

Airborne chemicals cause respiratory symptoms in individuals with contact allergy

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Exposure to fragrance chemicals causes various eye and airway symptoms. Individuals with perfume contact allergy report these symptoms more frequently than individuals with nickel allergy or no contact allergies. However, the associations between contact allergy and respiratory symptoms elicited by airborne chemicals other than perfumes are unclear. The study aimed to investigate the association between eye and airway symptoms elicited by airborne chemicals (other than perfumes) and contact allergy in a population-based sample. A questionnaire on respiratory symptoms was posted, in 2002, to 1189 individuals who participated in 1997/1998 in a Danish population-based study of allergic diseases. Questions about eye and airway symptoms elicited by different airborne chemicals and airborne proteins were included in the questionnaire. Data from the questionnaire were compared with data on patch testing and prick testing. Having at least 1 positive patch test (adjusted odds ratio 1.7, 95% CI 1.2–2.5) was associated with the symptoms, and the odds ratio increased with the number of positive patch tests (*P*-value for test for trend <0.05). Bronchial hyperreactivity, female sex and psychological vulnerability were independently associated with symptoms, but no association was found between prick test reactivity to proteins and the symptoms elicited by airborne chemicals.

Key words: contact sensitization; exposure; epidemiology; respiratory symptoms; airborne chemicals; sensory irritants; perfume. © Blackwell Munksgaard, 2005.

Accepted for publication 27 December 2004

Exposure to airborne fragrances is related to various immediate eye and airway symptoms, which make everyday life troublesome for many people (1). Individuals with hand eczema and perfume contact allergy report these symptoms more frequently than individuals with nickel contact allergy or no contact allergies (2). These findings suggest a link between skin and airways that warrants additional investigation.

The organic compounds in indoor air (OCIA) include ozone, and non-protein and non-glucan compounds (i.e. compounds with a molecular weight less than 500–1000 Da) (3). Some OCIA are chemically reactive and have been associated with ocular and respiratory symptoms (3) and many of these are also well-known contact allergens (e.g. acid anhydrides, acrylates and amines) (4). Most contact allergens are small, chemically reactive molecules with a molecular weight less than 400 Da (5) and may become airborne (4).

Volatile organic compounds (VOCs) are emitted from newspaper, laser printers and newly painted surfaces (6, 7); ambient air pollutants are emitted by vehicles with fossil fuel combustion engines (8). Short-term exposure to emissions from these agents is an everyday occurrence for many people.

Research in the field has mostly focused on exposure and evaluation of the irritation capacity of VOCs in animal- and human-exposure models (3, 9). The relative importance of individual factors has been little investigated (10, 11), and the associations have not been studied between having respiratory symptoms triggered by airborne chemicals and contact dermatitis.

The aim of this study was to investigate the associations between eye and airway symptoms elicited by exposure to airborne chemicals other than perfumes and previously recognized allergic contact sensitization in a population-based sample.

Materials and Methods

Study population

Investigations performed in 1997/1998. The study population ($n = 1216$) had previously participated in a population-based study of allergic diseases (The Copenhagen Allergy Study) (12, 13). Clinical examinations were between October 1997 and November 1998 and included patch testing, prick testing, methacholine bronchial challenge and questionnaires on respiratory symptoms, hand eczema, psychological, and social variables.

Investigations performed in 2002. In October 2002, a questionnaire on eye and respiratory symptoms elicited by exposures to various airborne agents was posted to 1189 individuals (97% of the baseline participants). The overall response rate to the questionnaire was 80%.

Design

Self-reported symptoms related to airborne chemicals and airborne proteins in 2002 were considered as outcome variables and were compared with data (predictor variables) collected during the health examination at baseline, 1997/1998.

Questionnaire in 2002

The potential symptom-eliciting agents comprised: newspaper (or printed magazines), laser printers, drying paint, car exhaust emissions (from vehicles with fossil fuel-combustion engines), furry animals, pollen, dust and mould.

1 question was asked for each of these agents: have you had symptoms from your eyes, nose, mouth or throat, or lungs elicited by 'the agent' within the last 12 months?

Development and testing of the questionnaire are described elsewhere (1). The retest validation on the 8 questions used in the present study gave a mean kappa value of 0.7.

Questionnaire at baseline in 1997/1998

At baseline, participants answered the following questions.

Within the last 12 months have you had episodes with

- (1) itchy eyes?
- (2) an itchy or stuffy nose or sneezing?
- (3) shortness of breath or troubled breathing?
- (4) wheezing?

Patch testing

The patch tests used were TRUE Test[®] (ALK-Abelló, Hørsholm, Denmark) (14–16). The hap-

tens in the panel differed from the European Standard Series by including thiomerosal and excluding primin. Directions on how to apply the patch tests to the upper back 2 days before the health examination were posted with the patch test to the participants. The patch tests were read 1 hr after removal at the Research Centre for Prevention and Health. Reactions were classified according to international guidelines (17). A positive reaction (+) was defined as a minimum of homogeneous redness and palpable infiltration in the test area. Reactions not fulfilling these criteria were classified as non-allergic reactions, irrespective of whether they were follicular reactions, erythema or typical irritant reactions.

Prick test

The prick tests were performed with a standard panel of 10 inhalation allergens, Soluprick SQ[®] (ALK-Abelló, Hørsholm, Denmark), as previously described (12). A positive prick test was defined as a mean wheal diameter of 3 mm or more for at least 1 allergen.

Hand eczema

All participants completed a questionnaire in 1997/1998 including questions about hand eczema. The questionnaire described eczema as follows: 'Eczema is an itching skin disease showing redness, dryness, and eventually vesicles and exudation. Eczema is present in the same skin area for some time'. The question was: have you had eczema on your hands within the last 12 months? An affirmative answer to this question was used to determine the 1-year prevalence of hand eczema.

Methacholine bronchial hyperreactivity

Methacholine bronchial hyperreactivity (BHR) was measured with a modification of the method of Yan (18) as previously described (1). Briefly, a maximal cumulated dose of 1200 µg methacholine was inhaled, and the cumulative dose of methacholine (PD₂₀) required to cause a 20% fall in forced expiratory volume in the first second was calculated.

Test of Psychological Vulnerability

Psychological vulnerability was based on a 22-item questionnaire completed by participants in 1997/1998. The score of psychological vulnerability was calculated as the overall sum of 12 items (possible score, 0–12) that constituted the test of

psychological vulnerability described by Kühl and Martini (19). The questions in the test and cut-off points on the vulnerability dimension according to age and sex are described elsewhere (20).

Social groups and educational level

Information about social group (white-collar worker, blue-collar worker and others) as well as overall educational level (≤ 9 , 10–11, 12–13 and ≥ 14 years) was based on questionnaire data collected at baseline.

Predictor variables

Patch test reactivity was defined as a positive patch test to at least 1 of the test substances in the panel or as the number of positive patch tests (range 0–4). Perfume contact allergy was defined as a positive patch test to 1 or more of the 3 test substances: fragrance mix (FM), balsam of Peru (PB) and colophony. Prick test reactivity was defined as a positive prick test to at least 1 of the allergens in the panel or as the number of positive prick tests. Bronchial hyperreactivity was expressed as PD₂₀, transformed into a dichotomous variable with a cut-off value of 1200 μ g (the maximal cumulative dose). Age was dichotomised in 2 groups: 20–45 and 46–82 years. The dimension of psychological vulnerability score was dichotomised according to Schapiro et al. (20). Smoking status was expressed as either currently smoking or not smoking in 1998. Incident cases were defined as those reporting no respiratory symptoms in the 1997/1998 questionnaire.

Outcome variables

Outcome variables were derived from the 2002 questionnaire and divided/indexed in 2 categories: eye and airway symptoms within 12 months elicited by (1) airborne chemicals and (2) airborne proteins. The questions indexed as airborne chemicals were respiratory symptoms elicited by newspaper (or printed magazines), laser printers, drying paint or car exhaust emission. The questions indexed as airborne proteins were respiratory symptoms elicited by furry animals, pollen, dust or mould.

Statistical analysis

Statistical analyses were performed with SPSS version 11.0 for Windows. Associations were expressed as odds ratio (OR) with 95% confidence intervals (CI). The associations between outcome variables [airborne chemicals or airborne proteins (and their causative agents)] and

the predictor variables (patch test reactivity and prick test reactivity) were further analysed in logistic regression models. Hand eczema, BHR, sex, psychological vulnerability, age and smoking habits were included in these models. Patch test reactivity and prick test reactivity were primarily included as categorical variables in the logistic regression models. In a second step, the *P*-value for test for trend was judged by including these (categorical) variables as continuous variables (trend variables) in the models. Groups were compared by using Chi-square or Fisher's exact test.

Results

Eye and airway symptoms within 12 months elicited by airborne chemicals were seen in 37% of the total population. Individuals with positive patch tests reported eye and airway symptoms elicited by exposure to newspaper, car exhaust emission, drying paint and laser printers within the last 12 months more frequently ($P < 0.05$) than those without contact allergy (Fig. 1). In a logistic regression model (including prick test reactivity, hand eczema, BHR, psychological vulnerability, sex, age and smoking habits), the association between respiratory symptoms elicited by airborne chemicals within the last 12 months and a positive patch test was an OR of 1.7 [95% confidence interval (CI) 1.2–2.5]. The association between patch test reactivity and respiratory symptoms increased with increasing number of positive patch tests (Fig. 2). This trend was statistically significant for women and borderline significant for men (Table 1). Women reported symptoms more often than men (43% versus 29%, $P < 0.05$), and 29% of women had at least 1 positive patch test compared to 11% of men. Individuals with respiratory symptoms elicited by airborne chemicals had a positive patch test in

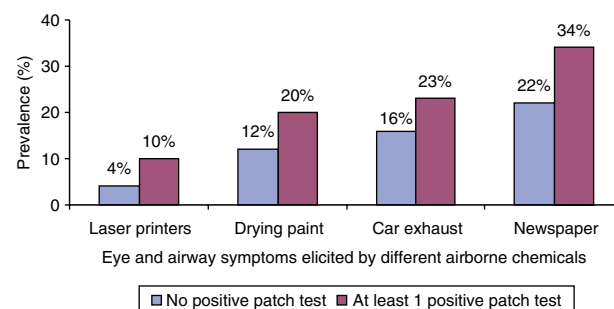


Fig. 1. The occurrences of eye and airway symptoms triggered by various agents within 12 months. The difference between the groups was statistically significant $P < 0.05$.

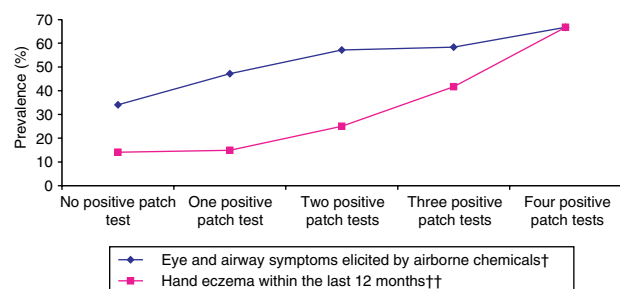


Fig. 2. The occurrence of eye or airway symptoms elicited by airborne chemicals in individuals with different patch test reactivity. †*P*-value for test for trend (airborne chemicals) <0.001. ††*P*-value for test for trend (hand eczema) <0.001.

28% of cases versus 17% when no symptoms to airborne chemicals were reported.

No associations were found between eye and airway symptoms elicited by airborne proteins and patch test reactivity, and no associations were found between prick test reactivity and respiratory symptoms elicited by airborne chemicals (Table 2). However, prick test reactivity showed a significant and precipitous dose-response relationship with symptoms elicited by airborne proteins (Table 2).

32% ($n = 301$) of the population ($n = 946$) reported no eye or airway symptoms in 1997/1998. The incidence of respiratory symptoms elicited by airborne chemicals in this subpopulation was 22% ($n = 65/301$). The associations between patch test reactivity and having respiratory symptoms elicited by airborne chemicals, but no previous history of respiratory symptoms (regarded as incident cases), are summarized in Table 3. The positive association between having 2 or more positive patch tests and symptoms elicited by airborne chemicals in the incident cases was significant ($P < 0.05$), also when adjusting for prick test reactivity, hand eczema, BHR, psychological vulnerability, sex, age and smoking habits (Table 3).

Eye and airway symptoms elicited by airborne chemicals other than perfume were associated with both perfume contact allergy (adjusted OR 2.4, 95% CI 1.2–4.7) and nickel contact allergy (adjusted OR 1.8, 95% CI 1.1–2.9). Individuals with perfume contact allergy had at least 2 positive patch tests in 51% compared with 30% in nickel-allergic individuals. This difference was statistically significant ($P < 0.05$). In the analysis, the presence of more than 1 positive patch tests to FM, PB, or colophony was regarded as having only 1 positive patch test, although no adjustment for cross-reactivity between nickel and cobalt was made. The ORs between respiratory symptoms elicited by airborne chemicals and patch test reactivity were essentially unchanged from the results in Table 1, when individuals with perfume contact allergy were excluded from analysis, and the test for trend of the dose-response was also significant ($P < 0.05$) in this subgroup.

The positive association between eye and airway symptoms elicited by airborne chemicals and hand eczema (crude OR 1.6, 95% CI 1.1–2.3) was not significant after adjustments in multivariable analysis ($P = 0.08$). The data were analysed further by creating additional predictor variables expressing the severity of hand eczema (hand eczema within the previous 12 months where the symptoms of hand eczema had or had not (1) persisted for more than 3 weeks and/or (2) been present more than once. Associations between these variables and the respiratory symptoms were positive and significant ($P < 0.05$) also when adjusting with variables in the logistic regression analysis (OR 1.7–1.9) and also when individuals with positive patch tests were excluded from analysis.

The association between hand eczema and patch test reactivity increased with the number of positive patch tests with a positive and significant ($P < 0.05$) trend (Fig. 2).

Table 1. The association between patch test reactivity and the occurrence of eye and airway symptoms elicited by airborne chemicals in women and men

	Eye and airway symptoms elicited by airborne chemicals ^a			
	In women		In men	
	% (n/total)	OR (95% CI) ^b	% (n/total)	OR (95% CI) ^b
Patch test reactivity				
No positive patch test	39.8 (144/362)	1; $P = 0.005^c$	28.0 (96/343)	1; $P = 0.055^c$
1 positive patch test	50.5 (54/107)	1.5 (1.0–2.4)	36.4 (12/33)	1.5 (0.7–3.1)
2 or more positive patch tests	58.8 (24/41)	2.1 (1.1–4.1)	55.6 (5/9)	3.2 (0.8–12.2)

^aEye and airway symptoms elicited by exposure to at least 1 of the following: newsprint, drying paint, car exhaust emission or laser printers within 12 months.

^bOdds ratio (95% confidence interval).

^c*P*-value for test for trend.

Table 2. Logistic regression model with eye and airway symptoms elicited by airborne chemicals or airborne proteins within 12 months as dependent variables and patch test reactivity and prick test reactivity as explanatory variables

	Eye and airway symptoms elicited by			
	Airborne chemicals ^a		Airborne proteins ^b	
	% (n/total)	OR (95% CI) ^c	% (n/total)	OR (95% CI) ^c
Patch test reactivity				
No positive patch test ^d	33.3 (227/682)	1; $P < 0.001^e$	51.8 (350/676)	1; $P = 0.3^e$
1 positive patch test ^d	47.8 (65/136)	1.6 (1.1–2.4)	53.9 (73/137)	1.0 (0.6–1.5)
2 or more positive patch tests ^f	58.3 (28/48)	2.2 (1.2–4.0)	71.4 (35/49)	1.7 (0.8–3.5)
Prick test reactivity				
No positive prick test	34.9 (184/527)	1; $P = 0.3$	33.1 (171/517)	1; $P < 0.001^e$
1 positive prick test ^g	41.0 (50/122)	1.2 (0.8–1.9)	69.8 (88/126)	5.0 (3.2–7.7)
2 or more positive prick test ^h	39.6 (86/217)	1.2 (0.8–1.7)	90.1 (199/219)	21.0 (12.6–35.1)

^aEye and airway symptoms elicited by exposure to at least 1 of the following: newsprint, drying paint, car exhaust emission, or laser printers within 12 months

^bEye and airway symptoms elicited by exposure to at least 1 of the following: furry animals, pollen, dust, or mould within 12 months.

^cOdds ratio (95% confidence interval) adjusted for the other values in the table and bronchial hyperreactivity, hand eczema, psychological vulnerability, plus age, sex, and smoking habits.

^dReactivity to exactly 1 of the 24 patches in the panel.

^e P -value for test for trend.

^fReactivity to 2 or more of the 24 patches in the panel.

^gReactivity to exactly 1 of the 10 prick tests in the panel.

^hReactivity to 2 or more of the 10 prick tests in the panel.

Bronchial hyperreactivity (OR 1.8, 95% CI 1.2–2.7), female sex (OR 1.7, 95% CI 1.3–2.3) and psychological vulnerability (OR 2.5, 95% CI 1.6–4.1) were independently associated with reporting symptoms elicited by airborne chemicals. A negative and significant association was found between smoking and reporting symptoms elicited by airborne chemicals (OR 0.7, 95% CI 0.5–0.99). No associations were found between

the age, educational level or social group and the symptoms.

In additional analyses, airborne chemicals and airborne proteins were separated into the reported causative agents (for definitions, see *Outcome variables*). Each agent was analysed in the logistic regression model. All the agents constituting airborne chemicals except for symptoms elicited by car exhaust emission were significantly

Table 3. Logistic regression analysis with incidences of eye and airway symptoms elicited by airborne chemicals and airborne proteins within 12 months as respectively dependent variables, and patch test- and prick test reactivity as explanatory variables

	Eye and airway symptoms elicited by			
	Airborne chemicals ^a		Airborne proteins ^b	
	% (n/total)	OR (95% CI) ^c	% (n/total)	OR (95% CI) ^c
Patch test reactivity				
No positive patch test ^d	19.8 (46/232)	1; $P < 0.02^e$	17.6 (40/227)	1; $P = 0.7^e$
1 positive patch test ^d	23.7 (9/38)	1.3 (0.6–2.8)	10.3 (4/39)	0.5 (0.2–1.8)
2 or more positive patch tests ^f	47.1 (8/17)	3.6 (1.3–9.9) ^g	23.5 (4/17)	1.2 (0.3–4.2)
Prick test reactivity				
No positive prick test	21.5 (52/242)	1; $P = 0.8^e$	13 (31/239)	1; $P < 0.001^e$
1 positive prick test ^h	25.0 (6/24)	1.0 (0.4–2.8)	21.7 (5/23)	1.8 (0.6–5.3)
2 or more positive prick test ⁱ	23.8 (5/21)	1.1 (0.4–3.1)	57.1 (12/21)	8.8 (3.4–22.6) ^g

Only individuals reporting no eye or airway symptoms in 1997/1998 ($n = 301/946$) were included in the analysis.

^aEye and airway symptoms elicited by exposure to at least 1 of the following: newspaper, drying paint, car exhaust emission or laser printers within 12 months.

^bEye and airway symptoms elicited by exposure to at least 1 of the following: furry animals, pollen, dust or mould within 12 months.

^cOdds ratio (95% confidence interval) adjusted for the other values in the table.

^dReactivity to 1 of the 24 patches in the panel.

^e P -value for test for trend.

^fReactivity to 2 or more of the 24 patches in the panel.

^gOdds ratios were significant after adjusting for sex, age, psychological vulnerability, BHR, hand eczema and smoking habits.

^hReactivity to exactly 1 of the 10 prick tests in the panel.

ⁱReactivity to 2 or more of the 10 prick tests in the panel.

($P < 0.05$) associated with patch test reactivity. Further, the ORs of respiratory symptoms elicited by newspaper increased with increasing numbers of positive patch tests (P -value for test for trend < 0.05). Respiratory symptoms elicited by the agents constituting airborne proteins were not associated with patch test reactivity in the logistic regression models.

Associations between having respiratory symptoms elicited by airborne chemicals other than perfume, and respiratory symptoms elicited by perfume and fragrance products were investigated by selecting all individuals who reported respiratory symptoms elicited by either airborne chemicals and/or airborne proteins ($n = 593$) in 2002. Having at least 1 respiratory symptom elicited by fragrance products as defined in Elberling et al. (2) was positively associated with respiratory symptoms elicited by airborne chemicals (OR = 4.3, $P < 0.05$), but not with reporting respiratory symptoms elicited by airborne proteins (OR = 1.0, $P = 1.0$) within this symptom group.

Discussion

The association between patch test reactivity and respiratory symptoms elicited by airborne chemicals other than perfume was significant, and the association increased with the number of positive patch tests.

No association was found between respiratory symptoms elicited by airborne chemicals and prick test reactivity, which is in agreement with the observation that patch test reactivity appears to be independent of prick test reactivity in the general population (21).

Airborne exposure, e.g. to rosin emitted from paper and preservatives emitted from painted surfaces, may cause eczema (22–24) and respiratory symptoms (25) in individuals with specific contact allergies. Exposure to newspaper can trigger nasal symptoms (26) and various respiratory symptoms has been related to exposure to newly painted surfaces, especially if solvent-based paint is applied (7, 27). The coarse particles (diameter about 7 μm) produced by vehicles with fossil fuel combustion are associated with ocular and nasal symptoms (28) as well as cough (8). The emissions from vehicles with fossil fuel-combustion engines also contribute to the ambient air level of ozone, a well-known respiratory irritant (29). When ozone is supplied to the indoor air (e.g. by ventilation from outdoors or indoor use of photocopying machines or laser printers), it may react with other indoor pollutants (e.g. terpenes) and produce products that are even stronger respiratory irritants than their precursors (9). However,

respiratory symptoms elicited by airborne chemicals differ from the clinical manifestation of allergic airborne contact dermatitis, and in addition, the majority of individuals with respiratory symptoms elicited by airborne chemicals had no positive patch tests, suggesting other mechanisms should also be considered. An endogenous predisposition to react with an inflammatory response to chemical exposure could explain the association between contact allergy and respiratory sensitivity to airborne chemicals. Individuals who are sensitized to more than 1 allergen [multiple sensitization (17)] may belong to a subgroup with increased susceptibility to chemicals (30). Enzymes involved in detoxification of xenobiotic chemicals are subject to genetic polymorphisms (31), which may have importance for development of contact allergies (32, 33) and which could also influence the development of respiratory symptoms elicited by airborne chemicals (34). In this relation, it is interesting to note that many airborne chemicals with respiratory irritation capacity (3) are also well-known contact allergens (4).

The association between hand eczema and respiratory symptoms elicited by airborne chemicals was not significant when adjusting in the logistic regression analysis. Nevertheless, the additional analysis suggests that severe hand eczema is significantly associated with the respiratory symptoms.

Environmental factors may influence the development of respiratory symptoms, and this study provided only little information about history of exposure to chemicals in skin and airways. However, we investigated the role of educational level and social group and found no association of significance.

Occupational exposures to low-dose chemicals are associated with the development of ocular and respiratory symptoms (35). Non-occupational exposure to paint, fuels, solvents, cleaning agents, self-care products and even paper in daily life may contribute to the development of ocular and respiratory symptoms. Different exposure patterns for women and men have been suggested as the most important factor of the higher prevalence of contact allergy (36), and hand eczema (37) seen in women. Differences in exposure pattern to airborne chemicals between men and women could also explain the increased frequency of respiratory symptoms elicited by airborne chemicals in women.

Analysis of the 301 cases, who had no general respiratory symptoms in 1997/1998, suggests that patch test reactivity is a predisposing risk factor of reporting respiratory symptoms to airborne

chemicals. However, this observation is built on the assumption that true incident cases were selected, but the baseline questionnaire did not include questions specific on ocular or respiratory symptoms elicited by airborne chemicals, which could bias the results. A true prospective study (including information about personal exposure pattern to chemicals in skin and airways) would provide a more valid study design to evaluate whether causality exists between patch test reactivity and the symptoms.

Individuals with positive patch tests did not report respiratory symptoms elicited by exposure to airborne proteins more frequently than individuals with no contact allergies. This suggests that the association between contact allergy and respiratory symptoms elicited by airborne chemicals was not due to a general tendency to report respiratory symptoms among individuals with contact allergy.

The consistency and excess of the association was too great to be explained by chance. Association bias could be a problem if, in the present study, exposure with the airborne chemicals had importance for the manifestation of eczema. However, the association was independent of hand eczema and the association was independent of individuals with colophony contact allergy in whom exposure to paper may have relevance for elicitation of eczema (38). Selection bias seems unlikely to explain the associations, as no difference was found between responders and non-responders concerning contact allergy, hand eczema, sex and psychological vulnerability in the study population (2). Item bias could be a problem when different items from a questionnaire are indexed into new variables. As respiratory symptoms elicited by car exhaust emissions were not associated with contact allergy when adjusting for possible confounders, it could indicate that emissions from vehicles with fossil fuel-combustion engines may not trigger airway symptoms in individuals with contact allergy more than it does in others. However, this lack of association did not contribute to bias, and the overall association was still positive and significant. The association was independent of the other possible confounders included in the analysis.

In conclusion, the association between eye and airway symptoms elicited by airborne chemicals other than perfumes and contact allergy was significant and increased with the number of positive patch tests. Having respiratory symptoms elicited by airborne chemicals may represent a syndrome, which is related to allergic contact dermatitis, and perhaps hand eczema, but not to IgE-mediated allergy to proteins. Although psychological fac-

tors play a significant role in reporting symptoms elicited by airborne chemicals, both endogenous and environmental factors may be of greater importance for the induction and elicitation.

Acknowledgements

We are grateful for the work of the staff at Research Centre for Prevention and Health, Glostrup University Hospital. Susanne Schweitz provided valuable secretarial assistance.

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