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European Surveillance System on Contact Allergies (ESSCA): Characteristics of patients patch tested and diagnosed with irritant contact dermatitis

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Abstract

Background: Irritant contact dermatitis (ICD) is caused by the acute locally toxic effect of a strong irritant, or the cumulative exposure to various weaker physical and/or chemical irritants.

Objectives: To describe the characteristics of patients with ICD in the population patch tested in the European Surveillance System on Contact Allergies (ESSCA; www.essca-dc.org) database.

Methods: Data collected by the ESSCA in consecutively patch tested patients from January 2009 to December 2018 were analyzed.

Results: Of the 68 072 patients, 8702 were diagnosed with ICD (without concomitant allergic contact dermatitis [ACD]). Hand and face were the most reported anatomical sites, and 45.7% of the ICD was occupational ICD (OICD). The highest proportions of OICD were found in metal turners, bakers, pastry cooks, and confectionery makers. Among patients diagnosed with ICD, 45% were found sensitized with no relevance for the current disease.

Conclusions: The hands were mainly involved in OICD also in the subgroup of patients with contact dermatitis, in whom relevant contact sensitization had been ruled out, emphasizing the need for limiting irritant exposures. However, in difficult-to-treat contact dermatitis, unrecognized contact allergy, or unrecognized clinical relevance of identified allergies owing to incomplete or wrong product ingredient information must always be considered.

KEYWORDS
body site, eczema, epidemiology, irritant contact dermatitis, occupational contact dermatitis, patch testing, RRID:SCR_001905, sensitization

1 | INTRODUCTION

Authors reporting results from the European Surveillance System on Contact Allergies (ESSCA) database have focused on specific allergens or allergen groups, occupational contact dermatitis, polysensitization, and sensitization profiles of various body parts.[1-7] However, results on patients eventually diagnosed with irritant contact dermatitis (ICD) from the ESSCA database have not yet been reported.

Contact dermatitis is a frequent problem and can negatively affect quality of life.[8,9] The two main types are ICD and allergic

contact dermatitis (ACD). ICD is caused by the toxic effect of various physical and/or chemical irritants on the skin and includes both acute and chronic manifestations. Acute ICD is often caused by a singular toxic event, usually with a strong irritant, whereas chronic ICD is caused by the cumulative exposure to weaker irritants.[9]

The exact pathophysiology of ICD is not yet fully elucidated. There is increasing evidence that tissue damage, followed by an immunological response resulting in the release of pro-inflammatory cytokines such as interleukin (IL)-1 and tumor necrosis factor (TNF)-α, activation of dendritic cells and T cells, which stimulate further cytokine and chemokine production, and eventually cutaneous inflammation, are involved in ICD.[10]

Most irritants that cause ICD are mild to moderate irritants (for example water or soap), where repeated and/or prolonged exposure is needed to cause tissue damage and ICD. However, the threshold concentration or duration may vary significantly from person to person. Whereby, atopic dermatitis (AD), atopic skin diathesis, and filaggrin gene (*FLG*) mutations are the most important endogenous risk factors for occupational ICD (OICD).[11,12]

Although several other papers report results of ICD and, mostly their occupational relation, not much attention is giving to affected body sites and sensitization profiles in ICD. Furthermore, ICD in such large numbers as the ESSCA database has never been studied before. This study aimed to evaluate the characteristics of patients diagnosed with ICD, without concomitant ACD, but with a possible other co-diagnosis, in the population patch tested at the departments of the ESSCA network from 2009 to 2018.

2 | METHODS

2.1 | Study design and population

The analysis is based on data collected by the ESSCA network as described previously.[13,14] Briefly, clinical and demographic data of all patients who were patch tested in the participating departments are documented electronically using different data-capture software and partly, the multilingual software WINALLDAT/ESSCA provided by the ESSCA.[15] Patch testing is done according to international recommendations.[16]

The case group includes all patients in whom ICD had been diagnosed as a first or second diagnosis, excluding patients with an additional diagnosis of ACD, whereas AD and other, non-dermatitis co-diagnoses were not an exclusion criterion. Moreover, patients had been patch tested with a baseline series (European, national, or departmental). The study period was 2009 to 2018, inclusive (10 years). Because the above case definition relies on a certain structure of the clinical documentation system, with two diagnoses and three sites to each of these, only departments using the WINALLDAT/ESSCA software or the WINALLDAT/IVDK sister software could be included in the present analysis. Thereby, this study included data from 32 departments in eight European countries: Austria, Germany, Italy, Lithuania, Poland, Spain, Switzerland, and The Netherlands (Table S1), except for the sub analysis about anatomical sites attributed to the ICD diagnoses stratified for country, where Italy and Lithuania were excluded because of missing data regarding anatomical sites (respectively, 87.3% and 69.5% of missing data). In case of multiple consultations during the study period, occurring in a minority of patients, one random consultation per patient was chosen.

For the purpose of the present analysis, different patch test preparations of one allergen, such as different concentrations, or TRUE Test vs pet.- or aq.-based allergens, were regarded as one, as the mostly slight differences noted between such preparations as reported previously both from the study period[3,7] and elsewhere, were not considered as possible confounders in this analysis.

For the total of patients patch tested in the study period, the ICD case group, and patients who were occupationally active and in whom their dermatitis was considered work-related (OICD), the Male, Occupational dermatitis, Atopic dermatitis, Hand dermatitis, Leg dermatitis, Face dermatitis, Age ≥40 years (MOAHLFA) index[17] and 'P' measure (the proportion of patients with at least one positive reaction to the baseline series) are given.[18]

A key information analyzed was the anatomical site affected by dermatitis. "Primary site", that is the skin region that is most affected or where the current dermatitis started, is used for the "HLF" part of the MOAHLFA index. In patients in whom this was not documented (n = 20 234), the first site to the first diagnosis was conventionally plugged-in; this was the case in n = 18 421 patients. For all other site-related analyses, in patients with ICD, site information strictly related to the diagnosis of ICD was utilized. Thereby, figures based on the primary site used for Table 1 and "site to diagnosis" as used in the remaining tables are not comparable.

The anatomical sites strictly related to the diagnosis of ICD in the ESSCA were aggregated into 10 body sites. This resulted in the following categories: head, face, arm, hand, trunk, anogenital, leg, foot, generalized, and other (see Table S2 for the details of this process). As the WINALLDAT/ESSCA software allows documentation of up to three anatomical sites to one diagnosis, patients could be classified into several different anatomical site categories. The group with generalized ICD represents patients with widespread eczema with more than three major body sites affected.

To evaluate OICD, all patients in the case group 16–68 years of age, representing persons potentially engaged in working life, with a documented current occupation were classified into occupational groups (on the 2- or 3-digit level of the International Standard Classification of Occupations version 1988 (ISCO-88)) and in full detail level of occupational classification (mostly on the 4-digit level of the ISCO-88 classification and partly on the 5-digit extensions introduced by ESSCA). In the ESSCA data, the relationship between occupational exposure and contact dermatitis is documented as "yes," "partial," "no," and "unknown." For the present analysis patients with clear or partial occupational causation (relationship between occupational exposure and contact dermatitis documented as "yes" or "partial") were defined as cases of OICD. Because the transition from the ISCO version 1988 to version 2008 was only partly made even at the end of the study period, the coding of the one department using WINALLDAT/ESSCA software having converted to ISCO-08 (Krakow,

TABLE 1 MOAHLFA index and "P" measure for all patients patched tested with a baseline series (European, national, or departmental) from 2009–2018 (overall, n = 68 072), patients with a diagnosis of irritant contact dermatitis (excluding an additional diagnosis of allergic contact dermatitis) (ICD, n = 8702), and the subgroup of patients with irritant contact dermatitis who are occupationally active in whom dermatitis was considered work-related (OICD, n = 3521)

	n(overall) n = 68 072	% (overall)	n(ICD) n = 8702	% (ICD)	n(OICD) n = 3521	% (OICD)
Male	23 382	34.35	3572	41.05	1698	48.22
Occupational dermatitis	13 563	19.92	3975	45.68	3521	100
Atopic dermatitis	16 170	23.75	2058	23.65	1152	32.72
Site: Hand	19 539	28.70	5509	63.31	3025	85.91
Site: Leg	4010	5.89	302	3.47	36	1.02
Site: Face	9664	14.20	927	10.65	112	3.18
Age 40+	43 479	63.87	5104	58.65	1912	54.30
"P' measure	40 285	59.18	3918	45.02	1659	47.12

Abbreviations: EBS, European Baseline Series; ICD, irritant contact dermatitis; MOAHLFA, Male, Occupational dermatitis, Atopic dermatitis, Hand dermatitis, Leg dermatitis, Face dermatitis, Age ≥ 40 years; OICD, occupational irritant contact dermatitis.
Note: "P' measure: the proportion of patients with at least one positive reaction to the baseline series.

Poland) were back-transformed to ISCO-88. The catalogue of occupations used by ESSCA is shown in Table S3.

2.2 | Statistical analysis

For data management, the statistical software R (version 3.6, <www.r-project.org>, RRID:SCR_001905) was used. Beyond descriptive analyses, log-binomial regression analyses were performed for each of the allergens of the European baseline series, with the dichotomous outcome positive (+, ++, and +++ on day 3 to day 5 inclusive) vs non-positive patch test reaction. As explanatory factor of interest a diagnosis of ICD vs all other diagnoses was examined in terms of quantifying the risk of a positive patch test reaction by the prevalence ratio (PR) accompanied by a corresponding 95% confidence interval (CI). As further adjustment factors, sex, age (dichotomized into <40 vs ≥40) and contributing department were employed.

3 | RESULTS

The ESSCA network reported data of 68 072 patients who were patch tested between 2009 and 2018. Altogether, 8702 (12.8%) patients diagnosed with ICD without concomitant ACD, but with a possible other co-diagnosis, were identified. Furthermore, 20 236 patients (29.7%) were diagnosed with ACD, without concomitant ICD. (See online supplemental figure S6 for the proportion of patients diagnosed with ICD among all patch tested patients per year).

3.1 | Clinical and demographic characteristics

In Table 1, the clinical and demographic characteristics of the ICD case group (n = 8702), the overall group of patients (n = 68 072), and the subgroup of ICD patients with OICD (n = 3521) are shown according to the MOAHLFA index, including the 'P' measure. Overall, the ICD case group included more males, more OICD, and a lower proportion of patients with at least one positive reaction to the baseline series compared to the overall group of patch tested patients. Similarly, lower percentages for previous or current diagnosis of AD were seen for the ICD case group compared with the overall group (23.7% and 23.8%, respectively), whereas for OICD, a higher percentage of patients with a previous or current diagnosis of AD was seen (32.7%). Hand as the primary site of dermatitis was more often reported for the ICD group compared to the overall group (respectively, 63.3% vs 28.7%). In addition, for OICD, the hand was the primary site in 85.9% of the cases. When looking at the MOAHLFA index stratified for country (see Table S4), the highest proportion of males were observed in Germany and The Netherlands (49.4% and 44.7%, respectively) and the lowest proportion of males in Lithuania and Austria (28.8% and 30.4%, respectively). The highest proportion of patients ≥40 years were observed in Spain and Germany (63.8% and 63.0%, respectively) and the lowest in Italy (40.5%). In addition, Germany had the highest percentage (68.5%) of OICD compared with the other countries.

3.2 | Anatomical sites

A more detailed presentation of aggregated anatomical sites involved in ICD, stratified for country, is presented in Table 2 (see Table S2 for details of this aggregating process). Of note, the overall share of a missing primary site information, after substitution as described in Methods, was n = 1813 (2.7%) and in the ICD case group it was n = 28 (0.3%). In all countries, the hand was clearly the most reported anatomical site that ICD was attributed to, ranging from 36.5% in Spain to 84.7% in Germany. The face was, with 10.6%, the second ranking anatomical site that ICD was attributed to. The most striking differences between countries were between Poland and Germany, with the face, trunk, and leg being reported as the most affected sites in patients with ICD in Poland compared to the other countries (respectively, 17.9%, 19.6%, and 17.6%), whereas the opposite was seen in Germany (respectively, 5.4%, 2.2%, and 2.4%). When looking

TABLE 2 Aggregated anatomical sites in patients diagnosed with irritant contact dermatitis (excluding an additional diagnosis of allergic contact dermatitis) (ICD), and the proportion of patients with irritant contact dermatitis who are occupationally active and in whom irritant contact dermatitis was considered occupation-related (OICD), stratified for country

Country	n(ICD)	Missing	OICD	Head	Face	Arm	Hand	Trunk	Anogenital	Leg	Foot	Generalized
AT	207	0 (0%)	79 (38.2)	12 (5.8%)	32 (15.5%)	28 (13.5%)	132 (63.8%)	8 (3.9%)	3 (1.4%)	7 (3.4%)	4 (1.9%)	3 (1.4%)
CH	1533	50 (3.3%)	287 (18.7)	61 (4%)	192 (12.5%)	108 (7%)	895 (58.4%)	85 (5.5%)	118 (7.7%)	66 (4.3%)	105 (6.8%)	107 (7%)
DE	2974	19 (0.6%)	2036 (68.5)	59 (2%)	162 (5.4%)	243 (8.2%)	2519 (84.7%)	64 (2.2%)	41 (1.4%)	70 (2.4%)	90 (3%)	18 (0.6%)
ES	1931	671 (34.7%)	444 (23.0)	84 (4.4%)	206 (10.7%)	109 (5.6%)	704 (36.5%)	122 (6.3%)	26 (1.3%)	65 (3.4%)	45 (2.3%)	46 (2.4%)
NL	486	7 (1.4%)	225 (46.3)	30 (6.2%)	70 (14.4%)	38 (7.8%)	324 (66.7%)	38 (7.8%)	6 (1.2%)	17 (3.5%)	26 (5.3%)	17 (3.5%)
PL	1253	63 (5%)	401 (32.0)	137 (10.9%)	224 (17.9%)	173 (13.8%)	612 (48.8%)	246 (19.6%)	35 (2.8%)	221 (17.6%)	152 (12.1%)	111 (8.9%)
Total	8384(100%)	810(9.7%)	3472 (41.4%)	371 (4.4%)	886(10.6%)	699(8.3%)	5186 (61.9%)	563 (6.7%)	229 (2.7%)	446 (5.3%)	422 (5.0%)	302 (3.6%)

Note: Note that up to three sites may have been documented and thus there are multiple occurrences of patients. Numbers of "other" sites not shown. Note that because the detailed anatomical sites are recoded to aggregated anatomical sites, the total number of cases is smaller for the aggregated anatomical site than for the detailed anatomical sites (see also Table S2). The group with generalized irritant contact dermatitis represents patients with widespread eczema with more than three major body sites affected. Italy and Lithuania were excluded because of missing data regarding anatomical sites (respectively, 87.3% and 69.5% of missing data). An identical analysis restricted to the patients with irritant contact dermatitis, a valid current occupation, age 16–68, and occupational irritant contact dermatitis is found in Table S5.

Abbreviations: AT, Austria; CH, Switzerland; DE, Germany; ES, Spain; ICD, irritant contact dermatitis; n, number; NL, The Netherlands; OICD, occupational irritant contact dermatitis; PL, Poland.

at aggregated anatomical sites in patients with a valid occupation and OICD, the hand and arm were the most reported anatomical sites were OICD was attributed to (respectively, 85.8% and 9.9%) (see Table S5).

3.3 | Occupational irritant contact dermatitis

Further focusing on occupation-related aspects, the ICD case group was narrowed to those between 16 and 68 years of age (inclusive) with an actual occupation documented, that is excluding non-formal activities like housewife/−husband. This yielded a subsample size of 6224 individuals, of whom 3521 had OICD. The number of persons with ICD per occupational group (ISCO-88 2 or 3-digit level) is shown in Table 3, along with the proportion of OICD. Only occupational groups with >75 cases of OICD were considered for analyses. The highest percentage of OICD was found in the occupations classified as blacksmiths, tool-makers, and related trades workers (84.8%) and machinery mechanics (82.0%). The lowest percentage of OICD was found in occupations classified as office clerks (9.7%) and teaching professionals (8.6%). Among nursing and midwifery associate professionals we found more individuals diagnosed with ICD compared to nursing and midwifery professionals (respectively, 26.4% vs 9.7%). By contrast, when comparing OICD, the proportions were similar (71.7% vs 69.2%).

In addition to the large subset of patients analyzed in Table 3, the following special groups were analyzed regarding the share of ICD within each of the groups: (a) retired (defined as age >68, 546 of a total of 8098 in that age group, ie, 6.7%); patients without documented current occupation, being 16–68 years of age (128 of 1839 without occupation, ie, 7%); unemployed patients (270 of 2027 unemployed, ie, 13.3%); and patients 15 years of age and younger (120 of 2033 within that age group, ie, 5.9%).

A similar analysis focusing on the full detail level of occupational classification, that is, the 4-digit level and 5-digit extensions partly introduced by ESSCA was done; results are shown in Table 4. The highest proportion of OICD, of all workers with ICD working in this occupation, were found in "Turners (metal)" (89.8%) and "Bakers, pastry-cooks, and confectionery makers" (72.4%). The lowest percentage of OICD was observed in "Building structure cleaners" (34.4%). However, the occupations with the lowest percentage of OICD in this table, have only the lowest percentage among the occupation with at least 75 cases of OICD.

3.4 | Patch test results

Patch test reactions to the 32 allergens of the European baseline series (EBS) and prevalence ratios for the subgroup of patients with ICD and for the whole group minus the ICD case group are shown in Table 5.

Patch test positivity to allergens in the EBS among patients with ICD varied from 14.9% (95%CI: 14.13–15.68) for nickel sulfate to

TABLE 3 The absolute and relative proportion of irritant contact dermatitis in the detailed occupational groups (classified on the 2- and 3-digit level of the ISCO-88 classification), and the percentage of occupational irritant contact dermatitis cases among the irritant contact dermatitis

ISCO-88	Occupational group	n(total)	n(ICD)	%(ICD)	n(OICD)	%(OICD)
7220	Blacksmiths, tool-makers, and related trades workers	747	244	32.7	207	84.8
7230	Machinery mechanics and fitters	1006	305	30.3	250	82.0
7310	Precision workers in metal and related materials	292	75	25.7	59	78.7
7120	Building frame and related trades workers	644	147	22.8	112	76.2
7410	Food-processing and related trades workers	601	131	21.8	98	74.8
8210	Metal- and mineral-product machine operators	311	85	27.3	62	72.9
3230	Nursing and midwifery associate professionals	1958	516	26.4	370	71.7
5140	Other personal services workers	1094	179	16.4	125	69 .8
2230	Nursing and midwifery professionals	802	78	9.7	54	69.2
7130	Building finishers and related trades workers	625	126	20.2	87	69.0
6110	Market gardeners and crop growers	437	84	19.2	58	69.0
3220	Modern health associate professionals (except nursing)	1164	243	20.9	160	65.8
9130	Domestic and related helpers, cleaners and launderers	1152	274	23.8	171	62.4
5120	Housekeeping and restaurant services workers	1994	427	21.4	257	60.2
3110	Physical and engineering science technicians	810	137	16.9	79	57.7
2220	Health professionals (except nursing)	1159	187	16.1	101	54.0
7140	Painters, building structure cleaners, and related trades workers	931	207	22.2	92	44.4
5220	Shop salespersons and demonstrators	1029	126	12.2	50	39.7
5200	Models, salespersons, and demonstrators	657	78	11.9	26	33.3
4200	Customer services clerks	977	207	21.2	24	11.6
4100	Office clerks	6365	444	7.0	43	9.7
2300	Teaching professionals	1051	81	7.7	7	8.6

Note: Only occupations with at least 75 cases of irritant contact dermatitis are shown in the table, ordered by decreasing proportion of occupational irritant contact dermatitis among the workers with irritant contact dermatitis in that group. Workers are defined as patients between 16 and 68 years of age with a documented current occupation. N(total), number of workers in the occupational group patch tested between 2009 and 2018; n(ICD), number of workers diagnosed with irritant contact dermatitis, %(ICD), % of workers diagnosed with irritant contact dermatitis among all the workers tested in the specific occupational group; n(OICD), number of workers diagnosed with occupational irritant contact dermatitis; %(OICD), % of occupational irritant contact dermatitis among all irritant contact dermatitis cases in that group.

Abbreviations: ICD, irritant contact dermatitis; ISCO-88, International Standard Classification of Occupations version 1988; n, number; OICD, occupational irritant contact dermatitis.

0.0% (95%CI: 0–0.12) for primin. For the whole group patch tested with EBS minus the ICD case group, positive patch test reactions ranged from 20.7% (95%CI: 20.37–21.03) for nickel sulfate to 0.4% (95%CI: 0.35–0.53) for clioquinol. Overall, as expected, patients diagnosed with ICD had a lower risk of a positive patch test reaction for all the EBS allergens compared to patients with (all) other diagnoses, the PR ranging from 0.1 (95%CI: 0.03–0.50) for mercapto mix to 0.7 (95%CI: 0.69–0.77) for nickel sulfate.

4 | DISCUSSION

This study describes the characteristics, including demographics, anatomical sites, occupation, and sensitization profile of patients who were patch tested and diagnosed with ICD in the ESSCA database. In this study, we found that 12.8% (n = 8702) of the patch tested persons with dermatitis from 32 departments in eight European countries between 2009 and 2018 were diagnosed with ICD, without having concomitant ACD. The frequency of ICD of this study is a little higher compared to a smaller single center study, which included patients who were referred for patch testing and reported 215/2321 (9.3%) patients diagnosed with ICD.[19] We included ICD with all possible combinations of other co-diagnoses (except for ACD), whereas the study of Turcic et al. included only solitary ICD. This might explain the higher frequency of ICD in our study. However, generally, the percentage of ICD in patch tested patients is assumed to be lower compared to the whole clinical population, the latter including varying proportions of patients with perhaps apparently clear-cut irritant dermatitis who are not suspected to be contact allergic, and thus not patch tested. Moreover, the characteristics of a department may play a role: In a tertiary referral center, more patients with prolonged course, and perhaps an initial diagnosis of ICD, are patch tested with

TABLE 4 The absolute and relative proportion of irritant contact dermatitis analyzed in occupations (on the 4-digit level of the ISCO-88 classification and 5-digit extensions partly introduced by ESSCA) with at least 75 cases of irritant contact dermatitis, ordered by decreasing proportion of occupational irritant contact dermatitis among all the workers with irritant contact dermatitis in that group

ISCO-88	Occupation	n(total)	n(ICD)	%(ICD)	n(OICD)	%(OICD)	Mean age	%(males)
72 231	Turners (metal)	254	88	34.6	79	89.8	45.3	88.6
7412	Bakers, pastry-cooks, and confectionery makers	335	76	22.7	55	72.4	31.9	36.8
5141	Hairdressers, barbers, beauticians, and related workers	954	165	17.3	116	70.3	32.8	4.2
3226	Physiotherapists and related associate professionals	367	89	24.3	62	69.7	37.9	14.6
5122	Cooks	744	179	24.1	122	68.2	34.6	40.8
7141	Painters and related workers	378	79	20.9	47	59.5	44.8	55.7
5121	Housekeepers and related workers	322	77	23.9	45	58.4	40.6	9.1
5123	Waiters, waitresses, and bartenders	619	145	23.4	78	53.8	37.7	19.3
2221	Medical doctors	462	88	19.0	42	47.7	36.0	17.0
7143	Building structure cleaners	496	125	25.2	43	34.4	45.3	4.8

Note: Workers are defined as patients between 16 and 68 years of age with a documented current occupation. N(total), number of workers in the occupational group patch tested between 2009 and 2018; n(ICD), number of workers diagnosed with irritant contact dermatitis, %(ICD), % of workers diagnosed with irritant contact dermatitis among all the workers tested in the specific occupational group; n(OICD), number of workers diagnosed with occupational irritant contact dermatitis, %(OICD), % of occupational irritant contact dermatitis among all irritant contact dermatitis cases in that group; mean age and %(males) refers to the patients with occupational irritant contact dermatitis in the respective occupation.
Abbreviations: ESSCA, European Surveillance System on Contact Allergies; ICD, irritant contact dermatitis; ISCO-88, International Standard Classification of Occupations version 1988; n, number; OICD, occupational irritant contact dermatitis.

TABLE 5 Positive patch test results to allergens of the baseline series in patients with irritant contact dermatitis and patients with (all) other diagnoses (non-irritant contact dermatitis), on the right the prevalence ratio (PR) with 95% confidence intervals (95%CI) quantifying the in- or decreased risk of a positive patch test reaction in patients diagnosed with irritant contact dermatitis vs non-irritant contact dermatitis diagnoses; additionally adjusted for sex, age (dichotomized at 40 years) and contributing department

	ICD			Non-ICD			Risk (ICD)
Allergen	Tested	n (pos.)	% (pos.; 95% CI)	Tested	n (pos.)	%(pos.; 95% CI)	PR (95% CI)
Potassium dichromate	8456	263	3.11 (2.75–3.5)	56 257	2949	5.24 (5.06–5.43)	0.54 (0.47–0.61)
Cobalt (II)-chloride	8399	382	4.55 (4.11–5.02)	57 048	4215	7.39 (7.18–7.61)	0.58 (0.52–0.64)
Nickel sulfate	8184	1219	14.89 (14.13–15.68)	57 502	11 901	20.7 (20.37–21.03)	0.73 (0.69–0.77)
Fragrance mix I	8259	288	3.49 (3.1–3.91)	56 299	4786	8.5 (8.27–8.73)	0.48 (0.43–0.54)
Fragrance mix II	8071	185	2.29 (1.98–2.64)	55 203	2771	5.02 (4.84–5.21)	0.53 (0.46–0.62)
HICC	8288	86	1.04 (0.83–1.28)	56 284	1110	1.97 (1.86–2.09)	0.53 (0.42–0.67)
Myroxolon pereirae (balsam of Peru)	8474	293	3.46 (3.08–3.87)	57 916	4087	7.06 (6.85–7.27)	0.56 (0.50–0.63)
Colophonium	8488	142	1.67 (1.41–1.97)	56 467	2016	3.57 (3.42–3.73)	0.50 (0.42–0.59)
Propolis	4690	107	2.28 (1.87–2.75)	31 675	1236	3.9 (3.69–4.12)	0.67 (0.54–0.81)
Formaldehyde	8482	84	0.99 (0.79–1.22)	57 904	1300	2.25 (2.13–2.37)	0.46 (0.37–0.58)
MCI/MI	8404	254	3.02 (2.67–3.41)	57 687	3698	6.41 (6.21–6.61)	0.44 (0.39–0.50)
Methylisothiazolinone	4201	143	3.4 (2.88–4)	35 186	2650	7.53 (7.26–7.81)	0.39 (0.33–0.47)
Paraben mix	8480	29	0.34 (0.23–0.49)	57 938	483	0.83 (0.76–0.91)	0.44 (0.30–0.65)
Quaternium 15	3887	12	0.31 (0.16–0.54)	29 109	315	1.08 (0.97–1.21)	0.26 (0.14–0.46)
Methyldibromo glutaronitrile	8541	130	1.52 (1.27–1.8)	57 968	2132	3.68 (3.53–3.83)	0.48 (0.40–0.57)
p-Phenylenediamine	4996	73	1.46 (1.15–1.83)	38 448	1622	4.22 (4.02–4.42)	0.35 (0.28–0.45)
Benzocaine	2662	7	0.26 (0.11–0.54)	18 926	197	1.04 (0.9–1.2)	0.25 (0.12–0.55)
Clioquinol	2056	1	0.05 (0–0.27)	20 691	89	0.43 (0.35–0.53)	0.13 (0.02–0.97)
Budesonide	4020	32	0.8 (0.55–1.12)	31 193	317	1.02 (0.91–1.13)	0.62 (0.42–0.90)
Tixocortol-pivalate	3999	8	0.2 (0.09–0.39)	38 655	360	0.93 (0.84–1.03)	0.26 (0.13–0.53)
Neomycin sulfate	4024	27	0.67 (0.44–0.97)	31 941	469	1.47 (1.34–1.61)	0.36 (0.24–0.53)
Thiuram mix	8469	133	1.57 (1.32–1.86)	58 025	1325	2.28 (2.16–2.41)	0.58 (0.48–0.70)

TABLE 5 (Continued)

Allergen	ICD			Non-ICD			Risk (ICD)
	Tested	n (pos.)	% (pos.; 95% CI)	Tested	n (pos.)	%(pos.; 95% CI)	PR (95% CI)
IPPD	7505	34	0.45 (0.31–0.63)	52 359	489	0.93 (0.85–1.02)	0.44 (0.31–0.63)
Mercapto mix (MBT,CBS,MBTS,MOR)	2864	2	0.07 (0.01–0.25)	24 834	191	0.77 (0.66–0.89)	0.12 (0.03–0.50)
Mercapto mix (CBS, MBTS, MOR)	6306	24	0.38 (0.24–0.57)	38 591	305	0.79 (0.7–0.88)	0.40 (0.26–0.62)
Mercaptobenzothiazole	8495	26	0.31 (0.2–0.45)	58 062	416	0.72 (0.65–0.79)	0.44 (0.29–0.66)
Sesquiterpenlactone mix	4074	6	0.15 (0.05–0.32)	30 457	273	0.9 (0.79–1.01)	0.24 (0.11–0.54)
Primin	2962	0	0 (0–0.12)	23 613	111	0.47 (0.39–0.57)	n.c.
Lanolin (wool fat) alcohols	8359	73	0.87 (0.69–1.1)	54 599	1379	2.53 (2.4–2.66)	0.52 (0.41–0.66)
Epoxy resin	8010	54	0.67 (0.51–0.88)	56 449	918	1.63 (1.52–1.73)	0.38 (0.29–0.51)
PTBFR	6204	31	0.5 (0.34–0.71)	45 191	481	1.06 (0.97–1.16)	0.45 (0.31–0.66)
Textile dye mix	479	6	1.25 (0.46–2.71)	4094	168	4.1 (3.52–4.76)	0.27 (0.12–0.60)

Abbreviations: CBS, *N*-cyclohexyl-2-benzothiazyl sulfenamide; CI, confidence interval; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde; ICD, irritant contact dermatitis; IPPD, *N*-isopropyl-*N*′-phenyl-*p*-phenylenediamine; MBT, 2-mercaptobenzathiazole; MBTS, dibenzothiazyldisulfide; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone; MOR, morpholinyl mercaptobenzothiazole; n, number; n.c., not calculable; pos., positive; PR, prevalence ratio; PTBFR, *p-tert*-butylphenol formaldehyde resin.

an extended range of allergens, which increases the likelihood of eventually correctly diagnosing ACD. By contrast, on the level of primary care—not well-represented in our network—the share of actual ICD, and of patients not patch tested, or patch tested with just a limited scope of allergens, may be higher, and thus the possibly partly erroneous diagnosis of ICD be made more often.

A variability in individual thresholds, and thereby the susceptibility of developing ICD, is known to be an important endogenous factor. Some individuals develop ICD following exposure to relatively low levels or short duration of exposure to irritants, whereas others tolerate much higher or longer exposures without skin complaints. In previous studies, sodium lauryl sulfate (SLS) was applied to the upper outer arm of volunteers at different concentrations, and a variability in the threshold irritant response was seen.[20,21] An important predisposing factor of developing OICD is AD.[11] The higher susceptibility of OICD in AD is attributed to an impaired skin barrier with higher transepidermal water loss and easier percutaneous penetration with higher diffusivity of irritants, even in non-involved AD skin.[22] In this study, similar percentages for a history or current diagnosis of AD were seen for both the ICD case group and the overall patch tested group (23.7% and 23.8%, respectively). The increased risk of OICD in patients with AD is confirmed in the current study.[11] Higher percentages for a history or current diagnosis of AD in the OICD group compared to the overall and the ICD group were seen. This might be explained by the greater exposure to irritants in an occupational setting, perhaps with mandatory use of occlusive personal protective equipment and per-protocol hygiene measures, compared to non-occupational settings.

4.1 | Anatomical sites

The hand and face, with respectively, 61.9% and 10.6%, were the most frequently reported anatomical sites for ICD. Because the current population consists of patch tested individuals, and the current recommendation of the working group of the European Society of Contact Dermatitis is to perform diagnostic patch testing in all patients with hand eczema with a duration of more than 3 months and/or relapse, this could partly explain the high percentage of hand involvement in ICD.[23] The high prevalence of ICD of both the hands and face could be explained by the higher amount of exposure to irritants to these body regions, especially for the hands. In a population-based study on exposure to irritants among 2128 patients with occupational skin disease (OSD), the most frequently mentioned irritant was work-related exposure to detergents (52%, in a nonspecific distribution for all occupational groups), which are mostly used on the hands.[24] In addition, wet work is known to be one of the most common triggers of ICD and almost always involves the hands.[25] For the face, exposure to cosmetic products and detergents could play a role in developing ICD. Recently, a 22-year retrospective cross-sectional analysis including 1332 male patients with facial dermatitis identified cosmetic products as the most common source of ICD, including both rinse-off and leave-on products (27.2%).[26] Factors possibly contributing to a higher susceptibility of the exposed skin are, among others, the thickness of the stratum corneum and absorption ability of the skin, which both vary considerably depending on anatomical site. This might particularly play a role in facial skin, as facial skin has the smallest number of cell layers of stratum corneum and the greatest absorption capacity compared to other anatomic sites such as the trunk, extremities, and palms and soles.[27,28] As a result, a lower threshold for developing ICD on the face induced by the same amount of exposure compared to other body regions can be assumed. Palmar skin has almost the largest number of cell layers of the stratum corneum, so that exogenous factors, like frequency of exposure, will play a larger role in this anatomical site compared to the thickness of the stratum corneum. Previously, an ESSCA study was performed on body sites in patients with ACD, which included cases with a minimum of one positive patch test reaction to the EBS and a final diagnosis of

ACD attributed to only one body site. The head (including the face) and hand were the most reported anatomical sites for ACD (respectively, 30.5% and 29.6%).[5] In a smaller retrospective study of 353 patients with contact dermatitis (ACD or ICD), the face (25%) and the hands (19%) were also the most frequently affected areas.[29] Because exposure is the causative factor, and products applied to the face and hands contain either irritants or allergens, or both, these anatomic regions prevail in both ICD and ACD. When stratifying for country, the highest percentage of patients with ICD attributed to the hand was seen in Germany (84.7%) and the lowest percentages were seen for Spain (36.5%) and Poland (48.8%). This difference might be explained partly by the low percentages of OICD in Spain and Poland (23.0% and 32.0%) in contrast to the highest percentage of OICD in Germany (73.5%), whereby in OICD the hands are more often involved compared with non-OICD. In addition, when looking at OICD, the hand was the most commonly reported anatomical site for OICD in Germany (95.4%) and the least reported anatomical site for OICD in Poland (55.1%). Another explanation for the high frequency of OICD in Germany might be the billing system of patch testing in Germany. In Germany, patients with suspected OSD are more often patch tested, since remuneration for the patch test is by the state accident insurance instead of the general health insurance covering non-OSD.[30] Other frequently reported anatomical sites in both ICD and OICD in Poland included the face, trunk, and leg. Another possible explanation might be that farmers are still a relatively large occupational group in Poland. Farmers are more likely to develop airborne dermatitis, for example, during harvest activities, especially during summer months when wearing less- protective clothing.

4.2 | Occupation-related ICD

ICD is often mentioned as a frequent OSD.[31] In the present study, 45.7% of the ICD was OICD. A previous study using data of the ESSCA database, with a partial overlap to the current period of analysis of 2 years, only analyzing patients with occupational contact dermatitis, included 10 617 patients between 16 and 68 years of age. Of these, 28.7% had ICD, 35.3% ACD, and 10.7% had both ACD and ICD. High percentages of OICD were found in waiters, waitresses, and bartenders (47.6%), bakers, pastry cooks, and confectionery makers (40.5%) and nursing and midwifery professionals (34.9%).[1]

A population-based study, including data of 5285 workers' compensation claims reported to a register of OSD, identified occupational groups at risk for ICD.[24] The highest incidence rates for OICD were found in hairdressers, bakers, and pastry cooks and ICD was the main diagnosis of OSD in pastry cooks (76%), cooks (69%), food-processing industry workers and butchers (63%), mechanics (60%), and locksmiths and automobile mechanics (59%). As the study did not use the same occupational group classification, a direct comparison for all the occupational groups is not possible. However, overlap based on job title is certainly conceivable.

In the current study, a remarkable difference in results was found for nursing and midwifery professionals on one hand, and nursing and midwifery associate professionals on the other. The overall prevalence of ICD was much lower in the former group compared to the latter group (respectively, 9.7% vs 26.4%). However, both occupational groups had comparable results regarding the relative proportion of OICD (respectively, 69.2% and 71.7%). This discrepancy could be explained by differences in job tasks, and thereby the level of occupational exposure between these two occupational groups. It is possible that nurses and midwifery professionals are more often involved in administrational tasks compared with nurses and midwifery associate professionals who are more often involved in, for example, wet work. If, however, the nursing professionals had developed ICD, it was as commonly OICD as in the associate professionals.

4.3 | Sensitization pattern

When comparing patients diagnosed with ICD to the group containing all other diagnoses, the sensitization pattern is very similar and largely overlapping when looking at the most common contact allergies in both groups. The highest prevalence of positive patch test reactions was seen to metals and fragrances, which have also often been seen in both the clinical population[3] and the general population.[32]

Overall, the proportion of ICD patients with at least one positive reaction to the EBS was 45.0%. This is higher compared to the general population in Europe. A cross-sectional study of 3119 patch tested persons from the general population in Europe showed that 27.0% had a positive reaction to at least one allergen of the EBS.[32] Approximately two to six times higher percentages were seen for the 10 allergens with the highest prevalence in the ICD case group compared to the general population. Per definition, as an additional diagnosis of ACD was excluded, all the positive reactions to the EBS in the ICD group had to be non-relevant for the current skin disease. These contact allergies could have been relevant in the past for other skin diseases at other body parts, or have become non-relevant for the current problem due to avoidance.

ICD is thought to predispose to the induction of skin sensitization.[33] According to the available human evidence for the impact of irritation on the elicitation of ACD, irritants lower the threshold elicitation concentration for allergens.[34] However, human evidence on the impact of irritants on the induction phase of ACD is limited due to ethical considerations. In animal models it was demonstrated that the presence of 5% SLS approximately doubled the rate of induction of sensitization from 38% to 78% to *p*-phenylenediamine in guinea pigs.[35] One study assessing 25 human volunteers demonstrated that pre-treatment of the skin with SLS increased the frequency of induction of sensitization from 8% to 54% compared to control skin.[36] Irritants seem to lower the threshold for induction of sensitization by inducing inflammation and increasing permeability of the horny layer. The predisposition to skin sensitization conveyed by irritants has been outlined previously as the "danger model," in which an antigenic signal will produce sensitization only in the presence of a danger signal (in ICD the activation of the innate immune system), and in the absence of a danger signal, tolerance will occur.[34]

4.4 | Limitations

A limitation of our study is that the type and amount of exposure to irritants is not systematically documented in the ESSCA database. An extended documentation on irritant exposure for hand dermatitis has been proposed previously to, partly, overcome this problem in the future.[37] Another limitation is that the current and past relevance of individual positive patch test reactions to the current dermatitis was not documented. However, this would be a limitation for studies addressing ACD, whereas a lack of current clinical relevance to a diagnosed contact allergen is in line with an exclusive diagnosis of ICD defining our study sample. Furthermore, to date, no definite common diagnostic criteria for ICD are available, thus a considerable country-to-country, center-to-center, and doctor-to-doctor variability has to be taken in to account.

In conclusion, the hand and face were the most reported anatomical sites for ICD, and the hands were mainly involved in OICD. Almost half of the patients with ICD had OICD. Furthermore, almost half of the patients diagnosed with ICD had at least one contact sensitization, with a similar sensitization pattern compared to the group containing all other diagnoses, albeit on a (much) lower level of relative frequency, if PRs are considered. The focus of prevention of ICD should include the identified high-risk occupations, with special attention given to exposure to the hands. In addition, in difficult-to-treat contact dermatitis, unrecognized contact allergy, or unrecognized clinical relevance of identified allergies owing to incomplete or wrong product, ingredient information must always be considered. Further research should focus on the type and duration of exposure to different kinds of irritants in individuals with ICD to gain more insight into the exposure patterns and identify further leads in the prevention of ICD.

CONFLICT OF INTERESTS

There was no funding. W.U. has accepted a honorarium for a presentation from mixed dermatopharmaceutical sponsors. T.R. has accepted honoraria for presentations from several pharmaceutical companies. The other authors have no conflicts of interest to report.

AUTHOR CONTRIBUTION (CRediT)

- Conceptualization: W.U., M.L.A.S., L.L.: (equal), M.P.(supporting)
- Data curation: all others except W.U.: (equal)
- Formal analysis: W.U. (lead)
- Funding acquisition: –
- Investigation: all others except W.U.: (equal)
- Methodology: W.U., M.L.A.S., L.L., M.P.: (equal)
- Project administration: all authors (equal)
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- Supervision: –
- Validation: all others except W.U.: (equal)
- Visualisation: all authors (equal)
- Writing – original draft: L.L. (lead), M.L.A.S, W.U, M.P (supporting)
- Writing – review & editing: all authors (supporting)

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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

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