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ORIGINAL ARTICLE

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Occupational contact allergy: The European perspective–Analysis of patch test data from ESSCA between 2011 and 2020

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Abstract

Background: Occupational skin diseases have led the occupational disease statistics in Europe for many years. Especially occupational allergic contact dermatitis is associated with a poor prognosis and low healing rates leading to an enormous burden for the affected individual and for society.

Objectives: To present the sensitization frequencies to the most relevant allergens of the European baseline series in patients with occupational contact dermatitis (OCD) and to compare sensitization profiles of different occupations.

Methods: The data of 16 022 patients considered having OCD after patch testing within the European Surveillance System on Contact Allergies (ESSCA) network between January 2011 and December 2020 were evaluated. Patients ($n = 46\,652$) in whom an occupational causation was refuted served as comparison group.

Results: The highest percentages of OCD were found among patients working in agriculture, fishery and related workers, metal industry, chemical industry, followed by building and construction industry, health care, food and service industry. Sensitizations to rubber chemicals (thiurams, carbamates, benzothiazoles) and epoxy resins were associated with at least a doubled risk of OCD. After a decline from 2014 onwards, the risks to acquire an occupation-related sensitization to methyl(chloro)isothiazolinone (MCI/MI) and especially to methylisothiazolinone (MI) seem to increase again. Sensitization rates to formaldehyde were stable, and to methyldibromo glutaronitrile (MDBGN) slightly decreasing over time.

Conclusions: Among allergens in the European Baseline Series, occupational relevance is most frequently attributed to rubber accelerators, epoxy resins and preservatives.

KEYWORDS
baseline series, clinical epidemiology, occupational contact allergy, patch testing, RRID:SCR_001905, surveillance

1 | INTRODUCTION

Up to 35% of all occupational diseases in Europe affect the skin. Worldwide incidence rates vary due to different definitions of occupational skin diseases (OSD), data collection methods and reporting systems and occupational exposures.[1–3] Economic costs of occupational skin diseases in the European Union (EU) amount up to approximately 5 billion €/year for treatment, pension and compensation payments and loss of productivity.[4] Moreover, occupational contact dermatitis OCD might be associated with a significant reduction in quality of life, unemployment and social decline.[5–9] Occupationally relevant sensitizations associated with an at least doubled risk for OCD were shown to be caused by thiurams, epoxy resins and preservatives, such as methylchloroisothiazolinone/methylisothiazolinone (MCI/MI), methyldibromo glutaronitrile (MDBGN) and formaldehyde.[10,11] Poor prognosis and low healing rates were associated with sensitization to occupationally relevant contact allergens and the number of positive patch test reactions.[12]

A prerequisite for targeted prevention in skin risk occupations is the knowledge of sensitizing agents at the workplaces, changes in sensitization rates over time and the discovery of emerging allergens. This can be obtained by continuous surveillance of contact allergy by contact allergy surveillance systems like the European Surveillance System on Contact Allergies (ESSCA)[13–15] or the database of the North American Contact Dermatitis Group (NACDG) and other national registries or databases.[16–19]

The aim of this study was to update the knowledge on the most relevant baseline series allergens and their sensitization frequencies in patients with OCD in Europe and to compare the sensitization profiles of different occupations.

2 | METHODS

The objective of the ESSCA is the clinical surveillance of contact allergy.[13–15] To this end, contributing departments (Table S1) submit

either all patch test results, or just patch test results of the European baseline series (or national or local adaptations thereof), obtained following ESCD standards,[20] to the data centre in Erlangen. This is accompanied by important demographic and clinical information, ranging from 'MOAHLFA index'[21] characteristics to a wider range of information according to the ESSCA 'minimal dataset' definition.[13,22] Data are quality checked, providing an 'internal report' for each contributing department for scrutiny and approval before pooling of the respective data.[14] Data from contributing departments are delivered in an anonymous format or partly, following national network standards and software usage (WinAlldat software),[22] in a pseudonymized format, where the pseudonym cannot be related to actual personal data except in the contributing department itself. Only in those departments using WinAlldat software, pseudonymized data enabled the elimination of duplicate patients (presently, in 1438 patients from Austria, Germany, Poland, Spain, Switzerland and The Netherlands). In such cases, a random selection of one of the multiple consultations of a patient was made. For the present analysis, further constraints were employed:

- Only patients aged between 16 and 68 (inclusive) were included.
- A valid occupational code, in this case, ISCO-88 still used by most departments as well as additions by ESSCA allowing to document activities beyond formal employments, such as homemaker, unemployed, and so on needed to be documented (coding '+': denotes job titles on the 3-digit level of groups in ISCO-88, for which a finer categorization is generally available, but had not been used in individual cases or when job titles were aggregated for analysis; all other job titles reported are on the 4-digit level of groups).
- Patients with occupation-related contact dermatitis tagged with 'occ' in MOAHLFA index after patch testing by the examining dermatologist/clinician were considered as cases of OCD. Patients in whom occupational causation was explicitly negated were tagged with 'non-occ' and these comprised the non-OCD group.
- Patients were tested with the baseline series as used locally.
- The association of OCD with any sensitization to an EBS allergen was investigated.

Data management and analysis were performed with the R software package (https://www.r-project.org; RRID:SCR_001905), version 4.0.3. For the calculation of 95% confidence intervals (CIs) to zero proportions an approximation to an exact CI was used.[23] The in- or decrease of risk to be sensitized to a particular allergen associated with OCD, compared to those patients in whom occupational causation of contact dermatitis was explicitly denied, was estimated with log-binomial regression analysis, adjusting for age (dichotomized in <40 vs. older) and sex, deriving a prevalence ratio (PR) accompanied by a 95% confidence interval (95% CI).

TABLE 1 Contributing countries.

Country	*N* (patients)	*N* (occ.)	% (occ.)
Austria	1711	349	20.4
Switzerland	9234	1383	15
Germany	16 064	6210	38.7
Spain	6090	1022	16.8
Finland	1170	721	61.6
Italy	10 507	873	8.3
Lithuania	2885	624	21.6
The Netherlands	9674	1805	18.7
Poland	5437	1154	21.2
Slovenia	8119	137	1.7
United Kingdom	18 886	1744	9.2
Total	89 777	16 022	17.8

Note: *N*, number; occ, patients with occupational contact dermatitis.

3 | RESULTS

Between January 2011 and December 2020, 89 777 patients fulfilled above-mentioned inclusion criteria. Among these, 16 022 were diagnosed with OCD, while in 46 652 occupational causation was explicitly negated. In 12 754, the occupational causation was unclear, and in the remainder (n = 14 349) information was altogether missing; these latter two groups were excluded from the comparisons. Contributing countries and respective patient numbers included are summarized in Table 1.

3.1 | Patients

The proportion of men was significantly higher in patients with OCD (44.5%) than in the non-OCD group (29.2%; Table 2). The proportion

TABLE 2 Demographic and clinical characteristics according to the MOAHLFA index.[4]

Factor	*N* (occ.)	% (occ.)	*N* (non-occ.)	% (non-occ.)	*p*-Value
Male	7126	44.5	13 609	29.2	<0.0001
Occupational	16 022	100	0	0	
Atopic eczema	5145	32.4	13 370	28.7	<0.0001
Site: hand	11 517	73.1	9383	21.2	<0.0001
Site: leg	242	1.5	2359	5.3	<0.0001
Site: face	1113	7.1	10 082	22.8	<0.0001
Age 40+	8470	52.9	29 224	62.6	<0.0001

Note: *N*, number; non-occ, patients without occupational contact dermatitis; occ: patients with occupational contact dermatitis.

TABLE 3 Characteristics of patients with OCD in occupational subgroups with a high level of occurrence of OCD (defined as >50 OCD cases and a relative frequency of at least 50% OCD) in detail, that is, on the four-digit ISCO level.

Occupation	*N* (occ.)	Mean age (years)	% males	% with ACD	% with ICD	% ACD + ICD
Hairdressers, barbers, beauticians and related workers	1329	33.1	7.1	48.8	24.0	7.0
Nursing and midwifery associate professionals	1137	39.9	10.1	20.4	37.5	4.8
Machinery mechanics and fitters	679	39.2	95.1	24.8	36.9	3.3
Cooks	437	35.6	54.9	28.7	31.1	5.4
Nursing and midwifery Professionals	420	42.4	9.8	56.0	19.2	5.6
Machine-tool setters and setter-operators	382	45.9	92.1	27.9	37.6	4.6
Physiotherapists and related associate professionals	232	37.8	19.0	21.8	34.8	5.2
Painters, Varnishers and related workers	232	41.2	87.1	38.3	23.8	2.8
Bakers, pastry-cooks and confectionery makers	222	34.2	52.3	35.3	26.4	2.5
Gardeners, horticulturists and nursery growers, NEC*	178	40.1	34.3	41.8	23.1	4.0
Metal- and mineral-products machine operators	170	44.0	88.8	29.6	33.8	4.1
Bricklayers and stonemasons	143	41.6	97.9	40.7	22.9	3.0
Chemical and physical science technicians	132	37.6	29.5	33.1	32.3	1.5
Electrical and electronic equipment mechanics and fitters	124	36.5	90.3	25.8	32.3	1.6
Dental assistants	119	33.3	0.8	34.2	29.1	3.4
Plumbers and pipe fitters	108	40.4	99.1	36.4	23.4	1.3
Metal-, rubber- and plastic-products assemblers	103	45.1	68.0	23.3	25.3	5.8
Other machine operators and assemblers	100	45.1	84.0	24.5	32.7	5.1
Wood treaters, cabinetmakers and related trades workers	94	39.8	86.2	29.7	21.2	4.3
Toolmakers and related workers	88	42.6	93.2	19.6	41.4	1.1
Dentists	87	39.6	23.0	50.0	18.3	3.7
Floor layers and tile setters	87	42.6	93.1	35.8	19.4	4.5
Welders and flame cutters	87	45.8	90.8	26.3	23.6	5.3
Metal wheel-grinders, polishers, and tool sharpeners	86	42.4	87.2	26.8	34.1	6.1
Carpenters and Joiners	84	44.1	90.5	40.3	29.9	0.0
Butchers, fishmongers, and related food preparers	84	40.1	51.2	20.8	34.2	2.4
Plant and machine operators and assemblers	82	44.7	92.7	11.4	38.0	6.3
Metal, machinery, and related trades workers	80	39.9	86.2	32.9	26.0	5.5
Precision workers in metal and related materials	73	41.2	38.4	34.3	35.7	2.7
Plastic-products machine operators	72	42.4	75.0	44.8	25.4	1.5
Building finishers and related trades workers	70	43.7	94.3	65.3	13.1	4.3
Precision-instrument makers and repairers	70	39.8	81.4	30.0	31.4	2.9
Modern health associate Professionals (except nursing)	61	44.0	23.0	47.1	30.1	5.7
Building frame and related trades workers	60	43.4	91.7	48.0	32.0	0.0
Food processing and related trades workers, NEC	60	40.3	40.0	43.3	21.6	8.1
Chemical-processing-plant operators	58	42.6	89.7	47.3	10.5	5.3
Mechanical engineering technicians	55	41.1	98.2	29.6	31.4	1.9
Baked-goods, cereal, and chocolate-products machine operators	54	39.0	3.7	18.5	27.7	1.9

Note: *N*, number; occ: patients with occupational contact dermatitis.
Abbreviations: ACD, allergic contact dermatitis; ICD, irritant contact dermatitis; NEC, not elsewhere classified.

of patients over 40 years of age was significantly lower in the OCD group compared to the non-OCD group (52.9% vs. 62.6%). Patients with current or previous atopic dermatitis were slightly overrepresented in OCD patients (32.4% vs. 28.7%). Hand was the predominant eczema location in OCD patients (73.1% vs. 21.2%).

3.2 | Risk of OCD in different occupations

In Table S2, the proportion of patients with OCD among all patients patch tested in the strata of occupational groups is shown. The highest risk for OCD with a share of >65% in occupational groups

TABLE 4 Risk of OCD associated with contact sensitization to allergens of the European baseline series, quantified with the PR with accompanying 95% CI.

Allergen (in petrolatum except where otherwise specified)	OCD-tested	OCD-positive	Non-OCD-tested	Non-OCD-positive	PR (95% CI)
Thiuram mix 1%	15 550	5.4% (5–5.7%)	46 139	1.2% (1.1–1.4%)	4.48 (4.03–4.98)
Epoxy resin (DGEBA) 1%	14 922	3.5% (3.2–3.8%)	44 635	0.9% (0.8–1%)	3.58 (3.14–4.09)
Carba mix 10%	4762	6.7% (6–7.4%)	22 818	2.2% (2–2.4%)	2.8 (2.44–3.22)
Mercaptobenzothiazole 0.5%	15 629	1.2% (1–1.3%)	46 135	0.4% (0.4–0.5%)	2.55 (2.08–3.12)
Mercapto mix 1% and 2%	10 997	1.2% (1–1.4%)	28 600	0.5% (0.4–0.6%)	2.35 (1.84–3)
IPPD 0.1%	13 525	1.2% (1–1.4%)	37 859	0.6% (0.5–0.7%)	1.85 (1.51–2.27)
Budesonide (0.1% and 0.01%)	7611	1% (0.8–1.3%)	26 728	0.6% (0.5–0.7%)	1.76 (1.34–2.32)
Formaldehyde 1% and 2%	15 466	2.7% (2.5–3%)	45 055	1.7% (1.6–1.9%)	1.66 (1.47–1.87)
Textile dye mix 6.6%	1530	5.9% (4.8–7.2%)	5311	3.8% (3.3–4.4%)	1.61 (1.26–2.05)
p-Phenylenediamine 1.0%	8773	5.1% (4.6–5.5%)	35 284	3.4% (3.3–3.6%)	1.6 (1.44–1.79)
MCI/MI 0.02% and 0.01% aq.	15 615	8.6% (8.2–9%)	46 153	5.7% (5.5–6%)	1.57 (1.47–1.68)
Colophonium 20%	15 616	4.2% (3.8–4.5%)	46 132	2.8% (2.7–3%)	1.55 (1.41–1.71)
Pot. Dichromate 0.5%	15 364	5.8% (5.5–6.2%)	45 103	3.8% (3.6–4%)	1.53 (1.42–1.66)
Quaternium 15 1.0%	7548	1.2% (0.9–1.4%)	26 052	0.8% (0.7–0.9%)	1.51 (1.18–1.94)
MI 0.2% and 0.05% aq.	11 021	9% (8.5–9.6%)	36 105	6.4% (6.2–6.7%)	1.49 (1.38–1.6)
ptBFR 1%	10 600	1% (0.8–1.2%)	36 486	0.8% (0.7–0.8%)	1.37 (1.09–1.72)
MDBGN 0.5%, 0.2% and 0.3%	14 202	3.6% (3.3–3.9%)	42 503	2.8% (2.7–3%)	1.36 (1.22–1.5)
Cobalt chloride 1%	15 485	7.8% (7.4–8.2%)	45 967	6.2% (6–6.4%)	1.32 (1.24–1.41)
Paraben mix 16%	14 145	0.8% (0.6–0.9%)	44 490	0.6% (0.5–0.6%)	1.31 (1.04–1.65)
SL mix 0.1%	7862	0.9% (0.7–1.1%)	27 627	0.8% (0.7–0.9%)	1.23 (0.93–1.62)
Neomycin sulfate 20%	8143	1.1% (0.9–1.4%)	31 199	1% (0.9–1.1%)	1.22 (0.97–1.54)
HICC 2.5%	14 189	1.8% (1.6–2%)	42 831	1.6% (1.5–1.8%)	1.19 (1.03–1.38)
Nickel sulfate 5%	15 241	19.4% (18.8–20%)	45 898	21.3% (20.9–21.7%)	1.09 (1.05–1.13)
Fragrance mix II 14%	15 013	4% (3.7–4.3%)	43 944	4.1% (3.9–4.3%)	1.06 (0.97–1.16)
Fragrance mix I 8%	15 122	7% (6.5–7.4%)	45 531	7.3% (7–7.5%)	1.05 (0.98–1.13)
Myroxylon pereirae 25%	15 155	5.5% (5.1–5.9%)	45 349	5.8% (5.6–6%)	1.01 (0.93–1.09)
Lanolin (wool alcohols) 30%	15 466	1.9% (1.7–2.2%)	44 956	2% (1.9–2.1%)	0.98 (0.86–1.12)
Tixocortol pivalate (0.1% and 1%)	8651	0.7% (0.5–0.9%)	33 078	0.8% (0.7–0.9%)	0.9 (0.68–1.19)
Primin 0.01%	5096	0.2% (0.1–0.4%)	17 728	0.3% (0.3–0.4%)	0.6 (0.31–1.17)
Benzocaine 5%	3842	0.5% (0.3–0.8%)	11 274	0.9% (0.7–1.1%)	0.59 (0.36–0.97)

Abbreviations: Aq, aqua; DGEBA, diglycidyl ether of bisphenol A; HICC, Hydroxylisohexyl 3-cyclohexene carboxaldehyde; IPPD, N-isopropyl-N′-phenyl-*p*-phenylenediamine; MDBGN, methyldibromo glutaronitrile; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone; Non-OCD, OCD negated; ptBFR: *p-tert*-butylphenol-formaldehyde resin; pot.: potassium; OCD, occupational contact dermatitis; PR, prevalence ratio; SL: sesquiterpenlactone mix: alantolactone, dehydrocostus lactone and costunolide; thiuram mix: tetramethylthiuram monosulfide, tetraethylthiuramdisulfide, tetramethylthiuramdisulfide, dipentamethylene thiuramdisulfide; carba mix: 1.3-diphenylguanidine, zinc dibutyldithiocarbamate, zinc diethyldithiocarbamate; mercapto mix (1% pet.): *N*-cyclohexylbenzothiazylsulfenamide, dibenzothiazyldisulfide, morpholinylmercaptobenzothiazole; 95% CI, 95% confidence interval.

comprising more than 50 patients was seen in metal workers, agricultural, fishery and related labourers, as well as in the rubber and chemical industry.

3.3 | Characteristics of patients working in occupations with a high occurrence of OCD

For patients working in occupations with a high occurrence of OCD, the distribution of ACD, ICD, and both diagnoses combined are shown in Table 3. Overall, the share of patients with ACD was 33.5%, of ICD 14.4% (both combined in 1.9%), and of current atopic eczema 11.8%, in 1.5% combined with ICD. ACD prevailed in building finishers and related trade workers (65.3%), nursing and midwifery professionals (56.0%), dentists (50%) and hairdressers, barbers, beauticians and related workers (48.8%). ICD was most common in toolmakers and related workers (41.4%), plant and machine operators and assemblers (38.0%), machine-tool setters and setters-operators (37.6%) followed by nursing and midwifery associate professionals (37.5%). A combined aetiology (ACD and ICD) was seen most frequently in food processing

and related trades workers (8.1%), hairdressers, barbers, beauticians, and related workers (7.0%), plant and machine operators and assemblers (6.3%) as well as metal wheel-grinders, polishers and tool sharpeners (6.1%).

3.4 | EBS allergens and association to OCD

The association of OCD with sensitizations to allergens of the European baseline series quantified with the prevalence ratio (PR) with accompanying 95% confidence interval is shown in Table 4. Occupationally relevant allergens with a doubled risk for occupational sensitization were rubber chemicals like thiuram mix (PR 4.48, 95% CI 4.03–4.98), carba mix (PR 2.8, 95% CI 2.44–3.22), mercaptobenzothiazole and mercapto mix (PR 2.55, 95% CI 2.08–3.12/2.35, 95% CI 1.8–3.0) and epoxy resin (diglycidyl ether of bisphenol A) (PR 3.58, 95% CI 3.14–4.09). The frequency of carba mix positivity (6.7%) was higher than that of thiuram mix sensitization (5.4%). (Table 4).

A comparison with the previous data analysis from Pesonen et al.[11] is shown in Table S3A–C. The most relevant data are reported here. Concerning thiuram-mix and mercaptobenzothiazoles, no relevant changes in overall sensitization rates and prevalence ratios (PR for positivity in OCD vs. non-OCD cases) compared to the analysis period from 2002 to 2010 were seen (Table S3A). For carba mix, no data from the former analysis period are available. *N*-isopropyl-*N*′-phenyl-p-phenylenediamine (IPPD) sensitization showed a downward trend in occupational relevance, as PR fell from 2.62 to 1.85.

No significant changes in epoxy resin sensitization rates were seen. However, there was a slight increase from 3.1% to 3.5%.

Sensitization rates to MCI/MI and MI showed a considerable increase as compared to the analysis period from 2002 to 2010, as MCI/MI increased from 4.0% to 8.6% in OCD patients and from 2.5% to 5.7% in non-OCD patients, and MI increased from 1.9% to 9.0% in OCD patients and from 0.5% to 6.4% in non-OCD patients. The likelihood of epidemiological relevance remained nearly the same for MCI/MI and clearly decreased for MI (PR 2.36 vs. PR 1.49). Sensitization rates in OCD and non-OCD patients peaked in 2014 and fell until 2018. Since then a slight upward trend with a peak in 2019 which is more pronounced in non-OCD patients, driven by MI sensitizations was seen. (Figure 1A, B). (Table S3C [biocides]).

Occupations with the highest risk of contact allergy to selected allergens are shown in Table S4A–F.

High rates of thiuram mix sensitization were seen in the construction and food industries. The highest sensitization rates were seen in builders (17.9%, 95% CI 8.9–30.4), followed by concrete placers, concrete finishers and related workers (17.1%, 95% CI 6.6–33.6) as well as in butchers, fishmongers and food preparers (14.1%, 95% CI 7.3–23.8) (Table S4A).

High rates of carba mix positivity were recorded in medical professions, construction and food industry. The highest positivity rates were seen in health professionals (except nursing) (26.0%, 95% CI 16.5–37.6), building finishers and related trades workers (19.4%, 95% CI 10.4–31.4), and cooks (13.1%, 95% CI 8.4–19.2) (Table S4B).

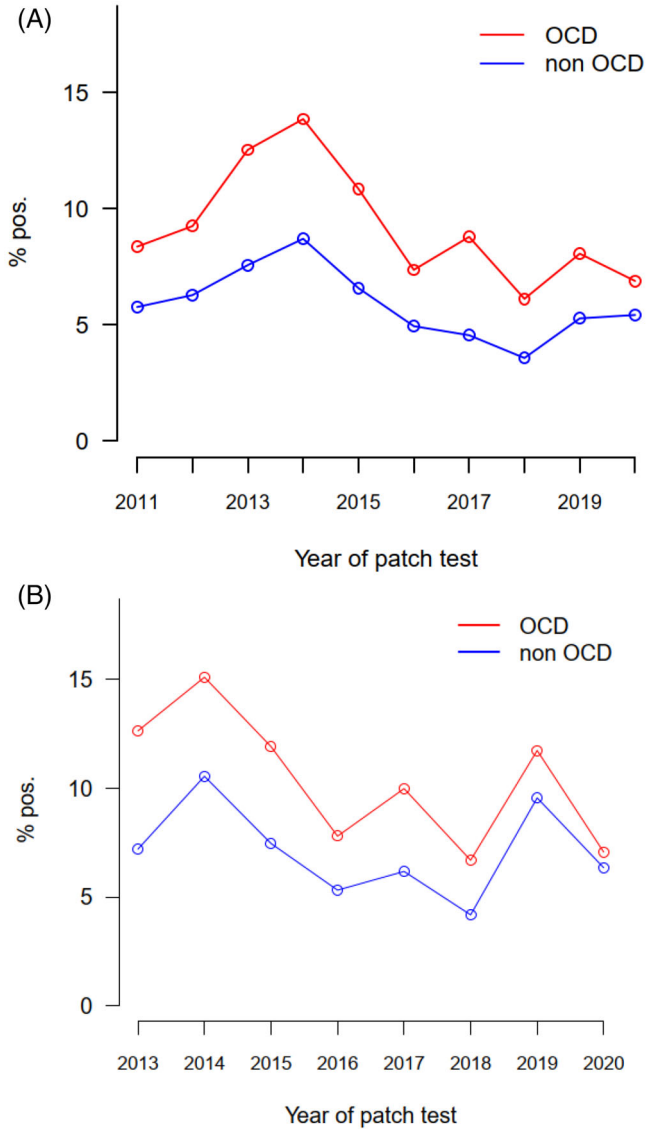

FIGURE 1 (A) Time trend of methylchloroisothiazolinone/methylisothiazolinone; (MCI/MI) contact sensitization in patients with occupational and non-occupational contact dermatitis, 2011–2020. (B) Time trend of and MI contact sensitization in patients with occupational and non-occupational contact dermatitis, 2011–2020.

Formaldehyde sensitization was observed in teaching professionals and in the metal industry. The highest sensitization rates were seen in teaching professionals (6.9%, 95% CI 2.6–14.4), machine-tool setters and setters-operators (6.7%, 95% CI 3.5–11.5) as well as turners (6.2%, 95% CI 3.1–10.8) (Table S4C).

MCI/MI sensitizations were found predominately in market gardeners and crop growers (31.2%, 95% CI 16.1–50), building finishers and related trades workers (21.7%, 95% CI 12.7–33.3) as well as in painters, building structure cleaners and related trades (17.6%, 95% CI 6.8–34.5) (Table S4D).

MI sensitizations were most prominent in building finishers and related trades workers (27.8%, 95% CI 17.9–39.6), painters and related workers (20.1%, 95% CI 13.8–27.8) as well as in chemical-processing-plant operators (20.0%, 95% CI 9.6–34.6) (Table S4E).

Sensitizations to epoxy resin were most prominent in craft occupations. The highest sensitization rates were seen in building construction labourers (34.1%, 95% CI 20.5–49.9), Floor layers and tile setters (27.2%, 95% CI 17.9–38.2) as well as in plumbers and pipe fitters (26.2%, 95% CI 18–35.8) (Table S4F).

Sensitization rates against MDBGN were less prominent in occupational (3.6%, 95% CI 3.3–3.9) and non-occupational settings (2.8%, 95% CI 2.7–3.0).

4 | DISCUSSION

Delayed type sensitizations to work-related allergens of the European baseline series in patients with OCD patches tested within the ESSCA network from 2011 to 2020 are dominated by sensitizations to rubber chemical accelerators as well as by epoxy resin. The occupational importance of sensitizations to preservatives has declined, compared to the previous analysis period from 2002 to 2010.[11] Concerning rubber chemical accelerators as well as epoxy resin these results are in line with recent data from the NACDG. However, occupational sensitization to preservatives, especially to MI, is still of great importance in the US and in Canada, where sensitization rates still rise.[24]

4.1 | Rubber chemicals

Accelerators added to rubber vulcanization processes represent the most common cause of contact sensitizations to rubber chemicals.[10,25–27]

Occupational rubber chemical sensitizations are mainly acquired by the use of occlusive rubber gloves.[28–31] Other allergen sources include rubber boots, rubber bands, rubber insulation material, car tires, machine belts, and rubber tool handles.[32–35]

Carbamates are the most common accelerators in medical rubber gloves nowadays, while thiurams are hardly used in their production anymore.[30] The persistently high rate of sensitization to the thiuram mix in patients with OCD is probably linked to occupational use of carbamate-containing gloves as thiurams and carbamates are a redox pair and thiurams are considered a better marker for a thiuram/carbamate sensitization.[31] In recent years, an overall increase in carba mix positivity,[32] especially in the health care sector was shown.[10,27,28,36] These results are supported by our data and the recent analyses by the NACDG.[24] Medical professionals with OCD showed positivity rates to carba mix from 7.2% in nursing and midwifery associates up to 26% in health professionals (except nursing). However, these results must be interpreted with caution because carba mix contains not only carbamates but 1,3-DPG, a problematic test substance frequently causing false-positive irritant reactions, which may explain the high positivity rate.[32,37–39] Therefore, the clinical relevance of carba mix sensitizations should be proven by testing the components of the carba mix, especially 1,3-DPG and by testing the thiuram mix or its components as well as patient's own material. A false positive reaction to carba mix has major consequences for the patient's occupational opportunities, because the selection of protective gloves is severely compromised when carbamates must be avoided.[40] However, one has to keep in mind that true allergic reactions to 1,3-DPG can occur, which was recently shown in health care workers wearing rubber gloves.[41,42]

In contrast, sensitization rates to mercaptobenzothiazoles derivates remained low in occupations with high OCD risk. Compared to the data of Pesonen et al 2015 even a slight downward trend was apparent.[11] However, the risk of acquiring occupational sensitizations to mercapto-compounds is still significantly increased. Highest rates were found in service and food industry (data not shown).

4.2 | Epoxy resin

Epoxy resin, for example, in epoxy paints, adhesives and protective coatings, is the emerging contact allergen of the last two decades due to the widespread use in craft trades and its high sensitization potential.[11,24,33,43–45]

Overall sensitization rates to epoxy resin (diglycidyl ether of bisphenol A) in Europe rose from 3.1 during 2001 to 2010 to 3.5% during 2011 to 2020. The NACDG reported sensitization rates to epoxy resin (bisphenol A epoxy resin) as high as 5.6% in OSD patients.[24] Differences in sensitization rates might be explained by real differences in exposure but also by the respective definition of OSD as well as by different patient selection criteria.

Contamination of the skin occurs by direct skin contact, contaminated surfaces, inappropriate personal protective equipment and by handling of uncured or not fully cured epoxy materials.[46] Sensitization rates to epoxy resin in exposed occupations further increased in the last decade. Most frequently sensitized were building and construction workers (34.1%) as well as floor layers and tile setters (27.2%). This is not surprising, since high sensitization rates in construction coating as well as by using adhesives, e.g. in tile setters are well known.[47] A dramatic increase compared to the previous analysis period from 2002 to 2010 in sensitization rates from 7.7%[11] to 26.2% was seen in plumbers and pipe fitters. High allergen exposure especially in epoxy injection casting or pipe lining techniques is likely responsible for the increasing sensitization rates in this occupational group.[48] Further occupations with a dramatic increase in epoxy resin (diglycidyl ether of bisphenol A) sensitization rates in the present and the previous analysis of ESCCA data are plastic-products machine operators (from 14.5% to 24.3%) and painters (from 16.5% to 22.6%). Practical guidelines for prevention of epoxy allergies are highly needed.[49]

Other components of epoxy resin systems namely hardeners, and reactive diluents, are potent allergens, too.[50–52] To detect these sensitizations, patch testing of an epoxy resin series besides the baseline series is highly recommended, because up to 20% of patients sensitized to a reactive diluent and up to 60% of the patients sensitized to an epoxy resin hardener show no positive patch test to epoxy resin.[51]

4.3 | Preservatives

4.3.1 | MCI/MI and MI

As a result of the guidance of Cosmetics Europe, the association of the cosmetic industry, as well as European legislation on the use of MI

in cosmetic products the sensitization to MI and MCI/MI decreased in Europe from 2014 onwards,[53,54] while in the United States and Canada, where legal regulations for consumer products are yet lacking, the upward trend is still ongoing.[24]

However, our data indicate that this downward trend ended in 2018. Since then, sensitization rates for MCI/MI and MI seem to increase again. Separate analyses for MCI/MI and MI showed that the peak in 2019 and the slight upward trend in non-occupational settings from 2018 onwards is again mainly driven by non-occupational MI sensitizations. The latter is most probably due to ongoing exposures to MCI/MI and MI in wall paints, household products such as wash machine powders and liquids, dish washing fluids, floor cleaning agents, shoeshine and so on.[55–58]

Besides private exposure, there is still pronounced occupational relevance for MCI/MI and MI. In the last 10 years, the spectrum of occupations at risk for MCI/MI and MI sensitizations changed and sensitization rates rose dramatically in distinct occupations. Pesonen et al. reported floor layers and tile setters, chemical processing plant operators and precision worker in metal and related materials to have the highest risk to acquire occupational MCI/MI sensitization.[11] In the current analysis, we found highest sensitization rates for MCI/MI in market gardeners and crop growers, in which almost one-third of the patch test population was sensitized, followed by building finishers and related trades as well as painters, building structure cleaners and related workers. For MI sensitization, building finishers and painters showed highest sensitization rates of 27.8% and 20.1%, respectively. In the recent analysis of the NACDG occupational relevance was assumed in 52.5% of positive reactions to MI.[24]

MCI/MI and MI exposure in painters and cleaners occurs via preserved water-based wall paints and cleaning products, respectively.[57,59,60] Market gardeners and crop growers might be exposed to MCI/MI- and MI-treated plants, fruits and vegetables used to reduce food-borne illnesses as well as microbial spoilage.[61,62] Occupational exposure of building finishers and related trades (roofer, floor layer and tile setters, plasterers, insulation workers, glaziers, plumbers and tile fitters, building and related electricians), might be related to occupational exposure to products like paints, adhesives, wall and joint mortars and cleansers which may contain isothiazolinones as preservatives. Non- and incorrect labelling of isothiazolinones still lead to considerable problems to identify the culprit allergen.[57,58]

4.3.2 | Formaldehyde

Formaldehyde and formaldehyde releasers are still frequently used as preservatives in household detergents, cosmetic and pharmaceutical products and various industrial products.[63,64] Sensitization rates to formaldehyde (1% and 2% aq.) were lower in Europe (2.7% [95% CI 2.5%–3%] compared to the United States and Canada 3.9%).[24] Continuous exposure might contribute to the constant level of sensitization rates to formaldehyde over the last 2 decades.[11] Current sensitization rates were highest in teaching professionals (6.9%), followed by metal workers (machine tool setters, turners: 5.6%–6.7%) and lower in health care (nurses and midwifes: 3.6%). When it comes to teaching professionals at vocational schools, sensitization might have been acquired by using formaldehyde-releaser-containing liquid soaps or other substances (e.g., metal working fluids) at the workplace. However, all the patients ($n = 6$) concerned were women between 37 and 50 years of age and they might as well have acquired formaldehyde sensitization by personal use of formaldehyde-releaser containing cosmetics or household products.[65]

High formaldehyde sensitization rates in metal workers are plausible due to regular contact to metal working fluids commonly preserved with a variety of different formaldehyde-releasers.[66,67]

4.3.3 | MDBGN

Sensitization rates to MDBGN slightly dropped in occupational and non-occupational settings by approximately 1%. Banned in cosmetics by the EU from 2007,[68] MDBGN may still be used in all product-type 6 (PT6) categories (preservatives for products during storage). PT6 sub-categories[69] are technical fluids, including washing and cleaning fluids, paints and coatings, metal working fluids and glues and adhesives. Labelling is not mandatory if concentration limits are not exceeding 0.1%. Other possible exposures are medical devices and medicinal products, where MDBGN is permitted.[69]

4.4 | Labelling

Due to the lack of full labelling of many products including technical and cleaning fluids, glues, adhesives and medical devices determining relevance of a sensitization as well as consecutive allergen avoidance is difficult. Legal regulations for full labelling are highly needed.[15,69,70]

5 | LIMITATIONS AND STRENGTH

A limitation of our study is, that the risk of sensitization is calculated from all positive patch tests, and not only from the relevant ones. The correct assessment of exposure at work is definitive to really confirm the occupational relevance.[71] However, in our data set we cannot ensure that the information on relevance is entirely reliable (e.g., based on workplace exposure analysis in every case), therefore, we opted for analysis of the entire data set.

Our data provide a broad epidemiological basis of the sensitization in Europe. However, aggregation of occupations within ISCO classification may have the effect, that important allergens in specific occupations could be overlooked. For these cases, occupation-specific analyses should be intended. Moreover, to comprehensively diagnose occupational allergic contact dermatitis in individual cases additional testing of occupation-related patch test series as well as patients' own products is commonly inevitable.

6 | CONCLUSION

From the EBS allergens, rubber chemicals—especially thiurams—and epoxy resin (DGEBA) were associated with a pronounced risk of OCD. High rates of sensitization continued to be detectable against preservatives, especially MCI/MI and MI. Since the previous analysis of OCD patients in ESSCA in 2002–2010, the MCI/MI and MI sensitization rates have increased in both OCD and non-OCD patients. Time will show whether the observed rise in their sensitization rate in 2019 which was largely driven by MI sensitizations represents a trend. Due to the necessity to test the single constituents anyway, testing of carba mix in the EBS should be reconsidered.

AUTHOR CONTRIBUTIONS

Andrea Bauer: Conceptualization; investigation; project administration; writing – original draft; writing – review and editing; resources; validation; methodology; supervision. **Maria Pesonen:** Investigation; writing – review and editing; resources. **Richard Brans:** Investigation; writing – review and editing; resources. **Francesca Caroppo:** Investigation; writing – review and editing; resources. **Heinrich Dickel:** Investigation; writing – review and editing; resources. **Aleksandra Dugonik:** Investigation; writing – review and editing; resources. **Francesca Larese Filon:** Investigation; writing – review and editing; resources. **Johannes Geier:** Investigation; writing – review and editing; resources. **Ana M. Gimenez-Arnau:** Writing – review and editing; investigation; resources. **Maddalena Napolitano:** Investigation; writing – review and editing; resources. **Cataldo Patruno:** Investigation; writing – review and editing; resources. **Thomas Rustemeyer:** Investigation; writing – review and editing; resources. **Dagmar Simon:** Investigation; writing – review and editing; resources. **Marie L.A. Schuttelaar:** Investigation; writing – review and editing; resources. **Radoslaw Spiewak:** Investigation; writing – review and editing; resources. **Luca Stingeni:** Investigation; writing – review and editing. **Marko Vok:** Investigation; writing – review and editing; resources. **Elke Weisshaar:** Investigation; writing – review and editing; resources. **Mark Wilkinson:** Investigation; writing – review and editing; resources. **Skaidra Valiukeviciene:** Investigation; writing – review and editing; resources. **Wolfgang Uter:** Investigation; writing – review and editing; resources; methodology; software; validation; funding acquisition; supervision; project administration; conceptualization; formal analysis; writing – original draft; data curation.

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CONFLICT OF INTEREST

Wolfgang Uter has accepted travel reimbursement and research funds from the cosmetic industry association IFRA. Thomas Rustemeyer has participated in patch test studies from SmartPractice and has given lectures for ALK Abello, Leo Pharma, Novartis, Sanofi Genzyme, UCB Pharma and Ypsomed. All other authors have no pertinent conflict of interests to declare.

DATA AVAILABILITY STATEMENT

Data sharing not possible owing to privacy restrictions (included patients had not been asked for consent for "open data" sharing).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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