

Clinicians vs. epidemiologists: Patch testing with methyldibromo glutaronitrile as a controversial issue.

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Conflicts of interest

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Key words

Methyldibromo glutaronitrile, MDBGN, patch test concentration, patch test validity, CAS 35691-65-7

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The preservative methyldibromo glutaronitrile (MDBGN) (CAS 35691-65-7) is known since long as an important contact allergen mainly used in cosmetics (Review: [1]). MDBGN was banned EU-wide from being used in leave-on products in 2005, for rinse-off products in 2008, and further restricted for non-cosmetic (technical) applications in 2010. However, positive reactions in patch testing (PT) continued to occur. MDBGN was patch tested at 0.2% in petrolatum (pet.) since August 2008 and at 0.3% since April 2016, because the 0.2% preparation was no longer available. We wondered if the downward trend of MDBGN sensitization had continued during 2010 to 2017 and if the compelled increase of the PT concentration from 0.2% (2010 - 2015) to 0.3% (2016 - 2017) did affect the quality and frequencies of patch test reactions. We analysed IVDK data on MDBGN between 2010 and 2017 according to the methods of the IVDK [2] and reviewed the literature on concomitant Repeated Open Application (ROATs) and patch testing (PTs), using ROAT results as (external) validity criterion for PT methods. Between 2010 and 2015, frequencies of sensitization to MDBGN decreased only slightly, but had remained at about 2% despite the ban (fig. 1). This may be explained by “historical sensitization”, but false positive reactions have to be considered also, as 2.9% of children ≤ 10 years of age with little chance to have ever been exposed to MDBGN reacted (weak (+)) positive. The increase of PT reactions up to >4% after increasing the PT concentration from 0.2% to 0.3%. is quite bewildering (fig. 1). Rare (technical) exposures cannot explain the magnitude of reactions, but may only give rise to very single cases. Thus the validity, in particular the specificity of the PT concentration of 0.3% can be questioned, in particular by referring to ROAT studies and concomitant PT with different concentrations [3, 4, 5]. The number of ROAT negatives but patch test positives (which we consider as “false” PT positives) increases dramatically with the patch test concentration (fig. 2), a relation found in other allergens as well [6]. However, in the IVDK ROAT all but 1 case were identified already with 0.2% MDBGN, very likely the best PT-concentration [7]. In addition, the Reaction Index (RI) [2], relating allergic and non-allergic reactions, and the Positivity Ratio (PR), the proportion of only weak (“+”) reactions, show that with MDBGN 0.3% compared to 0.2% the RI (ranging from -1 (all reactions non-allergic)

to +1 (all allergic)) decreased significantly from 0.22 to 0.01, and the PR increased significantly from 78.2% to 83.6%, meaning that with the higher concentration the proportion of non-allergic reactions and the proportion of weak positive reactions increased, a pattern probably indicative of an unknown number of false positive reactions. By contrast, MDBGN PT is recommended at 0.5% in the European baseline series [8, 9]. Even MDBGN 1% pet. was deemed necessary as with lower concentrations clinical relevant cases would be missed, and doubtful reactions in PT lower concentrations turned to allergic reactions with higher concentrations [3, 8, 10]. Regarding the best PT concentration, there are obviously two (legitimate) perspectives not yet considered: One of the clinician wanting “not to miss a case”, even at the expense of possibly wrong diagnoses in other cases, and one of the clinical epidemiologist striving for realistic frequencies of sensitization not artificially inflated by false positive cases. In those suspected to be false-negative to 0.2% higher concentrations could be patch tested. These results add a further argument: With MDBGN 0.3% the number of positives had more than doubled which cannot be regarded as relevant, as there is virtually no exposure.

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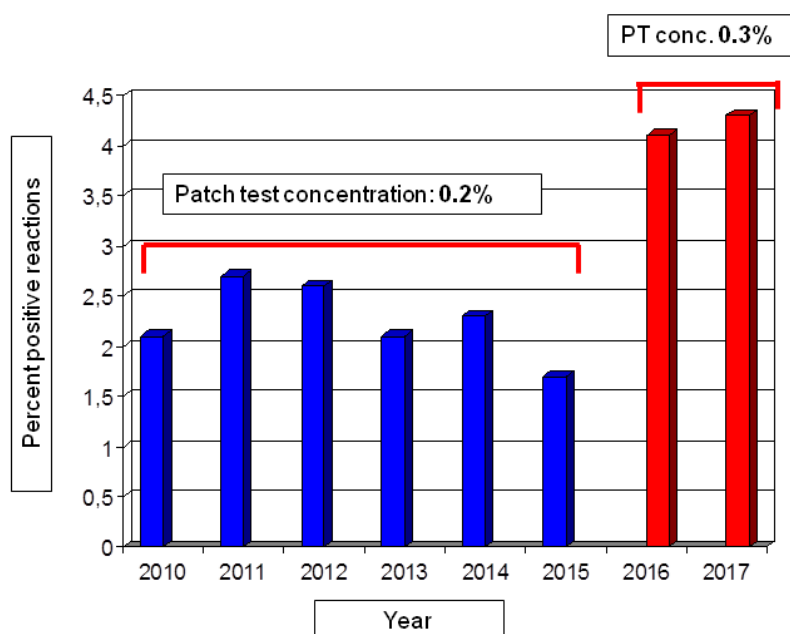
Legend to figure 1

Time trends of annual patch test results. Age- and sex-standardized percentages of positive reactions to MDBGN 0.2% pet. in 64,891 patients (2010-2015) and to MDBGN 0.3% pet. in 14,823 patients (2016-2017). The decline between 2010 and 2015 was significant (Cochran-Armitage trend test; $p = 0.0066$).

Legend to figure 2

Relation between ROAT and patch test reactivity. Distribution of positive and negative ROAT responses in numbers (n) for the respective patch—test reactivity levels in 3 studies (EECDRG [3], Malmø [4], and IVDK [5]). With increasing PT concentration, only a few or none (IVDK) relevant (i.e. ROAT-positive) cases are diagnosed, but from MDBGN 0.3 up to MDBGN 1.0 the percentage of false PT positives (i.e. ROAT-negatives) increases to 41% (Malmø) and 60% (EECDRG) of all positive PT reactions. In the IVDK study, all ROAT positive cases were diagnosed with MDBGN 0.2%. with the exception of one case remaining negative up to 0.5%. A maximum sensitivity of 94% (95% CI: 70-100%) is reached with a concentration of 0.2%, and is not further improved by increasing the concentration, whereas the specificity decreases from 88% (95% CI: 47-100%) with MDBGN 0.2% to a mere 12.5% (0-53%) with MDBGN 0.5%. (n.t.= not tested)

Fig 1



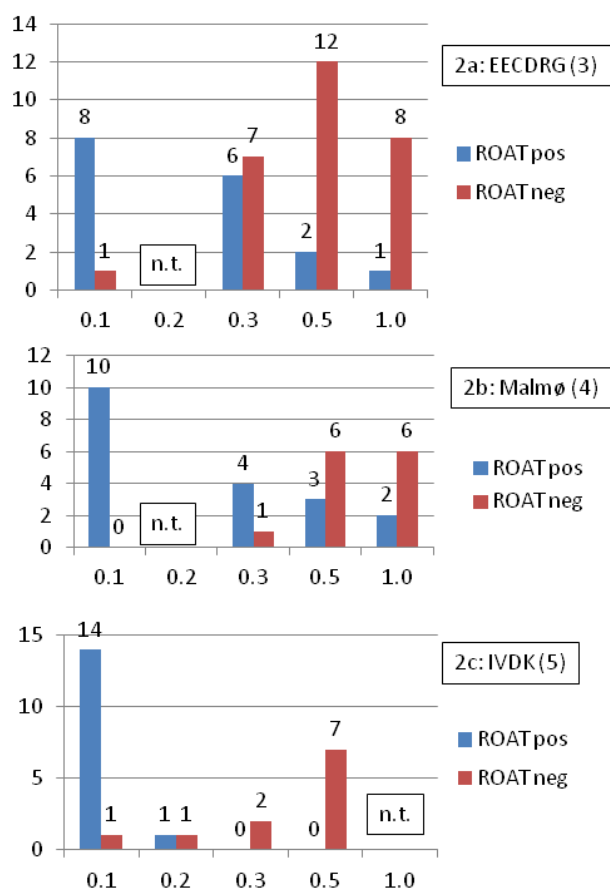


Fig. 2 a-c

Relation between ROAT and patch test reactivity

Fig. 2 a

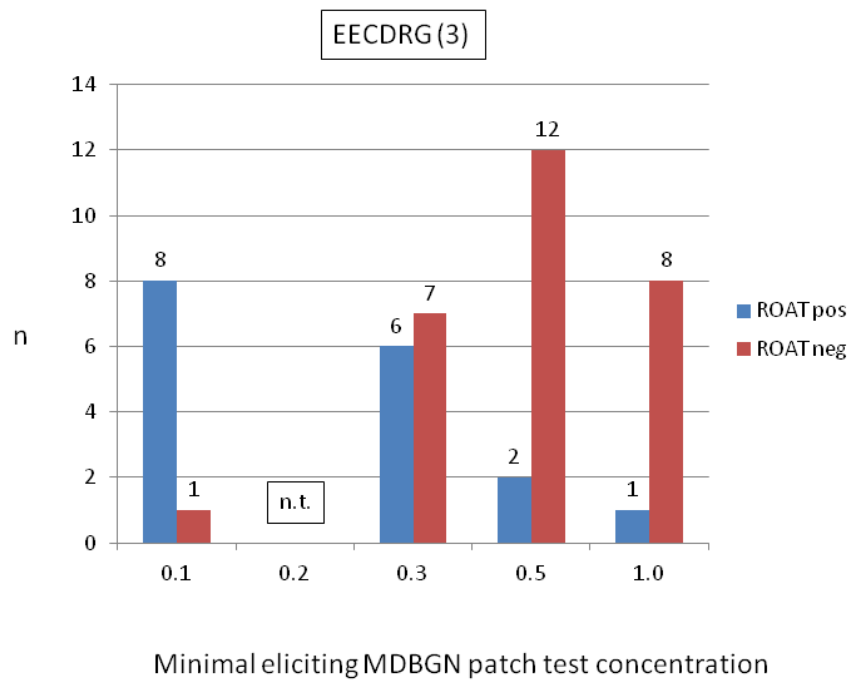


Fig. 2 b

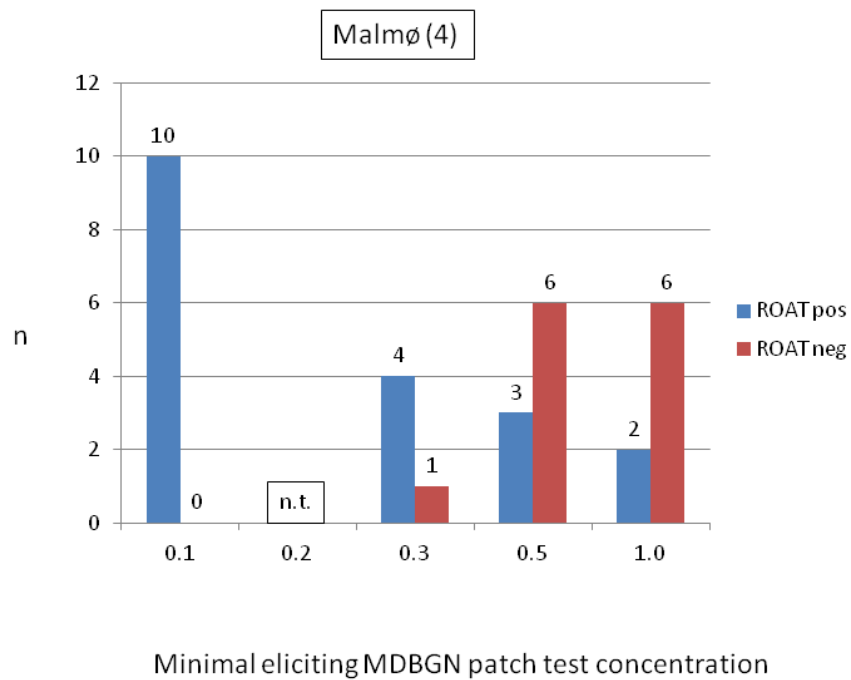
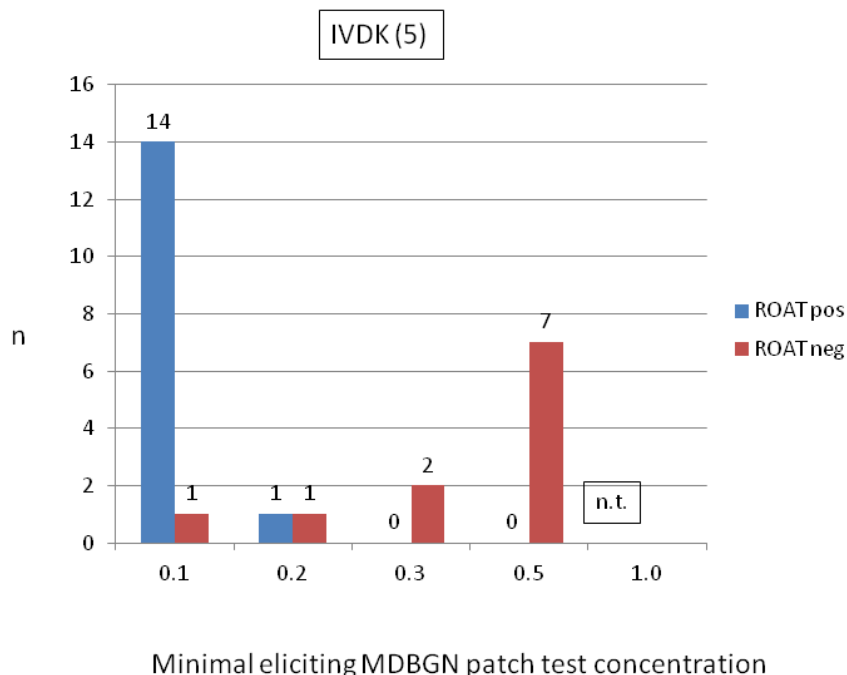


Fig. 2 c



Legend to Fig 2 (a-c)

Relation between ROAT and patch test reactivity. Distribution of positive and negative ROAT responses in numbers (n) for the respective patch—test reactivity levels in 3 studies (EECDRG [3], Malmø [4], and IVDK [5]). With increasing PT concentration, only a few or none (IVDK) relevant (i.e. ROAT-positive) cases are diagnosed, but from MDBGN 0.3 up to MDBGN 1.0 the percentage of false PT positives (i.e. ROAT-negatives) increases to 41% (Malmø) and 60% (EECDRG) of all positive PT reactions. In the IVDK study, all ROAT positive cases were diagnosed with MDBGN 0.2%, with the exception of one case remaining negative up to 0.5%. A maximum sensitivity of 94% (95% CI: 70-100%) is reached with a concentration of 0.2%, and is not further improved by increasing the concentration, whereas the specificity decreases from 88% (95% CI: 47-100%) with MDBGN 0.2% to a mere 12.5% (0-53%) with MDBGN 0.5%. (n.t.= not tested)