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Quaternium-15 sensitization in the North East of Italy, trend from 1996 to 2016 and occupational role

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Dear Editor,

Methenamine 3-chloroallylochloride (CAS 51229-78-8) or quaternium-15, is a quaternary ammonium salt that was used as preservative in many cosmetics, liquid soaps, moisturizers, eye make-up, bath gels, shaving creams and cleaning supplies (also non-cosmetic supplies, as floor waxes and inks).¹⁻³ It is a formaldehyde releaser with a broad spectrum antimicrobial and antifungal action that has been recently prohibited in cosmetics by the Commission Regulation (EU) 2019/831 of 22 May 2019. It is known from several studies that quaternium-15 can cause contact allergy³⁻⁶, and the sensitization trend was studied in other Countries, but there is no available data as far as Italy is concerned.

27381 patients with symptoms and/or signs of suspected allergic contact dermatitis were patch tested, from 1996 to 2016, in North-Eastern Italy⁷. Quaternium-15 was tested 1% in pet. The analysis of the data was performed using the statistical software STATA™ v. 13.1 (Stata Corp., LP, College Station, TX, USA).

The overall frequency of quaternium-15 sensitization was 0.49%. Patients sensitized to quaternium-15 resulted significantly younger than the non-sensitized patients did (40.5 ± 15 vs 43.1 ± 17.5 years old, $p < 0.05$), and women resulted more sensitized than men (Table 1). Quaternium-15 positivity resulted under 1% for all the considered years, with a significant decrease in the period 2008/2013. Sensitization by age classes did not show any significant trend. Sensitization to quaternium-15 resulted associated, as expected, to formaldehyde patch test positivity (OR 16.1; 95% CI 11.2-23.3), but also to other preservatives such methylchloroisothiazolinone/methylisothiazolinone (OR 4.9; 95% CI 3.1-7.6), methyldibromoglutaronitrile/phenoxyethanol (OR 2.8; 95% CI 1.3-6.1) and thimerosal (OR 1.7; 95% CI 1.02-3.0). Most of the co-sensitized subjects reacted to one other hapten (23%) while 19.3% of patients resulted monosensitized. Farmers and fishermen resulted more sensitized to this hapten compared to clerks (OR 3.7, 95% CI: 1.44-9.41) (table 2).

The overall frequency of patch test positivity to this hapten was lower than that reported in other European countries and in Australia ranging between 0.66 and 3.1%.^{3,6,5,8} Quaternium-15 sensitization is higher in USA reaching the 9.5%⁹ and 11.2% in patients with contact dermatitis associated to skin cleanser¹⁰. The higher prevalence of sensitization in North America can be

related to the double concentration used to patch test quaternium-15 (2% in pet in US instead of 1% in EU), but also to a possible higher exposure to quaternium-15 in cosmetics for different regulations between EU and USA.⁵

The lower percentage of sensitization in our population can be related to regulation and to the need of labeling cosmetics containing more than 0.05% of formaldehyde: the increase perception of formaldehyde as a dangerous chemical could have reduced the use of cosmetics with this labelling. However, it has been shown that cosmetic products containing 0.02-0.05% of free formaldehyde can induce dermatitis from short-term use in normal skin and at a lower exposure in compromised skin.⁵

As expected⁴, quaternium-15 sensitization was associated to that of formaldehyde and to other preservatives in line with the fact that multiple and continuative exposures are frequent. In our study mono-sensitization to quaternium-15 was seen in the 19.3% of the subjects, even though the most common outcome was a poly-sensitization to one, two or three other haptens.

The occupational role of quaternium-15 was limited probably due to the low numbers of sensitized workers (table 2) and only farmers and fishermen presented a significant higher sensitization to quaternium-15 possibly associated with the use of disinfectant containing quaternium-15 for cleaning the working areas.

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Table 1 Characteristics of patients sensitized and non-sensitized to quaternium-15 (in bold are reported significant values)

	Quaternium + n. 135	Quaternium – n. 27,246	OR (95% CI)
Age (years ± SD)	40.5 ± 15*	43.1 ± 17.5	
Female (%)	96 (71)	18435 (67.7)	1.2 (0.8-1.7)
Occupational dermatitis (%)	16 (11.8)	2083 (7.6)	1.6 (0.94-2.7)
Atopic eczema (%)	14 (10.4)	2295 (8.4)	1.35 (0.8-2.4)
Hand localization (%)	42 (31.1)	847 (31.1)	0.98 (0.67-1.4)
Leg localization (%)	7 (5.2)	1743 (6.4)	0.79 (0.4-1.7)
Face localization (%)	34 (22.2)	4386 (16.1)	1.5 (0.99-2.28)
Age ≥ 40 (%)	65 (48.1)	14,406 (52.9)	0.83 (0.6-1.2)
Concomitant reaction to:			
-Formaldehyde 1% n. (%)			16.1 (11.2-23.3)
Methylchloroisothiazolinon e/Methylisothiazolinone 0.02% aq n. (%)	45 (33.3) 24 (17.8)	768 (2.8) 1136 (4.2)	4.9 (3.1-7.6) 2.8 (1.3- 6.1)
- Methyldibromoglutaronitril e/Phenoxyethanol 2% n. (%)	7 (5.1) 15 (11.1)	538 (1.98) 1697 (6.23)	1.7 (1.02-3.0)
-Thimerosal 0.1% n. (%)			

* p<0.05

Table 5. Prevalence of quaternium-15 sensitizations in occupational groups considering clerks as reference category

Profession	Total, n	Quaternium +, n	%	O.R.	C.I 95%	n. possibly occupational cases	n. subjects cosensitized to formaldehyde 1%
Clerks	6933	41	0.59	1		0	0
Farmers and fishermen	233	5	2.15	3.7	1.44-9.41	2	0
Woodcraftsmen and similar	369	4	1.1	1.8	0.66-5.2	1	0
Hairdressers, barbers and beauticians	343	3	0.87	1.5	0.46-4.8	1	0
Mechanics	1270	10	0.79	1.33	0.66-2.7	2	1
Students	148	1	0.68	1.1	0.16-8.4	0	0
Healthcare workers	2747	17	0.62	1.05	0.59-1.84	4	1
Housekeepers	3192	18	0.56	0.95	0.55-1.7	0	0
Texile workers	568	3	0.53	0.89	0.27-2.9	0	0
Domestic workers and restauraners	1426	6	0.42	0.7	0.3-1.7	2	0
Workers of buildings and extraction	1202	5	0.42	0.7	0.28-1.8	0	0
Drivers	252	1	0.40	0.67	0.09-4.9	1	1
Unemployed	563	2	0.36	0.6	0.14-2.5	0	0
Retired	3984	10	0.25	0.42	0.21-0.84	0	0

Others (including paper machine and machine workers, teachers, chefs, delivery man)	4151	9	0.22	0.36	0.2-0.75	3	2
Total	27381	135				16	5

CI, confidence interval; OR, odds ratio. The ORs and 95% CIs were evaluated with multinomial logistic analysis adjusted for age and sex, with clerks as the reference category. Statistically significant results are in bold.