Contact allergy to 3-dimethylaminopropylamine in 5140 consecutive Italian patients: a one-year retrospective multicenter SIDAPA study

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/cod.13445

Keywords: 3-dimethylaminopropylamine, allergic contact dermatitis, cosmetic products, personal care products, SIDAPA baseline series, patch test.

Conflict of interest: the authors have no conflict of interest to declare.

3-Dimethylaminopropylamine (DMAPA) (CAS no. 109-55-7) is an aliphatic amine used for the synthesis of betaines and is often present in the final product as a contaminant,[1] and is able to induce contact allergy.[2-4] DMAPA may be contained in personal care products and several industrial products as agricultural chemicals, fabric softeners, water-resistant textile fibers, synthetic dyes and paints, etc. In this study, the prevalence of positive patch test reactions to DMAPA during the last year in the Italian population was assessed.

Methods

In 11 patch testing clinics evenly distributed across Italy, 5140 consecutive patients (1615 males, 3525 females; mean age 47.9 years, range 4-93) were patch tested for contact dermatitis between January and December 2018 with the SIDAPA (Società Italiana Dermatologia Allergologica, Professionale Ambientale) baseline series (FIRMA Diagent, Florence, Italy).[5] Patch tests were occluded for 2 days with Haye's Test Chambers (Haye's Service, Alphen aan den Rijn, The Netherlands) on Soffix tape (Artsana, Grandate, Italy), and readings were performed on day (D)2, D4, and D7.[5] Patients were asked to return in case of late reactions. Irritant and doubtful reactions were not considered.

Results

Among the 5140 patients tested, 68 (1.3%) (mean age 47.5 years, range 9-81) showed positive reactions to DMAPA, 31 males (1.9%) and 37 females (1.1%). No occupational cases were recorded. Irritant reactions were not registered. Clinical relevance was observed in 55 of 68

DMAPA-positive patients (80.9%): all the cases were related to the repeated daily use of skin cleaners containing betaines. Concomitant sensitizations were observed In 44 patients: nickel sulfate in 19 cases (27.9%), methylchloroisothiazolinone/methylisothiazolinone 3:1 in 11 cases (16.2%), cobalt chloride and methylisothiazolinone in 7 cases (10.3%). Twenty-two (32.3%) of 68 DMAPA-positive patients had a personal history of atopy. The reported duration of the skin lesions ranged from 3 months to 31 years (mean 3.8 years). The body sites most affected by the skin lesions were the face in 35 cases (51.5%), the trunk in 13 cases (19.1%), the upper limbs in 12 cases (17.6%), the hands in 11 cases (16.2%) and the scalp in 10 cases (14.7%).

Discussion

Our data from 5140 consecutively patch tested patients in Italy during a 1-year period showed a prevalence of 1.3% of contact allergy to DMAPA. This prevalence is lower compared to a previous Italian study,[2] although still remarkable. In this study, the authors showed 46 positive reactions (3.8%) to cocamidopropylbetaine 1% aq. among 1200 consecutively patch tested patients. Thirty out of these 46 patients were subsequently tested with DMAPA, turning out always positive, highlighting the sensitizing potential of DMAPA as an impurity of cocamidopropylbetaine.

The sensitizing potential of DMAPA is well known[6,7], but there is currently no regulation by the European Union or the United States defining a threshold for this substance in skin care products, nor obligation to report its presence and quantity on packaging labels. The North American Contact Dermatitis Group reported a 1.7% prevalence of positive reactions to DMAPA among

10877 patients patch tested between 2009 and 2014.[3] In 2012, the records of 1092 patch tests performed between 2002 and 2009 were reviewed at the Finnish Institute of Occupational Health reporting a 1.0% prevalence of occupational contact allergy due to DMAPA.[4] Of note, the authors found irritant reactions to patch tests with cocamidopropyl betaine and its impurities very common, that is, in 39% of the tested patients.

In December 2010, the Cosmetic Ingredient Review Expert Panel reviewed the safety of fatty acid amidopropyl dimethylamines concluding that they were safe when formulated in nonsensitizing levels, based on quantitative risk assessment[8]; DMAPA at a concentration of 0.01% in raw cocamidopropyl betaine in finished cosmetic products not being sensitizing[8]. In 2019, the Panel advised industry to continue minimizing the concentrations of the sensitizing impurities, highlighting that DMAPA in oleamidopropyl dimethylamine seems to exceed the limit recommended[9].

Despite this, we found that the majority of the DMAPA-positive patients (39/68; 57.3%), all with clinical relevance, reported the onset of the dermatitis during the last 2 years thus demonstrating that DMAPA is still present at sensitizing concentrations in many products as an impurity. All our patients did not report any recurrence of their dermatitis following strict avoidance of topical products containing betaines.

In conclusion, we believe that legislative interventions on DMAPA to improve consumer safety are advisable; as stated by Burnett CL et al,[9] DMAPA should be present in cosmetic products at a concentration lower than 0.01%. We would also stress that DMAPA should be tested in the baseline series.

References

1. U. S. National Toxicology Program. 3-Dimethylaminopropylamine. http://ntp.niehs.nih.gov/ntp/htdocs/chem_background/exsumpdf/dimethylaminopropylamine_508.pdf. Accessed July 23, 2019.
2. Angelini G, Foti C, Rigano L, Vena GA. 3-Dimethylaminopropylamine: a key substance in contact allergy to cocamidopropylbetaine? Contact Dermatitis. 1995;32(2):96-99.
3. Fowler JF Jr, Shaughnessy CN, Belsito DV, et al. Cutaneous delayed-type hypersensitivity to surfactants. Dermatitis. 2015;26(6):268-270.
4. Suuronen K, Pesonen M, Aalto-Korte K. Occupational contact allergy to cocamidopropyl betaine and its impurities. Contact Dermatitis. 2012;66(5):286-292.
5. Stingeni L, Bianchi L, Hansel K, et al. Italian Guidelines in Patch Testing - adapted from the European Society of Contact Dermatitis (ESCD). G Ital Dermatol Venereol. 2019;154(3):227-253.
6. Angelini G, Rigano L, Foti C, et al. Contact allergy to impurities in surfactants: amount, chemical structure and carrier effect in reactions to 3-dimethylaminopropylamine. Contact Dermatitis 1996;34(4):248–252.
7. Kanerva L, Estlander T, Jolanki R. Occupational allergic contact dermatitis from 3-dimethylaminopropylamine in shampoos. Contact Dermatitis 1996;35(2):122–3.
8. Burnett CL, Bergfeld WF, Belsito DV, et al. Final report of the cosmetic ingredient review expert panel on the safety assessment of cocamidopropyl betaine (CAPB). Int J Toxicol 2012;31(4 Suppl):77S-111S.

9. Burnett CL, Boyer I, Bergfeld WF, et al. Safety Assessment of Fatty Acid Amidopropyl Dimethylamines as Used in Cosmetics. Int J Toxicol 2019;38(1 Suppl):39S-69S.