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Contact Dermatitis / Early View

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Contact allergy to haptens in the Swedish baseline series: Results from the Swedish Patch Test Register (2010 to 2017)

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Abstract

Background

Allergic contact dermatitis has considerable public health impact and causative haptens vary over time.

Objectives

To report the prevalence of contact allergy to allergens in the Swedish baseline series 2010 to 2017, as registered in the Swedish Patch Test Register.

Methods

Results and demographic information for patients tested with the Swedish baseline series in 2010 to 2017 were analysed.

Results

Data for 21 663 individuals (females 69%) were included. Females had significantly more positive patch tests (54% vs 40%). The reaction prevalence rates were highest for nickel sulfate (20.7%), fragrance mix I (7.1%), *Myroxylon pereirae* (6.9%), potassium dichromate (6.9%), cobalt chloride (6.8%), methylchloroisothiazolinone/methylisothiazolinone (MCI/MI; 6.4%), MI (3.7%), colophonium (3.5%), fragrance mix II (3.2%), and formaldehyde

(3.2%). *Myroxylon pereirae* reaction prevalence increased from 5% in 2010 to 9% in 2017 and that for methyldibromo glutaronitrile from 3.1% to 4.6%. MCI/MI and MI reactions decreased in prevalence after 2014. Nickel reaction prevalence decreased among females aged 10 to 19 years.

Conclusions

Nickel remains the most common sensitizing agent, with reaction prevalence decreasing among females younger than 20 years. The changes in MCI/MI and MI reaction prevalence mirrored those in Europe. The register can reveal changes in contact allergy prevalence over time among patients patch tested in Sweden.

1 INTRODUCTION

Contact allergy to the most common sensitizing agents (haptens or allergens) affects approximately 20% of the population in Europe,[1] with metals, fragrances, and preservatives being the most common and largest groups of contact haptens.[2] Allergic contact dermatitis can have a considerable negative impact on patient's quality of life and a heavy socioeconomic burden.[3, 4]

The prevalence of contact allergy can be reduced through regulatory decrease of the exposure to specific haptens, such as nickel, chromate, and cosmetic ingredients (especially preservatives and fragrances), or through changing the behaviours of individuals.[5] In 2007, the European Chemicals Agency adopted the European Union Chemicals Regulation (REACH) to limit exposure to hazardous chemicals, including haptens (www.echa.europa.eu). The REACH regulation is dependent on continuous information on the occurrence of contact allergy and on changes in contact allergy prevalence in the population.

There are population-based studies[1, 5-9] of prevalence rates of allergies to common haptens. However, as performance of population-based studies is cumbersome, most prevalence data are obtained from patch testing at dermatology clinics. These often serve as a proxy for population-based data. Patch testing results give information on the occurrence of contact allergies among patients with contact dermatitis, but the problem of inference from clinical data to a population must be managed carefully. Nonetheless, using clinical patch test data, it has been possible to detect rather rapid changes in contact allergy frequencies for methylisothiazolinone (MI) in Europe[2] and trends in metal allergy in southern Sweden[10] and in nickel and chromate allergy in Denmark.[11, 12]

Thus, it is important to continuously monitor temporal trends of contact allergy, because changes in, for example, fashion and industrial technology expose people to different haptens over time. The most well-known database for monitoring contact allergy is the European Surveillance System on Contact Allergies (ESSCA)[13, 14] established in 1996 (www.essca-dc.org).

Data from ESSCA have been presented in several publications over the years.[2, 15] However, results from Sweden are not included in the ESSCA database.[16] Lindberg et al.[17] and Fall et al.[18] have previously reported patch test data for the Swedish baseline series at three timepoints: 1992, 2000, and 2009. Sensitization to nickel, cobalt, methylchloroisothiazolinone (MCI)/MI, and colophonium was shown to have decreased in 2009 and para-phenylenediamine (PPD) sensitization had increased since 1992. This increase was not found in another Swedish study covering the years 1993 to 2000.[19]

The aims of this study were to (a) to present the Swedish Patch Test Register (EpiReg) and (b) provide an update of contact allergy prevalence rates and trends for haptens in the Swedish baseline series during the period 2010 to 2017, as reported to EpiReg by dermatology clinics in Sweden.

2 METHODS

2.1 EpiReg

In 2009, the Swedish Contact Dermatitis Research Group (SCDRG) decided to establish a nation-wide register, EpiReg, for patch test results. EpiReg was designed to be a simple tool, making it possible to follow and detect changes in patch test outcomes at Swedish dermatology clinics. The data comprise results of testing with the Swedish baseline series and reporting is done by sending anonymous copies of patch test protocols, with information on test date, clinic, and patient sex and age to the administrator of EpiReg. All Swedish dermatology clinics (both the public sector and private practitioners) have been invited to participate. During the study period, several clinics—two of which were in the private sector—reported test results. However, not all clinics reported data each year. The database was administrated at the Dermatology Clinic of the University Hospital in Örebro using Microsoft Access and Excel.

2.2 Participants

All individuals who underwent patch testing with the Swedish baseline series (Table 1) from 2010 to 2017 at the clinics participating in EpiReg were eligible for inclusion. The indication for testing was suspected allergic contact dermatitis.

TABLE 1. The number of participating clinics and tested individuals for each year during the study

Year	2010	2011	2012	2013	2014	2015	2016	2017	Total
Number of clinics	7	13	15	14	19	16	17	14	22
Females	1213	1691	2098	1918	2218	1998	2053	1774	14 963
Males	534	852	946	836	953	866	917	796	6700

Year	2010	2011	2012	2013	2014	2015	2016	2017	Total
Total	1747	2543	3044	2754	3171	2864	2970	2570	21 663

2.3 Study design

Consecutive patch test results with the Swedish baseline series, including patient age and sex, test date and clinic, covering the period 2010 to 2017, were collected from EpiReg. Crude and sex-stratified prevalence rates were calculated and the age groups <40 years and ≥ 40 years were compared for each hapten and mixes of haptens.

2.4 Swedish baseline series

During the period 2010 to 2017, the Swedish baseline series contained 29 to 30 test preparations (Table 2). MI[20] was added in 2014, textile dye mix (TDM)[21] in 2015, and a phenol formaldehyde resin[22] in 2011. In 2014, the test concentration for formaldehyde was increased from 1.0% to 2.0% in aqua.[23] Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) 5.0% in petrolatum (pet.) was removed as an individual hapten[24] on December 31, 2013, as it is a component of fragrance mix (FM) II, tested at 2.5% in pet. Toluene sulfonamide formaldehyde resin 10.0% pet. was removed on December 31, 2014. Patch testing was performed in accordance with the European Society of Contact Dermatitis guidelines[25] (www.escd.org).

TABLE 2. Prevalence rates by sex and year. Variations within the period is analysed with linear-by-linear test. *P*-values for the analysis are given

Test substance	Sex	2010, %	2011	2012	2013	
Potassium dichromate	1	8.0	121	181	128	1917
0.5% in pet.	2	8.1	52	82	56	836
	T	8.0	173	263	184	2753

Test substance	Sex	2010, %	2011	2012	2013

Note: 1, females; 2, males; T, total number; n.a., not applicable; n.t., not tested. Significant variations are marked with bold. The table includes all tests substances used in the Swedish baseline series from 2010 to 2017. The number of tested individuals for each test substance is adjusted by excluding those not tested with the test substance.

Abbreviation: pet, petrolatum.

2.5 Outcome measures

Readings were graded based on the criteria established by the ICDRG.[26] A positive patch test result was defined as a 1+, 2++, or 3+++ reaction at day (D) 3/D4 and/or D7. An irritant response, doubtful response, or no response was considered to be a negative patch test result.

2.6 Statistics

Microsoft Excel, Statistica version 13 (data analysis software system, TIBCO Software Inc.), and IBM SPSS (version 21) were used for data management and statistical analyses. Chi-square tests, Mann-Whitney *U* test, and Spearman rank order correlation tests were used to analyse categorical data. Linear-by-linear analysis was used to determine variations for each hapten over the period 2010 to 2017 and the Z-test with Bonferroni correction was used to analyse changes between timepoints (years) for each hapten. Changes in the distribution of age and sex over time were analysed with logistic regression analysis. The level of statistical significance was set at $\alpha = .05$.

2.7 Ethics

This study was conducted in accordance with the Declaration of Helsinki. The Swedish Patch Test Register, EpiReg, does not contain personal information other than age and sex. The Regional Ethical Review Board in Uppsala, Sweden, approved the use of the register.

3 RESULTS

Between 2010 and 2017, a total of 21 663 individuals (females, n = 14 963 [69%]; males, n = 6700 [31%]) were patch tested with the Swedish baseline series, with data reported to

EpiReg. The median age was 44 years (interquartile range 28-58 years) for females and 44 years (interquartile range 30-58) for males. The annual age and sex distribution were similar throughout the study period, with no indication of a trend in any direction (Table 1). In 87.4% (n = 18 940) of the patch tests, the results were based on two readings (D3/4 + D7).

Crude and sex-stratified prevalence rates were analysed (Table 2). The 10 most common haptens or mixes of haptens with the highest crude prevalence rates for the period 2010 to 2017 were nickel sulfate (20.7%), FM I (7.1%), *Myroxylon pereirae* (balsam of Peru) (6.9%), potassium dichromate (6.9%), cobalt chloride (6.8%), MCI/MI (6.4%), MI (3.7%) (tested 2014-2017), colophonium (3.5%), FM II (3.2%), and formaldehyde (3.2%).

Statistically significant increases in prevalence rates (positive trends) were observed for *Myroxylon pereirae*, which increased from 4.9% in 2010 to 8.8% in 2017, and methyldibromo glutaronitrile (MDBGN), which increased from 3.1% to 4.6% (Figure 1). Contact allergy to MCI/MI increased significantly during the first study years and peaked in 2014, with a prevalence of 9.5%, after which a significant (50%) reduction was detected up until 2017, when the prevalence was 4.8%. MI was tested from 2014 with a prevalence of 8.4%, decreasing to 3.5% in 2017. The number of positive reactions to formaldehyde increased significantly after the test concentration was increased from 1.0% to 2.0%, from a mean of 2.2% (2010-2013) to a mean of 4.1% (2014-2017).

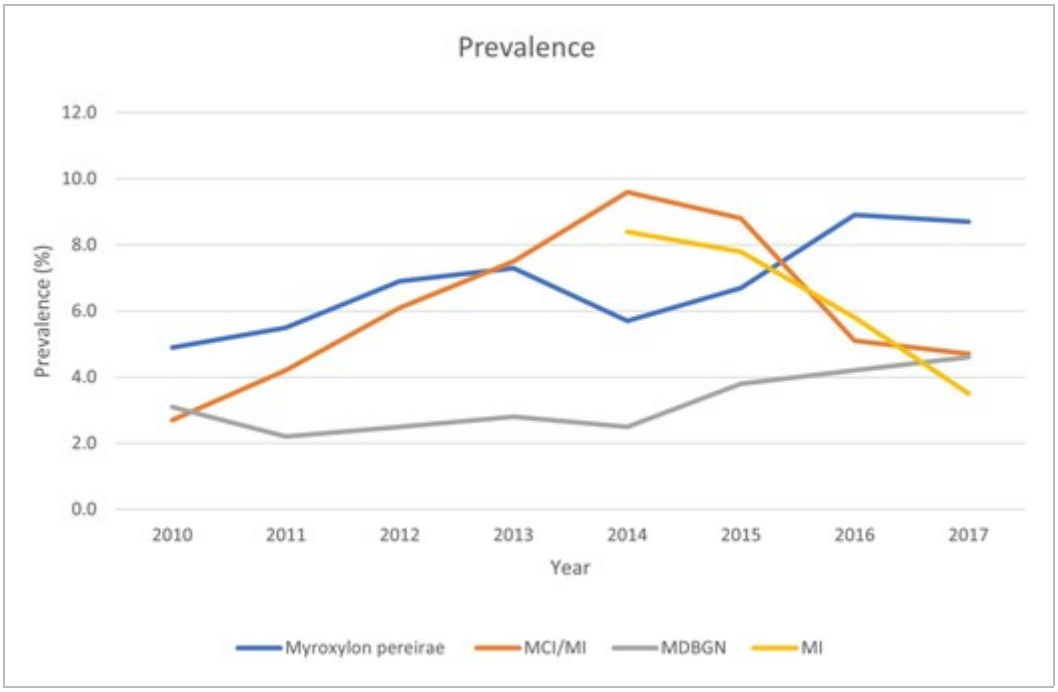

FIGURE 1

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Annual prevalence rates for the four haptens, where changes over time were found to be significant using Z-test and Bonferroni correction. MCI/MI, methylchloroisothiazolinone/methylisothiazolinone. MDBGN, methyldibromo glutaronitrile

Among those tested, a total of 10 926 individuals showed a negative patch test, with a significant difference between females (n = 6888 [46% of tested females]) and males (n = 4038 [60% of tested males]), $P < .001$. Among those with at least one positive patch test reaction (females, n = 8106 and males, n = 2671), there were significantly more positive reactions per tested individual among females than among males (1.90 vs 1.84; $P < .001$), a difference still significant after exclusion of reactions to nickel sulfate (1.83 vs 1.79; $P < .001$).

Analyses of differences between individuals younger or older than 40 years showed significant differences for 18 haptens among females, and for 14 among males (Table 3). For 12 haptens, there were differences in prevalence between sexes, with epoxy resin, *Myroxylon pereirae*, and lichen acid mix reactions being more common among males (Table 4).

TABLE 3. Comparison of prevalence rates for individuals younger than 40 years and 40 years or older, stratified by sex

Hapten	Prevalence (%)			
	Females		Males	
	<40 years	≥40 years	<40 years	≥40 years
Potassium dichromate, 0.5% in pet.	5.98	**7.76**	4.62	**7.86**
Para-phenylene diamine, 1% in pet.	3.34	**4.12**	1.97	1.69
Thiuram mix, 1% in pet.	1.13	**1.70**	1.15	1.15
Neomycin sulfate, 20% in pet.	0.82	**1.32**	0.57	**1.13**
Cobalt(II) chloride hexahydrate, 0.5% in pet.	7.89	7.39	5.45	**4.30**
Quaternium-15, 1% in pet.	1.51	**1.12**	0.97	1.20
Nickel(II) sulfate hexahydrate, 5% in pet.	24.06	**27.37**	9.10	9.01
Quinoline mix, 6% in pet.	0.29	**0.55**	0.21	**0.87**
Colophonium, 20% in pet.	2.42	**4.78**	2.01	**3.28**
Sesquiterpene lactone mix, 0.1% in pet.	0.36	**1.07**	0.43	**0.92**
Epoxy resin (Bisphenol A), 1% in pet.	0.54	**1.10**	1.65	1.84
Myroxylon pereirae, 25% in pet.	4.45	**8.25**	5.63	**8.80**
Fragrance mix II, 14% in pet.	2.49	**3.93**	1.93	**3.76**

Note: Bold figures are significant ($P < .05$) comparisons between females <40 and females ≥40 years or males <40 and

males ≥40 years.

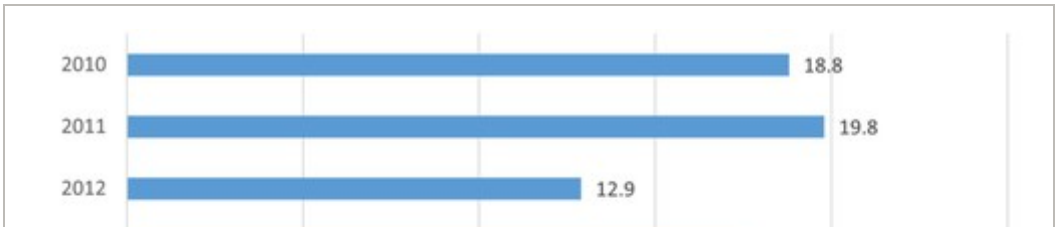
Abbreviations: HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral); MCI, methylchloroisothiazolinone; MDBGN, methyldibromo glutaronitrile; MI, methylisothiazolinone; pet., petrolatum; TDM, textile dye mix.

TABLE 4. Comparison of prevalence rates (%) between females and males. Analysis based on all patch tests results from 2010 to 2017. Only haptens or mixes with a significant difference are presented. Analysis with Mann-Whitney *U* test

Tested product	Females	Males	*P* value
Para-phenylenediamine, 1% in pet.	3.78	1.84	<.001
Cobalt(II)chloride hexahydrate, 0.5% in pet.	7.65	6.77	<.001
Nickel(II)sulfate hexahydrate, 5% in pet.	25.95	9.07	<.001
Colophonium, 20% in pet.	3.77	2.75	<.001
Epoxy resin (Bisphenol A), 1.0% in pet.	0.85	1.76	<.001
Myroxylon pereirae, 25% in pet.	6.62	7.48	.020
Fragrance mix I, 8% in pet.	7.57	6.04	<.001
MCI/MI, 0.02% in pet.	7.29	4.27	<.001
Lichen acid mix, 0.3% in pet.	1.02	1.40	.015
Tixocortol-21-pivalate, 0.1% in pet.	1.92	1.37	.003
MI, 0.2% in pet.	4.36	2.06	<.001
Formaldehyde, 1% or 2% in water.	3.41	2.67	.006

Abbreviations: MCI, methylchloroisothiazolinone; MI, methylisothiazolinone; pet., petrolatum.

With regard to positive nickel sulfate reactions among all females, no trend was observed during the study period. However, for females within the age group 10 to 19 years, the analysis showed a significant decreasing trend (Figure 2).



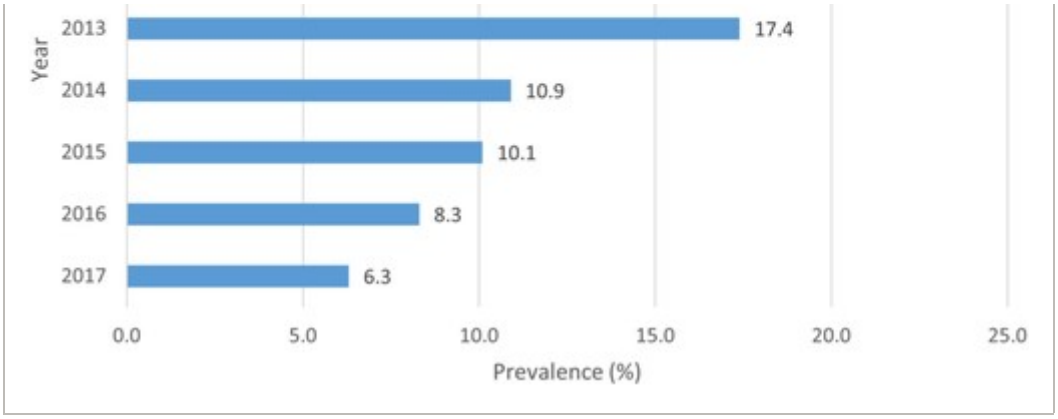


FIGURE 2

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Annual prevalence of positive nickel sulfate reactions for females aged 10 to 19 years. Analysis with Z-test and Bonferroni correction

Concomitant reactions to two or more haptens are of interest when evaluating test results. Results for FM II and HICC showed that 70% of HICC-positive individuals also reacted to FM II. A similar analysis of PPD and TDM showed that 47% of the PPD-positive patients and 43% of the TDM-positive patients had concomitant positive reactions. The correlation between *Myroxylon pereirae* and FM I was low (Spearman ρ = 0.265).

To highlight that EpiReg data can be used to discuss quality aspects of patch testing and readings, the relative occurrences of positive reactions (test readings) for each test preparation were retrieved (Figure 3). The proportions of doubtful and irritant reactions at the first reading (D3) that were negative at the second reading (D7) are presented in Figure 4. Figure 5 shows how many of the 1+ reactions at D3/D4 had disappeared at D7 readings. Figure 6 demonstrates the differences between the participating clinics regarding the ratio of 1+ to 3+ reactions.

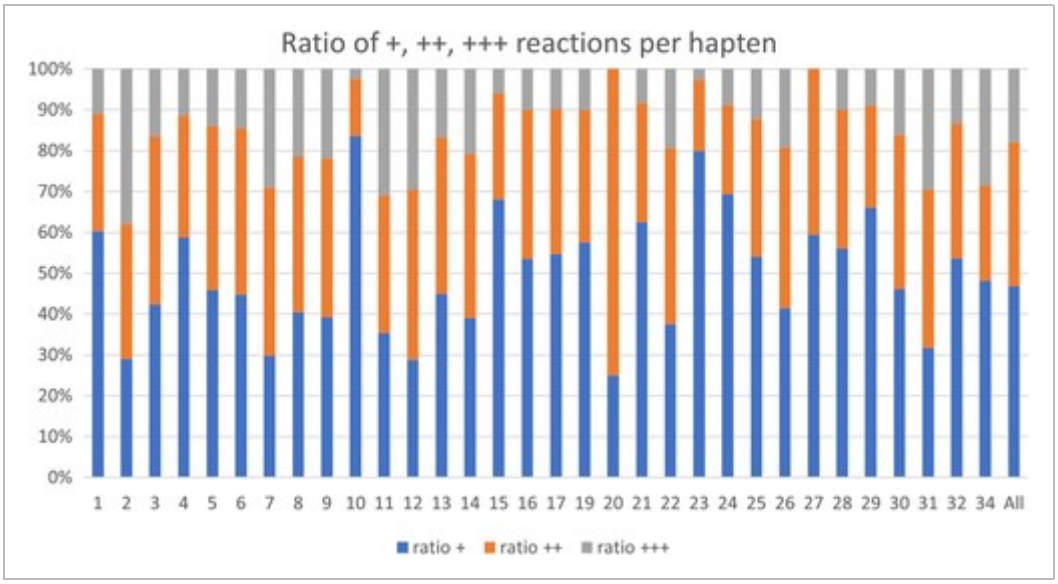

FIGURE 3

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Ratios of +, ++, and +++ reactions at the first reading (D3), stratified by hapten. 1, potassium dichromate; 2, *p*-phenylenediamine; 3, thiuram mix; 4, neomycin sulfate; 5, cobalt (II) chloride hexahydrate; 6, quaternium-15; 7, nickel (II) sulfate hexahydrate; 8, quinoline mix; 9, colophonium; 10, paraben mix; 11, black rubber mix; 12, sesquiterpene lactone mix; 13, mercapto mix; 14, epoxy resin (bisphenol A); 15, *Myroxylon pereirae*; 16, 4-tert-butylphenolformaldehyde resin (PTBP); 17, fragrance mix II; 19, fragrance mix I; 20, phenol formaldehyde resin (PFR2); 21, diazolidinyl urea; 22, methylchloroisothiazolinone/methylisothiazolinone (MCI/MI); 23, Amerchol L-101; 24, caine mix II; 25, lichen acid mix; 26, tixocortol-21-pivalate; 27, toluene sulfonamide formaldehyde resin; 28, budesonide; 29, methyldibromo glutaronitrile (MDBGN); 30, hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC); 31, methylisothiazolinone; 32, formaldehyde; 34, textile dye mix (TDM)

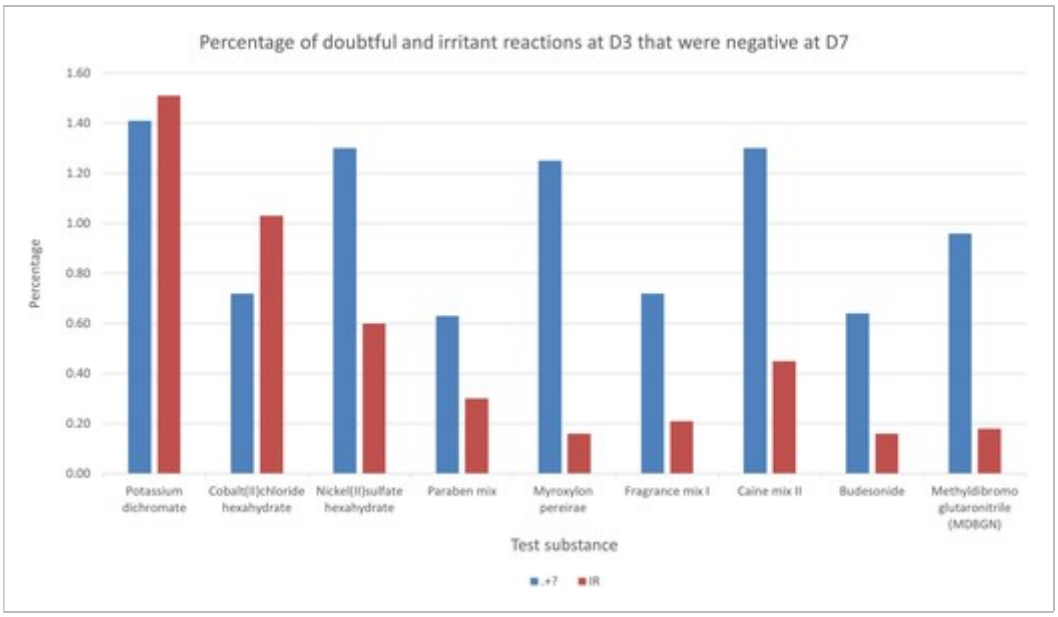

FIGURE 4

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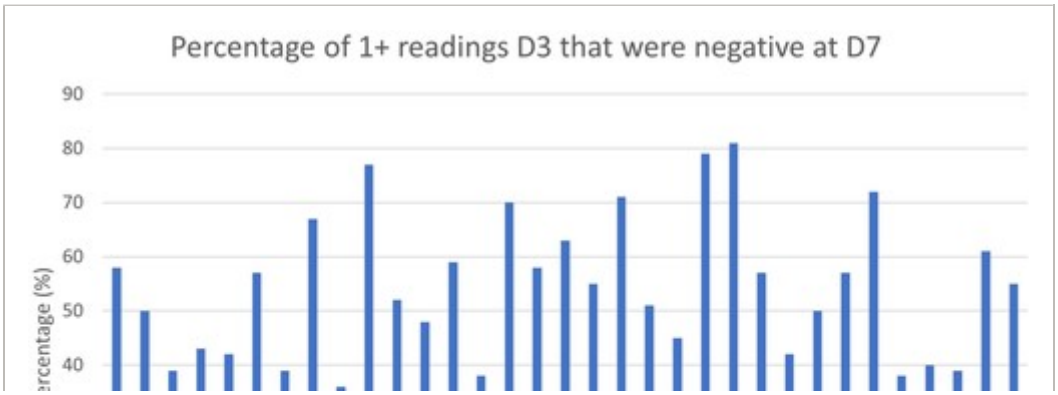
The proportion of doubtful and irritant reactions at day (D) 3 that became negative at the second reading at D7. All substances with prevalence rates for irritant and/or doubtful reactions higher than 0.5% are presented. +?, doubtful reactions; IR, irritant reaction



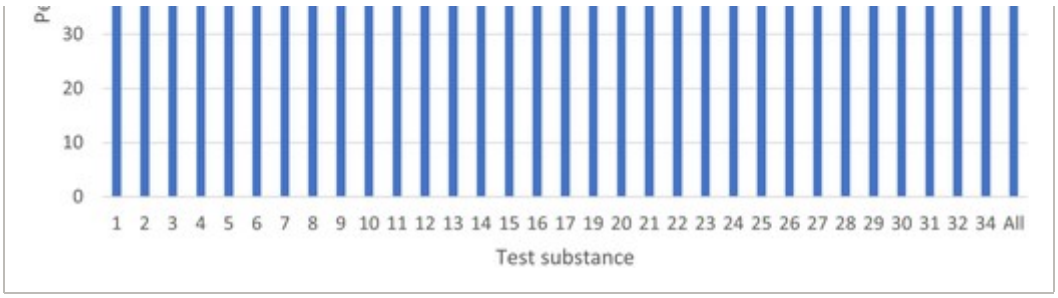


FIGURE 5

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Proportion of 1+ patch test reactions at the first reading (day [D] 3) that became negative at the second reading (D7). 1, potassium dichromate; 2, *p*-phenylenediamine; 3, thiuram mix; 4, neomycin sulfate; 5, cobalt(II)chloride hexahydrate; 6, quaternium-15; 7, nickel(II)sulfate hexahydrate; 8, quinoline mix; 9, colophonium; 10, paraben mix; 11, black rubber mix; 12, sesquiterpene lactone mix; 13, mercapto mix; 14, epoxy resin (bisphenol A); 15, *Myroxylon pereirae*; 16, 4-tert-butylphenolformaldehyde resin (PTBP); 17, fragrance mix II; 19, fragrance mix I; 20, phenol formaldehyde resin (PFR2); 21, diazolidinyl urea; 22, methylchloroisothiazolinone/methylisothiazolinone (MCI/MI); 23, Amerchol L-101; 24, caine mix II; 25, lichen acid mix; 26, tixocortol-21-pivalate; 27, toluene sulfonamide formaldehyde resin; 28, budesonide; 29, methyldibromo glutaronitrile (MDBGN); 30, hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC); 31, methylisothiazolinone; 32, formaldehyde; 34, textile dye mix (TDM)

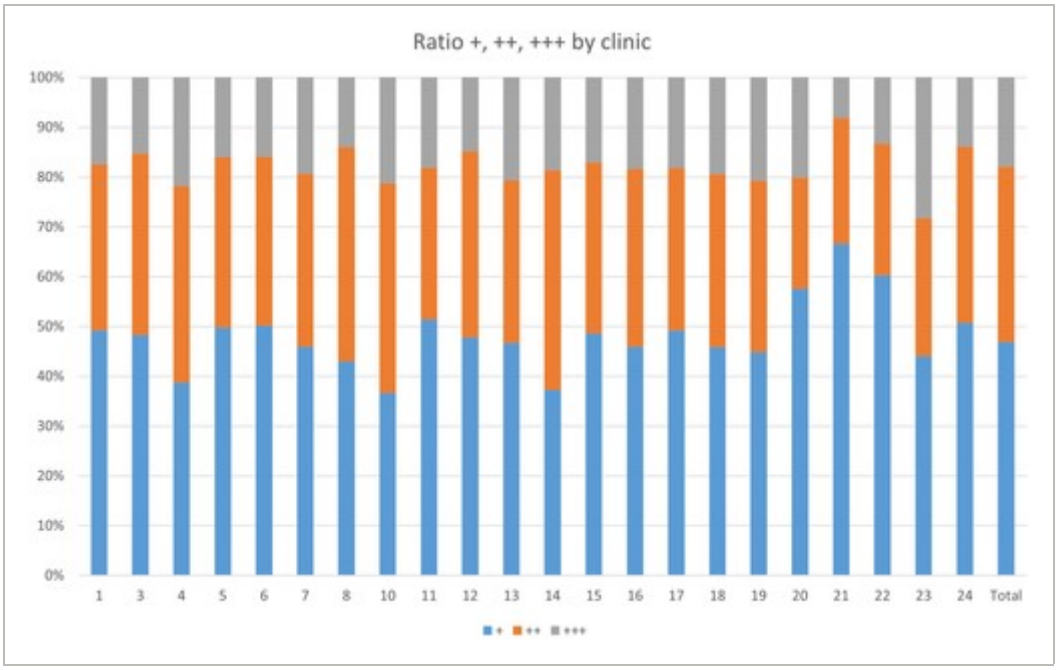

FIGURE 6

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Ratios of +, ++, and +++ reactions at the first reading (day [D] 3) stratified by the 24 participating clinics

4 DISCUSSION

This retrospective study of more than 20 000 participants who underwent patch testing with

the Swedish baseline series between 2010 and 2017 showed that the haptens most commonly causing positive reactions were nickel sulfate, FM I, and *Myroxylon pereirae*. Nickel remained the most common sensitizing agent in both sexes, echoing the results of Lindberg et al.[17] and Fall et al.,[18] who reported data based on the Swedish baseline series between 1992 and 2009.

To explore the possibility that the European Union (EU) regulation on nickel exposure might have had an impact on younger patients, those with positive nickel tests were divided into age groups. Among females, there was a significant decrease in nickel allergy in the age group 10 to 19 years between 2010 and 2017. However, the number of individuals was small and the finding merits further study.

Contact allergy to *Myroxylon pereirae* increased significantly during the study period, from approximately 5% in 2010 to 9% in 2017, which is a further and marked increase compared with previous data based on the Swedish baseline series.[18] In fact, the prevalence of contact allergy to *Myroxylon pereirae* now exceeds the prevalence rates recently reported from Central Europe.[2, 27] The reason for this is not known, but perhaps it reflects a change in the products available on the Swedish market.

As expected, positive readings increased when the test concentration for formaldehyde was increased from 1.0% to 2.0% in 2014, in line with recommendations from the European baseline series.[28] This study shows that the prevalence of contact allergy to formaldehyde doubled when the test concentration doubled.

HICC was previously patch tested both as an ingredient of FM II and as a separate test preparation. HICC was removed from the Swedish baseline series as a separate preparation in 2014 but remains as an ingredient of FM II. This was done based on the results of patch testing in more than 2000 patients at five clinics,[24] showing that the additional yield of contact allergy to HICC in patients without a concomitant positive reaction to FM II was below 0.5%. Generally, a contact allergy rate exceeding 0.5% is considered necessary to justify the presence of a sensitizer in a baseline patch test series.[29] In this study, with more than 10 000 patients tested simultaneously with FM II and HICC, the contact allergy rate was again below 0.5% for a positive reaction to HICC without a simultaneous reaction to FM II, which supports the removal of HICC as a separate preparation.

Two of the sensitizers with the highest proportion of strong (+++) reactions among the positive reactions were PPD and TDM (Figure 3). As expected, many patients reacted simultaneously to both: 47% of the patients allergic to PPD and 43% of the patients allergic to TDM. In those with a strong reaction to TDM, 85% have a concomitant strong reaction to PPD. These strong reactions are most likely due to cross-reactivity between PPD and disperse Orange 3 in TDM.[30] Ongoing studies by the SCDRG and ICDRG are investigating what it would mean to remove disperse Orange 3 from TDM.

The crude prevalence of reactions to chromium did not change between 2010 and 2017, in

line with the findings of Fall et al.[18], who covered the study period 1992 to 2009. However, in the study by Fall et al., there was a significant increase in reactions among younger females and a decrease among older males, with the latter result thought to be attributable to the restriction of chromium levels in cement. In the present study, there was no difference between sexes or age groups. Nowadays, exposure to leather is thought to be the major culprit in chromium allergy.

In 2015, the EU restricted the concentration of hexavalent chromium in leather goods to a maximum of 3 ppm, and a recent study from Denmark showed a decrease in the contact allergy rate from 2010 to 2017,[12] attributed to this legislation.

The rise and fall of contact allergy to MCI/MI, which has been thoroughly reported by others,[31] is also clearly noticeable in Sweden. After a peak in 2014, with a prevalence of 9.5%, positive readings decreased markedly, showing a 50% reduction, which corresponds to the trend seen in the rest of Europe.[31] This is due to simultaneous reductions in the use of MI and in the concentration of MI used in Europe.

MDBGN reactions increased, in contrast to what could be expected following the prohibition of MDBGN use in hygiene products in 2007 (European Commission 2007/17/EF). Uter et al.[2] recently published similar data indicating that the prevalence of MDBGN reactions is, in fact, not decreasing, which indicates a possible unknown or uncontrolled mode of exposure to this preservative. It has recently been stated by Lidén and White that “the use of MDBGN/dibromodicyanobutane (DBDCB)” in the EU is regulated, but that its use is largely undisclosed (in labelling of chemical products and medical devices) owing to insufficiently protective legislation.[32] DBDCB (dibromodicyanobutane) is the name for MDBGN used in noncosmetic products.

The female-to-male ratio among tested individuals and the proportion of positive reactions per tested individual were higher than in previous reports.[18, 33] It is probable that such changes can have an impact on prevalence rates when reported from dermatology clinics. Whether this represents a shift in the selection of patients for patch testing or a true change in the population has to be studied further. For example, our finding that males had more negative patch test results might indicate a selection bias for patch testing.

To obtain reliable patch testing results, there is a need for constant education and training. The results in Figures 3-6 demonstrate the variability in reported results between test substances and clinics. Some variation can be a result of regional differences in exposure and patient selection (eg, testing with Compositae mix).[34] However, it might also be attributed to a lack of calibration of patch testing techniques or differing clinical readings and interpretations of patch tests, especially in the case of 1+, irritant, and doubtful reactions.[35-37] EpiReg is believed to be a potentially useful tool for education about and calibration of patch testing in Sweden.

4.1 Strengths and limitations

As shown by others, EpiReg is a simple and effective tool that can be used to detect dynamic changes, such as those for MI and MCI/MI during the relevant period. It also revealed an increase of positive reactions when the test concentration of formaldehyde was increased. Although there was a variation in the number of clinics reporting results between years, the age and sex distribution remained stable. Further, results from EpiReg can be used to discuss and develop the quality of patch testing in Sweden. A major limitation is that it is not known if each clinic has reported all their patch test results. Another possible limitation is the fact that not all clinics deliver results every year, which might increase the variance in the results. Besides, the test results were not accompanied by information such as (male, occupational dermatitis, atopic dermatitis, hand dermatitis, leg dermatitis, facial dermatitis, age >40 years) indices.[14, 15] Lastly, assessment of clinical relevance of the outcome of the patch tests should be included in EpiReg.

5 CONCLUSION

This study demonstrates that EpiReg is a simple and reliable register that can be used to monitor the results of patch testing with the Swedish baseline series in Sweden. Nickel remains the most common sensitizing agent and no decreasing trend was observed, except among females aged 10 to 19 years. A significant increase of contact allergy to *Myroxylon pereirae* and MDBGN was detected during the study period and sensitization to MCI/MI and MI followed the same pattern as that reported from the rest of Europe. When the test concentration of formaldehyde was increased, a directly proportional increase in contact allergy could be seen.

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AUTHOR CONTRIBUTIONS

Daniel Andernord: Data curation (lead); investigation (lead); methodology (lead); project administration (lead); supervision (lead); validation (lead); visualization (lead); writing – original draft (lead); writing – review and editing (lead). **Magnus Bruze:** Formal analysis (supporting); investigation (equal); methodology (equal); project administration (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). **Ing-Liss Bryngelsson:** Methodology (equal); project administration (equal); writing – original draft (equal); writing – review and editing (equal). **Johanna Bråred Christensson:** Methodology (equal); project administration (equal); writing – original draft (equal); writing – review and editing (equal). **Bo Glas:** Methodology (equal); project administration (equal); writing – original draft (equal); writing – review and editing (equal). **Lina Hagvall:** Methodology (equal); project administration (equal); writing – original draft (equal); writing – review and editing (equal). **Marléne Isaksson:** Methodology (equal); project administration (equal); writing – original draft (equal); writing – review and editing (equal). **Mihály Matura:** Methodology (equal); project administration (equal); writing – original draft (equal); writing – review and editing (equal). **Gunnar Nyman:** Methodology (equal); project administration (equal); writing – original draft (equal); writing – review and editing (equal). **Berndt Stenberg:** Methodology (equal); project administration (equal); writing – original draft (equal); writing – review and editing (equal). **Cecilia Svedman:** Methodology (equal); project administration (equal); writing – original draft (equal); writing – review and editing (equal). **magnus lindberg:** Conceptualization (lead); data curation (lead); formal analysis (lead); funding acquisition (lead); investigation (lead); methodology (lead); project administration (lead); resources (lead); software (lead); supervision (lead); validation (lead); visualization (lead); writing – original draft (lead); writing – review and editing (lead).

CONFLICTS OF INTEREST

M.B. is a member of an expert panel on fragrance safety (www.fragrancesafetypanel.org). The other authors have no conflicts of interest to declare.

Open Research

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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