

## Original Research Article

# Trend in the variation of sensitization of the European standard battery allergens over 26 years

Aïcha Brahem\*, Asma Gaddour, Mohamed Bouhlel, Asma Chouchene, Asma Aloui, Imen Kacem, Maher Maoua, Houda Kalboussi, Olfa ElMaalel, Souhaeil Chatti, Najib Mrizek

Department of Occupational Medicine, University Hospital Farhat Hached, Faculty of Medicine of Sousse, University of Sousse, Tunisia

**Received:** 04 March 2021

**Accepted:** 07 April 2021

**\*Correspondence:**

Dr. Aïcha Brahem,

E-mail: brahemaicha@yahoo.fr

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### ABSTRACT

**Background:** Epidemiological monitoring of sensitization rates to common allergens and identification of emerging allergens are needed to assess preventive measures. The aim of this study was to assess trends in the frequencies of sensitization to the different allergens in the European standard battery over a 26 year period from 1989 to 2015.

**Methods:** It's a descriptive study of the trend of sensitization to BSE allergens over a period of 26 years, at the dermatology-allergology unit of occupational medicine department of Farhat Hached university hospital-Sousse (Tunisia), based on the results of patch tests of all patients who consulted the unit between 1989 and 2015.

**Results:** During the study period, 1716 patients were patch tested, 48048 patch tests were performed with 886 positive tests to at least one allergen (51.6%). Between 1989 and 2015, the number of positive patch tests has shown a significantly positive trend with an annual percentage change (APC) of 10.03% ( $p < 10^{-3}$ ). However, the overall frequency of sensitization to BSE allergens decreased with an APC of -0.87%,  $p = 0.2$ . The APC of chromium sensitization was -2.57% ( $p < 10^{-3}$ ). The frequency of cobalt sensitization showed a non-significant decrease (APC = -0.28%,  $p = 0.9$ ). The frequency of nickel sensitization increased with an APC of +2.7%,  $p = 0.1$ . Overall, there was a statistically significant growth between 1989 and 2015 in the BSE preservatives sensitization trend with an APC of +5.54% per year ( $p < 10^{-3}$ ). The frequency of sensitization to mix fragrances increased from 2004 to 2015, with a significantly positive trend (APC = +24.33%,  $p < 10^{-3}$ ).

**Conclusions:** Although the frequency of some BSE allergens sensitization tends to decrease, it remains high. Consistent preventive measures should be focused, mainly on sensitization to perfumes and preservatives used in the cosmetic industry.

**Keywords:** Allergic contact dermatitis, Epidemiology, Occupational allergies, Patch-tests

### INTRODUCTION

Contact allergy dermatitis is a non-infectious inflammatory skin disease caused by delayed

hypersensitivity reaction a reaction to haptens.<sup>1</sup> Since the industrialization of modern civilization, the number of allergens has continued to increase.<sup>2</sup> The prevalence of sensitization to at least one of the common allergens of standard batteries in the general European and American

population is estimated between 12.5% and 40.6% with a mean of 21.2%.<sup>2</sup> It has been shown that allergic contact dermatitis has a significant impact on the quality of life of patients especially on their everyday life activities and life satisfaction, in addition to a significant economic impact due to a reduction in worker productivity.<sup>3-5</sup>

In addition to the large number of allergens to which we are exposed, it has been shown that the development of allergies also depends on several factors, in particular individual predisposition lifestyle and occupational environment.<sup>6</sup>

These parameters differ from one population to another and also over time, which could explain in part the variation in the allergological profile among populations and over time.

Thus, epidemiological surveillance is required to monitor the rate of sensitization to common allergens and identify emerging allergens, in order to evaluate preventive measures already in place and/or eventually implement new appropriate preventive measures.

In this context, we carried out an epidemiological study to assess trends in the frequencies of sensitization to the different allergens in the European standard battery over a 26 year period from 1989 to 2015.

## METHODS

We conducted a descriptive study of the trend of sensitization to BSE allergens over a period of 26 years, at the dermatology-allergy unit of occupational medicine department of Farhat Hached university hospital-Sousse (Tunisia), based on the results of patch tests of all patients who consulted the unit between 1989 and 2015. All the patients were tested by the European Standard BSE.

The consent of the patients was obtained verbally after having explained to them the application and the reading modalities of the patch tests.

The results were read according to the recommendations of the international contact dermatitis research group (ICDRG).<sup>7</sup>

The evaluation of the trend of sensitization was performed using the national cancer institute's 'join point regression program' version 4.5.0.1 software.<sup>8</sup>

The ethics committee of the university hospital Farhat Hached of Sousse has given its favorable agreement for the realization of this study.

The study data is available on request via the email of the corresponding author.

## RESULTS

During the study period, 1716 patients were patch tested, 48048 patch tests were performed with 886 positive tests to at least one allergen (51.6%) (Figure 1).

The allergens with highest frequency of positive reactions were metals (chromium, nickel and cobalt) with frequencies of 37%, 34% and 24%, respectively. Table 1 presents the different sensitization frequency of the tested allergens.

Between 1989 and 2015, the number of positive patch tests has shown a significantly positive trend with an APC of 10.03% ( $p < 10^{-3}$ ). However, the overall frequency of sensitization to BSE allergens decreased with an APC of -0.87%,  $p = 0.2$  (Figure 2).

### Metal sensitization trend

The frequency of chromium sensitization has been steadily decreasing over time. Indeed, the annual percentage change was -2.57% ( $p < 10^{-3}$ ). Similarly, the frequency of cobalt sensitization showed a non-significant decrease (APC=-0.28%,  $p = 0.9$ ). The frequency of nickel sensitization increased with an APC of +2.7%. However, this increase was not statistically significant ( $p = 0.1$ ).

### Preservative sensitization trend

Overall, there was a statistically significant growth between 1989 and 2015 in the BSE preservatives sensitization trend with an APC of +5.54% per year ( $p < 10^{-3}$ ).

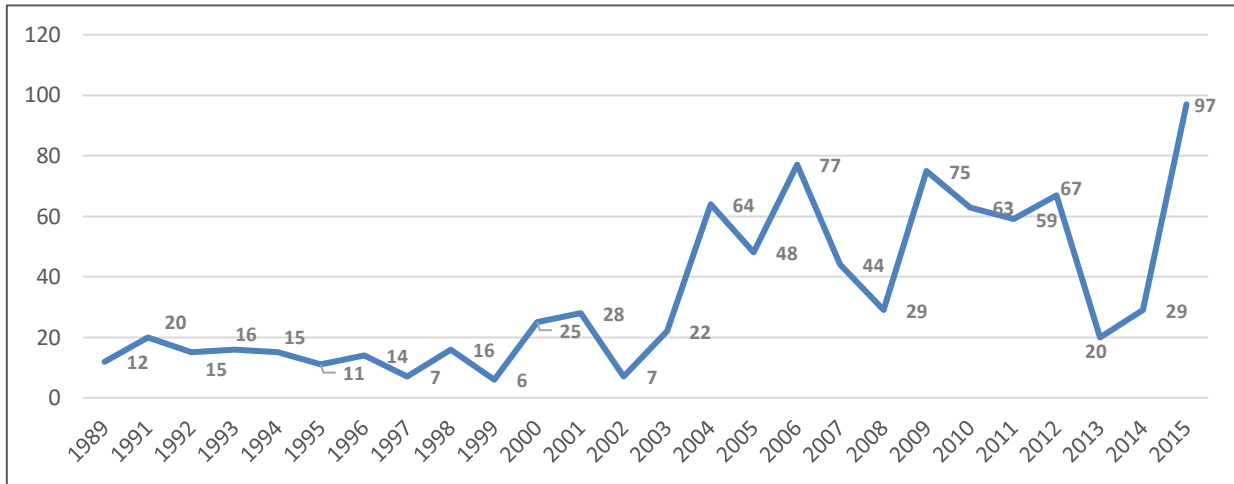
The study of the trend of each separate preservatives showed a statistically significant increase in the frequency of sensitization by methyl dibromoglutaronitrile since its introduction into BSE allergens in 2005.

In contrast, a statistically significant reduction in the frequency of sensitization by paraben mix (between 2006 and 2015) and quaternium 15 was observed (Table 2).

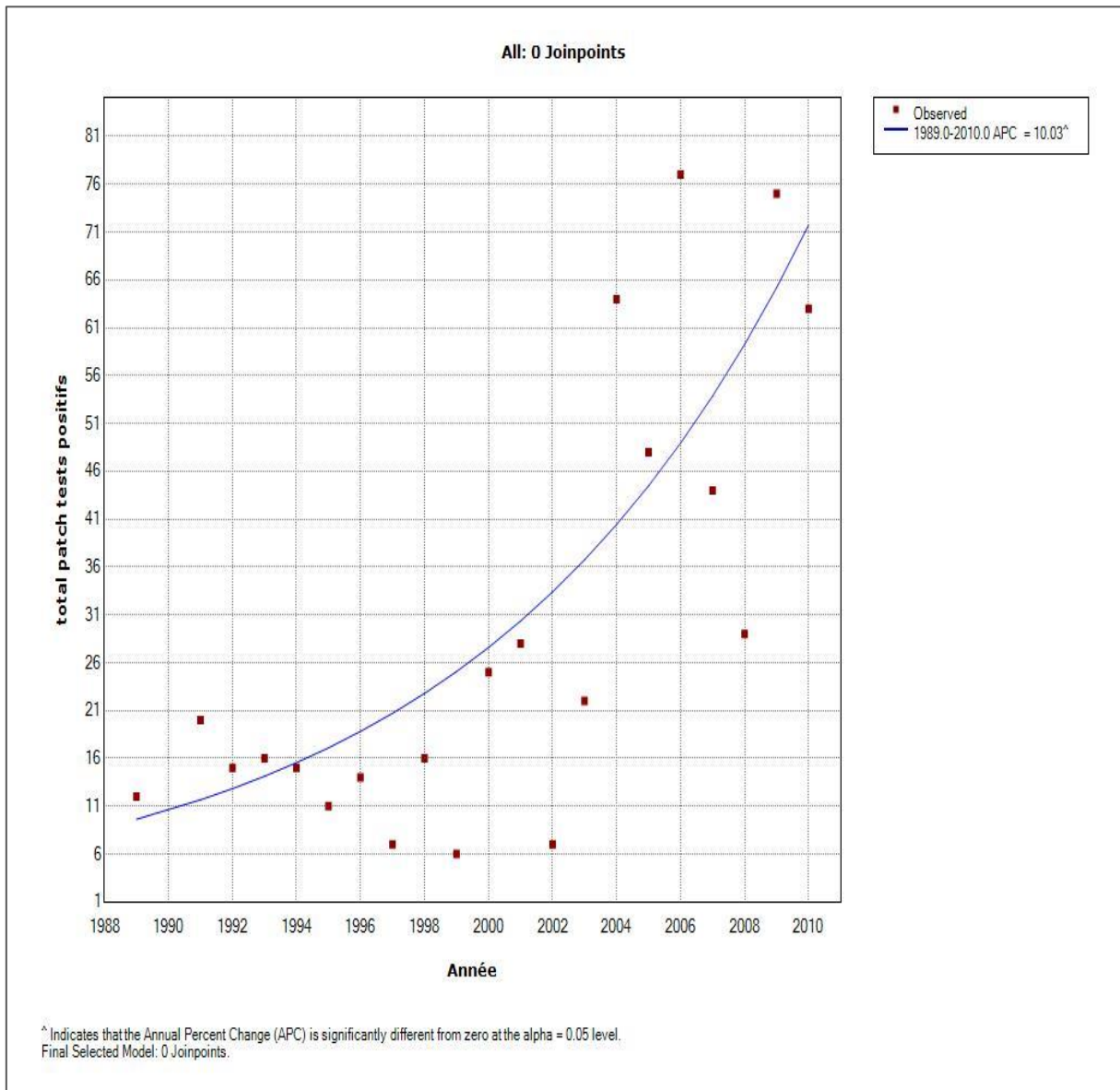
### Fragrance mix sensitization trend

The frequency of sensitization to mix fragrances has evolved in three times: from 1989 to 2001, there was a statistically significant increase in the frequency of sensitization (APC=+15.19%,  $p < 10^{-3}$ ); from 2001 to 2004, a decrease in sensitization was noted but not statistically significant (APC=-46.33%,  $p = 0.3$ ); from 2004 to 2015, a significantly positive trend was observed (APC=+24.33%,  $p < 10^{-3}$ ).

Table 3 gives details of the observed trends in the frequencies of sensitization to various BSE allergens between 1989 and 2015.



**Figure 1: Distribution of the number of subjects sensitized to one or more BSE allergens.**



**Figure 2: Trend in the number of positive patch tests for one of BSE allergens between 1989 and 2015.**

**Table 1: Frequency of sensitization to different BSE allergens.**

Allergens	Positive patch-tests	
	N	%
Balsam of Peru	79	8.93
Benzocaine	26	2.92
Budesonide	05	0.56
Chromium (potassium dichromate)	328	37.06
Clioquinol	20	2.26
Cobalt chloride	212	24
Colophonium	58	6.55
Formaldehyde	36	4.06
Fragrance mix	60	6.77
Kathon CG	22	2.48
Sesquiterpene lactone-mix	16	1.80
Lanolinalcohol	19	2.14
Mercaptobenzothiazole	23	2.59
Mercapto mix	25	2.82
Methyldibromoglutaronitrile	29	3.27
Neomycinsulphate	35	3.95
Nickel sulphate	305	34
N-isopropyl-N-phenylparaphenylenedia-mine (IPPD)	34	3.8
Parabenmix	35	3.95
Paraphenylenediamin	35	3.95
Tixocortol-21-pivalate	03	0.34
Primin	22	2.49
Quaternium 15	17	1.92
Epoxy resin	37	4.18
Paratertiarybutylphenol-formaldehyderesin	50	5.65
Thiuram mix.	55	6.21

**Table 2: Trends in sensitization to BSE preservatives between 1989 and 2015.**

Preservatives	Period	APC	P trend
Formaldehyde	1989-2015	-3,85	0.1
Kathon CG	1989-2015	-3,13	0.1
Paraben Mix	1989-2006	4,33	0.1
	2006-2015	-17.25	<10 <sup>-3</sup>
Quaternium 15	1989-2015	-2.98	<10 <sup>-3</sup>
Methyldibromoglutaronitrile	2005-2015	34.4	<10 <sup>-3</sup>

**Table 3: Trends in frequency of sensitization to different BSE allergens.**

Allergen	Période	APC (%)	p trend
Balsam of Peru	1989-2015	-0.20	0.9
Benzocaine	1989-2015	-2.32	0.2
Budesonide	-	-	-
Chromium (potassium dichromate)	1989-2015	-2.57	<10 <sup>-3</sup>
Clioquinol	1989-2015	-4.42	0.1
Cobalt chloride	1989-2015	-0.28	0.9
Colophonium	1989-2015	1.13	0.6
Formaldehyde	1989-2015	-3.23	0.1
Fragrance mix	1989-2001	15.19	<10 <sup>-3</sup>
	2001-2004	-46.33	0.3
	2004-2015	24.33	<10 <sup>-3</sup>

Continued.

Allergen	Période	APC (%)	p trend
<b>Kathon CG</b>	1989-2015	-2.50	0.2
<b>Sesquiterpene lactone-mix</b>	1989-2015	-2.51	0.1
<b>Lanolinalcohol</b>	1989-2012	-4.80	<10 <sup>-3</sup>
	2012-2015	84.57	0.2
<b>Mercaptobenzothiazole</b>	1989-2002	0	1
	2002-2005	-38.57	0.5
	2005-2012	34.46	<10 <sup>-3</sup>
	2012-2015	-42.02	0.1
<b>Mercapto mix</b>	1989-2015	0.03	1
<b>Méthyldibromoglutaronitrile</b>	2005-2015	34.4	<10 <sup>-3</sup>
<b>Neomycinsulphate</b>	1989-2015	-2.32	0.3
<b>Nickel sulphate</b>	1989-2015	2.70	0.1
<b>N-isopropyl-N-phenylparaphenylenediamin (IPPD)</b>	1989-2015	-0.10	1
<b>Paraben mix</b>	1989-2015	-2.02	0.2
<b>Paraphenylenediamin</b>	1989-2015	-0.71	0.7
<b>Tixocortol-21-pivalate</b>	-	-	-
<b>Primin</b>	1989-2015	-2.71	0.1
<b>Quaternium 15</b>	1989-2015	-2.36	0.1
<b>Epoxy resin</b>	1989-2015	-4.91	0.1
<b>Paratertiarybutylphenol-formaldehyderesin</b>	1989-2015	1.38	0.4
<b>Thiuram mix.</b>	1989-2015	-0.46	0.8
<b>APC : Annual percent change</b>			

## DISCUSSION

### *Sensitization frequency*

Our study showed a significantly increasing trend in the number of positive patch test results between 1989 and 2015 while the percentage of sensitization was almost constant. This was likely related to the growth in the total number of patients with suspected allergic contact dermatitis referred to our consultation for patch tests.

### *Metal sensitization*

Metals were the most common allergens with a sensitization frequency of 37%, 34% and 24% for potassium dichromate, nickel sulfate and cobalt chloride, respectively. These results were similar to those reported in European studies where these three metals are among the five most common allergens in Europe.<sup>10,11</sup>

This result could be explained by the ubiquitous nature of these metals, widely found in our occupational and non-occupational environment all over the world. However, the frequency of sensitization to these three metals was much higher in our study compared to European studies which reported a frequency ranging from 3.9% to 8.8% for cobalt chloride, from 2.4% to 5.9% for potassium dichromate and 17.25% for nickel sulfate.<sup>9-14</sup>

This disparity would not be surprising considering the implementation by the European union of different

prevention strategies to limit metals sensitization. As an example, a European directive which aimed at reducing the maximum concentration of nickel sulfate in products in prolonged contact with the skin was established in 1994.<sup>9</sup>

An extension of this limitation was implemented in Europe in 2009, prohibiting the sale of cell phones releasing nickel sulfate.<sup>15</sup> Another example is the European directive 2003/53/EC, limiting the amount of hexavalent potassium dichromate in cement.<sup>16</sup>

The frequency of potassium dichromate sensitization has steadily decreased between 1989 and 2015 with an APC of -2.57%. This result could be explained, in part, by a better awareness by citizens of the allergenic risk of these products and therefore a change in their habits and practices.

### *Preservative sensitization*

Preservatives are widely used in various products such as household products, cosmetics and industrial products. The purpose of preservation is to eliminate microbial growth, but often a higher concentration than necessary is applied. This increases the risk of sensitization preservatives are potential allergens and can cause allergic contact dermatitis. In this context, real epidemics of conservative contact dermatitis have been described during the last decades.<sup>17</sup>

In this study, preservatives were second only to metals in terms of frequency of sensitization. Formaldehyde was the most common preservative responsible for a quarter of the preservative sensitizations and 4% of all sensitizations. This result was far superior to that reported by European studies.

Indeed, the French study conducted by Schoeffler A et al reported a frequency of formaldehyde sensitization between 1981 and 2011 of 1.69%.<sup>9</sup> The international agency for research on cancer (IARC) classified formaldehyde as carcinogenic to humans (upper airways) in 2004. The implication of this classification was a reduction in its use in several countries, particularly in France, which resulted in a significant decrease in the percentage of formaldehyde sensitization.<sup>9</sup>

The overall frequency of sensitization trend of BSE preservatives tends towards a statistically significant increase with an APC of +5.54%. This is somewhat predictable if we consider their increasingly ubiquitous use in our environment.

The present study reveals a statistically significant decrease in the frequency of sensitization to parabens mix (2006) and quaternium and the emergence of dibromodicyanobutane sensitization.<sup>15</sup> The study by Schnuch A et al showed a significant trend towards a decrease in the frequency of Sensitization to paraben mix.<sup>11</sup>

### ***Fragrance sensitization***

Fragrances were among the most common allergens responsible for sensitization. This finding is consistent with those in the literature.<sup>18-20</sup>

The frequency of fragrance sensitization trend increased significantly with an APC of 15.19% between 1989 and 2001 and 24.33% between 2004 and 2015.

This result could be explained by their frequent use. Fragrances are used not only in cosmetics, household and industrial products but also in topical medications.

It would be important to draw attention to one particular aspect of the use of fragrances. In fact, it's often applied to potentially traumatized skin areas such as shaved skin areas (beard, legs, underarms), areas of occlusion (mainly underarms), or areas of high absorption (eyelids) and even chronic skin lesions in the case of topical medication. This use would promote the penetration of haptens and therefore the development of allergy.

To reduce this risk, it was important to reduce the use of these allergens and also to limit their concentration in cosmetic and industrial products.

## **CONCLUSION**

The aim of this study was to identify the most common BSE allergens with a higher frequency of sensitization in our environment and assess their trends over time.

Although the frequency of chromium sensitization tends to decrease, it remains high. The frequency of sensitization to perfumes and preservatives, which was initially high, has continued to increase over time.

These findings imply the need to develop regulatory directives limiting the use and/or concentration of these allergenic substances. Such measures applied in various countries, particularly in Europe, have already proven their effectiveness.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the institutional ethics committee*

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**Cite this article as:** Brahém A, Gaddour A, Bouhleb M, Chouchene A, Aloui A, Kacem I, Maoua M, Kalboussi H, ElMaalel O, Chatti S, Mrizek N. Trend in the variation of sensitization of the European standard battery allergens over 26 years. *Int J Res Dermatol* 2021;7:364-70.