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Occupational exposure to inhalative irritants and methacholine responsiveness[1]

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Objectives Occupational exposures to inhalative irritants have been associated with an increased reporting of respiratory symptoms in previous studies. Methacholine responsiveness represents a continuous measure of airway responsiveness. As such, it may be less subject to recall bias and more sensitive to detecting effects of occupational exposure on airways. Such effects may be stronger among atopic persons. The objective of the study was to examine the relationship between self-reports of occupational exposure to dusts, gases, vapors, aerosols, and fumes and methacholine responsiveness.

Methods A sample was studied of never smokers (N=3044) chosen randomly from 8 areas in Switzerland. Atopy was defined as any positive skin test to 8 inhalative allergens. Nonspecific bronchial reactivity was tested using methacholine chloride and quantified by calculating the slope of the dose-response.

Results The methacholine slopes were 19% [95% confidence interval (95% CI) 6—32] higher for never smokers with exposure to dusts, fumes, vapors, gases, or aerosols than for the unexposed group. When only atopic never smokers were examined, the increase was larger (37%, 95% CI 7—75), and for persons with ≥2 positive skin prick tests the effect was still higher (42%, 95% CI -1.5—104). Exposure to vapors and aerosols was strongly associated with increased methacholine slopes among the atopic subjects.

Conclusions Occupational exposure, particularly to dusts and fumes, was associated with increased bronchial reactivity in never smokers in this study. The magnitude of the effect was larger among atopic subjects.

Key terms allergy skin tests, bronchial hyperreactivity, human adults, methacholine challenge.

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Long-term exposure to urban air pollution may increase bronchial responsiveness in a general population sample. Studies of occupational cohorts with high levels of exposure to dusts, fumes, or gases have shown associations with both respiratory symptoms and chronic obstructive pulmonary disease (1—8). Moderate levels of occupational exposure to organic and inorganic dust have been associated with loss of pulmonary function in a longitudinal study of Parisian workers by Kauffmann and her co-workers (9). Chronic respiratory symptoms and pulmonary impairment have also been associated with occupational exposures to dusts and gases in general population studies (7, 10, 11). These studies are critical because they avoid selection bias and because the levels of exposure involved are generally much lower than under experimental conditions. The study of Krzyzanowski & Kauffmann (11) even excluded manual workers to assure that the exposure levels would be relatively low. They reported some evidence of a sensitive subgroup for occupational exposure, consisting of persons with a history of wheezing, which they took as indicative of increased airway reactivity. Both that study and the study of Korn et al (10) grouped all types of occupational exposures together.

While bronchial responsiveness may be a predisposing factor for sensitivity to occupational exposure, it is possible that occupational exposure leads to increased bronchial responsiveness (12). This is certainly the case with occupational asthma, especially isocyanate asthma (2). Increased bronchial responsiveness has also been observed in potroom workers (13), papermill workers (14) and cotton mill operatives (15). Relatively little is known about the association between reported occupational exposure and bronchial responsiveness from general population surveys. The present paper examines this issue in the SAPALDIA cross-sectional study of the adult Swiss population. It is possible that the lower levels of occupational exposure seen in such a study will only be associated with increased bronchial responsiveness in sensitive persons. It was hypothesized that atopy was such a predisposing factor (16), and this analysis also reports on those results. Finally, while previous general population surveys have lumped all occupational exposures together, we have tried to see if there were distinctive patterns for different types of occupational exposure. The aim of the present study was thus to examine the relationship between self-reports of occupational exposure to dusts, gases, vapors, aerosols or fumes and methacholine bronchial responsiveness among atopic and nonatopic never smokers.

Subjects and methods

Study population

The Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) is a multicenter study designed to examine the potential association between air pollution and respiratory outcomes (17—19). The 8 study areas (Aarau, Basle, Davos, Geneva, Lugano, Montana, Payerne, and Wald) were chosen to represent a range of urbanization, altitude, air pollution, and meteorology. A random sample of adults aged 18—60 years was drawn from the register of inhabitants of each town. The subjects had to be resident in the area for at least 3 years to be included in the study. Subjects with complete questionnaire data were included in the study (N=9651). They represented 59% of all the persons randomly selected to participate (17). The questionnaire was an expanded version of the European Respiratory Health Survey (20). The responses given by each participant were recorded online on a computer by a trained technician. Subjects who declined to participate had the same probability of being never smokers as the group under study (17, 18).

Occupational exposure was substantially more prevalent among current smokers than among never smokers. If the impact of smoking on methacholine slope is imperfectly controlled for, the results could be biased (16, 21). Even a subgroup analysis of smokers could give biased results if the effects of current smoking were not adequately controlled for. Given this risk and the large number of never smokers in this sample, we have restricted our analyses to lifetime nonsmokers (never smokers) (N=3044).

Table 1 shows the characteristics of the never smokers with complete and sufficient data for analysis

Table 1. Characteristics of the subsamples of never smokers. ($FEV_{1.0}$ = forced expiratory volume in 1 second)

Characteristic	Age (years)		Female (%)	Asthma, ever (%)	Wheeze apart from cold (%)	Allergic rhinitis, including hay fever	Skin test positive (%)	$FEV_{1.0}$ (l)			
								Men		Women	
	Mean	SD						Mean	SD	Mean	SD
Never smokers with complete and sufficient data[a] (N=3044)	39.1	12.4	57.9	5.5	3.8	20.1	25.9	4.31	0.66	3.08	0.53
Never smokers with incomplete or insufficient data (N=1185)	43.2	12.3	65.2	10.0	7.4	21.3	25.6	3.88	0.87	2.85	0.63

[a] Complete and sufficient data on the base-line $FEV_{1.0}$ value conforming to criteria of the American Thoracic Society, methacholine responsiveness, smoking status, and occupational exposure.

(N=3044) in comparison with never smokers with incomplete or insufficient data (ie, excluded from the test or unwilling to participate, N=1185). The prevalence of asthma and wheezing was higher in the latter group, in which excluded persons predominate, and the forced expiratory volume in 1 second ($FEV_{1.0}$) was lower. There was little difference between the subsamples in the prevalence of positive skin prick tests or of self-reported allergic rhinitis (including hay fever).

The allergy tests included skin prick tests to 8 inhalative allergens (ie, cat fur, dog epithelia, house dust mite (*Dermatophagoides pteronyssinus*), molds (*Cladosporium herbarum* and *Alternaria tenuis*), Timothy grass pollen (*Phleum pratense*), birch pollen (*Betula verucosa*), and pellitory pollen (*Parietaria officinalis*). They were performed with Phazet lancets (Kabi-Pharmacia, Uppsala, Sweden) on the volar side of the forearm and compared with a negative (uncoated lancet) and a positive control (10 mg of histamine dihydrochloride). A positive skin prick test for a given allergen was defined as an adjusted mean wheal diameter (ie, observed mean wheal diameter minus mean wheal diameter of the negative control) of greater than or equal to 3 mm (22). "Any positive skin prick test" was used to define atopy.

Spirometry measurements were done using a SensorMedics 2200 pulmonary function system SP (Bilthoven, The Netherlands). This is an open sensor device which meets the quality criteria of the American Thoracic Society. The SensorMedics spirometer displays an error code after each forced expiration to inform the technician about the acceptability of the maneuver and the reproducibility between the trials using the standard quality criteria defined by the American Thoracic Society (23). The trials were recorded electronically on a personal computer as they were done. Calibration was done at least once daily, using a 3-liter syringe. All the spirometry technicians were trained together according to a standardized protocol and were tested with the use of volunteers (24).

Nonspecific bronchial reactivity was tested using methacholine chloride (Provocholine®, Roche, Nutley, New Jersey, United States) prepared in 0.39, 1.56, 6.25, and 25.0 mg/ml solutions in a phosphate buffer without phenol. Methacholine was administered at progressing doses up to a cumulative dose of 2 mg (8.37 µmol) through an aerosol dosimeter (Mefar MB3, Bovezzo, Italy). Each inhalation delivered 0.01 ml. The first inhalation was a saline control. The schedule was then 4 inhalations at 0.39 mg/ml (total dose 0.016 mg), 3 inhalations at 1.56 mg/ml (cumulative dose 0.062 mg), 3 inhalations at 6.25 mg/ml (cumulative dose 0.25 mg), 3 inhalations at 25.0 mg/ml (cumulative dose 1 mg), and 4 inhalations at 25.0 mg/ml (total cumulation dose 2 mg). If a $FEV_{1.0}$ decrease of more than 10% from the basal level was obtained at any intermediate point of the test, smaller increments were introduced. Testing continued until the final dose of 2 mg, or until a 20% reduction in $FEV_{1.0}$, was reached. Under this protocol the cumulative doses of methacholine converted in micromoles at each level were 0, 0.065, 0.26, 1.06, 4.18, and 8.37. At each level, the subjects were asked to inhale slowly from their functional residual capacity up to their vital capacity. The subjects were instructed to keep a full inspiration for 4 seconds before a slow normal exhalation. After each dose level of methacholine, 2 forced expiratory maneuvers were performed at 1 and 2 minutes after the end of the methacholine inhalation and the best of the 2 $FEV_{1.0}$ values was considered (20).

Methacholine responsiveness was quantified by calculating a dose-response slope for each subject as suggested by O'Connor et el (21). In order to avoid negative slopes, the absolute decline in $FEV_{1.0}$ was defined as the difference between the maximum $FEV_{1.0}$ over all the tested levels and the $FEV_{1.0}$ at the last level measured. The slope was defined as the ratio between the percentage decline in $FEV_{1.0}$ and the total cumulative dose of methacholine (in micromoles) administered. As the distribution of these slopes was skewed, a logarithmic transformation was used to obtain a more symmetrical distribution better suitable for statistical analyses. In order not to lose a few zero values, a small constant (ie, c=0.01) was added before the logarithm was taken. This constant was small enough not to bias the effect estimates to a relevant degree. Moreover, the Kolmogorov-Smirnov distance between the distribution of residuals of ln (slope + 0.01) and the normal family was close to its minimum over all the positive values of c when the regression model estimating the effect of "any current occupational exposure" on the dose-response slope among never smokers was considered.

Bronchial hyperreactivity to methacholine was defined as a decline in $FEV_{1.0}$ from the baseline saline control by at least 20% after a cumulative dose of methacholine up to 8.37 µmol.

Subjects were excluded from the methacholine testing if they had a base-line FEV_1/FVC ratio (FVC = forced vital capacity) of less than 80% of the predicted, had an $FEV_{1.0}$ of less then 70% of the predicted, had difficulty performing the spirometry maneuver, were pregnant, or refused to participate. The exclusions reduced the sample size to 6936 (among them, 3044 never smokers).

Occupational exposure was assessed by the questionnaire used by the SAPALDIA group (17), which is an expanded version of the European Community Respiratory Health Survey (20). Professional status and environment were detailed by asking 56 questions regarding professional training, present occupational situation, change of jobs for breathing problems, current exposure to a variety of substances (individually enumerated), protective measures at work, current health problems at work,

and exposure to irritants (enumerated) during leisure time. No attempt was made to quantify exposures.

Within our study sample of never smokers, current occupational exposure to one or more of the airborne irritants dusts, gases, vapors, aerosols, or fumes was mentioned by 38.2% of the men and by 19.9% of the women.

Multiple regression analysis of the logarithm of the methacholine slope was used to examine the association between occupational exposure and bronchial responsiveness. These regression analyses controlled for area of study, gender, age, and $FEV_{1.0}$value. Since the association between the logarithm of the methacholine slope and the base-line $FEV_{1.0}$ was nonlinear, the square of the $FEV_{1.0}$ was also included in the model. This approach is likely to be conservative, since, as already noted, occupational exposure may be associated with a loss of $FEV_{1.0}$ (9), and exposed persons with decreased base-line pulmonary function were excluded from the methacholine challenge test. Unlike other studies (2), ours did not support evidence of an association between atopy and workplace exposure to airborne irritants. Therefore, atopy was not included as a covariate in the basic regression models. However, to examine the role of atopy as a potential modifier of the effects of occupational exposure on bronchial reactivity, we also computed separate regression models for different categories of atopic persons and for the group of nonatopic subjects. At each stage of the analysis, a first model was computed for "exposure in general" (ie, exposure to at least one of the irritants considered), and then separate models were estimated for the different types of irritants. When the standard errors of the regression estimates were computed, the heteroscedasticity of residuals was taken into account by using the asymptotic covariance matrix output by the Statistical Analysis System (SAS) under option ACOV. A complementary multiple logistic regression analysis was performed for the dichotomous variable "bronchial hyperreactivity", which is more commonly used among clinicians than the methacholine slope is. The covariates used in this model were the same as in the model for the logarithm of methacholine slope.

Results

The estimated percentage of change in the slope of the methacholine responsiveness associated with different types of occupational exposure among the never smokers is shown in table 2. Among the never smokers, significantly increased methacholine slopes were found for the group of subjects with any kind of exposure ("any exposure" group) and for the persons exposed to dusts or fumes. The other occupational exposures were only associated with small increases in bronchial responsiveness, and the increases were not statistically significant.

Table 3 shows the estimated percentages of change in the slope of the methacholine responsiveness in

Table 2. Estimated percentage of change[a] in the slope of methacholine responsiveness [and 95% confidence interval (95% CI)] associated with different types of occupational exposures of never smokers (N=3044). ($FEV_{1.0}$ = forced expiratory volume in 1 second)

Exposure[b]	Estimated change (%)	95% CI
Any exposure	18.6	6.2—32.4
Dusts	25.4	11.1—41.5
Fumes	45.5	15.2—83.8
Vapors	17.9	-2.2—42.1
Gases	18.4	-2.7—44.1
Aerosols	4.6	-20.2—37.0

[a] Adjusted for gender, age, area of study, and level of base-line $FEV_{1.0}$.
[b] A separate regression model was computed for each exposure variable.

Table 3. Estimated percentage of change[a] in the slope of methacholine responsiveness [and 95% confidence interval (95% CI)] associated with different types of occupational exposures of never smokers according to the degree of atopy. (SPT = skin prick test, $FEV_{1.0}$ = forced expiratory volume in 1 second)

Exposure[b]	Degree of atopy					
	Negative SPT (N=2192)		Positive SPT (N=766)		≥2 positive SPT (N=334)	
	Estimated change (%)	95% CI	Estimated change (%)	95% CI	Estimated change (%)	95% CI
Any exposure	13.6	0.9—27.9	36.9	7.3—74.7	41.9	-1.5—104.4
Dusts	19.5	5.0—36.1	43.5	9.7—87.7	39.5	-9.0—113.8
Fumes	35.7	6.0—73.7	92.2	13.3—226.1	109.0	12.4—288.6
Vapors	5.3	-13.7—28.5	77.5	19.3—164.0	81.1	8.4—202.6
Gases	9.9	-11.5—36.5	49.5	-0.9—125.6	69.0	3.1—177.1
Aerosols	-10.8	-34.5—21.4	76.7	14.6—172.4	203.0	68.5—445.0

[a] Adjusted for gender, age, area of study, and level of base-line $FEV_{1.0}$.
[b] A separate regression model was computed for each exposure variable.

association with different types of occupational exposure among the never smokers, according to the degree of atopy, as assessed by skin prick test reactivity. Among the never smokers with negative skin prick tests (N=2192), exposure to dust and fumes remained significantly associated with an increased slope for methacholine responsiveness. On the other hand, occupational exposure to vapors and aerosols was a significant predictor of increased bronchial responsiveness only among the atopic subjects (N=766). In addition, the estimated increase in the slope of the methacholine responsiveness for each single exposure other than dust and for any exposure appeared to be even larger for the subjects with two or more positive skin prick tests (N=344 of 766).

We also examined the possibility that subjects with different types of skin prick test reactivities may have different sensitivities to occupational exposure. The subjects were divided into those sensitized to perennial indoor allergens (housedust mite, cat, dog) (N=419) and those sensitized to pollen but no indoor allergens (N=347). These results are shown in table 4. For exposure to fumes, vapors, gases, and aerosols the magnitude of the increase in the methacholine slope was larger among subjects with positive skin prick tests to indoor allergens.

Table 5 presents the estimated odds ratio of bronchial hyperreactivity between never smokers with and without occupational exposure. The odds ratios of being hyperreactive were significantly increased for any exposure, dust exposure, and fume exposure. These findings are thus concordant with those obtained using the slope of the methacholine responsiveness as the outcome variable (table 2).

The final 2 analyses addressed 2 potential sources of bias in our study. First, subjects who develop symptoms may remember better that they have been occupationally exposed. One approach to avoid this potential source of bias is to analyze the data excluding subjects with asthma (ie, subjects with positive answers to the questions "Are you suffering from asthma?" and "Was this confirmed by a doctor?"] Second, it is possible that increased symptom reporting by occupationally exposed workers may be confounded by socioeconomic differences between exposed and unexposed persons. The increases in the methacholine slope associated with occupational dust exposure and occupational aerosol exposure remained significant when subjects with asthma were excluded. In contrast, the increases in methacholine slope associated with exposure to gases, vapors, and fumes were substantially lower among the nonasthmatic subjects and no longer statistically significant. Control for education had little impact on any of the associations between occupational exposure and bronchial responsiveness (data not shown).

Table 4. Estimated percentage of change[a] in the slope of methacholine responsiveness [and 95% confidence interval (95% CI)] associated with different types of occupational exposures of never smokers according to type of atopy. (SPT = skin prick test, $FEV_{1.0}$ = forced expiratory volume in 1 second)

Exposure[b]	Type of atopy			
	Positive SPT to pollen only (N=347)		Positive SPT to indoor allergens (N=419)	
	Estimated change (%)	95% CI	Estimated change (%)	95% CI
Any exposure	38.9	-1.1—95.2	32.6	-6.4—87.8
Dusts	55.0	8.4—121.6	34.2	-9.1—98.2
Fumes	0.3	-41.0—70.4	153.5	24.3—416.8
Vapors	34.4	-26.0—144.1	122.1	29.9—279.8
Gases	3.0	-42.4—84.2	84.9	4.5—227.2
Aerosols	45.4	-7.7—129.1	114.0	5.8—333.0

[a] Adjusted for gender, age, area of study and level of base-line $FEV_{1.0}$.
[b] A separate regression model was computed for each exposure variable.

Table 5. Estimated odds ratios[a] [and 95% confidence intervals (95% CI)] for bronchial hyperreactivity[b] associated with different types of occupational exposures of never smokers. ($FEV_{1.0}$ = forced expiratory volume in 1 second)

Exposure[c]	Estimated odds ratio of being hyperreactive (exposed versus unexposed) (N=3044)	95% CI
Any exposure	1.38	1.10—1.73
Dusts	1.55	1.22—1.98
Gases	1.24	0.82—1.87
Vapors	1.24	0.88—1.75
Aerosols	1.37	0.86—2.17
Fumes	2.18	1.43—3.31

[a] Adjusted for gender, age, area of study, and level of base-line $FEV_{1.0}$ in the logistic regression model.
[b] Bronchial hyperreactivity: decline in $FEV_{1.0}$ from the base-line saline control by at least 20% after a cumulative dose of methacholine of up to 2 mg (= 8.38 μmol).
[c] A separate logistic regression model was computed for each exposure variable.

Discussion

Occupational exposure was associated with increased bronchial reactivity to methacholine among the never smokers in this study. When the different types of occupational exposure were considered for the nonatopic subjects, the association was significant only for dust and fume exposure. The fume-induced changes were larger than those induced by dust exposure. Moreover, for all the categories of occupational exposure, the magnitude

of the effect was larger among the atopics. For instance, exposure to vapors and aerosols was significantly associated with increased bronchial responsiveness only among the atopics. This finding suggests that atopy, as shown previously (12, 15, 16), is a significant risk modifier for the effect of different categories of occupational exposure. It has been shown that the association between atopy and bronchial hyperresponsiveness decreases with age (16). This trend, however, was not observed in the present study.

Further evidence for the interaction with atopy is given by the results comparing subjects with negative skin prick tests with those with positive skin prick tests and with the subgroup with at least 2 positive skin prick tests. While the smaller sample size reduced the significance of the associations, it was noted that the estimated increase in the methacholine slope was larger among the more severe atopics. Thus atopy may act as an amplifier of bronchial responsiveness in never smokers exposed to occupational agents. For vapor, gas, fume, and aerosol exposure, the magnitude of the increase in the methacholine slope was larger among the subjects sensitized to indoor allergens than among those sensitized only to pollen. Only dust exposure was associated with an increased methacholine slope among the subjects sensitized only to seasonal allergens (pollen), a finding suggesting that occupational dust exposure needs less coexposure to perennial allergens (indoor allergens) to manifest an impact on bronchial responsiveness. Previous studies have shown that dust exposure was associated with an increased prevalence of chronic respiratory symptoms, decreased pulmonary function, and accelerated functional decline (3, 9).

The association of dust, vapor, and aerosol exposures with increased bronchial reactivity in atopic persons is probably not due to recall bias among asthmatic subjects since it was also found after these subjects were excluded. However, such an exclusion, while reducing the potential for upward bias due to better recall among subjects who have become symptomatic, increases the risk of downward bias. If occupational exposure increases bronchial reactivity, and as a result some workers become asthmatic, excluding the asthmatics will underestimate the impact of occupational exposure. Hence the weaker evidence for other exposure categories seen in this analysis should be considered with caution. Overall, the exposure that showed the strongest and most consistent relationship across all strata was occupational dust exposure. In contrast to dust exposure, the vapor and aerosol exposures were only associated with increased methacholine slopes among the subjects with predisposing factors to bronchial hyperreactivity, such as positive skin test reactivity. Sensitivity analyses implied that these associations were not confounded by socioeconomic factors.

It has been suggested that this increase in bronchial responsiveness may be due to inflammation (25) with an increased number of eosinophils (26) or basophils (27). Indeed, a statistically significant relation has been found between serum immunoglobulin E levels, blood eosinophils, and bronchial hyperresponsiveness (26). In addition, a direct correlation has been observed between the long-term evolution of bronchial reactivity and long-term changes in airway basophils. These results are consistent with those of other studies that have found occupational exposure to dusts, fumes, and other substances (such as isocyanates (2), platinum salts (28), and substances emitted during the electrolytic extraction of aluminum (13) at levels currently permitted) to be associated with respiratory changes which may persist for years. Our epidemiologic approach did not allow us to address this specific question.

In conclusion, our study confirms that the level of bronchial responsiveness is associated with the inhalation of occupational irritants and that atopy is a significant risk modifier for the effect of such exposure. Increased slopes of methacholine according to the degree of atopy, distinctive patterns of bronchial responsiveness for different types of occupational exposure, and the role of perennial indoor allergens as a stronger amplifier of methacholine responsiveness in comparison with pollen sensitization appear as original findings. These results have significant public health impact and may be of use in the occupational counseling of apprentices or of workers with work-related respiratory symptoms or diseases.

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