

Type IV allergy in the food processing industry: sensitization profiles in bakers, cooks and butchers

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Data about the impact of allergic contact dermatitis in food processing occupations are scarce. The objective of this study was to identify the most frequent allergens and sensitization profiles in employees of the food processing industry. The results of patch testing performed in 873 bakers, cooks and butchers suspected of having occupational allergic contact dermatitis from 33 dermatological departments of the Information Network of Departments of Dermatology (IVDK) from 1992 to 1999 were analysed. A final diagnosis of allergic contact dermatitis was made in 213 patients (24.4%). Qualitative and quantitative differences in allergen profiles could be identified. Significantly higher sensitization rates were found in employees in the food processing industry, compared to the total test population, for nickel sulphate (22.4% versus 17.2%, $p < 0.0005$), thiuram mix (4.9% versus 2.6%, $p < 0.0005$), formaldehyde (3.5% versus 2.1%, $p < 0.005$) and Compositae mix (6.2%, $p < 0.0005$). Significantly lower sensitization rates were found for thimerosal (4.5% versus 6.9%, $p < 0.05$). For patch testing in food workers, we recommend the standard, the rubber and the Compositae series, as well as patients' own products according to the individual history.

Key words: allergens; allergic contact dermatitis; Compositae; food industry; formaldehyde; nickel sulphate; occupational hand dermatitis; patch testing; thiuram. © Blackwell Munksgaard, 2002.

Accepted for publication 18 March 2002

Occupational skin disease (OSD) is an important problem in the food processing trades. In 1998, occupational skin disease ranked second after baker's asthma in the occupational disease statistics of the social liability insurer of the food processing industry (BGN). Particularly bakers and confectioners were affected, as well as cooks and caterers (1).

The most common diagnosis is irritant contact dermatitis, due to continual wet work, contact with irritant food ingredients, as well as contact with detergents and disinfectants. Not only experienced workers are at risk. The disease history of employees starts early in their vocational training, when up to one third of baker's apprentices develop OSD in the first 6 months and continue to have it until the end of their training (2, 3). The continual contact of eczematous skin with occupational allergens may be followed by the development of allergic contact dermatitis (ACD). Tacke *et al.* (4) reported allergic contact dermatitis in 12% of bakers, 10% of confectioners and 5% of cooks included in a population-based study on the frequency of OSD from 1990 to 1993 in North Bavaria (4). Gebhardt *et al.* (5) evaluated IVDK patch test data in 88 bakers suspected of having occupational allergic contact dermatitis and found allergic contact dermatitis in 28.4% of the employees (5). Besides one big survey in workers of the food industry (6), current knowledge of the relevant allergens is mainly based on various case reports, reviews of selected food allergens or small

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case series (5, 7–16). Concerning the negative impact of occupational sensitization, possibly leading to loss of job, retraining and unemployment, reliable data on sensitization rates and profiles in the food processing industry are urgently needed. The aim of this study was to identify the most frequent allergens, the sensitization profiles and the relative sensitization risks causing Type IV allergies in bakers, cooks and butchers, thus providing reliable data for preventive, diagnostic and therapeutic strategies.

Patients and Methods

A retrospective data analysis of the patch test data of 873 employees (340 bakers, 403 cooks and 130 butchers) in the food processing industry was performed. The workers had been tested for occupational allergic contact dermatitis from 1992 to 1999 in 33 departments co-operating in the Information Network of Departments of Dermatology (IVDK). To secure a high standard of quality in the performance of test procedures, data collection and processing in the individual co-operating clinics, standardized procedures are in place. Moreover, quality control of the data transferred to the IVDK headquarters is performed regularly with every data delivery. Workshops of the IVDK, where data quality aspects are discussed, are held twice a year (17, 18). Sensitization rates were compared to the total test population of 71,872 patients without food processing occupations from 1992 to 1999. To decrease contamination from leisure-time allergens, data of patients were only analysed if they had been tested on suspicion of an occupational disease. In 817 (94%) of patients the dermatitis was localized on the hands. 425 (48.7%) of the patients from food processing occupations were male, and 233 (26.7%) were 40 years or older. 209 patients (23.9%) reported past or present atopic dermatitis, 191 patients (21.9%) reported allergic rhinitis, and 73 patients (8.4%) had bronchial asthma. The standard series recommended by the German Contact Dermatitis Research Group (DKG) was tested in 816 patients (93.5%). Other specific allergens were tested when indicated by the patients' histories. Tests were performed according to internationally accepted recommendations (19–22). Patch test substances were mainly purchased from Hermal (Reinbek, Germany). Finn Chambers on Scanpor (27 depts.), Hayes test chambers (3 depts.), Curatest F Lohmann (2 depts.) and Leukotest (1 dept.) were used for application of the test substances. Patch tests were applied for 24 h in 338 patients (38.7%) and for 48 h in 535 patients (61.3%). Readings were done after 48 and 72 h. For this analysis, only readings at day

3 (72 h) were considered. Sensitization rates rather than data on the relevance of the patch test results were used for the analysis. Data on both the sensitization rates and the relevance of patch test results were routinely documented in the IVDK. At present, there is no commonly agreed concept for the evaluation of relevance (23–25). Therefore, we regarded relevance data, apart from their importance to the individual patient, to be less reliable than sensitization rates for this analysis. For comparability, patch test data were standardized by age and sex, following the recommendations on PAFS (population adjusted frequency of sensitization) (26, 27), where appropriate. Differences between the sensitization rates in the study group and the control group were tested by χ^2 test statistics for standardized rates. Odds ratios (95% confidence limits) for the leading allergens in bakers, cooks and butchers were calculated (28, 29). Hypothesis testing was applicable for allergens tested in at least 90% of the study population and the control group (Table 1, allergens 1–14). Data for the remaining allergens (Table 1, allergens 15–20) must be interpreted with caution, because these allergens were tested in less than 90% of the study population. A sensitivity analysis was performed. Statistics were performed using the statistical packages of SAS (SAS Institute, Cary, NC, USA) and SPSS 10, Windows NT.

Results

A final diagnosis of allergic contact dermatitis was made in 213 patients (24.4%). Irritant contact dermatitis was diagnosed in 334 (38.3%) and atopic dermatitis in 197 patients (12.2%). Protein contact dermatitis was diagnosed in 24 (2.7%) and contact urticaria in 13 patients (1.5%). The remaining cases were due to other defined dermatological diseases, e.g. psoriasis and fungal infections. 434 patients (49.7%) had positive patch test reactions to 1109 allergens (each substance was counted only once per patient). Thus, the average was 2.55 allergens per patient (median = 2). 168 patients (19.2%) reacted to 1 allergen, 111 patients (12.7%) to 2 allergens, 60 (6.9%) to 3 allergens, 37 (4.2%) to 4 allergens, and 58 (6.7%) to 5 or more allergens. The 20 most frequent allergens are listed in Table 1. The allergens of the standard series are listed from ranks 1 to 14. For the allergens 15–20 direct comparison of sensitization rates between test population and control group, as well as hypothesis testing, must be interpreted with caution, because the allergens were tested in varying proportions in both populations. This could lead to an overestimation of the sensitization rates in food processing occupations due to selective testing.

Table 1. Most frequent allergens in food processing employees (bakers, cooks and butchers) compared to the total IVDK test population (without food processing occupations). The table shows age- and sex-adjusted sensitization rates, the total number of tested patients and the total number of positive test results for each allergen in employees working as bakers, cooks and butchers who were tested because of suspected occupational contact dermatitis between 1992 and 1999. The control group consisted of all patients tested for allergic contact dermatitis during this time period (without bakers, cooks and butchers)

Allergen	Food processing occupations	Bakers	Cooks	Butchers	Total IVDK test population
	% std./n-tested/ n positive	% std./n-tested/ n positive	% std./n-tested/ n positive	% std./n-tested/ n positive	% std./n-tested/ n positive
1. Nickel sulphate (5% pet.)	22.4*/815/160 $p < 0.0005$	22.2*/312/54 $p < 0.0005$	25.1*/385/90 $p < 0.0005$	14.6*/124/18 $p < 0.0005$	17.2/64860/10454
2. Fragrance mix (8% pet.)	10.4/814/77	9.7/314/34	9.8/382/36	8.7/124/7	11.5/65381/7756
3. Balsam of Peru (25% pet.)	7.1/815/48	10.2/315/19	7.4/382/27	1.4*/124/2 $p < 0.05$	7.8/65406/5531
4. Cobalt chloride (1% pet.)	5.8/812/46	6.9/314/14	6.0/380/22	6.3/124/10	5.2/65726/3272
5. Thimerosal (0.1% pet.)	4.5*/807/43 $p < 0.05$	7.1/316/25	3.8*/376/16 $p < 0.05$	1.6/121/3	6.9/64834/4078
6. Potassium dichromate (0.5% pet.)	5.1/816/31	5.7/315/10	5.0/383/15	4.0/124/6	4.3/65789/2871
7. p-Phenylene-diamine (1% pet.)	4.6/811/31	6.0/312/10	3.7/381/14	7.0/124/7	4.6/65397/3100
8. Thiuram mix (1% pet.)	4.9*/815/31 $p < 0.0005$	5.0*/314/6 $p < 0.01$	6.4*/383/21 $p < 0.0005$	2.3/124/4	2.6/65406/1781
9. Colophonyium (Rosin) (20% pet.)	4.1/812/28	5.6/314/8	3.9/381/15	3.0/123/5	3.7/65397/2520
10. Mercury amide chloride (ammoniated mercury) (1% pet.)	2.4/814/22	1.6/314/9	3.3/382/12	/	2.5/65243/1663
11. Formaldehyde (1% aq.)	3.5*/816/19 $p < 0.005$	2.6/315/5	3.6/383/11	4.1/124/3	2.1/65554/1372
12. Methylidibromo glutaronitrile/2-Phenoxyethanol (1% pet.)	3.4/790/18	1.6/305/5	4.0/367/11	1.1/123/2	2.7/63436/1771
13. Lanolin alcohol (30% pet.)	1.7*/813/14 $p < 0.003$	4.4/314/4	1.2*/381/6 $p < 0.01$	2.0/124/4	3.4/64814/2391
14. (Chloro)methylisothiazolinone (100 p.p.m.)	1.8/784/9	/	2.7/370/8	0.7/121/1	2.5/64144/1627
15. Benzoyl peroxide (1% pet.) ^a	5.5/283/19	5.4/162/12	4.9/94/5	2.9/28/2	8.9/17986/1558
16. Tetramethyl-thiuram monosulphide (0.25 pet.) ^a	7.3/259/18	/	5.7/168/9	10.8/43/6	5.2/10975/569
17. Compositae mix (6% pet.) ^a	6.2*/211/15 $p < 0.0005$	/	10.0*/105/12 $p < 0.0005$	/	2.4/14660/366
18. Tetraethylthiuramdisulphide (0.25% pet.) ^a	6.8/258/14	/	7.9/167/10	5.9/43/3	5.5/10953/598
19. Tetramethyl-thiuram disulphide (0.25% pet.) ^a	6.0/255/13	/	4.7/166/7	7.8/43/4	3.7/10912/407
20. Glutaraldehyde (1% pet.) ^a	3.0/418/10	2.6/129/4	2.5/228/5	/	2.0/20227/398

std., age and sex standardized (PAFS) (21, 22). /, no data available.

*Significant difference between the food processing employees and the control group ($p < 0.05$).

^aThese allergens were tested in less than 90% of the patients in food processing occupations and the control group. Sensitization rates may be biased by selective testing. Therefore no direct comparison of the sensitization rates is possible.

The allergen spectrum in these latter occupations resembles that of all patients tested in 1992–97, but there are specific sensitization risks in employees in the food processing industry, particularly concerning fragrance-related allergens, preservatives and rubber chemicals (Table 1). Employees in the food processing occupations mentioned (22.4%), and particularly cooks (25.1%), showed significantly higher sensitization rates ($p < 0.0005$) to nickel sulphate than the control group (17.2%). Only 10.4%

of all food processing employees were sensitized to fragrance mix, compared to 11.5% of the control group. High occupation-specific sensitization rates were found for Compositae mix. 6.2% of the food processing employees ($p < 0.0005$), and particularly cooks (10%, $p < 0.0005$), were sensitized compared to 2.4% of the control group. As mentioned above, these rates could be overestimated. To test the robustness of the data, a sensitivity analysis was performed. The difference in Compositae mix sensit-

Table 2. Odds ratios (95% confidence intervals (CI)) in food processing occupations, bakers, cooks and butchers. This table shows the Odds ratios (OR) and confidence intervals (CI) for sensitization to allergens in different food occupations. OR were calculated for each allergen using the figures of the control group as reference OR (OR = 1)

Allergen	Food processing occupations	Bakers	Cooks	Butchers
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
<i>Fragrance associated allergens</i>				
Balsam of Peru	0.84 (0.66–1.09)	1.22 (0.85–1.77)	0.86 (0.58–1.26)	0.18 (0.04–0.72)
Colophony	1.05 (0.74–1.50)	1.52 (0.94–2.45)	1.02 (0.61–1.72)	0.84 (0.31–2.27)
Fragrance mix	0.87 (0.69–1.09)	0.79 (0.54–1.14)	0.80 (0.57–1.12)	0.72 (0.39–1.34)
Compositae mix	2.63 (1.49–4.65)	/	4.69 (2.49–8.83)	/
<i>Rubber ingredients</i>				
Thiuram mix	1.84 (1.34–2.54)	1.92 (1.16–3.18)	2.50 (1.66–3.75)	0.89 (0.28–2.79)
<i>Preservatives</i>				
Thimerosal	0.70 (0.50–0.97)	1.12 (0.72–1.72)	0.58 (0.34–0.98)	0.25 (0.06–1.01)
Mercury amide chloride	0.99 (0.63–1.55)	0.62 (0.25–1.50)	1.35 (0.77–2.35)	/
Methyldibromo glutaronitrile + 2PE	1.26 (0.24–1.41)	0.58 (0.24–1.41)	1.48 (0.88–2.49)	0.29 (0.04–2.04)
Formaldehyde	1.72 (1.19–2.51)	1.22 (0.60–2.47)	1.78 (1.04–3.04)	1.97 (0.80–4.82)

/, no data available. bold figures, significant increase/decrease of relative risk ($p < 0.05$).

ization rates between the food processing occupations/cooks and the control group stayed significant up to a hypothetical overestimation of the sensitization rates in the former of 33% ($p < 0.04$) and 42% ($p < 0.02$), respectively. 4.9% in the food processing occupations were sensitized to thiuram mix (control group 2.6%; $p < 0.0005$). Again, cooks were the most affected group (6.4%, $p < 0.0005$). Sensitization rates to benzothiazoles and carbamates were negligible in food processing employees. The sensitization profiles in food workers concerning preservatives and disinfectants were heterogeneous. Sensitization to organic mercury components was less frequent in food processing employees, compared to the control group. 4.5% patients from food processing occupations were sensitized to thimerosal ($p < 0.05$), compared to 6.9% in the central group. The opposite was true for formaldehyde (3.5% in the former versus 2.1% in the latter, $p < 0.005$). Here, sensitization was more frequent in food processing employees. Significantly increased sensitization risks were found in such occupations for thiuram mix, formaldehyde and nickel sulphate. Sensitization rates to Compositae mix were noteworthy, but have to be interpreted with caution, as mentioned above. Cooks were the occupational group with the most

and the highest risks for occupational Type IV sensitizations (Table 2).

Discussion

Irritant contact dermatitis was the leading diagnosis (38.3%, $n = 334$) in employees in the food processing occupations, patch tested for occupational allergic contact dermatitis in 33 departments co-operating in the IVDK. But such occupations also bore an important morbidity risk for Type IV sensitizations. In 24.4% ($n = 213$) of the patients, allergic contact dermatitis was considered to be responsible for the skin lesions. The age and sex standardized sensitization rates of food processing employees showed qualitative and quantitative differences from the sensitization profile of the control group. The main occupational allergens for which employees in such occupations showed higher sensitization risks than the control group were food related, like Compositae mix, or linked with current preventive measures, like thiuram mix in rubber gloves, as well as allergens in disinfectants and cleaning agents like formaldehyde. Moreover nickel sulphate seemed to be a relevant allergen, which could be released from stainless steel cooking instruments.

Fragrance mix and balsam of Peru (Myroxylon Pereirae resin)-related allergens

Case reports and case series suggested that Type IV sensitization to spices, foods and flavouring agents played an important role in food processing occupations (9–13, 15, 16). Van der Akker *et al.* (30) showed that many sensitizations to clove, nutmeg, cinnamon and cayenne pepper could be detected by screening with fragrance mix and balsam of Peru (30). In our evaluation of this large group of food processing employees, sensitization rates to fragrance mix and balsam of Peru were lower than in the control group. If spices really were frequent sensitizers in the study group, this should be reflected in higher sensitization rates to fragrance mix and balsam of Peru. Moreover, Kanerva *et al.* (12) described 5 cases of occupational Type IV sensitizations to spices in employees of the hotel and restaurant trades, where only 1 showed positive patch test reactions to fragrance mix and balsam of Peru (12). Fragrance mix and balsam of Peru should not uncritically be regarded as screening substances, but rather spices or flavouring agents should be tested additionally depending on the individual's history. In our study group only a few butchers and cooks were sensitized to cinnamon (butchers $n = 2$), cinnamic aldehyde (butchers $n = 6$; cooks $n = 1$), limonene (butchers $n = 2$; cooks $n = 1$), oil of clove (butchers $n = 3$) and vanilla (butchers $n = 2$, cooks $n = 1$). These sensitizations represented single cases due to individual occupational histories. No broad sensitization to flavouring agents or spices in food processing occupations can be inferred from this.

Compositae mix

Highly significant sensitization rates to Compositae mix were found. 6.2% of food processing employees and 10% of cooks were sensitized to Compositae mix, compared to 2.4% of the control group. Direct skin contact with Compositae, like lettuce, chicory, endive, iceberg lettuce, artichoke, mugwort, etc., is common in cooks and other caterers, which could explain our findings. Sensitization potency varies from weak for mugwort and lettuce to medium for artichoke. Sesquiterpene lactones show cross-reactivity. Therefore local therapy with chamomile, marigold and arnica in popular topical remedies could provoke relapse and exacerbation (31–34). But, as mentioned above, the high sensitization rate to Compositae mix in food processing occupations must be interpreted with caution, due to the fact that the allergen was tested in less than 90% of the test population and therefore an overestimation of the sensitization rates in this

study group could have appeared. However, test results were robust, as shown in the sensitivity analysis, allowing for a considerable hypothetical overestimation of the sensitization rates up to 33% (food processing employees) and 42% (cooks), respectively. Therefore, advice to reduce direct skin contact with Compositae in such occupations seems reasonable.

Rubber chemicals

Employees in food processing occupations had a 1.84-fold (95% CI 1.34–2.54) increased relative risk of becoming sensitized to thiuram mix. Thiurams, like carbamates and benzothiazoles, are rubber vulcanizing accelerators widely used in rubber production. Testing with thiuram mix revealed most sensitizations to be to tetramethylthiuram-monosulphide (TMTM), tetramethylthiuram-disulphide (TMTD) and tetraethylthiuram-disulphide (TETD). Sensitization to dipentamethylene-thiuram-disulphide (PTD) did not play an important role. The main allergen source was probably rubber gloves used to prevent irritant contact dermatitis. Due to environmental conditions, occlusion and sweating, thiurams could readily be released from such products (35). Cooks had the highest (2.5-fold) relative risk increase in becoming thiuram-sensitized compared to all occupations studied. One could speculate that cooks have acquired such sensitization because they might have worn gloves more often than employees in other food processing occupations. However, there are no studies to support this hypothesis. Another allergen source in such occupations could be rubber boots, rubber handles of knives or other kitchen instruments. Thiuram mix sensitization is no isolated problem in food processing employees. Increasing sensitization rates have been shown in many other occupations, especially in healthcare workers due to more frequent protective glove wearing (36, 37). Nowadays, many manufacturers provide thiuram-free gloves for the hospital sector. To prevent a further rise in sensitization rates to thiurams in food processing occupations, it is essential that thiuram-free products should be made available. Additionally, information must be provided for employers and employees to make the right choices within the wide range supplied.

Disinfectants and cleansers

Work organization and hygiene regimens force food processing employees to spend a considerable amount of their work time on cleaning and disinfecting of work surfaces, cutlery, machines and instruments (3). Employees in such occupations had a significantly higher risk of formaldehyde sensit-

ization (1.72-fold) than the control group. 3% of the study group were sensitized to glutaraldehyde. These biocides are commonly used in surface disinfecting in occupational settings. Glutaraldehyde sensitization in food processing occupations should be monitored carefully and interventions may be necessary to prevent the development that occurred in the health services, where glutaraldehyde recently became the most important allergen in healthcare workers due to its replacement of formaldehyde (37–39). Interestingly, sensitizations to the organic mercury compound thimerosal was significantly lower in the study group compared to the control group. The low thimerosal sensitization rates could be an indicator of a lower immunization uptake in such employees (40). Sensitization to other preservatives, particularly those used in skin care and cosmetic products, like methyldibromoglutaronitrile + 2-phenoxyethanol and MCI/MI was less important for employees in the study group, underpinning the occupational relevance of the above-mentioned industrial biocides.

Other allergens

Benzoyl peroxide was banned as a flour improver in Denmark and the Netherlands in the early 1930s followed by most of the other European countries (41). This act proved to be effective concerning occupational sensitizations over recent decades (5, 42), and benzoyl peroxide sensitization no longer plays an important role today. Sensitization to persulphates, gallates and sulfites was only found occasionally. They did not have a broad impact on sensitization rates and look likely to remain the domain of case reports and reviews (7, 8, 41). Bakers and especially cooks showed significantly higher sensitization rates to nickel sulphate than did the control group. Nickel sensitization is commonly acquired by wearing costume jewelry and the higher sensitization rates in study group could be an expression of specific fashion trends in such occupations (43, 44). However, particularly cooks and caterers regularly handle nickel-releasing stainless steel cutlery, tools, pans and pots. The impact of occupationally acquired nickel sulphate sensitizations is debatable. But there is some evidence that sensitization to nickel, independently of whether it was acquired in leisure time or under occupational conditions, plays a role in occupational settings, especially in employees involved in wet work (45–50).

Conclusions

Sensitization patterns in food processing occupations were quite homogeneous within these oc-

cupations, but varied significantly from sensitization rates in the total patch test population, indicating the occupational relevance of such patterns. Cooks were the occupation with the highest sensitization risk. Based on our data, for diagnostic purposes in such occupations we recommend patch testing with the standard series recommended by the German Contact Dermatitis Research Group, or a comparable standard series containing the relevant allergens at risk like thiuram mix and formaldehyde. Moreover, a rubber series, a Compositae series and individual workplace substances should be patch tested according to the patients' work environment. Preventive strategies must provide information about sensitization risks to work-related allergens in food or other workplace substances, like cleansing and disinfectant agents. Moreover, for preventive and therapeutic purposes it is essential to advise employers to remove thiuram-containing gloves from workplaces and to provide workers with thiuram-free protective gloves to prevent new sensitization in healthy, as well as disease exacerbation in sensitized, employees. Generally, there is an urgent need to improve preventive strategies in the food processing occupations to reduce the frequencies of occupational irritant contact and allergic contact dermatitis.

Acknowledgements

This study was supported by a grant of the Thuringian Ministry of Science, Research and Art (Thüringer Ministerium für Wissenschaft, Forschung und Kunst), Business Plan 2000, Chapter 1524/TG84.

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