

# Epidemiological data on airborne contact dermatitis – results of the IVDK

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## Summary

**Background.** Airborne contact dermatitis (AirbCD) is not uncommon, according to a large number of published case reports and review articles. Epidemiological data on AirbCD based on larger clinical samples have not yet been published.

**Objectives.** To investigate demographic characteristics and patch test reactivity in patients diagnosed with both occupational and non-occupational AirbCD.

**Methods.** A retrospective analysis of data from the Information Network of Departments of Dermatology (IVDK), 1994–2013, including 201 344 consecutively patch tested patients, was performed.

**Results.** One thousand two hundred and three patients (0.6%) were diagnosed with AirbCD, 421 (35.0%) of these with an occupational background. Occupational dermatitis and face involvement were more prevalent than in patients without AirbCD ( $n = 200\ 141$ ). Sensitization to epoxy resin and sensitization to methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI) were significantly associated with AirbCD, and there was a trend for sensitization to Compositae mix and/or sesquiterpene lactone mix to be associated with AirbCD. Adhesives, plastics, construction materials, paints and varnishes in occupational cases, and plants in non-occupational cases, were the most commonly documented culprit product categories.

**Conclusions.** AirbCD is more common in patients with occupational dermatitis than in patients with non-occupational dermatitis. In our clinical sample, components of epoxy resin systems, MCI/MI and Compositae allergens were the most important contact allergens associated with AirbCD. Patch testing with additional allergens is important.

**Key words:** airborne contact dermatitis; contact allergy; face dermatitis; occupational contact dermatitis; patch test.

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Airborne contact dermatitis (AirbCD) is defined as contact dermatitis (CD) caused by a variety of contact allergens and/or irritants transported by air, among them fibres, dust particles, sprays, vapours, and gases (1), affecting exposed skin areas. Skin lesions of airborne allergic CD have been reported to be eczematous, commonly symmetrical, and located in uncovered body parts. AirbCD may be misdiagnosed as facial allergic CD caused by direct contact of offending agents with the skin, or as atopic dermatitis, seborrhoeic dermatitis, and other dermatoses located primarily on the face. It should be noted that 'extrinsic'-type

atopic dermatitis may be triggered by aeroallergens (e.g. house dust mites and pollens), either by skin contact or by inhalation (2, 3); in the following, we will refer only to delayed hypersensitivity reactions to haptens.

Many case reports and case series have been published on AirbCD, mainly in the context of occupational settings. These cases have been summarized in several review articles, providing a good overview of offending agents, among them fragranced products, preservatives (e.g. isothiazolinones), plants (e.g. sesquiterpene lactones), woods, plastic resin systems and varnishes (e.g. epoxy resins), and drugs (e.g. corticosteroids) (1, 4–7).

The occurrence of AirbCD may be underestimated, as many cases are never published, and, occasionally, the term 'airborne' does not appear in the keywords, so that the publication is not found and considered in review articles (5). The proportion of AirbCD among patients with suspected allergic CD is largely unknown, as no epidemiological data from large-scale patient registries have been published yet. Swinnen and Goossens have recently reported AirbCD in 81 cases from 2548 patients patch tested in their department, but it is unclear whether this proportion (3.2%) is generally representative (7).

As the proportion of AirbCD among patch tested patients, the demographic and clinical characteristics of these patients and frequencies of sensitization to common allergens are not well known, we performed a retrospective analysis of data from the Information Network of Departments of Dermatology (IVDK) over the last two decades.

## Methods

The IVDK ([www.IVDK.org](http://www.IVDK.org)) is an epidemiological surveillance system on contact allergy that collects clinical and patch test data from 56 departments of dermatology in Germany, Austria, and Switzerland. The methods used by the IVDK have been described in detail elsewhere (8, 9). Patch tests are performed and evaluated according to international guidelines (10), as further refined by the German Contact Dermatitis Research Group (DKG) (11). Patch test material was obtained from Almirall Hermal (Reinbek, Germany) during the study period. Patch test results of every reading, a standardized history (sex, age, atopic diseases, current and former occupation, and up to three different presumptive causal exposures per patient), final diagnoses, anatomical site of dermatitis and information on suspected occupational causation are transferred in an anonymized format to the data centre at the University of Göttingen, where they are processed according to published standards after quality control (12, 13).

For the present data analysis, patch test reactions on D3 were selected. In a few exceptional cases, the D4 reaction was taken instead, if no reading was performed on D3, but a reading was performed on D4. Frequencies of sensitization (as percentage of patients tested) were calculated both as crude proportions and as proportions standardized for sex and age, supplemented with 95% confidence intervals (CIs) (14). Differences in the proportions of clinical or demographic characteristics among subgroups of patients were tested for statistical significance with the  $\chi^2$ -test; a *p*-value of < 0.05 was considered to indicate significance. For data management and analysis, the statistical software package SAS™ (version 9.3; SAS Institute, Cary, NC, USA) was used.

All patients patch tested in the years 1994–2013 in the departments of dermatology joining the IVDK (*n* = 201 344) were included in this data analysis. Patients whose final diagnosis was AirbCD on the basis of the clinical picture, medical history and diagnostic results (*n* = 1203) were compared with the remaining patients not diagnosed with AirbCD (*n* = 200 141; 'control group', i.e. patients with CD caused by direct contact of agents with the skin, atopic eczema, seborrhoeic eczema and others). Moreover, for a more detailed characterization, we compared data of AirbCD patients with occupational (*n* = 421) versus non-occupational causation (*n* = 782) of the disease. Diagnostic criteria for occupational CD included (i) an exposure-dependent course of the disease, and (ii) localization of skin lesions in areas of occupational exposure to allergens or irritants.

## Results

### Population characteristics and clinical features of AirbCD patients

Demographic and clinical characteristics according to the MOAHLFA index are shown in Table 1. The sex and age distributions were similar among AirbCD patients and the control group (mean age  $\pm$  standard deviation:  $45.5 \pm 15.4$  versus  $48.7 \pm 18.5$  years; no significant difference). As expected, the face was significantly more frequently involved in AirbCD patients, whereas the hands or legs were significantly less often affected. Remarkably, the proportion of occupational dermatitis patients was significantly higher among AirbCD patients than in the control group. When we compared AirbCD patients with and without occupational dermatitis, we found significantly more men, more patients with hand dermatitis and more patients aged < 40 years in the occupational dermatitis group.

Additional investigation of clinical data beyond the MOAHLFA index showed that there were significantly

**Table 1.** Demographic characteristics of patients with a final diagnosis airborne contact dermatitis, further itemized by occupational and non-occupational causation, and the control group, according to the items of the MOAHLFA index

|                             | Control group |       | Airborne contact dermatitis |       | Occupational airborne contact dermatitis |        | Non-occupational airborne contact dermatitis |       |
|-----------------------------|---------------|-------|-----------------------------|-------|------------------------------------------|--------|----------------------------------------------|-------|
|                             | n             | %     | n                           | %     | n                                        | %      | n                                            | %     |
|                             | 200 141       | 100.0 | 1203                        | 100.0 | 421                                      | 100.0  | 782                                          | 100.0 |
| M (male)                    | 73 461        | 36.7  | 468                         | 38.9  | 217                                      | 51.5   | 251                                          | 32.1  |
| O (occupational dermatitis) | 30 122        | 15.1  | 421                         | 35.0  | 421*                                     | 100.0* | 0*                                           | 0.0*  |
| A (atopic dermatitis)       | 37 640        | 18.8  | 268                         | 22.3  | 78                                       | 18.5   | 190                                          | 24.3  |
| H (hand dermatitis)         | 55 356        | 27.7  | 152                         | 12.6  | 84                                       | 20.0   | 68                                           | 8.7   |
| L (leg dermatitis)          | 21 213        | 10.6  | 8                           | 0.7   | 0                                        | 0.0    | 8                                            | 1.0   |
| F (face dermatitis)         | 30 683        | 15.3  | 826                         | 68.7  | 276                                      | 65.6   | 550                                          | 70.3  |
| A (age ≥ 40 years)          | 134 215       | 67.1  | 791                         | 65.8  | 239                                      | 56.8   | 552                                          | 70.6  |

\*Owing to group definition.

more patients with generalized eczema in the control group than among AirbCD patients (10.0% versus 4.0%).

### Presumptive causal exposures

The 15 most frequent allergen sources suspected, before patch testing, by the physician of having caused dermatitis in AirbCD patients are shown in Table 2. Patients with AirbCD were significantly more often than individuals in the control group to be suspected of suffering from dermatitis caused by plants, perfumes, deodorants or aftershaves, adhesives, paints and varnishes, plastics, construction materials, that is, cement and tiling adhesives, chemicals not further specified, and house dust.

Among the patients with occupational AirbCD, presumptive causal exposures were most frequently adhesives, plastic materials, disinfectants, paints, and other construction materials, whereas among the non-occupational cases, cosmetics, plants, topical drugs, perfumes etc. were more frequently documented (Table 3). Patients with occupational AirbCD were more often employed as health professionals, for example nurses, nursing assistants, and dental assistants (10.9% versus 5.8% in the control group), as painters (7.6% versus 0.6%), as mechanics, machine operators, or toolmakers (5.9% versus 2.9%), in the building trade (4.8% versus 0.9%), as florists or gardeners (4.3% versus 0.7%), as farmers (3.6% versus 0.5%), as engineers or technicians (3.3% versus 2.2%), in cleaning professions (3.3% versus 1.7%), and as plastic processors (2.9% versus 0.2%), reflecting the presumptive causal exposures in this patient group. The job titles of patients with non-occupational AirbCD were similar to those in the control group, and were unspecific, with 29.8% working in occupations with indefinite exposures, 20.1% working in office occupations, and 11.0% being housewives.

**Table 2.** Most frequent presumptive causal exposures in patients with airborne contact dermatitis (n = 1203) and, for comparison, corresponding data of the control group (n = 200 141)

| Exposures                         | Airborne contact dermatitis |      | Control group |      |
|-----------------------------------|-----------------------------|------|---------------|------|
|                                   | n                           | %    | n             | %    |
| Cosmetics                         | 389                         | 32.3 | 62 119        | 31.0 |
| Plants (food excluded)            | 149                         | 12.4 | 3305          | 1.7  |
| Drugs (topical)                   | 127                         | 10.6 | 42 856        | 21.4 |
| Perfumes, deodorants, aftershaves | 103                         | 8.6  | 7025          | 3.5  |
| Adhesives                         | 99                          | 8.2  | 3449          | 1.7  |
| Paints, varnishes                 | 87                          | 7.2  | 2991          | 1.5  |
| Disinfectants                     | 85                          | 7.1  | 12 340        | 6.2  |
| Plastics                          | 68                          | 5.7  | 3733          | 1.9  |
| Soap, shower gel, shampoo         | 59                          | 4.9  | 11 927        | 6.0  |
| Chemicals (not specified)         | 56                          | 4.7  | 2662          | 1.3  |
| Construction materials            | 56                          | 4.7  | 3815          | 1.9  |
| Rubber                            | 54                          | 4.5  | 12 269        | 6.1  |
| Gloves (leather, rubber, fabric)  | 51                          | 4.2  | 12 046        | 6.0  |
| House dust                        | 48                          | 4.0  | 1329          | 0.7  |
| Cleaning agents                   | 45                          | 3.7  | 5472          | 2.7  |

### Patch test results

*Patch tests with commercial preparations.* A positive reaction to at least one allergen was observed in 724 of 1203 patients with AirbCD (60.2%). Among these, the average number of incriminated allergens was 3.2 allergens per patient. In the control group, 101 535 of 200 141 patients (50.7%) had at least one positive reaction, with an average of 2.8 reactions per patient.

Among the 1203 AirbCD patients, the DKG baseline series was tested in 1039 patients (86%). Special patch test series were tested as follows: ointment bases (696 patients; 58%), preservatives (512 patients; 43%), plastics

**Table 3.** Most frequent presumptive causal exposures in patients with occupational (n = 421) and non-occupational (n = 782) airborne contact dermatitis

| Occupational airborne contact dermatitis |    |      | Non-occupational airborne contact dermatitis |     |      |
|------------------------------------------|----|------|----------------------------------------------|-----|------|
| Exposures                                | n  | %    | Exposures                                    | n   | %    |
| Adhesives                                | 64 | 15.2 | Cosmetics                                    | 346 | 44.2 |
| Plastics                                 | 55 | 13.1 | Plants (food excluded)                       | 116 | 14.8 |
| Disinfectants                            | 55 | 13.1 | Drugs (topical)                              | 111 | 14.2 |
| Cosmetics                                | 43 | 10.2 | Perfumes, deodorants, aftershaves            | 90  | 11.5 |
| Paints, varnishes                        | 43 | 10.2 | Soap, shower gel, shampoo                    | 55  | 7.0  |
| Construction materials                   | 37 | 8.8  | Paints, varnishes                            | 44  | 5.6  |
| Gloves (leather, rubber, fabric)         | 35 | 8.3  | House dust                                   | 43  | 5.5  |
| Rubber                                   | 34 | 8.1  | Adhesives                                    | 35  | 4.5  |
| Plants (food excluded)                   | 33 | 7.8  | Disinfectants                                | 30  | 3.8  |
| Cleaning agents                          | 29 | 6.9  | Hair cosmetics (colours, perms)              | 25  | 3.2  |
| Metalworking fluids                      | 22 | 5.2  | Chemicals (not specified)                    | 22  | 2.8  |
| Metals                                   | 18 | 4.3  | Textiles                                     | 20  | 2.6  |
| Drugs (topical)                          | 16 | 3.8  | Rubber                                       | 20  | 2.6  |
| Perfumes, deodorants, aftershaves        | 13 | 3.1  | Paints in freshly painted areas              | 20  | 2.6  |
| Hair cosmetics (colours, perms)          | 13 | 3.1  | Construction materials                       | 19  | 2.4  |

and glues (255 patients; 21%), fragrances (246 patients; 20%), rubber (233 patients; 19%), disinfectants (213 patients; 18%), and plant materials (202 patients; 17%). Additional series were tested in < 100 patients each. Percentages of positive reactions to allergens from single test series showed that, beyond the very 'efficient' baseline series (at least one positive reaction in 52% of the patients tested), testing with the plastics and glue series, plant material series and special fragrance series was the most rewarding (positive reactions in 29%, 25% and 19% of the patients tested, respectively).

Allergens that were included in the baseline series for several years during the study period are listed in decreasing order of frequency in Table 4 for patients with AirbCD as compared with the control group. As can be seen from the non-overlapping 95% CIs of the age-standardized and sex-standardized reaction frequencies, there were some significant differences. Patients with AirbCD were more frequently sensitized to epoxy resin based on bisphenol A diglycidyl ether (BADGE) and methylchloroisothiazolinone (MCI)/methylisothiazolinone (MI). Less pronounced increases were seen with colophonium, nickel, fragrance mixes, and formaldehyde. In Table 4, only those allergens that were included in the baseline series and were therefore patch tested in almost all consecutive patients in both groups are listed. Hence, a comparison without selection bias is possible. However, further allergens were applied in selected patients of the study population, according to their individual histories. Among the patients with AirbCD, high sensitization prevalence rates were observed for sesquiterpene lactone mix [positive reactions in 47 of 350 (13.4%) patch tested patients], Compositae mix [tested as

four different commercial preparations in the course of the study period; in all, 63 of 915 (6.9%) patients with a positive reaction to at least one of the mixes], MI [34 of 356 (9.6%)], and several reactive diluents of epoxy resin systems.

The proportion of patients with at least one positive patch test reaction was significantly higher among patients with occupationally caused AirbCD than among those with no occupational background (65.8% versus 57.2%). A comparison of sensitization prevalence rates in patients with occupational and non-occupational AirbCD is shown in Table 5. Patients with occupational AirbCD were significantly more often sensitized to epoxy resin based on BADGE and significantly less often sensitized to MCI/MI. Of the 421 patients with occupational AirbCD, 343 were patch tested with BADGE epoxy resin, and 61 (17.8%) reacted positively. Of the 61 epoxy resin-positive patients, 31 also reacted to reactive diluents, and 12 to amine hardeners. In 149 patients, plants were suspected to have caused AirbCD. Of these, 107 were patch tested with sesquiterpene lactone mix, and 36 (33.6%) reacted positively. A Compositae mix was patch tested in 106 patients, and, of these, 32 (30.2%) reacted positively. Of the 103 patients in whom perfumes, deodorants etc. were the suspected allergen sources, 92 were patch tested with the fragrance mix, and, of these, 21 (22.8%) reacted positively. Sixteen of 92 patients (17.4%) reacted to *Myroxylon pereirae* (balsam of Peru), and 8 of 54 (14.8%) to fragrance mix II. Single fragrance compounds were patch tested in 25–55 patients, and of these, only a few (< 5 patients for each allergen) reacted positively. Among the 99 patients with adhesives as the suspected allergen

**Table 4.** Prevalence rates of sensitization to baseline series allergens in decreasing order of frequency in patients with airborne contact dermatitis (n = 1203), and comparison with the respective frequencies in patients of the control group (n = 200 141)

| Allergen                                       | Airborne contact dermatitis        |                                                             | Control group                      |                                                             |
|------------------------------------------------|------------------------------------|-------------------------------------------------------------|------------------------------------|-------------------------------------------------------------|
|                                                | Crude % positive reactions (95%CI) | Age-standardized and sex-standardized prevalence, % (95%CI) | Crude % positive reactions (95%CI) | Age-standardized and sex-standardized prevalence, % (95%CI) |
| Nickel sulfate 5.0%                            | 17.3 (15.1–19.8)                   | 20.0 (17.3–22.6)                                            | 14.9 (14.8–15.1)                   | 16.9 (16.7–17.1)                                            |
| Fragrance mix I 8.0%                           | 12.2 (10.3–14.4)                   | 12.1 (10.0–14.2)                                            | 9.7 (9.5–9.8)                      | 9.0 (8.9–9.1)                                               |
| Epoxy resin based on BADGE 1.0%                | 8.4 (6.8–10.3)                     | 8.1 (6.4–9.8)                                               | 1.4 (1.4–1.5)                      | 1.3 (1.3–1.4)                                               |
| <i>Myroxylon pereirae</i> (balsam of Peru) 25% | 7.5 (6.0–9.3)                      | 6.9 (5.3–8.5)                                               | 8.5 (8.4–8.7)                      | 7.4 (7.3–7.5)                                               |
| Colophonium (rosin) 20%                        | 6.4 (4.9–8.0)                      | 6.1 (4.5–7.6)                                               | 4.2 (4.1–4.3)                      | 4.0 (3.9–4.1)                                               |
| Fragrance mix II 14%*                          | 6.3 (4.6–8.5)                      | 5.3 (3.6–7.0)                                               | 5.1 (4.9–5.2)                      | 4.6 (4.5–4.8)                                               |
| MCI/MI 100 ppm in water                        | 5.7 (4.4–7.3)                      | 5.3 (3.9–6.7)                                               | 2.8 (2.7–2.9)                      | 2.7 (2.6–2.8)                                               |
| Cobalt chloride 1.0%                           | 5.6 (4.3–7.2)                      | 6.7 (4.9–8.4)                                               | 5.4 (5.3–5.5)                      | 5.9 (5.8–6.0)                                               |
| Potassium dichromate 0.5%                      | 3.9 (2.8–5.3)                      | 3.7 (2.5–4.9)                                               | 4.4 (4.3–4.5)                      | 4.2 (4.1–4.3)                                               |
| Methyldibromo glutaronitrile 0.2%/0.3%†        | 3.8 (2.6–5.4)                      | 3.6 (2.2–4.9)                                               | 3.8 (3.7–3.9)                      | 3.4 (3.3–3.5)                                               |
| Lanolin alcohols 30.0%                         | 3.4 (2.4–4.6)                      | 2.8 (1.8–3.7)                                               | 3.3 (3.2–3.3)                      | 3.0 (2.9–3.1)                                               |
| Propolis 10.0%‡                                | 3.1 (2.1–4.4)                      | 2.8 (1.7–3.9)                                               | 2.7 (2.7–2.8)                      | 2.5 (2.4–2.6)                                               |
| Thiuram mix 1.0%                               | 2.8 (1.9–4.0)                      | 3.0 (1.8–4.1)                                               | 2.4 (2.3–2.5)                      | 2.4 (2.3–2.4)                                               |
| Oil of turpentine 10.0%                        | 2.8 (1.9–4.0)                      | 2.4 (1.5–3.3)                                               | 2.0 (1.9–2.0)                      | 1.8 (1.8–1.9)                                               |
| Formaldehyde 1.0% in water                     | 2.7 (1.8–3.8)                      | 2.8 (1.7–3.9)                                               | 1.5 (1.4–1.6)                      | 1.5 (1.4–1.6)                                               |

BADGE, bisphenol A diglycidyl ether; CI, confidence interval; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone.

All allergens in petrolatum, except where indicated.

\*Fragrance mix II has been included in the German Contact Dermatitis Research Group (DKG) baseline series since 2005.

†Methyldibromo glutaronitrile has been included in the DKG baseline series since 1997; its test concentration has been changed over the years.

‡Propolis has been included in the DKG baseline series since 1999.

source, epoxy resin was the leading allergen, with 30 of 89 reacting positively (33.7%). Paints and varnishes and/or staying in freshly painted rooms were the presumptive allergen sources in 110 patients. MCI/MI was patch tested in 101 of these patients, and 21 (20.8%) reacted positively. MI was tested in 40 patients, and 12 (30.0%) of these reacted positively. Epoxy resin gave positive reactions in 14 of 100 (14.0%) patients. In contrast, no particular pattern of sensitization was found among the 85 patients with disinfectants as the presumptive allergen source; reactions to formaldehyde were seen in 4 of 69 patients (5.8%), and to glutaraldehyde in 3 of 62 patients (4.8%).

**Patch testing with patients' own drugs.** In 16 patients with occupational AirbCD, 80 patch tests with systemic drugs brought in by patients were performed. Five of these patients were veterinarians, and the other 11 patients were employed as nurses or nurse assistants. Positive reactions were observed in 6 patients, who reacted to tetrazepam (4 of 5 patients), tylosin (1 of 3 patients), and pantoprazole (1 of 1 patient). No reactions were seen to other drugs (Table S1).

## Discussion

To the best of our knowledge, this is the first large-scale epidemiological analysis addressing AirbCD. It is based on a large patient sample of > 200 000 patients patch tested for suspected CD in 56 dermatology departments networking in the IVDK. Only 0.6% of these patients were diagnosed with AirbCD, which is considerably lower than the frequency reported by Swinnen and Goossens (3.2%) (7). The proportion of patients suffering from AirbCD in a clinical patient sample largely depends on the patient population analysed, and therefore may not be representative when recruited in a single department. The difference in frequency between our data analysis and that of Swinnen and Goossens probably arises from the fact that the department of dermatology in Leuven is a renowned contact allergy centre, and complicated or severe cases, including most AirbCD patients, accumulate there. Our data confirm that AirbCD should be considered particularly in patients presenting with eczema localized on the face. However, other uncovered body parts may be affected if exposed to the airborne allergen, for example when the individual is working while wearing short sleeves or trousers.

**Table 5.** Prevalence rates of sensitization to baseline series allergens in decreasing order of frequency in patients with occupational airborne contact dermatitis (n = 421), and comparison with the respective frequencies in patients with non-occupational airborne contact dermatitis (n = 782)

| Allergen                                      | Occupational airborne contact dermatitis |                                                             | Non-occupational airborne contact dermatitis |                                                             |
|-----------------------------------------------|------------------------------------------|-------------------------------------------------------------|----------------------------------------------|-------------------------------------------------------------|
|                                               | Crude % positive reactions (95%CI)       | Age-standardized and sex-standardized prevalence, % (95%CI) | Crude % positive reactions (95%CI)           | Age-standardized and sex-standardized prevalence, % (95%CI) |
| Epoxy resin based on BADGE 1.0%               | 17.8 (13.9–22.2)                         | 13.4 (10.2–16.6)                                            | 3.8 (2.5–5.5)                                | 4.0 (2.3–5.6)                                               |
| Nickel sulfate 5.0%                           | 16.5 (12.8–20.8)                         | 19.8 (15.2–24.4)                                            | 17.8 (15.0–20.8)                             | 19.8 (16.5–23.1)                                            |
| Fragrance mix I 8.0%                          | 10.2 (7.2–13.9)                          | 10.6 (7.1–14.2)                                             | 13.3 (10.8–16.0)                             | 12.4 (9.8–15.0)                                             |
| <i>Myroxylon perei</i> (balsam of Peru) 25.0% | 7.9 (5.3–11.3)                           | 8.1 (5.1–11.1)                                              | 7.3 (5.4–9.5)                                | 6.0 (4.3–7.8)                                               |
| Cobalt chloride 1.0%                          | 6.6 (4.2–9.8)                            | 7.7 (4.6–10.8)                                              | 5.1 (3.6–7.0)                                | 5.9 (3.9–8.0)                                               |
| Fragrance mix II 14.0%*                       | 6.5 (3.6–10.7)                           | 6.4 (2.8–10.1)                                              | 6.3 (4.1–9.0)                                | 4.5 (2.7–6.4)                                               |
| Colophonium (rosin) 20.0%                     | 5.7 (3.5–8.7)                            | 5.3 (2.8–7.7)                                               | 6.7 (4.9–8.8)                                | 6.6 (4.6–8.6)                                               |
| Thiuram mix 1.0%                              | 4.6 (2.6–7.3)                            | 5.1 (2.5–7.6)                                               | 1.9 (1.0–3.2)                                | 2.0 (0.8–3.1)                                               |
| Potassium dichromate 0.5%                     | 4.0 (2.2–6.6)                            | 3.4 (1.5–5.2)                                               | 3.9 (2.6–5.7)                                | 4.0 (2.4–5.7)                                               |
| Methyldibromo glutaronitrile 0.2%/0.3%†       | 3.9 (2.0–6.9)                            | 4.1 (1.5–6.6)                                               | 3.7 (2.3–5.8)                                | 3.4 (1.7–5.0)                                               |
| Formaldehyde 1.0% in water                    | 3.4 (1.8–5.8)                            | 3.9 (1.7–6.1)                                               | 2.3 (1.3–3.7)                                | 2.6 (1.2–4.0)                                               |
| MCI/MI 100 ppm in water                       | 3.4 (1.8–5.8)                            | 2.9 (1.2–4.6)                                               | 7.0 (5.2–9.1)                                | 6.7 (4.7–8.7)                                               |
| Oil of turpentine 10.0%                       | 3.4 (1.8–5.9)                            | 2.7 (1.1–4.3)                                               | 2.5 (1.4–3.9)                                | 2.2 (1.1–3.4)                                               |
| Propolis 10.0%‡                               | 3.1 (1.5–5.6)                            | 2.9 (1.0–4.8)                                               | 3.1 (1.9–4.8)                                | 2.7 (1.4–3.9)                                               |
| Lanolin alcohols 30.0%                        | 2.8 (1.4–5.1)                            | 2.5 (0.8–4.1)                                               | 3.6 (2.4–5.3)                                | 2.9 (1.7–4.1)                                               |

BADGE, bisphenol A diglycidyl ether; CI, confidence interval; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone.

All allergens in petrolatum, except where indicated.

\*Fragrance mix II has been included in the German Contact Dermatitis Research Group (DKG) baseline series since 2005.

†Methyldibromo glutaronitrile has been included in the DKG baseline series since 1997; its test concentration has been changed over the years.

‡Propolis has been included in the DKG baseline series since 1999.

We analysed allergen sources suspected, before patch testing, to have induced dermatitis. As expected, not every presumptive causal exposure was confirmed on patch testing. However, most exposures suspected of having caused dermatitis in AirbCD patients were typical airborne agents, that is, plants, perfumes, deodorants, paints and varnishes, adhesives, plastics, and construction materials. On the other hand, in many patients, cosmetics and topical drugs were (also) suspected of having caused skin lesions pre-patch testing. Probably, in these patients facial dermatitis was initially attributed to direct skin contact with these products, but was finally diagnosed as AirbCD after the patch test results were available.

As one limitation, it has to be considered that (i) the IVDK documentation does not differentiate between allergic and irritant AirbCD, and (ii) this is a retrospective data analysis and not an in-depth report of single cases. Not every contact allergy diagnosed is related to the patients' AirbCD; there may also be contact allergies related to other diagnoses, including allergens with past relevance, or chance 'non-relevant' findings. It was not the aim of our study to present and discuss a full review on airborne allergens reported in published case reports. Therefore, we have focused our discussion on allergens

with a significantly increased frequency of sensitization among AirbCD patients, the potential for airborne exposure, and a plausible relationship with the patients' exposure. On the whole, sensitization frequencies matched the suspected allergen sources. The significantly higher proportion of epoxy resin sensitization can be explained by airborne exposure to adhesives, varnishes, plastics, and construction materials, the high frequency of sensitization to MCI/MI and MI by exposure to water-based paints, which are frequently preserved with these biocides (15), and the increased number of reactions to fragrance mix by airborne exposure to perfumes and spray-on deodorants. However, we have no conclusive explanation from the available routine data for the significantly higher proportion of contact allergy to colophonium. Colophonium, on the one hand, and sesquiterpene lactone mix or at least one of the four variations of the Compositae mix used in the course of the 20 years (1994–2013), on the other hand, were patch tested in parallel in 930 AirbCD patients. Of these, 62 (6.7%) reacted positively to colophonium, and 71 (7.6%) to sesquiterpene lactone mix and/or Compositae mix. Only 13 of these patients reacted to both colophonium and sesquiterpene lactone mix/Compositae mix. Hence, the majority of the reactions to colophonium can probably not be explained by sensitization to terpenes,

which are also present in *Compositae*. Finally, formaldehyde reactions were significantly more common in AirbCD patients, albeit being seen in only 28 patients. With the share of patients with occupational dermatitis and nurses being increased among the formaldehyde-positive AirbCD patients (data not shown in detail), this was a plausible but not significant explanation.

In more than one-third of all patients diagnosed with AirbCD, skin lesions were related to occupational exposure. This corresponds to the high proportion of published case report of AirbCD occurring in occupational settings and the data reported by Swinnen and Goossens (7). As expected, a large proportion of patients with occupational AirbCD in our clinical sample also had hand involvement, presumably because of either airborne or direct skin contact with offending allergens. Patients with occupational AirbCD were, on average, younger than patients with non-occupational AirbCD, and there was a higher proportion of male patients, in line with the finding that many patients with occupational AirbCD were employed in 'typical' craft occupations, for example as painters, as varnishers, as mechanics, as machine operators, as toolmakers, or in the building trade, even though the most common occupation was aggregated health professions. Accordingly, characteristic volatile or fine-particulate occupational exposures were suspected of having caused skin lesions in patients with occupational AirbCD, mainly adhesives, plastics, paints, varnishes, construction materials, and disinfectants.

The high prevalence of sensitization to epoxy resin based on BADGE in patients with occupational CD can easily be attributed to the fact that most epoxy resins systems are composed of a resin based on BADGE, diluents, and hardeners, and almost all may induce (airborne) contact allergy. It is remarkable that, among occupational AirbCD patients, the frequency of sensitization to epoxy resin based on BADGE is 10-fold higher than in the general IVDK patient population (16).

Unexpectedly, the prevalence of sensitization to the isothiazolinone preservative mixture MCI/MI was higher in patients with non-occupational AirbCD than in patients with occupational AirbCD. MCI/MI is primarily used in industrial products, but also in consumer products such as cleaning products and, with decreasing frequency, in cosmetics and toiletries. Regarding industrial products, MCI/MI is added to water-based paints and varnishes, but also to many other industrial fluids (17). In recent years, MI has increasingly been used as a single preservative in cosmetics and industrial products, particularly in paints (15). Among painters and varnishers, the rates of sensitization to MI are rising (18). Cases of AirbCD caused by MI and MCI/MI contained in

water-based paints have been reported (19, 16). However, paints and 'staying in freshly painted rooms' were the suspected sources of allergen exposure in ~40% of both patients with occupational AirbCD and patients with non-occupational AirbCD sensitized to MCI/MI, which suggests that exposure to MCI/MI in paints may also have contributed to the high sensitization prevalence in patients with non-occupational AirbCD.

Regarding the suspected exposure to plants, high prevalence rates of sensitization to constituents of plants (*Compositae* mix and sesquiterpene lactone mix) were found both in patients with occupational AirbCD and in those with non-occupational AirbCD. Sesquiterpene lactones are contained in *Compositae*, but also in plants of related and unrelated plant families, such as *Magnoliaceae*, *Laureaceae*, and *Frullaniae* (20).

The role of drugs as a cause of AirbCD has been frequently described in case reports in recent years (21–25). For 16 of the occupational AirbCD patients, systemic drugs brought in by the patients were patch tested, and 6 of them reacted positively. Remarkably, tetrazepam was the leading allergen among these patients. Tetrazepam [7-chloro-5(cyclohex-1-enyl)-1,3-dihydro-1-methyl-2H-1,4-benzodiazepin-2-one] is a benzodiazepine. It has been used as a muscle relaxant and sedative in geriatric nurseries. Case series and single cases of occupational AirbCD in geriatric nurses caused by tetrazepam have been reported by several groups in recent years (21, 23–25). Worsening of skin lesions occurred in the work environment, where they had to pulverize tetrazepam tablets with a mortar, leading to the production of drug dust. A case of occupational AirbCD caused by tetrazepam in a repair technician employed in the pharmaceutical industry was reported by Ferran et al. (26). Because numerous life-threatening drug reactions after intake of tetrazepam had occurred in the past, the European Commission suspended the registration of drugs containing tetrazepam in January 2013.

In conclusion, AirbCD is not uncommon, particularly in occupational dermatology, and is possibly underestimated. In our patients, components of epoxy resin systems, MCI/MI and *Compositae* allergens (including sesquiterpene lactones) were the most important contact allergens associated with AirbCD. Patch testing with additional allergens is important, according to the patient's individual exposure, to identify contact allergy relevant for AirbCD.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Patch tests (n = 80) with internal drugs in patients with occupational airborne contact dermatitis (n = 16).

## References

- Lachapelle J-M. Airborne contact dermatitis. In: *Kanerva's Occupational Dermatology*, 2nd edition, Rustemeyer T, Elsner P, John S M, et al. (eds): Berlin, Heidelberg, Springer-Verlag, 2012: pp. 175–184.
- Darsow U, Laifaoui J, Kerschenlohr K et al. The prevalence of positive reactions in the atopy patch test with aeroallergens and food allergens in subjects with atopic eczema: a European multicenter study. *Allergy* 2004; **59**: 1318–1325.
- Werfel T, Kapp A. Environmental and other major provocation factors in atopic dermatitis. *Allergy* 1998; **53**: 731–739.
- Dooms-Goossens A, Deleu H. Airborne contact dermatitis: an update. *Contact Dermatitis* 1991; **25**: 211–217.
- Santos R, Goossens A. An update on airborne contact dermatitis: 2001–2006. *Contact Dermatitis* 2007; **57**: 353–360.
- Schloemer J A, Zirwas M J, Burkhart C G. Airborne contact dermatitis: common causes in the USA. *Int J Dermatol* 2015; **54**: 271–274.
- Swinnen I, Goossens A. An update on airborne contact dermatitis: 2007–2011. *Contact Dermatitis* 2013; **68**: 232–238.
- Schnuch A, Geier J, Uter W et al. National rates and regional differences in sensitization to allergens of the standard series. Population adjusted frequencies of sensitization (PAFS) in 40,000 patients from a multicentre study (IVDK). *Contact Dermatitis* 1997; **37**: 200–209.
- Schnuch A, Geier J, Lessmann H, Arnold R, Uter W. Surveillance of contact allergies: methods and results of the Information Network of Departments of Dermatology (IVDK). *Allergy* 2012; **67**: 847–857.
- Lindberg M, Matura M. Patch testing. In: *Contact Dermatitis*, 5th edition, Johansen J D, Frosch P J, Lepoittevin J P (eds): Berlin, Heidelberg, Springer-Verlag, 2011: pp. 439–464.
- Schnuch A, Aberer W, Agathos M et al. Performing patch testing with contact allergens. *J Dtsch Dermatol Ges* 2008; **6**: 770–775.
- Uter W, Schnuch A, Gefeller O. Guidelines for the descriptive presentation and statistical analysis of contact allergy data. *Contact Dermatitis* 2004; **51**: 47–56.
- Uter W, Mackiewicz M, Schnuch A, Geier J. Interne Qualitätssicherung von Epikutantest-Daten des multizentrischen Projektes 'Informationsverbund Dermatologischer Kliniken' (IVDK). *Dermatol Beruf Umwelt* 2005; **53**: 107–114.
- Schnuch A. PAFS – population adjusted frequency of sensitization (I) – influence of sex and age. *Contact Dermatitis* 1996; **34**: 377–382.
- Schwensen J F, Lundov M D, Bossi R et al. Methylisothiazolinone and benzisothiazolinone are widely used in paint: a multicentre study of paints from five European countries. *Contact Dermatitis* 2015; **72**: 127–138.
- Bohn S, Niederer M, Brehm K, Bircher A J. Airborne contact dermatitis from methylisothiazolinone in wall paint. Abolition of symptoms by chemical allergen inactivation. *Contact Dermatitis* 2000; **42**: 196–201.
- Friis U F, Menné T, Flyvholm M A, Bonde J P, Lepoittevin J P, Le Coz C J, Johansen J D. Isothiazolinones in commercial products at Danish workplaces. *Contact Dermatitis* 2014; **71**: 65–74.
- Uter W, Geier J, Bauer A, Schnuch A. Risk factors associated with

- methylisothiazolinone contact sensitization. *Contact Dermatitis* 2013; **69**: 231–238.
- 19 Alwan W, White I R, Banerjee P. Presumed airborne contact allergy to methylisothiazolinone causing acute severe facial dermatitis and respiratory difficulty. *Contact Dermatitis* 2014; **70**: 320–321.
  - 20 Lovell C R. Plants. In: *Kanerva's Occupational Dermatology*, 2nd edition, Rustemeyer T, Elsner P, John S M, et al. (eds): Berlin, Heidelberg, Springer-Verlag, 2012: pp. 793–805.
  - 21 Breuer K, Worm M, Skudlik C, Schröder C, John S M. Occupational airborne contact allergy to tetrazepam in a geriatric nurse. *J Dtsch Dermatol Ges* 2009; **7**: 896–898.
  - 22 Corazza M, Baldo F, Osti F, Virgili A. Airborne allergic contact dermatitis due to budesonide from professional exposure. *Contact Dermatitis* 2008; **59**: 318–319.
  - 23 Landeck L, Skudlik C, John S M. Airborne contact dermatitis to tetrazepam in geriatric nurses – a report of 10 cases. *J Eur Acad Dermatol Venereol* 2012; **26**: 680–684.
  - 24 Swinnen I, Ghys K, Kerre S, Constandt L, Goossens A. Occupational airborne contact dermatitis from benzodiazepines and other drugs. *Contact Dermatitis* 2014; **70**: 227–232.
  - 25 Vander Hulst K, Kerre S, Goossens A. Occupational allergic contact dermatitis from tetrazepam in nurses. *Contact Dermatitis* 2010; **62**: 303–308.
  - 26 Ferran M, Giménez-Arnau A, Luque S, Berenguer N, Iglesias M, Pujol R M. Occupational airborne contact dermatitis from sporadic exposure to tetrazepam during machine maintenance. *Contact Dermatitis* 2005; **52**: 173–174.

**Table S1.** Patch tests (n=80) with internal drugs in patients with occupational airborne contact dermatitis (n=16). Numbers of patients tested with the respective drug in parentheses.

| ATC code                                          | Internal drugs                                                                                                             | Positive reactions |
|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|--------------------|
| A02 Drugs for acid related disorders              | Omeprazole (1), Pantoprazole (1), Esomeprazole (1), Ranitidine (2), Calcium carbonate (1)                                  | Pantoprazole (1)   |
| A10 Drugs used in diabetes                        | Acarbose (1), Glibenclamide (1), Glimepiride (1)                                                                           | -                  |
| B03 Antianaemic preparations                      | Ferrous sulphate (2)                                                                                                       | -                  |
| C01 Cardiac therapy                               | Digitoxin (1)                                                                                                              | -                  |
| C03 Diuretics                                     | Furosemide (3), Torasemide (2), Xipamide (1), Spironolactone (1)                                                           | -                  |
| C05 Vasoprotectives                               | Isosorbiddinitrate (1)                                                                                                     | -                  |
| C07 Beta blocking agents                          | Metoprolol (2), Bisoprolol (1)                                                                                             | -                  |
| C08 Calcium channel blockers                      | Verapamil (1)                                                                                                              | -                  |
| C09 Agents acting on the renin-angiotensin system | Captopril (1), Enalapril (1)                                                                                               | -                  |
| C10 Lipid modifying agents                        | Simvastatin (1)                                                                                                            | -                  |
| H02 Corticosteroids for systemic use              | Prednisolone (1)                                                                                                           | -                  |
| H03 Thyroid therapy                               | L-Thyroxine (1),                                                                                                           | -                  |
| J01 Antiinfectives for systemic use               | Benzylopicillin (1), Amoxicillin (2), Cefuroxim (1), Ofloxacin (1)                                                         | -                  |
| J07 Vaccines                                      | Tetanus toxoid (1)                                                                                                         | -                  |
| N02 Analgesics                                    | Acetylsalicylic acid (1), Metamizole (1), Morphine (1)                                                                     | -                  |
| N03 Antiepileptics                                | Valproic acid (1), Carbamazepine (2), Clonazepam (1)                                                                       | -                  |
| N04 Anti-parkinson drugs                          | Levodopa (2), Amantadine (1), Selegiline (1)                                                                               | -                  |
| N05 Psycholeptics                                 | Diazepam (1), Chlorpromazine (2), Clozapine (1), Pipamperone (1), Risperidone (1), Chlorprothixene (1), Zuclopenthixol (1) | -                  |
| N06 Psychoanaleptics                              | Antidepressants: Mirtazapine (1), Amitriptyline (1), Memantine (1), Pyracetam (1)                                          | -                  |
| M01 Antiinflammatory and antirheumatic products   | Ibuprofen (1), Meloxicam (1)                                                                                               | -                  |
| M03 Muscle relaxants                              | Tetrazepam (5), Baclofen (1)                                                                                               | Tetrazepam (4)     |
| M04 Antigout preparations                         | Allopurinol (2)                                                                                                            | -                  |
| R05 Cough and cold preparations                   | Codeine (1), Acetylcysteine (1)                                                                                            | -                  |
| No ATC code: Veterinary drugs                     | Tylosine (3), Tiamuline (1), Enrofloxacin (1), Oxytocin (1), Olaquinox (1)                                                 | Tylosine (1)       |