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Patch test results with the European baseline series and additions thereof in the ESSCA network, 2015-2018

Wolfgang Uter[1] | Andrea Bauer[2] | Anna Belloni Fortina[3] | Andreas J. Bircher[4,5] | Richard Brans[6] | Timo Buhl[7] | Susan M. Cooper[8] | Magdalena Czarnecka-Operacz[9] | Heinrich Dickel[10] | Aleksandra Dugonik[11] | Johannes Geier[12] | Ana M. Giménez-Arnau[13] | Margarida Gonçalo[14] | Jeanne D. Johansen[15] | Graham A. Johnston[16] | Vera Mahler[17] | Thomas Rustemeyer[18] | Javier Sanchez-Perez[19] | Marie L.A. Schuttelaar[20] | Dagmar Simon[21] | Radoslaw Spiewak[22] | Skaidra Valiukevičienė[23] | Elke Weisshaar[24] | Ian R. White[25] | Mark Wilkinson[26] | ESSCA Working Group

[1]Department of Medical Informatics, Biometry and Epidemiology, University of Erlangen/Nürnberg, Erlangen, Germany

[2]Department of Dermatology, University Allergy Centre, Medical Faculty Carl Gustav Carus, Technical University Dresden, Dresden, Germany

[3]Dermatology Unit, Department of Paediatrics, University of Padova, Padova, Italy

[4]Allergy Unit, Department of Dermatology, University Hospital Basel, Basel, Switzerland

[5]Faculty of Biomedicine, Università della Svizzera Italiana, Lugano, Switzerland

[6]Department of Dermatology, Environmental Medicine and Health Theory, University of Osnabrück, Osnabrück, Germany

[7]Department of Dermatology, Venereology and Allergology, University Medical Center Göttingen, Göttingen, Germany

[8]Department of Dermatology, Oxford University Hospitals NHS Trust, Oxford, UK

[9]Department of Dermatology, Poznan University of Medical Sciences, Poznań, Poland

[10]Department of Dermatology, Venereology and Allergology, St. Josef Hospital, Ruhr University Bochum, Bochum, Germany

[11]Department of Dermatology, University Medical Centre Maribor, Maribor, Slovenia

[12]Information Network of Department of Dermatology, University Medical Center, Göttingen, Germany

[13]Department of Dermatology, Hospital del Mar. Universitat Autònoma and Pompeu Fabra, Barcelona, Spain

[14]Department of Dermatology, Coimbra University Hospital and Faculty of Medicine, University of Coimbra, Coimbra, Portugal

[15]National Allergy Research Centre, Department of Skin and Allergy, Gentofte Hospital, Hellerup, Denmark

Collaborators: ESSCA working group: Werner Aberer, Department of Dermatology, Medical University of Graz, Graz, Austria; Barbara Ballmer-Weber, Department of Dermatology, University Hospital Zürich and Clinic of Dermatology and Allergology, Kantonsspital St. Gallen, Zürich, Switzerland; Detlef Becker, Department of Dermatology, University of Mainz, Mainz, Germany; Ulrike Beiteke, Department of Dermatology, Dortmund, Germany; Jochen Brasch, Department of Dermatology, University of Schleswig-Holstein, Campus Kiel, Kiel, Germany; Mahbub M. Chowdhury, Welsh Institute of Dermatology, Cardiff, UK; Maria Teresa Corradin, Dermatology Unit, Santa Maria degli Angeli Hospital, Pordenone, Italy; Cecilia Dietrich, Department of Dermatology, University of Schleswig-Holstein, Campus Kiel, Kiel, Germany; Rosella Gallo, Clinica Dermatologica, IRCCS – AOU San Martino – IST and Department of Health Sciences, University of Genoa, Genoa, Italy; Jürgen Grabbe, Department of Dermatology, Kantonsspital Aarau, Aarau, Switzerland; Swen Malte John, Institute for Interdisciplinary Dermatologic Prevention and Rehabilitation (iDerm), University of Osnabrück, Lower Saxony Institute for Occupational Dermatology (NIB), Osnabrück, Germany; Maja Kalac Pandurovic, Outpatient Clinic of Dermatology, Maribor, Maribor, Slovenia; Nada Kecelj, Outpatient Clinic of Dermatology, Ljubljana, Slovenia; Tanja Kmecl, Department of Dermatology, General Hospital Celje, Celje, Slovenia; Birger Kränke, Department of Dermatology, Medical University of Graz, Graz, Austria; Francesca Larese Filon, Department of Public Health, Occupational Medicine, University of Trieste, Trieste, Italy; Tomaž Lunder, Department of Dermatology, University Medical Center, Ljubljana, Slovenia; Pedro Mercader, Dermatology Department, Hospital General Universitario Morales Meseguer, Murcia, Spain; Alexander Navarini, Department of Dermatology, University Hospital Zürich, Zürich, Switzerland; Andrea Peserico, Department of Dermatology, University of Padova, Padova, Italy; Maria Pesonen, Occupational Medicine, Finnish Institute of Occupational Health (FIOH), Helsinki, Finland; Inmaculada Ruiz, Department of Dermatology, Complejo Asistencial de León, León, Spain; Anna Sadowska-Przytocka, Department of Dermatology, Poznań University of Medical Sciences, Poznań, Poland; Kathrin Scherer-Hofmeier, Allergy Unit, Dept. of Dermatology, University Hospital Basel, Basel, Switzerland; Sibylle Schliemann, Department of Dermatology and Allergology, University Hospital Jena, Jena, Germany; Mojca Simončič Godnič, Department of Dermatology, Novo Mesto, Slovenia; Luca Stingeni, Dermatology Section, Department of Medicine, University of Perugia, Perugia, Italy; Natalie Stone, Aneurin Bevin Health Board, Newport, Gwent, UK; Marko Vok, Outpatient Clinic of Dermatology, Izola, Slovenia; Nicola Wagner, Department of Dermatology, University of Erlangen-Nürnberg, Erlangen, Germany; Thomas Werfel, Medizinische Hochschule Hannover, Department of Immunodermatology and Experimental Allergy, Hannover, Germany.

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[16]Department of Dermatology, Leicester Royal Infirmary, Leicester, UK

[17]Department of Dermatology, University Hospital Erlangen, Erlangen, Germany, Paul-Ehrlich-Institut, Langen, Germany

[18]Department of Dermatology, Free University of Amsterdam, Amsterdam, The Netherlands

[19]Dermatology Department, Hospital Universitario de la Princesa, Instituto de Investigación Sanitaria la Princesa (IIS-IP), Madrid, Spain

[20]Department of Dermatology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[21]Department of Dermatology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

[22]Department of Experimental Dermatology and Cosmetology, Jagiellonian University Medical College, Krakow, Poland

[23]Department of Skin and Venereal Diseases, Lithuanian University of Health Sciences, Kaunas, Lithuania

[24]Department of Clinical Social Medicine, Occupational and Environmental Dermatology, University Hospital Heidelberg, Heidelberg, Germany

[25]Cutaneous Allergy Team, St. John's Institute of Dermatology, Guy's Hospital, London, UK

[26]Dermatology Department, Leeds Teaching Hospitals NHS Trust, Leeds, UK

Correspondence
Dr. Wolfgang Uter, Department of Medical Informatics, Biometry and Epidemiology, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Waldstrasse 6, D-91054 Erlangen, Germany.
Email: wolfgang.uter@fau.de

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Abstract

Background: Clinical surveillance of the prevalence of contact allergy in consecutively patch tested patients is a proven instrument to continually assess the importance of contact allergens (haptens) assembled in a baseline series.

Objectives: To present current results from the European Surveillance System on Contact Allergies, including 13 countries represented by 1 to 11 departments.

Methods: Anonymized or pseudonymized patch test and clinical data from various data capture systems used locally or nationally as transferred to the Erlangen data centre were pooled and descriptively analysed after quality control.

Results: In the 4 years (2015-2018), data from 51 914 patients patch tested with the European baseline series (EBS) of contact allergens were analysed. Contact allergy to nickel was most frequent (17.6% positive), followed by contact allergy to fragrance mix I (6.9%), methylisothiazolinone (MI; 6.2%), and *Myroxylon pereirae* resin (balsam of Peru; 5.8%).

Conclusions: While the prevalence of MI contact allergy decreased substantially following regulatory intervention, the persistently high levels of allergy to metals, fragrances, other preservatives, and rubber chemicals point to problems needing further research and, potentially, preventive efforts. Results with national additions to the baseline series provide important information on substances possibly to be considered for inclusion in the EBS.

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

1 | INTRODUCTION

The value of surveillance of contact allergy using scientific networks has been repeatedly illustrated (for example, see Uter et al 2020[1] for a summary on this topic) and shall not be further expanded on. In the United States and Canada, continual reporting by the North American Contact Dermatitis Research Group, for example,[2] provides a regular audit of the value of patch testing, and of the importance of single allergens (possibly in subgroups of the patch tested population) and time trends, as does the work of the European Surveillance System on Contact Allergies (ESSCA, https://www.essca-dc.org) in Europe.[3] A series of reports presenting results of patch testing with the European baseline series (EBS; see[4] for the current version) and partly also with national or some local additions to it has been published. Continuing this series, 4-year results, obtained from 2015 to 2018, are presented and discussed herein.

2 | METHODS

The ESSCA is a working group of the ESCD (https://www.escd.org). Its objective is the clinical surveillance of contact allergy.[1,5] To this end, contributing departments (Table S1) submit either all patch test results or just patch test results obtained with the EBS (or national or local

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adaptations thereof), obtained following ESCD standards,[6] to the data centre in Erlangen. This is accompanied by important demographic and clinical information, ranging from "MOAHLFA" characteristics to a wider range of information according to the ESSCA minimal dataset definition.[1,7] Data from contributing departments are delivered in an anonymous format or partly, following national network standards, in a pseudonymized format, where the pseudonym cannot be related to actual personal data except in the contributing department itself. This difference is of importance, as only with pseudonymized data can re-investigations of patients be identified and eliminated, to avoid duplication of entries. For the purpose of the present analysis, a random selection among two or more consultations documented in the database, involving testing the baseline series, was made. Data were quality checked, providing an internal report for each contributing department for scrutiny and approval before pooling of the respective data.[5] Two departments contributed aggregated (ie, no individual) data on results, stratified for gender, namely, Gentofte/Denmark and Coimbra/Portugal. Test results with different preparations of the same allergen, for example, concerning methylisothiazolinone (MI), are presented separately. Concerning MI, 0.05% and 0.2% aqueous (aq.) had been tested most commonly. Following an overall decline of patient numbers patch tested from 2015 to 2018, patch testing with MI 0.05% aq. also decreased, by 37.7%, whereas patch testing with MI 0.2% aq. decreased by 29.1% ($P < .0001$, chi-square test). Data management and analysis were performed with the R software package (www.rproject.org; RRID:SCR_001905), version 3.6. For the calculation of 95% confidence intervals (CIs) to zero proportions an approximation to an exact CI was used.[8]

Data from the subset of departments from Austria, Germany, and Switzerland participating in the Information Network of Departments of Dermatology (IVDK, https://ivdk.org/en) and in the ESSCA (these departments roughly cover one-third of all investigations included in the IVDK) were also included in the presentation of 2007 to 2018 IVDK results with the German baseline series recently published.[9]

3 | RESULTS

In total, data of 51 914 patients patch tested with the EBS from 2015 to 2018 (inclusive) were analysed. The individual contribution by country and department is shown in Table S1. Population characteristics according to the MOAHLFA index,[10] extended by the P-measure, that is, the proportion of patients positive to at least one allergen from the baseline series,[11] are illustrated in Table 1. The share of patients with one, two, and three or more positive reactions to unrelated allergens[12] applied in the baseline series was 23.3%, 12%, and 16.8%, respectively. A considerable variation of all MOAHLFA factors is evident. In the present data, the share of patients aged 40 or older is just slightly higher in males (62.9%) than in females (61.6%, $P = .005$). The overall share of patients with trunk or generalized dermatitis was 5% and 5.6%, respectively.

Patch test results with the EBS, in the version valid at the time,[13,14] are shown in Table 2 as crude overall prevalence and sex-stratified prevalences, respectively. A supplemental analysis stratified for three age groups is presented in Table S2 for the EBS and in supplemental Table S3 for additions thereof. A further analysis presenting age- and sex-standardized, instead of age- and sex-stratified, results is presented in Table S4, for direct comparison with previous ESSCA analyses using the same standardization.[15] Patch testing results to the three metals, the four fragrance allergens, and the preservatives shown in Table 2 are as follows: 21.9% were positive to at least one metal, 12.1% to at least one of the fragrance markers, and 11.1% to at least one of the preservatives listed.

The currently used textile dye mix (TDM) 6.6% petrolatum (pet.) contains Disperse Orange 3 1%, which strongly cross-reacts with *p*-phenylenediamine (PPD). The cross-reactivity between TDM and PPD was thus assessed: Of the 11 996 patients tested with both TDM and PPD, 184 (1.5%) reacted to TDM and PPD, 152 (1.3%) only to TDM, and 209 (1.7%) only to PPD. An odds ratio (OR) of 66.3 indicates very marked cross-reactivity.

In many departments temporary or long-term additions were tested along with the EBS in consecutive patients; these results are shown in Table 3 in a format identical to Table 2. "Carba mix" contains not only two dithiocarbamates (zinc dibutyldithiocarbamate and zinc diethyldithiocarbamate [ZDEC]) but also 1,3-diphenylguanidine. Of 18 796 patients patch tested with both thiuram and carba mix, 111 (0.59%) reacted to both, whereas 388 (2.06%) were positive only to carba mix and 188 (1%) only to thiuram mix. Of all 500 positive reactions to carba mix, 86.6% were weak positive, with the remainder either strong (12.4%) or extreme (1%) positive. None of the patients

TABLE 1 Demographic and clinical characteristics according to the MOAHLFA index[10] with "P-measure,"[11] that is, the proportion of patients with at least one positive reaction to a baseline series allergen, excluding one purely paediatric department (Padova Paediatric Department)

Factor		Minimum %	Average %	Median %	Maximum %
Male	M	20.5	32.9	32.3	58.8
Occupational	O	2.4	16.1	13.9	70.1
Atopic dermatitis	A	7.5	27.5	21.7	70.5
Hand	H	7.0	27.0	29.0	87.5
Leg	L	0.0	5.3	5.8	19.3
Face	F	1.4	17.9	18.1	39.0
Age 40+	A	35.2	62.6	65.1	77.5
Positive to at least one baseline series hapten	P	35.0	52.1	53.1	80.0

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TABLE 2 Patch test results (days 3 to 5) with the European baseline series, 2015 to 2018, in the 48 active departments of the European Surveillance System on Contact Allergies (ESSCA), additionally stratified for sex

Allergen	Conc.	Tested	% ? +/IR	% +	% + +/+++	% positive (95% CI)	Females: % positive (95% CI)	Males: % positive (95% CI)
Metals								
Potassium dichromate	0.5	48 610	3.43	2.11	1.7	3.73 (3.56-3.9)	3.39 (3.2-3.59)	4.42 (4.1-4.75)
Cobalt(II) chloride hexahydrate	1	48 579	3.63	3.14	2.39	5.39 (5.19-5.6)	6.09 (5.84-6.36)	3.93 (3.63-4.24)
Nickel(II) sulfate hexahydrate	5	48 421	2.47	6.58	11.25	17.65 (17.31-17.99)	22.99 (22.53-23.45)	6.65 (6.26-7.04)
Fragrances								
Fragrance mix I	8	47 697	2.53	3.92	3.05	6.95 (6.72-7.18)	7.49 (7.2-7.78)	5.82 (5.45-6.2)
Fragrance mix II	14	49 760	2.21	2.24	1.51	3.72 (3.56-3.89)	3.95 (3.75-4.17)	3.26 (2.99-3.55)
HICC	5	44 355	0.83	0.78	0.63	1.41 (1.3-1.53)	1.54 (1.4-1.68)	1.16 (0.99-1.35)
Myroxylon pereirae (balsam of Peru)	25	44 687	2.82	3.77	2.24	5.8 (5.58-6.02)	5.86 (5.59-6.13)	5.68 (5.31-6.07)
Preservatives								
Formaldehyde	1[a]	32 290	1.29	1.16	0.96	2.12 (1.97-2.28)	2.19 (2-2.39)	1.98 (1.73-2.27)
Formaldehyde	2[a]	16 989	0.79	0.98	1	1.98 (1.78-2.2)	2.14 (1.88-2.42)	1.65 (1.33-2.03)
MCI/MI	0.01[a]	38 345	1.35	2.49	2.23	4.73 (4.52-4.95)	4.99 (4.73-5.26)	4.19 (3.84-4.55)
MCI/MI	0.02[a]	10 566	5.44	2.9	2.86	5.74 (5.3-6.2)	6.28 (5.73-6.87)	4.6 (3.93-5.36)
Methylisothiazolinone	0.01[a]	709	1.51	0.99	1.27	2.26 (1.3-3.64)	2.61 (1.36-4.52)	1.55 (0.42-3.92)
Methylisothiazolinone	0.02[a]	4143	0.25	2.49	3.72	6.2 (5.49-6.98)	7.03 (6.15-7.99)	3.79 (2.72-5.12)
Methylisothiazolinone	0.05[a]	17 208	1.59	3.06	2.27	5.33 (5-5.68)	5.39 (4.98-5.83)	5.22 (4.68-5.8)
Methylisothiazolinone	0.2[a]	25 462	1.35	1.95	3.18	5.29 (5.02-5.57)	5.68 (5.34-6.03)	4.44 (4-4.91)
Paraben mix	16	47 093	1.22	0.43	0.21	0.61 (0.54-0.69)	0.47 (0.4-0.55)	0.9 (0.76-1.07)
Quaternium-15	1	29 481	0.23	0.38	0.34	0.7 (0.61-0.8)	0.79 (0.67-0.92)	0.51 (0.37-0.68)
Methyldibromo glutaronitrile	0.2	5058	2.33	1.23	0.42	1.64 (1.31-2.03)	1.28 (0.92-1.73)	2.28 (1.64-3.06)
Methyldibromo glutaronitrile	0.3	28 640	3.32	2.72	0.62	3.29 (3.09-3.51)	3.26 (3.02-3.53)	3.36 (3-3.74)
Methyldibromo glutaronitrile	0.5	13 687	2.9	0.71	3.49	3.89 (3.58-4.23)	3.61 (3.24-4)	4.54 (3.93-5.21)
Medicaments, excipients								
Benzocaine	5	18 643	0.53	0.2	0.54	0.69 (0.58-0.82)	0.67 (0.54-0.83)	0.74 (0.53-1)
Clioquinol (iodochlorhydroxyquine)	5	15 677	0.56	0.12	0.18	0.29 (0.21-0.38)	0.29 (0.2-0.41)	0.28 (0.15-0.48)
Budesonide	0.01	19 268	1.76	0.38	0.31	0.67 (0.56-0.8)	0.6 (0.48-0.74)	0.84 (0.62-1.11)
Budesonide	0.1	13 671	1.24	0.18	0.09	0.29 (0.21-0.4)	0.31 (0.21-0.45)	0.25 (0.13-0.45)
Tixocortol pivalate	0.1	20 849	1	0.27	0.28	0.56 (0.46-0.67)	0.53 (0.42-0.66)	0.62 (0.44-0.84)
Tixocortol pivalate	1	15 713	0.67	0.56	0.25	0.81 (0.68-0.97)	0.82 (0.66-1.01)	0.8 (0.57-1.09)
Neomycin sulfate	20	34 530	0.57	0.5	0.74	1.23 (1.11-1.35)	1.38 (1.23-1.53)	0.89 (0.72-1.09)
Lanolin (wool) alcohols	30	44 607	1.33	1.27	0.51	1.73 (1.61-1.86)	1.72 (1.58-1.88)	1.75 (1.54-1.97)
Rubber additives								
Thiuram mix	1	48 416	0.87	0.85	1.04	1.91 (1.79-2.03)	1.79 (1.65-1.94)	2.15 (1.93-2.39)
N-isopropyl-*N*′-phenyl-*p*-phenylenediamine	0.1	45 703	0.73	0.37	0.34	0.7 (0.62-0.78)	0.54 (0.46-0.63)	1.02 (0.86-1.19)
Mercapto mix (MBT, CBS, MBTS, MOR)	2	27 416	0.25	0.21	0.24	0.46 (0.39-0.55)	0.43 (0.34-0.53)	0.55 (0.4-0.74)
Mercapto mix (CBS, MBTS, MOR)	1	20 322	0.87	0.32	0.24	0.54 (0.45-0.65)	0.42 (0.32-0.55)	0.76 (0.57-0.99)
Mercaptobenzothiazole	2	48 706	0.6	0.27	0.26	0.52 (0.46-0.59)	0.46 (0.39-0.54)	0.66 (0.54-0.8)

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TABLE 2 (Continued)

Allergen	Conc.	Tested	% ? +/IR	% +	% + +/+++	% positive (95% CI)	Females: % positive (95% CI)	Males: % positive (95% CI)
Resins/glues								
Colophonium	20	48 694	1.09	1.33	1.8	3.11 (2.95-3.26)	3.25 (3.06-3.45)	2.81 (2.56-3.08)
Epoxy resin	1	47 014	0.64	0.54	0.72	1.24 (1.14-1.34)	0.85 (0.75-0.95)	2.05 (1.83-2.29)
PTBFR	1	34 453	0.7	0.31	0.31	0.64 (0.55-0.73)	0.68 (0.58-0.79)	0.54 (0.41-0.7)
Other								
p-Phenylenediamine	1	37 377	0.77	1.28	2.18	3.44 (3.26-3.63)	4.02 (3.79-4.27)	2.13 (1.87-2.41)
Sesquiterpene lactone mix	0.1	27 963	0.75	0.31	0.46	0.8 (0.7-0.91)	0.8 (0.68-0.93)	0.82 (0.64-1.03)
Primin	0.01	22 031	1.39	0.12	0.17	0.28 (0.21-0.36)	0.34 (0.25-0.44)	0.13 (0.06-0.25)
Textile dye mix	6.6	14 021	3.74	0.8	2.04	2.77 (2.51-3.06)	3.03 (2.7-3.39)	2.21 (1.79-2.68)

Abbreviations: Conc., concentration in %, tested in petrolatum, except where otherwise indicated; CBS, N-Cyclohexylbenzothiazyl sulfenamide; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde; IR, irritant; MBT, 2-Mercaptobenzothiazole; MBTS, Dibenzothiazyl disulfide; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone; MOR, 2-(4-Morpholinylmercapto)benzothiazol; PTBFR, *p-tert*-butylphenol formaldehyde resin.
[a]Aqueous (aq.).

TABLE 3 Patch test results (day 3 to day 5) with additions to the European baseline series, 2015 to 2018, in those departments of the European Surveillance System on Contact Allergies (ESSCA) testing these in consecutive patients

Allergen	Concentration	Tested	% ? +/IR	% +	% + +/+++	% positive (95% CI)	Females: % positive (95% CI)	Males: % positive (95% CI)
Oil of turpentine	10.00	14 176	1.01	0.58	0.23	0.81 (0.67-0.97)	0.77 (0.6-0.98)	0.88 (0.64-1.17)
MDBGN + 2-phenoxyethanol	0.50	227		0.88	0.00	0.88 (0.11-3.15)	1.22 (0.15-4.34)	0 (0-5.69)
MDBGN + 2-phenoxyethanol	1.00	548		0.91	2.01	2.92 (1.68-4.7)	2.44 (1.12-4.58)	3.91 (1.59-7.89)
MDBGN + 2-phenoxyethanol	1.50	1820	0.62	0.22	0.16	0.38 (0.15-0.79)	0.26 (0.05-0.75)	0.62 (0.17-1.58)
Diazolidinyl urea	2.00	22 276	0.3	0.44	0.15	0.59 (0.49-0.7)	0.58 (0.46-0.71)	0.61 (0.44-0.83)
Imidazolidinyl urea	2.00	22 115	0.27	0.39	0.08	0.47 (0.38-0.56)	0.24 (0.03-0.85)	0 (0-1.16)
Imidazolidinyl urea	1.00	1167		0.17	0.00	0.17 (0.02-0.62)	0.48 (0.38-0.61)	0.41 (0.28-0.59)
2-Bromo-2-nitropropane-1,3-diol	0.25	5805	0.25	0.78	0.14	0.91 (0.68-1.19)	0.98 (0.7-1.32)	0.75 (0.39-1.3)
2-Bromo-2-nitropropane-1,3-diol	0.30	2525	0.04	0.00	0.51	0.51 (0.27-0.88)	0.76 (0.41-1.3)	0 (0-0.45)
2-Bromo-2-nitropropane-1,3-diol	0.50	8454	0.19	0.35	0.15	0.51 (0.37-0.68)	0.51 (0.34-0.73)	0.51 (0.28-0.85)
Iodopropynyl butylcarbamate	0.20	22 978	3.29	1.03	0.13	1.17 (1.03-1.31)	1.12 (0.96-1.3)	1.25 (1.02-1.52)
Caine mix III (benzocaine, dibucaine, tetracaine)	10.00	13 742	0.79	1.11	0.28	1.45 (1.26-1.66)	1.31 (1.09-1.57)	1.74 (1.37-2.17)
Propolis	10.00	21 807	3.6	2.36	0.60	2.96 (2.74-3.19)	2.9 (2.63-3.19)	3.07 (2.69-3.48)
Sodium metabisulfite	1.00	13 088	0.96	2.97	1.00	3.97 (3.64-4.32)	3.19 (2.84-3.57)	5.75 (5.05-6.51)
Fusidic acid, sodium salt	2.00	4585	0.13	0.15	0.02	0.17 (0.08-0.34)	0.22 (0.09-0.45)	0.07 (0-0.41)
Zinc diethyldithiocarbamate	1.00	15 605	0.39	0.35	0.25	0.6 (0.48-0.73)	0.59 (0.45-0.77)	0.6 (0.42-0.84)
Carba mix	3.00	19 792	1.64	2.27	0.35	2.61 (2.39-2.84)	1.97 (1.74-2.22)	4 (3.53-4.52)
Compositae mix	6.00	733	0.41	0.14	0.27	0.41 (0.08-1.19)	0.22 (0.01-1.2)	0.74 (0.09-2.63)
Compositae mix	5.00	15 354	0.88	0.85	0.59	1.45 (1.26-1.65)	1.27 (1.06-1.51)	1.74 (1.42-2.12)
Compositae mix	2.50	3306	0.16	0.15	0.33	0.48 (0.28-0.78)	0.53 (0.28-0.93)	0.38 (0.1-0.96)
Cetearyl alcohol	20.00	25 213	0.93	0.34	0.13	0.47 (0.39-0.56)	0.47 (0.37-0.59)	0.47 (0.34-0.64)

Note: Compositae mix 5% contained the following extracts and single compounds, respectively: *Anthemis nobilis* 1.2%, *Chamomilla recutita* 1.2%, *Achillea millefolium* 1%, *Tanacetum vulgare* 1%, *Arnica montana* 0.5%, and parthenolide 0.1%; in the 2.5% version, the same ingredients were included at half the concentration; 6% contained *Tanacetum vulgare* 1%, *Arnica montana* 0.5%, *Tanacetum parthenium* 1%, *Matricaria chamomilla* 2.5%, and *Achillea millefolium* 1%. All allergens in petrolatum (pet.). conc., concentration in %; IR, irritant; MDBGN, Methyldibromo glutaronitrile.

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TABLE 4 Patch test results (day 3 to day 5) with the TRUE Test allergens, 2015 to 2018, in those six departments (partially) using it

Allergen	Conc. (μg/cm^2)	Tested	% ?+/IR	% +	% ++/+++	% positive (95% CI)
Metals						
Potassium dichromate	54	2591	0.72	1.58	1.54	3.13 (2.49-3.87)
Cobalt (II) chloride	20	2588	1.32	3.63	2.01	5.64 (4.78-6.6)
Nickel (II) sulfate	200	2571	3.04	8.95	12.37	21.31 (19.75-22.95)
Fragrances						
Fragrance mix I	500	2592	1.03	2.35	1.43	3.78 (3.08-4.59)
Myroxylon pereirae (balsam of Peru)	800	2591	0.47	1.47	0.73	2.2 (1.67-2.84)
Preservatives						
Formaldehyde	180	2592	0.76	0.81	0.35	1.16 (0.78-1.65)
MCI/MI	4	2593	0.27	2.58	6.44	9.02 (7.95-10.19)
Paraben mix	1000	2592	0.53	0.23	0.12	0.35 (0.16-0.66)
Quaternium-15	100	2592	0.45	0.73	0.5	1.23 (0.85-1.74)
Diazolidinyl urea	550	2581	0.4	0.35	0.08	0.43 (0.21-0.76)
Imidazolidinyl urea	600	2578	0.2	0.23	0.08	0.31 (0.13-0.61)
Quinoline mix	190	1082		0.18	0.18	0.37 (0.1-0.94)
Thiomersal	7	2591	0.8	1.35	1.16	2.51 (1.94-3.19)
Medicaments, excipients						
Caine mix III (benzo-, dibu-, tetracaine)	630	2591	0.53	0.62	0.73	1.35 (0.94-1.87)
Budesonide	1	2590	1.46	0.19	0.19	0.39 (0.19-0.71)
Tixocortol pivalate	3	2594	1.16	0.42	0.42	0.85 (0.53-1.28)
Hydrocortisone-17-butyrate	20	2241	3.19	0.18	0.13	0.31 (0.13-0.64)
Neomycin sulfate	600	2591	0.2	0.27	0.15	0.42 (0.21-0.76)
Lanolin (wool) alcohols	1000	2595	1.2	0.89	0.12	1 (0.66-1.46)
Rubber additives						
Thiuram mix	27	2590	1.06	1.2	0.85	2.05 (1.54-2.67)
p-Phenylenediamine (black rubber) mix	75	2590	0.73	0.46	0.46	0.93 (0.59-1.38)
Mercapto mix (CBS, MBTS, MOR)	75	2591	0.4	0.62	0.5	1.12 (0.75-1.6)
Mercaptobenzothiazole	75	2588	0.27	0.46	0.31	0.77 (0.47-1.19)
Carba mix	250	2578	2.7	2.56	1.01	3.57 (2.89-4.36)
Resins/glues						
Colophonium	1200	2591	0.54	1.27	0.96	2.24 (1.7-2.88)
Epoxy resin	50	2587	1.19	1.04	1.04	2.09 (1.57-2.71)
PTBFR	45	2591	0.93	1.39	0.89	2.28 (1.74-2.93)
Other						
p-Phenylenediamine	90	2570	0.72	1.48	2.18	3.66 (2.97-4.46)
Ethylenediamine-HCl	50	2591	0.49	0.35	0.46	0.81 (0.5-1.24)

Abbreviations: CBS, N-Cyclohexylbenzothiazyl sulfenamide; MBTS, Dibenzothiazyl disulfide; MCI, methylchloroisothiazolinone; MDBGN, methyldibromo glutaronitrile; MI, methylisothiazolinone; MOR, 2-(4-Morpholinylmercapto)benzothiazol; PTBFR, *p-tert*-butylphenol formaldehyde resin.

had been tested with both carba mix and ZDEC, but 15 549 with both thiuram mix and ZDEC. Among these, 71 reacted to both allergen preparations, 325 only to thiuram mix, and 19 to ZDEC, but not to thiuram mix.

Regarding reactivity to sesquiterpene lactone (SL) mix vs the three different Compositae mixes, 3305 patients were tested with SL mix and Compositae mix 2.5% pet.; of these, 10 reacted positive to both, 6 only to Compositae mix, and 9 only to SL mix. Fewer patients (n = 1154) had been tested with both SL mix and Compositae mix 5% pet., with 0 reacting positive to both, 2 only to Compositae mix 5%, and 4 only to SL mix. Compositae mix 6% pet. had not been tested in parallel with SL mix in a significant number of patients. Finally, cross-reactivity between colophonium and oil of turpentine was examined. Both allergens had been applied in 14 150 patients, with positive

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reactions in 65 (0.46%) to both allergen preparations, and in 492 (3.48%) only to colophonium and 48 (0.34%) only to oil of turpentine (OR 37.3, $P < .0001$). Oil of turpentine could be viewed as a fragrance allergen, owing to its use as raw fragrance material. Cross-reactivity to both fragrance mix (FM) I and *Myroxylon pereirae* resin was less, with ORs of 6.2 and 5.2, respectively, but still highly significant (both $P < .0001$).

Altogether, 25 141 patients were routinely tested with both lanolin (wool) alcohols and cetearyl (cetostearyl) alcohol, almost exclusively in the IVDK departments and in the UK. While the prevalence of positive reactions to lanolin alcohols was not significantly different between IVDK and UK departments ($P = .4$), that of positive reactions to cetearyl alcohol was 0.7% in the former vs 0.2% in the latter ($P < .0001$). Co-reactivity between the two emulsifiers was limited, with 24 (0.1%) patients reacting to both, 498 (1.98%) only to lanolin alcohols, and 95 (0.38%) only to cetearyl alcohol.

Propolis is a long-standing constituent of the baseline series in German-speaking countries. The prevalence of positive reactions was 4% in the participating departments of the three countries (Austria, Germany, and Switzerland) which are also members of the IVDK, and 1% in the others testing it, namely, departments from Italy, Lithuania, UK, and, to a limited extent, The Netherlands and Poland, $P < .0001$. While propolis is not a fragrance allergen, cross-reactivity to FM I (OR 5.6) and *M pereirae* (OR 7.5) was substantial (both $P < .0001$).

Finally, patch test results with the TRUE Test are shown in Table 4; the departments using this test system as a part of their baseline patch test work-up supplemented this with investigator-loaded test allergens to (mostly) conform with the EBS. These latter results are included in Table 2, for example, concerning MI.

4 | DISCUSSION

The present analysis of routine surveillance data collected by the ESSCA follows up on previous reports and is a continuation of a series of similar reports on data from 2002/2003,[16] 2004,[17] 2005/2006,[18] 2007/2008,[19] 2009 to 2012,[20-25] and lastly, 2013/2014.[3] The changing patterns of contact allergy can therefore be observed and interpreted, albeit from the background of a partly changing contribution to the network, which needs to be considered.

With increasing geographical contribution to the ESSCA network, extreme proportions of the characteristics of patients as described by the MOAHLFA index have partly increased, while the changes in the mean values are less pronounced. For instance, compared with the first reporting period, in which a table identical to Table 1 had been incorporated,[16] the share of males slightly dropped from 37.1% to 32.9%, whereas the percentage of patients with occupational dermatitis increased slightly from 13.1% to 16.1%. In accordance with observations elsewhere, but not quite as marked,[26] there was a trend of patients being older in the recent period, with a share of 62.6% aged 40 and older, compared with 57.8% in the first ESSCA report. The most striking increase was seen in the proportion of patients with a history or current diagnosis of atopic dermatitis, from 18.0% to the current figure of 27.5%. However, there is no uniform definition of (a history of) atopic dermatitis, leading to considerable heterogeneity of this characteristic, and thus difficulties in interpreting this change, also owing to the changing and expanding nature of ESSCA. Concerning anatomical sites of dermatitis, a shift from leg (9.1% to 5.3%) to face (from 13.4% to 17.9%) and a largely stable share of hand dermatitis (28.7% vs 27.0%) was observed. A decrease of leg dermatitis may be due to a change of treatment paradigms, with less allergenic products used in more recent times.[27] The increase in face dermatitis can, at least partly, be attributed to the recent epidemic of MI sensitization with many cosmetic-related cases of face dermatitis.[28]

The overall yield of the baseline series, in terms of at least one positive reaction to one of its allergens, had been suggested as another descriptor of a patch tested patient population.[11] However, as this measure summarizes rather complex effects, as more extensively discussed in Uter et al,[20] its interpretation is not straightforward; notwithstanding, the broad range of positivity does stimulate speculation.

4.1 | European baseline series (version 2015)

Taken together, and certainly dominated by nickel, the three metals included in the EBS most commonly cause contact allergies. Age-stratified results indicate a lower prevalence of nickel allergy in the youngest age group, compared with the quite broadly defined middle age group. This may reflect to some extent a, albeit limited, decline of nickel contact allergy.[29] However, despite a considerable success of preventive efforts, nickel exposure prevention needs further improvement.[30] The prevalence of chromium contact allergy is lowest in the youngest age group; however, because chromium is a less ubiquitous allergen, the success of prevention (reduction of hexavalent chromium in cement and more recently, in leather) should best be reviewed in particularly exposed subgroups, for example, in the building industry[31] and in patients with shoe (foot) dermatitis. Cobalt, in contrast to the other two metals, does not display any age pattern. Given the general difficulty in identifying clinical relevance for sensitization to cobalt,[32] it is difficult to identify relevant exposures which need to be addressed by further research and, ultimately, prevented.

Fragrances are the next most common group of substances or mixtures causing contact allergy. Positive patch test reactions to FM I show a well-known age gradient,[33] possibly owing to the life-long cumulative exposure and steadily increasing risk of sensitization. It is unclear, at least by just looking at the FM I results, whether the lower prevalence in the younger patients also reflects self-regulatory concentration restrictions concerning FM I constituents in cosmetics taken in the past. A similar pattern is seen for FM II and its main allergenic constituent, hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC). In view of the recent ban of HICC, and the de facto ban of *Evernia prunastri* (oak moss) due to the restrictions on (chlor)atranol,[34] a re-design of the mixes could be considered in due time, to adapt these to the currently relevant exposure conditions in Europe. The age gradient of positive reactions to *M. pereirae* (balsam of Peru) is

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even more marked than that of FM I. This "ill-defined natural fragrance mix" is an apparently important, but also enigmatic allergen, concerning the consequences of a positive patch test for the patient, as recently reviewed by de Groot.[35]

The dramatic increase of contact allergy prevalence to MI and, parallel to this, to the mixture methylchloroisothiazolinone (MCI)/MI 3:1 in the recent past, and the decline since 2013/2014 have been repeatedly reported and discussed,[9,36] and shall not be expanded on here. The fact that MI 0.02 and 0.05% aq. elicited a slightly higher share of positive reactions than MI 0.2% as recommended appears counter-intuitive, but should not be overinterpreted: (a) different subgroups of patients had been patch tested, and (b) the prevalences are not significantly different, if overlapping 95% CIs are considered. The lesser decrease of MI 0.2% aq., as compared with 0.05% aq., during the study period characterized by a marked decrease of MI sensitization prevalence may have partly contributed to the seemingly similar yield of patch reactions with the two concentrations. The same holds true for formaldehyde, while MCI/MI and methyldibromo glutaronitrile (MDBGN) show a pattern one would expect. In 2005, the European Union (EU) banned the use of MDBGN in leave-on cosmetic products, and then in 2007 banned it also in rinse-off cosmetic products. The fact that patients up to the age of 30 years had positive patch test reactions to MDBGN in 2015 to 2018 (Table S3) may imply that these individuals were all sensitized to MDBGN in cosmetics by the age of 20 years. Alternatively, or additionally, there may be exposure from rogue cosmetics, unregulated use in medical devices, cosmetic products marketed as medical devices, undeclared exposure,[37] or noncosmetic sources such as paints, glues, or technical fluids, although such broad exposure to MDBGN is largely unknown presently. From this background, reporting on patients with currently relevant contact allergy to MDBGN[37,38] is encouraged. A cautionary note is that false-positive reactions particularly to MDBGN 0.5% pet. may occur.[39] As sensitization to paraben mix and quaternium-15 is now uncommon (Table 2), the continued inclusion of these allergens in the EBS may be only marginally justifiable.

The EBS contains two corticosteroids assumed to cover different antigenic classes,[40] namely, budesonide and tixocortol pivalate. A Spanish multicentre study involving 3699 consecutively patch tested patients added six other corticosteroids (methylprednisolone aceponate, mometasone furoate, prednicarbate, clobetasol propionate, betamethasone 17-valerate, and betamethasone 17, 21-dipropionate). Overall, 1.46% (n = 54) showed a positive reaction to at least one of the eight corticosteroids and, among these, 39 to one of the six additional corticosteroids. Interestingly, 24 of those 39 were not positive to any of the two screening markers; hence, contact allergy would have been missed when relying solely on these.[41] In other words, the two EBS markers failed to detect corticosteroid allergy in about 40% of the patients in that study, which probably depends on country- or region-specific exposure/prescription. Of note, the Spanish study used a day 7 reading, which was mostly lacking in the present data, and in the outcome definition, which must be regarded as a shortcoming leading to underestimation of the sensitization prevalence particularly of the corticosteroids by up to 30%.[42] It is recommended to test with a full series of corticosteroids in case allergic contact dermatitis to these is suspected.

Clioquinol contact allergy has become a rarity, justifying its recent elimination from the EBS.[4] Benzocaine was replaced by Caine mix III in 2019, and at least in the present analysis the detection rate of the latter is higher; however, further patch test studies on Caine mix III are warranted to further assess its diagnostic validity and the clinical relevance of positive reactions. Neomycin sulfate is a topical antibiotic rarely used in some countries, while it is a popular, sometimes over-the-counter remedy, in others; this heavily impacts the prevalence of sensitization. From this background, the German Contact Dermatitis Research Group decided several years ago to remove neomycin sulfate from its baseline series; however, in other countries, and certainly the United States, it is still an important part of the baseline series.[43]

Compared with thiuram mix, sensitization to the other rubber allergens, including *N*-isopropyl-*N*′-phenyl-*p*-phenylenediamine, is relatively rare. Of note, thiurams, including the mix, are considered to detect contact allergy to dithiocarbamates, as corresponding thiurams and dithiocarbamates constitute redox pairs.[44] Positive patch test reactions to the benzothiazoles are almost twice as common in the youngest, compared with the oldest age group, likely pointing to occupational exposure and sensitization, for example, in the healthcare sector, or perhaps to fashion-related exposures. In general, if (occupational) exposure to rubber additives is suspected to cause allergic contact dermatitis, testing with a dedicated rubber series, pieces of rubber products, or ultrasonic extracts thereof is indicated.[44] Patch testing with rubber constituents has been discussed in-depth elsewhere,[25,44] particularly the problem of irritant patch test reactions to 1,3-diphenylguanidine,[45] which has been found, at the same time, to be an important allergen in synthetic rubber gloves.[46]

The sensitization prevalence of PPD is largely stable, with a preponderance of females (Table 2) and a weak variation across age groups (Table S2). Contact allergy to PPD is often related to exposure to oxidative hair dyes.[47] Hence, a much reduced share of PPD-containing hair dye products and replacement with only partially cross-reacting PPD derivatives recently observed at least in Germany[48] could be expected to contribute to a lessening of sensitization frequency. The marked cross-reactivity of PPD with TDM, owing to the presence of Disperse Orange 3 in the latter, has been confirmed in the present data. To avoid unnecessary, possibly strong, or extreme patch test reactions, a TDM without Disperse Orange 3 should be evaluated.[49]

The frequency of sensitization to epoxy resin largely remained stable over the previous years;[3] contact allergy is mostly observed in patients with occupational dermatitis.[50] This suggests that further efforts to improve occupational hygiene are necessary, especially in (spray) painting and at construction sites or in pipe relining.[51]

4.2 | Additional, consecutively tested allergens

Among the allergens still not part of the EBS in the study period, propolis and caine mix III, along with 2-hydroxyethyl methacrylate, have

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been incorporated in the 2019 version of the EBS. With a sensitization prevalence of around 3%, remarkably similar between the sexes and with just a slight increase with age, propolis seems indeed a worthwhile addition. Accordingly, propolis had been identified as an emerging allergen in a recent analysis of long-term data from the IVDK (of which the present data sample constitutes a fraction, see the "Methods" section).[9] A comparison between results from "IVDK countries" and the remaining countries testing with propolis shows a highly significant difference in prevalences, with a prevalence of 1% in the latter, illustrating the well-known geographical variation of contact allergy to this natural product.[19] Further results are awaited, together with information on clinical relevance and exposure in patients with positive patch test reactions. With a prevalence of positive reactions well above 1%, caine mix III also seems a worthwhile addition or rather replacement in the EBS; notwithstanding further studies, for example, comparing mix with break-down results. 2-Hydroxyethyl methacrylate had not been consecutively tested in a sufficient number of departments to warrant presentation. However, owing to the massively increased exposure in terms of cosmetic acrylic nail usage, contact allergy to this allergen is expected to escalate.[52]

Data suggest that SL mix alone is insufficient as a screen to diagnose Compositae allergy, but the ideal combination is not yet established. Some suggest a combination with Compositae mix II 2.5% pet. and parthenolide 0.1% pet.[53] However, while the original Compositae mix I 5% pet. induced active sensitization, others feel that the 5% concentration of the Compositae mix II is not sensitizing and contains parthenolide 0.1%[54] rather than feverfew extract that was in the mix I.

The question as to whether different formaldehyde releasers, including quaternium-15, which is a longstanding constituent of the EBS, should be tested in addition to formaldehyde (ideally 2% aq.) has been addressed by another, dedicated analysis and shall not be discussed here.[55] The present results with the different formaldehyde releasers are largely similar to the more detailed, department-wise analysis of 2013/2014 data.[56] The mixture of MDBGN and 2-phenoxyethanol 1:4 (eg, Euxyl K 400 as trademark) is still tested to a limited extent by some departments. Iodopropynyl butylcarbamate (IPBC) 0.2% pet., tested in more than 20 000 consecutive patients, caused over 1% positive, mostly weak positive, reactions and about three times as many doubtful or irritant reactions. However, other studies found a lower sensitization prevalence (eg, 0.53%).[57] IPBC liberates iodine, which has also been supported by observing simultaneous contact allergy to IPBC and iodine.[58] Owing to possible endocrine interference, use concentrations are restricted to between 0.02% in rinse-off products and 0.0075% in deodorants/antiperspirants for many years (SCCNFP/0826/04, EU Cosmetics Regulation, Annex V/56). It would be of interest to further investigate IPBC regarding the clinical relevance of (weak) positive patch test reactions. Similar to propolis, cetearyl alcohol also exhibits significant geographical differences, albeit on a much lower level, presently not justifying inclusion into the EBS. While sodium metabisulfite yields a considerable number of positive reactions (Table 3) and has thus been recommended to be added to the EBS,[4] fusidic acid seems to be a rare allergen not warranting consecutive testing.

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CONFLICTS OF INTEREST

W.U. has accepted travel reimbursement and research funds from the cosmetic industry association IFRA and has received a lecture fee from dermatology-related sponsors for an educational lecture on contact allergy. The IVDK, maintained by the IVDK e.V., of which J.G. is an employee, is sponsored by the cosmetic and fragrance industry (associations) as well as by public funds. M.G. has received honoraria for advisory boards and lectures from Novartis and Sanofi-Genzyme. M.W. has received travel reimbursement to attend meetings with the cosmetic industry. The other authors have no pertinent conflict of interests to declare.

AUTHOR CONTRIBUTION (CRediT)

Wolfgang Uter, Andrea Bauer, Anna Belloni Fortina, Andreas J. Bircher, Richard Brans, Timo Buhl, Susan M. Cooper, Magdalena Czarnecka-Operacz, Heinrich Dickel, Aleksandra Dugonik, Johannes Geier, Ana M. Giménez-Arnau, Margarida Gonçalo, Jeanne D. Johansen, Graham A. Johnston, Vera Mahler, Thomas Rustemeyer, Javier Sanchez-Perez, Marie L.A. Schuttelaar, Dagmar Simon, Radoslaw Spiewak, Skaidra Valiukeviciene, Elke Weisshaar, Ian R. White, and Mark Wilkinson: Conceptualization; Andrea Bauer, Anna Belloni Fortina, Andreas J. Bircher, Richard Brans, Timo Buhl, Susan M. Cooper, Magdalena Czarnecka-Operacz, Heinrich Dickel, Aleksandra Dugonik, Johannes Geier, Ana M. Giménez-Arnau, Margarida Gonçalo, Jeanne D. Johansen, Graham A. Johnston, Vera Mahler, Thomas Rustemeyer, Javier Sanchez-Perez, Marie L.A. Schuttelaar, Dagmar Simon, Radoslaw Spiewak, Skaidra Valiukeviciene, Elke Weisshaar, Ian R. White, and Mark Wilkinson Data curation (equal); Formal analysis Wolfgang Uter (lead); Margarida Gonçalo (equal) and Mark Wilkinson (equal): Funding acquisition; Andrea Bauer, Anna Belloni Fortina, Andreas J. Bircher, Richard Brans, Timo Buhl, Susan M. Cooper, Magdalena Czarnecka-Operacz, Heinrich Dickel, Aleksandra Dugonik, Johannes Geier, Ana M. Giménez-Arnau, Margarida Gonçalo, Jeanne D. Johansen, Graham A. Johnston, Vera Mahler, Thomas Rustemeyer, Javier Sanchez-Perez, Marie L.A. Schuttelaar, Dagmar Simon, Radoslaw Spiewak, Skaidra Valiukeviciene, Elke Weisshaar, Ian R. White, and Mark Wilkinson: Investigation (equal); Wolfgang Uter, Andrea Bauer, Anna Belloni Fortina, Andreas J. Bircher, Richard Brans, Timo Buhl, Susan M. Cooper, Magdalena Czarnecka-Operacz, Heinrich Dickel, Aleksandra Dugonik, Johannes Geier, Ana M. Giménez-Arnau, Margarida Gonçalo, Jeanne D. Johansen, Graham A. Johnston, Vera Mahler, Thomas Rustemeyer, Javier Sanchez-Perez, Marie L.A. Schuttelaar, Dagmar Simon, Radoslaw Spiewak, Skaidra Valiukeviciene, Elke Weisshaar, Ian R. White, and Mark Wilkinson: Methodology (equal and supporting); Wolfgang Uter, Andrea Bauer, Anna Belloni Fortina, Andreas J. Bircher, Richard Brans, Timo Buhl, Susan M. Cooper, Magdalena Czarnecka-Operacz, Heinrich Dickel, Aleksandra Dugonik, Johannes Geier, Ana M. Giménez-Arnau, Margarida Gonçalo, Jeanne D.

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Johansen, Graham A. Johnston, Vera Mahler, Thomas Rustemeyer, Javier Sanchez-Perez, Marie L.A. Schuttelaar, Dagmar Simon, Radoslaw Spiewak, Skaidra Valiukeviciene, Elke Weisshaar, Ian R. White, and Mark Wilkinson: Validation (equal); Wolfgang Uter, Andrea Bauer, Anna Belloni Fortina, Andreas J. Bircher, Richard Brans, Timo Buhl, Susan M. Cooper, Magdalena Czarnecka-Operacz, Heinrich Dickel, Aleksandra Dugonik, Johannes Geier, Ana M. Giménez-Arnau, Margarida Gonçalo, Jeanne D. Johansen, Graham A. Johnston, Vera Mahler, Thomas Rustemeyer, Javier Sanchez-Perez, Marie L.A. Schuttelaar, Dagmar Simon, Radoslaw Spiewak, Skaidra Valiukeviciene, Elke Weisshaar, Ian R. White, and Mark Wilkinson: Visualization: (equal and supporting); Wolfgang Uter: Writing – original draft (lead); Wolfgang Uter, Andrea Bauer, Anna Belloni Fortina, Andreas J. Bircher, Richard Brans, Timo Buhl, Susan M. Cooper, Magdalena Czarnecka-Operacz, Heinrich Dickel, Aleksandra Dugonik, Johannes Geier, Ana M. Giménez-Arnau, Margarida Gonçalo, Jeanne D. Johansen, Graham A. Johnston, Vera Mahler, Thomas Rustemeyer, Javier Sanchez-Perez, Marie L.A. Schuttelaar, Dagmar Simon, Radoslaw Spiewak, Skaidra Valiukeviciene, Elke Weisshaar, Ian R. White, and Mark Wilkinson: Writing – review & editing: (equal and supporting). **Wolfgang Uter:** Conceptualization; formal analysis; methodology; project administration; resources; software; visualization; writing-original draft; writing-review and editing. **Andrea Bauer:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Anna Belloni Fortina:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Andreas Bircher:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Richard Brans:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Timo Buhl:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Susan Cooper:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Magdalena Czarnecka-Operacz:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Heinrich Dickel:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Aleksandra Dugonik:** Conceptualization; data curation; investigation; methodology; project administration; resources; software; validation; visualization; writing-review and editing. **Johannes Geier:** Conceptualization; data curation; funding acquisition; methodology; project administration; resources; software; validation; visualization; writing-review and editing. **Ana Giménez-Arnau:** Conceptualization; data curation; investigation; methodology; project administration; resources; software; validation; visualization; writing-review and editing. **Margarida Gonçalo:** Conceptualization; data curation; funding acquisition; investigation; methodology; project administration; resources; software; validation; visualization; writing-original draft; writing-review and editing. **Jeanne Duus Johansen:** Data curation; investigation; methodology; resources; supervision; writing-original draft; writing-review and editing. **Graham Johnston:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Vera Mahler:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Thomas Rustemeyer:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Javier Sanchez-Perez:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Marie-Louise Schuttelaar:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Dagmar Simon:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Radoslaw Spiewak:** Conceptualization; data curation; investigation; methodology; project administration; resources; software; validation; visualization; writing-review and editing. **Skaidra Valiukeviciene:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Elke Weisshaar:** Conceptualization; data curation; investigation; methodology; project administration; resources; validation; visualization; writing-review and editing. **Ian White:** Conceptualization; data curation; investigation; methodology; project administration; resources; software; validation; visualization; writing-review and editing. **Mark Wilkinson:** Conceptualization; data curation; funding acquisition; investigation; methodology; project administration; resources; software; validation; visualization; writing-original draft; writing-review and editing.

DATA AVAILABILITY STATEMENT

Data not available due to privacy/ethical restrictions

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ORCID

Wolfgang Uter https://orcid.org/0000-0002-4498-3710
Andrea Bauer https://orcid.org/0000-0002-4411-3088
Anna Belloni Fortina https://orcid.org/0000-0001-5791-0775
Timo Buhl https://orcid.org/0000-0002-3139-129X
Johannes Geier https://orcid.org/0000-0002-5047-8948
Margarida Gonçalo https://orcid.org/0000-0001-6842-1360
Jeanne D. Johansen https://orcid.org/0000-0002-3537-8463
Vera Mahler https://orcid.org/0000-0001-6471-1811
Thomas Rustemeyer https://orcid.org/0000-0001-7580-0684
Dagmar Simon https://orcid.org/0000-0001-8965-9407
Radoslaw Spiewak https://orcid.org/0000-0001-5968-0555

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