

Occupational anaphylaxis—Data from the anaphylaxis registry

Margitta Worm¹  | Veronika Höfer¹  | Sabine Dölle-Bierke¹  | Maria Beatrice Bilo^{2,3}  | Karin Hartmann^{4,5}  | Dominique Sabouraud-Leclerc⁶ | Regina Treudler⁷ 

¹Division of Allergy and Immunology, Department of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

²Department of Clinical and Molecular Sciences, Università Politecnica delle Marche, Ancona, Italy

³Allergy Unit, Department of Internal Medicine, University Hospital Ospedali Riuniti di Ancona, Torrette, Italy

⁴Division of Allergy, Department of Dermatology, University Hospital Basel and University of Basel, Basel, Switzerland

⁵Department of Biomedicine, University Hospital Basel and University of Basel, Basel, Switzerland

⁶Praticien Hospitalier, Pédiatre Allergologue, Service Pédiatrie A, Pôle Femme/Parents/Enfant, AMH 2, Reims, France

⁷Department of Dermatology, Venereology and Allergology, Universitätsklinikum Leipzig, Leipzig, Germany

Correspondence

Margitta Worm, Division of Allergy and Immunology, Department of Dermatology and Allergology, Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany.
Email: margitta.worm@charite.de

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Abstract

Background: Epidemiologic data on occupational anaphylaxis is scarce, and there is a need of more knowledge about work-related anaphylactic episodes.

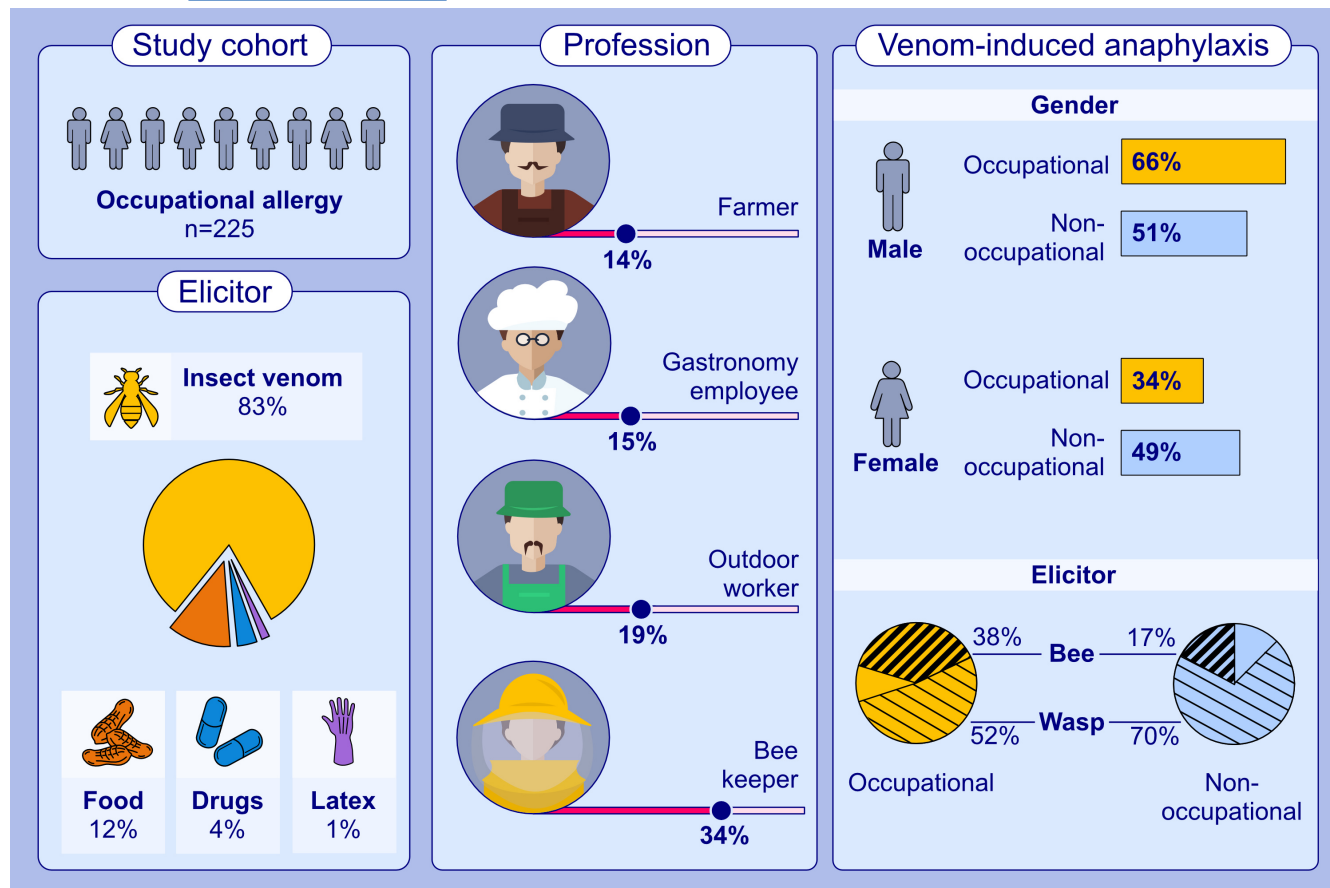
Methods: Based on the data of the Anaphylaxis Registry, we identified cases related to occupational exposure and analyzed the elicitors, demographics, severity of clinical reaction and management.

Results: Since 2017, 5851 cases with an information about the occupational relation of the anaphylactic episode were registered whereby 225 (3.8%) were assigned to be caused by an occupational allergen. The vast majority of these occupational anaphylaxis cases were caused by insects ($n=186$, 82.7%) followed by food ($n=27$, 12.0%) and drugs ($n=8$, 3.6%). Latex elicited occupational anaphylaxis in only two cases. Beekeepers, gardeners, farmers, and individuals working in professions associated with food handling, for example, employees in restaurants, bakery, pastry, and cooks were most frequently affected. The comparison of the occupational insect venom-induced anaphylaxis to a group of non-occupational insect anaphylaxis in adults ($n=1842$) revealed a significant younger age in occupational anaphylaxis (46 vs. 53 years), a predominance of bee-induced cases (38% vs. 17%), and a higher rate of venom immunotherapy in a primary care setting (3.3% vs. 1.3%, $p=.044$). In the occupational- versus non-occupational adults with food-induced anaphylaxis atopic dermatitis as concomitant atopic disease was observed more frequently ($n=486$; 20% vs. 10%), although this was not significant.

Conclusion: Our data demonstrate the impact of venom allergy in work-related anaphylaxis. Foods and drugs are less frequently elicitors, and latex-induced occupational anaphylaxis was rare. More data are needed to determine risk factors associated with occupational anaphylaxis.

KEYWORDS

food allergy, drugs, latex, occupational anaphylaxis, venom



GRAPHICAL ABSTRACT

Insect venom, followed by food were the most frequent elicitors of occupational anaphylaxis. Anaphylaxis to bee venom was more frequent in occupational anaphylaxis than non-occupational anaphylaxis in adults. Occupational anaphylaxis to drugs was rare and most frequently induced by antibiotics. Only two occupational cases were latex-induced. Beekeepers, outdoor workers (e.g., gardeners), and farmers were the most frequently affected occupations.

1 | INTRODUCTION

Occupational allergy is defined as an entity characterized by the fact that the allergic reaction is acquired and/or triggered by allergens in an individual who is exposed within the professional context. In principle, occupational allergy can be induced via type I or type IV sensitization towards proteins and in case of type IV sensitization also to various chemicals. Type IV allergens are inducing an allergic contact dermatitis, which plays a major role in occupational dermatology, for example, occupational hand eczema. By contrast occupational anaphylaxis is much less frequent. Anaphylaxis occurring in the workplace may not only be induced by workplace exposures but may also arise from non-workplace exposures manifesting at work. Anaphylaxis due to non-occupational allergens, occurring at or exacerbated by the workplace, can be common. In a European survey, 5.9% of food anaphylaxis occurred at workplace.¹ Therefore, reactions require careful evaluation before being labeled as “occupational.”

In an EAACI task force consensus statement from 2015, the current scientific evidence linking exposure to occupational triggers and the risk of anaphylaxis including a proposal regarding possible preventive measures was published.²

In detail mechanisms, diagnosis, the identification of triggers and a general approach to management, early detection and prevention were suggested in this paper. The position paper also pointed out the need of epidemiologic data on occupational anaphylaxis and the need of more knowledge about the proportion of anaphylactic episodes that relate to work.

So far the limited literature on this topic suggests that venom and latex, and to a lesser extent food and drugs are among the most frequent elicitors of occupational anaphylaxis.²

The aim of this study was to extract cases related to occupational exposure based on the data of the anaphylaxis registry and to analyze these in respect to elicitors, concomitant diseases, severity, but also its management.

2 | METHODS

2.1 | Data

The anaphylaxis registry is gathering real-life anaphylaxis ranging from moderate to severe allergic reactions. The registry was launched in 2007 in German-speaking countries and expanded to other countries in 2011. More than 100 specialized tertiary allergy centers from 11 European countries (Germany, Switzerland, France, Italy, Austria, Poland, Spain, Ireland, Greece, Bulgaria, Romania) and Brazil participate in the registry. Data capture is standardized by an access- and password protected online questionnaire (<https://www.anaphylaxie.net/en/>) that comprehensively collects information regarding elicitor(s), symptoms, course of reaction, cofactors, diagnostic procedures, emergency treatment, and preventive/long-term management. The data about the occupational context of the anaphylactic episode were initially introduced into the questionnaire 2017 (asking whether the eliciting allergen was occupational) and further developed by the introduction of an additional question about the occupation of the patient at the time of the reaction. Patients who had experienced anaphylaxis within the past 12 months before presenting to the participating allergy centers were included. Additional inclusion criteria for data entries only considered severe allergic reactions encompassing symptoms of the lower respiratory tract and/or the cardiovascular system and only unintended allergic reactions. After obtaining written informed consent from patients, de-identified data were captured by trained health care professionals on-site through the web interface. Data were submitted after completion of the diagnostic workup. The diagnostic certainty of the triggering allergen sources was documented at the level of confirmed or highly suspected, based on the local allergy specialist's individual judgment. The confirmation of the elicitor is the responsibility of the physician recording the reaction.

2.2 | Data sample extraction

For the current analysis, cases were extracted from the anaphylaxis registry based on affirmative responses to the question of whether

it is an occupational allergen. In addition, only cases that met the modified criteria of the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network were included.³ For the comparison of occupational versus non-occupational anaphylaxis, only adults were included in the non-occupational group.

2.3 | Data analysis

Statistical analysis was performed using R version 4.2.1 (2022-06-23)⁴ and the gtsummary-package.⁵ GraphPad Prism, version 9.5.1 for Windows, GraphPad Software, Boston, Massachusetts USA, www.graphpad.com was used for visualization. Descriptive analysis was performed, and statistical significance was analyzed using chi-square test, Fisher's exact test for categorical and Wilcoxon test for non-normally distributed continuous variables. Relative frequencies were calculated only among cases with known answers per question. Statistical significance was defined as $p < .05$.

3 | RESULTS

3.1 | Overall description of the cohort

Within the anaphylaxis registry in total 15,748 cases were registered until March 2023. The question regarding the role of the allergen in an occupational context has been introduced into the questionnaire in 2017. Considering this time point as reference the registered cases account to 5851 cases with information about the occupational relation. Detailed reports about cases per countries are depicted in Table S1. Out of these 225 (3.8%) cases were assigned to be caused by an occupational allergen. In 214 cases (95%), the elicitor was confirmed and in 11 (5%) highly suspected. The most frequent triggers of the 225 cases of occupational anaphylaxis are shown in Figure 1 and indicate that the vast majority of these cases were caused by insects ($n=186$, 82.7%) followed by food ($n=27$, 12%) and drugs ($n=8$, 3.6%). By contrast, latex was only in two cases given as the eliciting allergen for the

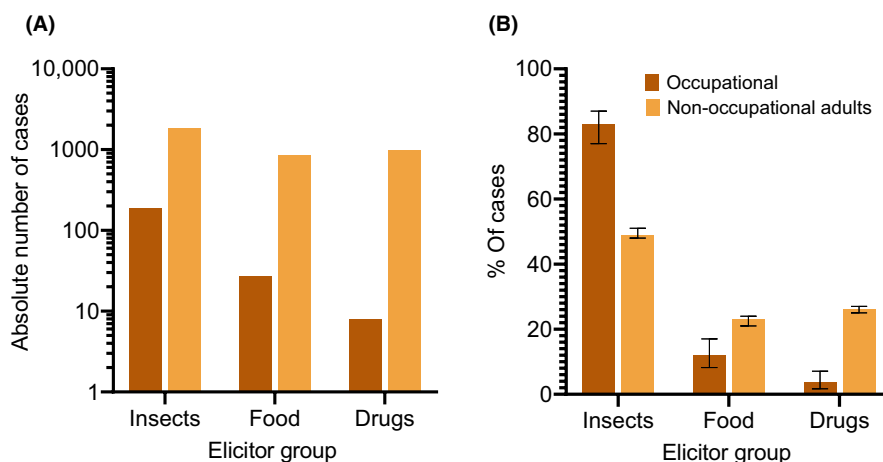


FIGURE 1 Elicitors of occupational versus non-occupational anaphylaxis. Data from the anaphylaxis registry 2017–2023. Non-occupational cases include only adults.

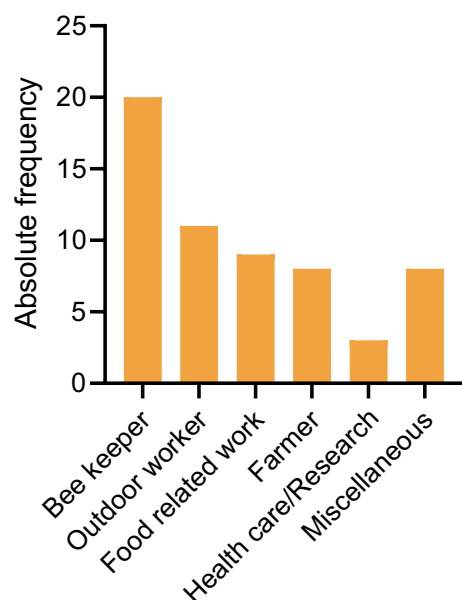


FIGURE 2 Professions among cases with occupational anaphylaxis reported to the anaphylaxis registry between 2017 and 2023.

occupational anaphylaxis (0.9%). The detailed list about all single elicitors is shown in Table S2.

The mean age of the total occupational anaphylaxis group is 44 years, and 97.8% are adults ($n=220$). One case was fatal (yellow jacket), and in three cases, a mastocytosis was identified as a co-disease (1.6%). As it concerns severity grades, grade II was observed in $n=145$ (64%), grade III in $n=75$ (33%), and grade IV in $n=5$ (2.2%) according to Ring & Messmer.⁶ The professions within the group of occupational anaphylaxis were most frequently beekeepers (34%) followed by outdoor workers (e.g., gardeners; 19%), individuals working in professions associated with food handling, for example, employees in restaurants, bakery, pastry, or cooks (15%) and farmers (14%). Other potential risk groups like firefighters were not reported to be affected in this cohort. The detailed information about the professions in this cohort is provided in Figure 2.

3.2 | Venom as an elicitor in occupational anaphylaxis

To investigate in more detail venom-induced occupational anaphylaxis, we analyzed the data in comparison to all other adult venom-induced anaphylaxis cases (Table 1), which were reported to the anaphylaxis registry within the similar time frame ($n=1842$). We observed that venom anaphylactic individuals who experienced anaphylaxis within their occupation were significantly younger (46 vs. 53 years, $p<.001$) and bee was more frequently an elicitor in occupational cases (38% vs. 17%, $p<.001$), while wasp-induced anaphylaxis was more frequent in non-occupational anaphylaxis (52% vs. 70%; $p<.001$). No differences between occupational and non-occupational were observed regarding the severity grades and the

TABLE 1 Venom-induced anaphylaxis without (only adult patients) and with occupational association.

Characteristic	Occupational association		p-Value ^a
	No association ^b	Occupational association ^b	
Sex			
Female	898 (49%)	64 (34%)	<.001
Male	944 (51%)	122 (66%)	
Age in years	53 (40, 63)	46 (35, 55)	<.001
Eliciting insect			
Yellow jacket (wasp)	1297 (70%)	97 (52%)	<.001
Bee	304 (17%)	71 (38%)	
Hornet	216 (12%)	17 (9.1%)	
Bumblebee	6 (0.3%)	1 (0.5%)	
Horse fly	0 (0%)	0 (0%)	
Mosquito	0 (0%)	0 (0%)	
Other	14 (0.8%)	0 (0%)	
Unknown	5 (0.3%)	0 (0%)	
Severity grade (Ring & Messmer)			
Grade II	1155 (63%)	121 (65%)	.8
Grade III	650 (35%)	61 (33%)	
Grade IV	37 (2.0%)	4 (2.2%)	
Previous reaction	448 (26%)	48 (28%)	.5
Prescription of emergency medication			
No	28 (1.5%)	5 (2.7%)	.4
Yes	1767 (96%)	177 (95%)	
Unknown	47 (2.6%)	4 (2.2%)	
SIT overall	1495 (83%)	145 (80%)	.2
SIT prior to reaction	20 (1.1%)	3 (1.6%)	.5
SIT offered in acute reaction	25 (1.4%)	2 (1.1%)	>.9
SIT in primary care	23 (1.3%)	6 (3.3%)	.044
SIT in allergology center	1454 (81%)	138 (76%)	.093
No SIT offered	300 (17%)	37 (20%)	.2
AAI prescribed overall ^c	1685 (98%)	172 (100%)	.10
AAI available prior to reaction ^c	105 (6.1%)	9 (5.2%)	.6
AAI prescribed in acute reaction ^c	383 (22%)	42 (24%)	.5
AAI prescribed in primary care ^c	493 (29%)	45 (26%)	.5
AAI prescribed in allergology center ^c	953 (56%)	91 (53%)	.5
No AAI prescribed ^c	30 (1.7%)	0 (0%)	.10
Number of AAI ^c			
>2	1 (<0.1%)	1 (0.8%)	.2
1	935 (72%)	89 (73%)	
2	360 (28%)	32 (26%)	

TABLE 1 (Continued)

Characteristic	Occupational association		p-Value ^a
	No association ^b	Occupational association ^b	
Concomitant mastocytosis (overall)	43 (2.6%)	3 (1.9%)	.8
Current concomitant mastocytosis	41 (2.5%)	3 (1.9%)	>.9
Admission to hospital	679 (42%)	60 (36%)	.2

Note: Data from the anaphylaxis registry 2017–2023. *p*-values < 0.05 are considered significant (printed in bold).

Abbreviations: AAI, adrenaline autoinjector; SIT, specific immunotherapy.

^aPearson's chi-squared test; Wilcoxon rank sum test; Fisher's exact test.

^b*n* (%); Median (IQR).

^cAmong those who received a prescription for emergency medication.

onset of previous reactions. However, venom immunotherapy (VIT) was initiated as a therapeutical consequence more frequently in occupational venom anaphylaxis in a primary care setting in these patients (*p* = .044).

3.3 | Food-induced occupational anaphylaxis

The identified food allergens of this cohort inducing occupational anaphylaxis show a broad range of different elicitors. However, the grouping of the different food allergens revealed that the largest groups identified were peanut, tree nuts and sesame (*n* = 7) and fruits and vegetables (*n* = 5) followed by mussels, shellfish and salmon (*n* = 4), rye, wheat and buckwheat flour (*n* = 5), meat (*n* = 4), and cow's milk (*n* = 2).

Also in the food allergen-induced occupational anaphylaxis group the mean age of affected individuals was lower in comparison to the all other food-induced anaphylaxis cases among adults (35 vs. 39 years, *p* = .058, not significant) and the severity was a bit higher (41% grade III compared to 35% grade III reactions; *p* = .086, not significant, Table 2). Except of a slightly higher rate of current atopic dermatitis (20% vs. 10%, *p* = .3, not significant) and a higher frequency of prescription of two adrenaline autoinjectors (AAI) (36% vs. 17%, not significant), this group did not differ from non-occupational adult food-induced anaphylaxis cases (Table 2).

3.4 | Drug-induced occupational anaphylaxis

In this group, eight cases were identified (Table S3). Interestingly, five cases (63%) were due to antibiotics, four were induced by beta lactams (three cephalosporins/one penicillin) and one by a quinolone. Two cases were attributed to COVID-19 vaccinations (one Biontech Pfizer and one AstraZeneca) and one to a GnRH-analogue. Within

TABLE 2 Food-induced anaphylaxis without (only adult patients) and with occupational association.

Characteristic	Occupational association		p-Value ^a
	No association ^b	Occupational association ^b	
Sex			
Female	486 (57%)	13 (48%)	.4
Male	369 (43%)	14 (52%)	
Age in years	39 (27, 52)	35 (23, 46)	.058
Severity grade (Ring & Messmer)			
Grade II	550 (64%)	15 (56%)	.086
Grade III	302 (35%)	11 (41%)	
Grade IV	3 (0.4%)	1 (3.7%)	
Eliciting food			
Animal-products (including meat and seafood)	182 (21%)	10 (37%)	
Cereals	115 (13%)	5 (19%)	
Fruits	100 (12%)	2 (7.4%)	
Tree nuts	122 (14%)	2 (7.4%)	
Vegetables	65 (7.6%)	2 (7.4%)	
Legumes (including peanut)	123 (14%)	1 (3.7%)	
Spices/seeds (including sesame)	48 (5.6%)	1 (3.7%)	
Additives	8 (0.9%)	0 (0%)	
Others	48 (5.6%)	1 (3.7%)	
More than one food allergen suspected ^c	44 (5.1%)	3 (11%)	
Previous reaction	354 (47%)	12 (57%)	.3
Prescription of emergency medication			
No	28 (3.3%)	1 (3.7%)	.8
Yes	794 (93%)	25 (93%)	
Unknown	33 (3.9%)	1 (3.7%)	
AAI prescribed overall ^d	715 (94%)	22 (96%)	>.9
AAI available prior to reaction ^d	89 (12%)	2 (8.7%)	>.9
AAI prescribed in acute reaction ^d	108 (14%)	4 (17%)	.6
AAI prescribed in primary care ^d	90 (12%)	3 (13%)	.7
AAI prescribed in allergology center ^d	500 (66%)	15 (65%)	>.9
No AAI prescribed ^d	48 (6.3%)	1 (4.3%)	>.9
Number of AAI ^d			
1	391 (83%)	9 (64%)	.085
2	82 (17%)	5 (36%)	

(Continues)

TABLE 2 (Continued)

Characteristic	Occupational association		p-Value ^a
	No association ^b	Occupational association ^b	
Concomitant mastocytosis (overall)	9 (1.2%)	0 (0%)	>.9
Current concomitant mastocytosis	8 (1.1%)	0 (0%)	>.9
Concomitant AD (overall)	103 (14%)	5 (25%)	.2
Current concomitant AD	80 (10%)	4 (20%)	.3
Concomitant asthma (overall)	189 (25%)	8 (35%)	.3
Current concomitant asthma	162 (21%)	7 (30%)	.3
Concomitant rhinitis (overall)	400 (50%)	12 (50%)	>.9
Current concomitant rhinitis	350 (44%)	10 (42%)	.8
Concomitant food allergy (overall)	179 (23%)	6 (29%)	.6
Current concomitant other FA	167 (21%)	5 (24%)	.8
Admission to hospital	265 (35%)	11 (50%)	.14

Note: Data from the anaphylaxis registry 2017–2023.

Abbreviations: AAI, adrenaline autoinjector; FA, food allergy.

^aPearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test.

^bn (%); Median (IQR).

^cAmong n = 1 peanut or hazelnut; n = 1 peanut or scampi, n = 1 hazelnut or shellfish.

^dAmong those who received a prescription for emergency medication.

this group, the percentage of affected females accounted 75% and 63% (n = 5/8) were admitted to a hospital during the acute reaction.

4 | DISCUSSION

In this report, we describe a large cohort of 225 individuals who experienced an occupational anaphylaxis and were registered within the anaphylaxis registry (NORA e. V). To better understand the clinical characteristics of these patients we analyzed this cohort in comparison with cases of non-occupational anaphylaxis of the same elicitor group. Our data are in line with the literature showing venom frequently accounting for occupational anaphylaxis. Venom counted also in this cohort for more than 80% cases (especially bee venom = 71, 31.5% and yellow jacket/hornet n = 114, 50.6%) the main elicitor. However, in contrast to the previous literature the second most frequent elicitor group

was not latex (only 2 cases—0.9%), but rather food allergens. Drugs accounted for up to 3.6% of occupational anaphylaxis.^{7,8}

4.1 | Venom-induced occupational anaphylaxis

Hymenoptera stings have been described as common occupational triggers and have been reported to induce anaphylaxis in beekeepers and forestry workers.^{9,10}

In the general population, Hymenoptera venom allergy has a prevalence of approximately 5%.^{11,12} Of patients with Hymenoptera venom allergy, 17% were reported to have at least one allergic reaction at work, for example, beekeepers, gardeners, firemen, or forest rangers.¹² In a recent study, 14% of Spanish firefighters with increased exposure to hymenoptera stings at work reported large local reactions and 6% reported systemic reactions.¹³

Sting incidence was reported to be 98.1% in Japanese forest workers¹⁰ and 59% in pest control operators.¹⁴ Italian forestry workers reported a sting incidence between 59% and 87%, depending on the geographical location within the country. A total of 13% of them reported large local reactions and 9% even systemic reactions after a Hymenoptera sting.¹⁵ In an Israeli population, 44% reported adverse reactions of their Hymenoptera venom allergy on their occupational activities,¹⁶ confirmed by an Italian study of 181 patients, where 17% reported work disability.^{12,17}

Primary and secondary prevention measures in venom anaphylaxis should include the reduction of exposure including protective clothing. In patients who experienced a severe anaphylaxis VIT should be considered and continued for the duration of the hazardous occupation. In venom-induced occupational anaphylaxis, VIT was not significantly more frequently offered to the affected individuals. However, we observed that VIT was initiated in these occupational patients mostly in a primary care setting. The cause might be related to the possibility that the affected individuals were living in more rural areas, where no tertiary allergy center was available.

In respect to the initiation of VIT, it has to be taken into consideration that repetitive stings in an exposed individual, for example, bee keeper can cause natural tolerance over time.¹⁸ However, in certain individuals, for example, males with increased tryptase levels and coexisting cardiovascular disease such procedure may be a risk for a given patient.¹⁹ More data regarding this topic are necessary for a better risk assessment in the future.

Other insects may also cause occupational anaphylaxis, for example, tick bites, Chironomidae larvae used by aquarists as fish food or mosquito bites,^{20,21} but are only in exceptional cases the cause of occupational anaphylaxis.

4.2 | Food allergy as a cause of occupational anaphylaxis

Although food allergens are well known to induce occupational asthma or protein contact dermatitis, the data on food-induced

occupational anaphylaxis are limited. In this cohort, we identified 27 individuals with food-induced anaphylaxis in the context of occupational exposure. The most frequent elicitors were peanut, tree nuts and sesame ($n=7$) and fruits and vegetables ($n=5$) suggesting PR-10, LTP- and storage proteins as sensitizing allergens. As we do not have more details on the individual sensitization profile and the occupational allergen exposure, we do not know how the sensitization was acquired in these patients. Seafood like mussels, shellfish, and salmon ($n=4$) were less commonly reported as causes of occupational anaphylaxis in our cohort. In the literature, data on workers handling with seafood reported a prevalence of occupational asthma from 7% to 36% and contact dermatitis from 3% to 11%.²² Bakers asthma is a well-known entity,²³ and also in this dataset, we identified a few cases of (rye and wheat) flour ($n=4$) induced anaphylaxis and one case due to buckwheat. Buckwheat is a known, though uncommon, allergen in occupational settings. It has recently gained popularity as healthy food and as an ingredient in gluten-free diets. A series of six patient cases with occupational immediate allergy to buckwheat was recently published. Three cooks, two bakers, and a worker in a grocery store were occupationally exposed to buckwheat flour and developed immediate allergy to buckwheat, which was confirmed by skin prick testing and measurement of specific immunoglobulin E antibodies. Four of the patients were diagnosed with occupational asthma, four with occupational rhinitis, and two with occupational contact urticaria caused by buckwheat. Three of the six patients suffered anaphylaxis as consequence of their occupational buckwheat allergy after ingestion of food that contained buckwheat.²⁴

Other cases of occupational food allergy have been reported in other food processing working places, for example, a spice factory with an anaphylaxis due to coriander.²⁵ Another interesting, although not reported allergen in an occupational setting is Psyllium (from *Plantago ovata*; ispaghula). It is used as a dietary supplement and supplied in the form of husk, granules, capsules, or powder. Consumers using psyllium-containing laxatives, healthcare workers handling these, and pharmaceutical workers in laxative-manufacturing plants are known to be at risk of sensitization and subsequent rhinitis, asthma, contact urticaria, and even anaphylaxis.²⁶ Finally, our data set also unraveled a few cases of animal mammal protein dependent anaphylaxis—meat and cow's milk were reported to elicit an occupational anaphylactic reaction in two cases each. Alpha-gal as an allergen has been reported in forest workers and led to the identification of tick bites as the sensitizing source.²⁷ More recently, meat has been reported as a cause of an occupational anaphylaxis in a cook.²⁸

4.3 | Drug-induced occupational anaphylaxis

Drug-induced occupational anaphylaxis was not frequent in our cohort (3.2%). However, it is noteworthy that beta lactam antibiotics accounted for half of the cases reported (4/8). This is not surprising as these drugs are commonly used and also known to be one

of the most important elicitor group of drug-induced anaphylaxis.²⁹ A recent study from the anaphylaxis network indicated that antibiotics are besides analgetics the most frequent inducer of drug-induced anaphylaxis. Remarkably our small group of drug-induced occupational anaphylaxis included more females, a finding we also observed in larger groups of drug-induced anaphylaxis²⁹ and which may be further increased to the higher proportion of females working in hospital settings. In the literature, we only found one case of a piperacillin-induced occupational anaphylaxis, underpinning the observation that drug-induced occupational anaphylaxis is a rather rare event. Interestingly, we also had two reports on occupational anaphylaxis with the COVID-19 vaccination. However, after the initial report on two healthcare workers from Great Britain directly after the initiation of the vaccine campaign³⁰ only few reports followed thereafter. Finally, anaphylaxis in the context of COVID-19 vaccination turned out to be a rare event with less than 0.5–2 per 100,000.^{31,32}

4.4 | Latex-induced occupational anaphylaxis

Latex was a major occupational allergen in the 1990s, and the sensitization rates among healthcare workers reached 10%–15%.³³ After the introduction of non-powdered gloves, low protein gloves, and synthetic rubber gloves, the sensitization rates decreased³⁴ and which is also reflected by our data where we had only two cases of latex-induced occupational anaphylaxis (0.9%).

5 | CONCLUSIONS

All in all this analysis shows for the first time data from a large group of occupational anaphylaxis obtained within the anaphylaxis registry. This enabled us not only to describe this cohort regarding elicitors and severity in more detail, but also to unravel characteristics in comparison with non-occupational anaphylaxis. Further data in the future are needed to get a better insight on country specific issues, but also professional exposures in order to develop optimized prevention.

AUTHOR CONTRIBUTIONS

MW designed and conceptualized the study, contributed to data acquisition, interpreted the data, and wrote the manuscript. VH and SD-B conducted statistical analysis, contributed to data acquisition, and interpreted the data. MBB contributed to data acquisition and data interpretation. KH contributed to data acquisition and data interpretation. DS-L contributed to data acquisition and data interpretation. RT contributed to data acquisition and data interpretation. All authors have read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

ORCID

Margitta Worm  <https://orcid.org/0000-0002-3449-1245>

Veronika Höfer  <https://orcid.org/0000-0002-8538-3439>

Sabine Dölle-Bierke  <https://orcid.org/0000-0002-3339-0709>

Maria Beatrice Bilo  <https://orcid.org/0000-0002-9324-6039>

Karin Hartmann  <https://orcid.org/0000-0002-4595-8226>

Regina Treudler  <https://orcid.org/0000-0002-9642-4742>

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SUPPORTING INFORMATION

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

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