

Letter to the Editor

Both mercaptobenzothiazole and mercapto mix should be part of the standard series

Dear Sir,

We have read with interest the paper by Diepgen et al. (1) addressing the question whether mercaptobenzothiazole (MBT) or the mercapto mix, or both of them, should be patch tested in the standard series. Based on their retrospective analysis of data from the European Environmental Contact Dermatitis Research Group (EECDRG), the authors concluded that testing with both, MBT and mercapto mix, is necessary because otherwise an unacceptably large proportion of allergic patients would be missed. This largely confirms the findings of an earlier study published in 2002 in the *American Journal of Contact Dermatitis* on behalf of the German Contact Dermatitis Research Group (DKG) and the Information Network of Departments of Dermatology (IVDK) (2). However, some topics, in particular differences between the 3-component and the 4-component mercapto mix, are worth being discussed in the light of existing knowledge as this has not been disclosed to the readers in the paper by Diepgen et al.

Diepgen et al. analysed patch test results obtained with MBT 2% pet. and a mercapto mix consisting of 4 components at 0.5% pet. each: MBT, *N*-cyclohexyl-2-benzothiazylsulfenamide (CBS), dibenzothiazylsulfide (MBTS), and morpholinylmercaptobenzothiazole (MOR). The basis of their retrospective analysis was data from 32 475 patients tested with the European standard series in 11 European centres from 1996 to 2000. They found that 327 patients (1.00%) reacted to MBT and/or the mix, but only 254 (0.78%) to MBT and 261 (0.80%) to mercapto mix. Hence, by testing with only 1 of the 2 test preparations, 22% or 20%, respectively, of the patients allergic to MBT and/or its derivatives would not have been detected (see Table 1).

A retrospective IVDK data evaluation based on 2260 patients tested between 1990 and 1993 focusing on the sensitivity of patch tests with rubber mixes including the same 4-component mercapto mix was published in 1995(3). Using the data depicted in table 3 of this paper, the cross-tabulation

renders virtually the same proportions like in the EECDRG study (Fisher's exact test: no significant differences) (see Table 1).

The DKG/IVDK study published in 2002 was based on patch test results of 7198 patients, in whom MBT 2% pet., a mercapto mix including 3 components (CBS, MBTS, MOR, but not MBT) at 0.33% each, and each of the 3 single-mix components, had been tested because of suspected rubber allergy between 1995 and 1999. Primarily, this study addressed in detail the question of sensitivity and specificity of MBT and the mix in detecting contact allergy to MBT and/or its derivatives. However, the same calculation as given by Diepgen et al. can be derived from data presented in table 4 of the publication (2). Among the 163 patients (2.26%) reacting to MBT and/or the mix, 131 (1.82%) reacted to MBT and 116 (1.61%) to the mix. Thus, patch testing with MBT only would have missed 20%, and patch testing with the mix only would have missed 29% of the patients sensitized to MBT or its derivatives (see Table 1). Hence, although the proportion of patients reacting to MBT and/or its derivatives was higher in the DKG/IVDK study, because of different patient selection, the proportions of sensitizations potentially missed when patch testing with MBT only were virtually the same. The proportion of cases missed by testing with mercapto mix only was significantly lower in the EECDRG study than in the DKG/IVDK study (20% versus 29%; Fisher's exact test, $P = 0.04$). This can be explained by the differing test concentration and mix composition, namely 2% pet. with MBT in the EECDRG study and 1% pet. without MBT in the DKG/IVDK study. From the DKG/IVDK study (2), it was evident that neither MBT alone nor the 3-component mercapto mix alone had a satisfying sensitivity (0.69 and 0.60, respectively) to indicate contact allergy to MBT and/or its derivatives. Testing with both allergen preparations in parallel would increase the sensitivity to 0.77. Therefore, it was recommended to patch test both, MBT and the 3-component mercapto mix, for screening purposes (2).

Table 1. Number and percentage of patients reacting to MBT or mercapto mix

	EECRDG ^a (1), n (%)			IVDK ^a (3), n (%)			DKG/IVDK ^b (2), n (%)		
	MBT pos.	MBT neg.	Total	MBT pos.	MBT neg.	Total	MBT pos.	MBT neg.	Total
Mercapto mix pos.	188 (58)	73 (22)	261 (80)	40 (57)	13 (19)	53 (76)	84 (51)	32 (20)	116 (71)
Mercapto mix neg.	66 (20)	—	66 (20)	17 (24)	—	17 (24)	47 (29)	—	47 (29)
Total	254 (78)	73 (22)	327 (100)	57 (81)	13 (19)	70 (100)	131 (80)	32 (20)	163 (100)

MBT, mercaptobenzothiazole; EECRDG, European Environmental Contact Dermatitis Research Group; IVDK, Information Network of Departments of Dermatology; DKG, German Contact Dermatitis Research Group; pos., positive; neg., negative.

^a4-component mix, consisting of MBT, CBS, MBTS, and MOR.

^b3-component mix, consisting of CBS, MBTS, and MOR.

Diepgen et al. discuss patch testing with MBT and the mercapto mix at different concentrations and with different composition of the mix, suggesting that there is no compulsive reason for preferring one test preparation over the other. However, there has been a decisive reason why Hermal (Trolab) switched from the 4-component mix ($4 \times 0.5\%$, including MBT) to the 3-component mix ($3 \times 0.33\%$, without MBT) in 1995: chemical analyses had shown that the concentration of MBT was unstable in the 4-component mix. In contrast, the concentration of CBS, MBTS, and MOR in the 3-component mix proved to be stable during shelf life (4). Consequently, obeying Good Manufacturing Practice regulations for drugs, the 4-component mix had to be abandoned.

As cited in Diepgen et al., Hansson and Agrup (5) showed that CBS, MBTS, and MOR are rapidly converted into MBT in the presence of glutathione, which is abundantly present in the living cells of the epidermis. They assumed that MBT is probably the true hapten of all mercapto mix compounds. As mentioned above, the sensitivity of patch tests with rubber mixes has been analysed by 2 of the authors on the basis of IVDK data from 1990 to 1993 (3). At that time, the 4-component mercapto mix was still in use in Germany. We could show that, with 0.57, the sensitivity of the mix in detecting sensitization to 1 of its 4 components was not satisfying. Additionally, it was demonstrated that MBT and the 4-component mercapto mix virtually had the same sensitivity (0.65 and 0.64, respectively) in detecting contact allergy to the MBT derivatives CBS, MBTS, or MOR. Considering the results of Hansson and Agrup, we recommended to switch from the 4-component mercapto mix to MBT in the standard series at that time, because, according to our data, this switch would not mean a lack in diagnostic sensitivity. However, nowadays, this recommendation is obsolete anyway as the 4-component mercapto mix should no longer be used because of the unstable MBT concentration (4).

In conclusion, we would like to comment on 3 statements made by Diepgen et al. (1) in their discussion.

- (1) Research into the best solution how to screen for contact allergy to MBT and its derivatives is not lacking (2, 3, 5).
- (2) A comparison of patch test results obtained with the 3-component mercapto mix and the 4-component mercapto mix is part of the DKG/IVDK study published in 2002 (2).
- (3) Considering the chemical instability of the 4-component mercapto mix (4), we do not agree that it is advisable to continue patch testing MBT and the 4-component mercapto mix in the European standard series. Instead, we would like to repeat our recommendation to use MBT and the 3-component mercapto mix for screening purposes in the patch test standard series (2).

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