96} Prior to the wide use of rubber in shoes, shoe dermatitis was mostly due to dyes and leather.⁹⁷ By the 1950s, several reports had confirmed that rubber had become a major cause of shoe dermatitis,^{96,98,99} and MBT was among the most frequently mentioned sensitizers.^{2,96,98} Contact dermatitis due to shoes occurs most often on the dorsa of the feet and toes, but other locations on the feet are possible.^{100–102} For example, in one study, 45 of 65 patients (69%) with foot dermatitis on the soles of their feet were allergic to mercapto mix.⁷⁷ Marcussen recognized that chemical additives may diffuse throughout the shoe and impregnate layers that do not necessarily contain rubber, which can contribute to the wide variety of presentations of shoe dermatitis.⁹⁸ Leaching of antigens may peak initially or occur after the initial coating on an object wears off, resulting in increased leaching as the object ages.⁷⁵

Diagnosis is also problematic because shoe allergy can masquerade as a wide variety of conditions, including tinea pedis, psoriasis, and dyshidrosis.^{14,103} Shoe dermatitis from MBT allergy has also been reported to spread to the hands,¹⁰⁴ further complicating the diagnosis of shoe allergy. Additionally, socks that have been in contact with MBT may also perpetuate shoe dermatitis. It has been shown that MBT persists in amounts sufficient to cause allergic contact dermatitis even after the socks have been washed and boiled.¹⁰⁵

MBT and its derivatives are among the most common sensitizers in patients with shoe contact dermatitis. Cronin's review of 213 patients with shoe dermatitis in 1966 described 100 patients (47%) who were sensitive to rubber, 96 (45%) who were sensitive to leather, and 17 (8%) who were sensitive to both. The 100 patients who were sensitized to rubber were patch-tested with MBT and tetramethylthiuram disulfide, and 82 (82%) were allergic to MBT, making it the most common rubber allergen in this study.⁴⁵ When Nurse reviewed the charts of 486 patch-tested patients at the Royal Melbourne Hospital, he found that 11 patients had dermatitis of the feet and that 10 of these 11 (90%) reacted positively to MBT or a mercapto mix.¹⁰¹ However, the prevalence of mercapto allergy in foot dermatitis may be decreasing in comparison to the high numbers reported in these two studies. In 1986, Foussereau and colleagues reported testing 13 patients who were suspected of having foot dermatitis and found that 2 of 13 (15%) were allergic to MBT 1% pet.¹⁰⁶ In 1993, 50 patients who were suspected of having foot dermatitis and 30 control patients were tested with a shoe series by Saha and colleagues. No patients in the control group

reacted to MBT 1% pet, but 7 (14%) patients in the footwear dermatitis group had reactions to MBT 1% pet.¹⁰⁷ Other authors reported sensitivity rates of 7.1 to 20.2% to mercapto compounds when patients with suspected shoe dermatitis were patch-tested.^{77,108,109} In a recent study of 53 patients with allergic contact dermatitis of the feet, a mercapto mix 2% pet caused 10 (11.4%) of the 90 positive reactions seen in this group, thus tying with nickel sulfate for the highest number of positive reactions.¹¹⁰ Children develop shoe dermatitis due to mercapto allergies as well. In a prospective study, Weston and colleagues patch-tested 34 children who were under the age of 14 years and who had foot dermatitis. Of these children, 4 (11.8%) reacted to a mercapto mix 1% pet and MBT 1% pet.¹¹¹

The prevalence of shoe allergy due to MBT and its derivatives in a given population is influenced by the forms of footwear that are popular in the population. In Taiwan, where rubber slippers are common, a recent retrospective study of 2,235 patch-tested patients found an overall prevalence of 1.1% allergy to a mercapto mix. However, among the patients with a mercapto allergy, 14 (56%) had foot dermatitis.²⁵ In Israel, 140 patients with suspected shoe contact dermatitis were patch-tested with a shoe tray; a total of 88 positive reactions were seen, only 3 (3.3%) of which were due to MBT. When the same group was tested with the European Standard series, a total of 45 reactions were seen, 2 (4.4%) of which were reactions to an MBT mix.¹¹² In India, 105 patients with foot dermatitis were patch-tested by Bjaj and colleagues. Relatively low rates of shoe dermatitis due to mercapto allergy (4 of 105 [3.8%]) were reported whereas allergies to leather (28.6%) and chrome (35.2%) were much more common.¹¹³ A large number of these cases were caused by the straps of sandals (presumably leather) rather than the soles of shoes, where rubber products containing MBT are more likely to be found. In general, the prevalence of shoe allergy to MBT and its derivatives is relatively high, and suspicion of foot contact dermatitis warrants patch-testing with mercapto compounds.

Epstein theorized that contact dermatitis from rubber compounds in shoes may be a self-perpetuating reaction. In skin disrupted by dermatitis, allergens may continually cross the skin barrier, further provoking type IV reactions. In fact, when he examined cases of shoe dermatitis, Epstein occasionally observed resolution of dermatitis when shoes that produced reactions were not worn for a period of months to years. He particularly noted that this occurred with children who discontinued wearing dermatitis-provoking shoes. After not wearing the shoes for a time,

these children were able to wear rubber footwear again without recurrence of the dermatitis.¹⁰⁰ However, it still appears that most adults who develop contact allergy have a lifelong sensitivity and do best when they are able to completely avoid mercapto compounds. Not only the offending shoes but also socks worn with those shoes must be replaced to eliminate exposure to the antigen.¹⁰⁵

Cross-Reactions to Mercapto Compounds

Mercapto compounds do not appear to present a high rate of cross-reaction with chemicals outside of their own group. A list of chemicals considered to be part of the mercapto group but not included in mercapto mix is available in *Occupational Contact Dermatitis*.¹⁵ Adams patch-tested MBT-sensitized patients with mercaptobenzimidazole and found that 2 of 17 (12%) patients reacted.¹¹⁴ Morpholine and MOR have also been studied for cross-reactions due to their shared morpholine group. In guinea pig studies, reactions to morpholine 2% pet in animals initially sensitized to MOR and MBT elicited reactions to MOR in only 1 of 10 animals whereas none reacted to MBT.⁷¹ A literature search revealed no reports of cross-sensitization between these compounds in humans.

A comprehensive literature search found no reports of systemic contact dermatitis due to ingestion of substances that cross-react with mercapto compounds. Gaig and colleagues reported a woman who developed a generalized pruriginous maculopapular rash. She underwent prick and patch testing with several angiotensin-converting enzyme (ACE) inhibitors and MBT 1% pet and also underwent oral tolerance tests with other ACE inhibitors.¹¹⁵ MBT was chosen because it contained a sulfhydryl group similar to captopril's sulfhydryl group. All reactions except those to the patch test with captopril were negative at 48 hours.

It is not uncommon for patients who are sensitized to one rubber accelerator to be sensitized to others. Cosensitization, rather than cross-reaction, most likely explains this finding. Cronin reviewed the cases of 100 patients sensitized to rubber between 1953 and 1966 and found that 37 (37%) of patients reacted to both tetramethylthiuram disulfide and MBT.⁴⁵ Rudzki and colleagues patch-tested 2,075 patients with a variety of rubber accelerators including several mercapto compounds. They found that only 16 (0.8%) of the patients were allergic to more than one accelerator. Only the coincident reactions between thiurams and carbamates were considered to be true cross-reactions whereas the remainder were considered to be cosensitizations.¹¹⁶ Cronin also described 356 patients who had glove dermatitis; 43 (12.1%) of the patients had

reactions to both MBT and thiuram, but only 26 (7.3%) reacted to MBT alone, and 287 (80.6%) reacted to thiuram alone.³¹ In a study that analyzed systems designed to visualize multiple sensitivity in patch-test databases, data on 2,881 patients were used to determine which allergies were likely to occur together. A mercapto mix was found to have the highest association with other allergens (a high "multiple sensitivity index").¹¹⁷ Brasch and colleagues conducted a retrospective analysis of data on 7,501 patients who had multiple positive patch-test reactions and found that positive reactions to a mercapto mix coincident with positive reactions to other allergens occurred more often than would be expected with independent distribution. Positive reactions to a mercapto mix were found to have strong associations with N-isopropyl-N'-phenyl-p-phenylenediamine (OR, 16.90; 95% CI, 11.03–25.91), thiuram mix (OR, 11.70; 95% CI, 8.52–16.08), zinc diethyldithiocarbamate (OR, 9.39; 95% CI, 4.89–18.05), and p-tert-butylphenol formaldehyde (OR, 6.40; 95% CI, 3.75–10.91).¹¹⁸ It is possible that these individuals with numerous allergies have a predisposition to the development of type IV reactions¹¹⁷ or that an initial dermatitis allows for the penetration of other allergens and subsequent sensitization to them.¹¹⁶

Patch-Test Considerations

Patch-test screening is generally considered to be quite sensitive when used carefully and within the correct patient population. Combining patch tests with chemical analysis has proved to be useful in identifying exactly which compounds in rubber products are responsible for sensitization,^{119–123} but this form of analysis is not widely available. Therefore, most allergies to MBT and its derivatives are detected by using standard allergens as screening tools. MBT and mercapto mix (in differing compositions and concentrations) have been and currently are included in the NACDG standard allergen series, the European Standard series, and the International Contact Dermatitis Research Group (ICDRG) standard Series.^{124,125}

Testing with mixes saves time and space when using substances like the mercapto compounds, which have a relatively low frequency of sensitization in the general population.^{126,127} However, when a mercapto mix was left for 3 weeks at room temperature, Hansson and Agrup found that the major remaining component of the mix was MBTS.³² Therefore, the true composition of a mercapto mix likely varies, depending on the duration of storage and the conditions under which the mix is stored.

The NACDG changed the composition of mercapto mix after a 1976 report of a study by Mitchell and colleagues

showed that the concentration of MBT in the mercapto mix 1% pet containing MBT, MOR, CBS, and MBTS (each in a concentration of 0.25%) was too low and occasionally resulted in patients reacting positively to MBT but negatively to the mercapto mix.¹²⁸ The mixture was switched to a mercapto mix 1% pet containing only MBT, MOR, and CBS (each in a concentration of 0.33%). However, in the early 1980s, Lynde and colleagues reported data on 2,297 patients tested with the “new” mix and found that 8 patients still reacted positively to the mix and negatively to MBT. In addition, 26 patients had positive reactions to MBT and negative reactions to the mix. The authors concluded that there was still no ideal screening mix for the mercapto compounds.¹²⁹ Similarly, when Geier and colleagues retrospectively compared results from the IVDK in Germany, they found that a mercapto mix 2% pet lacked sensitivity.¹³⁰ After changing the formula in the mid-1990s to a new mercapto mix (1% pet, with MOR, CBS, and MBTS) and testing with MBT separately, they found that the difference in sensitivity for the old mercapto mix (2% pet) and the new mercapto mix (1% pet) was not statistically significant ($p = .66$).¹³¹ The NACDG now includes MBT 1% pet and a mercapto mix 1% pet consisting of 0.25% each of MBT, MOR, MBTS, and CBS in its standard series. The ICDRG standard series also includes MBT 1% pet in addition to a mercapto mix 1% pet containing 0.25% each of CBS, MBTS, MOR, and MBT. The European Standard series includes MBT 2% pet and a mercapto mix 2% pet containing 0.5% each of CBS, MBTS, MOR, and MBT. Both the European Standard series and the ICDRG series are commercially available from Chemotechnique Diagnostics (Malmö, Sweden).¹²⁵ The TRUE Test (commercially available in the United States from Allerderm Laboratories, Petaluma, CA [www.true-test.com]) contains 0.075mg/cm² of MBT, with 0.0203 mg each of CBS, MOR, and MBTS).

Caution should be exercised when patch-testing with commercial products. It is important to realize that in some substances that contain MBT, such as cutting fluids, the concentration may be too low to provoke a reaction. In addition, these substances often contain strong irritants,¹³² so patch-testing with the industrial product is generally not recommended. When testing “chunky personals” such as shoes, Jordan recommended soaking pieces in water for 15 minutes before application, to “enhance percutaneous absorption.”¹⁰³ He also recommended that solid samples be 2 to 4 cm² and without rough or sharp edges. When patch-testing with items that may have different chemicals on the inside and on the outside (such as condoms), Fisher recommended testing squares of the outside

and inside portions; if both portions produce reactions, the allergy is likely due to a rubber chemical.¹³³

If suspicion of a contact allergy is high and initial patch-test results are negative, there are several options. Repeat patch tests with a wider variety of allergens could be considered. Also, re-application of certain nonirritating substances after 48 hours may elicit relevant reactions.¹³⁴ In the case of equivocal prick and patch-test results when glove dermatitis is suspected, Heese and colleagues suggested glove use exposure tests in which patients wear gloves for 2 hours daily for 3 consecutive days.⁸⁷

Summary

Allergic contact dermatitis from mercapto compounds is relatively uncommon. Despite this fact, recognition and treatment of this problem is important as mercaptobenzothiazole and its derivatives continue to be used in industry and are part of everyday exposures for most people throughout the world. More studies are needed to identify the best concentration and composition of the mercapto mix used for patch testing. Further studies are also needed to elucidate potential cross-reactions between mercapto compounds.

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