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Respiratory Morbidity Induced by Occupational Inhalation Exposure to Formaldehyde

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Abstract: The potential of formaldehyde to produce chronic respiratory tract disease remains a controversial issue. The main purpose of this study was to investigate the respiratory effects, if any, of long term occupational exposure to formaldehyde. This cross-sectional study was carried out at a local melamine-formaldehyde resin producing plant. The study population consisted of seventy exposed and 24 non-exposed (referent) employees. Using respiratory questionnaire, data on respiratory symptoms were gathered. Atmospheric concentrations of formaldehyde were measured at different contaminated areas of the plant. Similarly, the parameters of pulmonary function were measured at the beginning (preshift) and at the end (postshift) of the first working day of the week. The results showed that airborne concentrations of formaldehyde exceeded current permissible levels. Additionally, significant decrements in some preshift and postshift parameters of pulmonary function of exposed workers were noted. However, a relative recovery in lung functional capacity observed following temporary cessation of exposure (preshift values). Furthermore, exposed workers had higher prevalence rates of regular cough, wheezing, phlegm, shortness of breath, chest tightness and episodes of chest illness associated with cold. The findings of this study collectively indicate that exposure to formaldehyde may induce respiratory symptoms, acute partially reversible and chronic irreversible functional impairments of the lungs.

Key words: Formaldehyde, Occupational exposure, Respiratory symptoms, Functional impairments of the lungs

Introduction

Formaldehyde is an important industrial chemical that has been used for more than 60 yr in manufacturing of resins, adhesives and plastics[1]. It has also been used in processing of anatomic and pathologic specimens, as an antimicrobial agent in cosmetics, a fumigant in agriculture, and in the production of crease-resistant garments. Although the heaviest exposures to formaldehyde have occurred occupationally, it is also encountered residentially, where it arises from several sources, including particle board made with formaldehyde-based resins (which are used in furniture) and cavity insulation with urea formaldehyde foam.

In industry, one of the most common uses of formaldehyde is in the production of melamine-formaldehyde resins. Reaction of formaldehyde with melamine yields melamine formaldehyde which is delivered in solution or powder form for further processing.

The possible effects of formaldehyde exposure on respiratory tract have been investigated in a few studies. While in some studies a higher incidence of upper respiratory disease or a reduction in forced expiratory volume in the first second (FEV_1) in formaldehyde-exposed individuals compared to control subjects has been reported, others have failed to find any significant changes in the parameters of pulmonary function. For

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instance, two separate studies in wood-processing plant revealed that the incidence of upper respiratory disease in workers exposed to formaldehyde was higher than that of controls[2, 3]. Similarly, others have reported that symptoms involving the eyes and throat as well as chest oppression were significantly more common in the formaldehyde-exposed subjects than in the non-exposed controls. They also reported that the parameters of pulmonary function (e.g. FEV_1) were normal on the Monday morning before exposure to formaldehyde, but reduced significantly after a day of work and exposure to formaldehyde, suggesting bronchoconstriction[4]. Kriebel *et al*. (2001) in a study on anatomy laboratory students also found that exposure to 1.1ppm of formaldehyde for 2.5 h/wk reduced peak expiratory flow (PEF) by 1% per ppm[5]. Similar results have been reported by Erdem *et al*. in smoking formaldehyde exposed individuals[6].

In contrast, Schoenberg and Mitchell[7] did not observe any significant changes in the parameters of pulmonary function among workers exposed to formaldehyde level of 0.5 to 1 mg/m^3. Similarly, no significant bronchoconstriction (FEV_1 test) was noted among 15 non-smoking healthy volunteers exposed to 2.4 mg/m^3 formaldehyde for 40 min on two consecutive days[8]. Likewise, Main and Hogan (1983) found no differences in the parameters of lung functions between workers exposed to formaldehyde (0.14–1.9 mg/m^3 equal to 0.11–1.55 ppm) and non-exposed controls. However, significantly more complaints of eyes and throat irritation, headache and fatigue were reported by the exposed individuals[9]. Comparison of pre-shift to post-shift pulmonary function test among fiberglass wool manufacturing workers who were exposed to formaldehyde showed no association between exposure and decrements in the parameters of pulmonary function[10]. The same findings were reported by Slaughter *et al*. who found no association between changes in FEV_1, FVC, or $FEF_{25–75}$ from preshift to postshift[11].

Given the above, the potential of formaldehyde to produce chronic respiratory tract disease remains a controversial issue and evidence for associations between exposure to formaldehyde and either respiratory symptoms or functional impairments of the lungs has not been conclusive and requires further elucidation. The main objectives of this study were, therefore, two fold:

- Firstly, to investigate, after adjusting for confounding variables of age, smoking habits, etc., whether long term occupational exposure to formaldehyde is associated with any significant decrement in the parameters of pulmonary function.
- Secondly, to determine if chronic exposure to formaldehyde may significantly increase the prevalence of respiratory symptoms.

Materials and Methods

Study subjects

This cross-sectional study was carried out at a local melamine-formaldehyde resin producing factory. The study population consisted of all 70 male workers with current occupational exposure to formaldehyde with a work history of ≥ 2 yr (exposed group) as well as 24 healthy males from the same industry with almost identical socioeconomic and demographic status (sex, ethnic background, education, smoking habits, income as well as family size) and without present or history of past exposure to formaldehyde or other chemicals known to cause respiratory morbidity that served as the referent group. Both groups were volunteer subjects. No selected subjects refused to participate in the study. Additionally, the study was conducted in accordance with the Helsinki Declaration of 1964 as revised in 2000[12].

Measurement of Study Variables

Respiratory illness

Subjects were interviewed and respiratory symptom questionnaire, as suggested by the American Thoracic Society (ATS)[13], with a few modifications, was administered to all of them. These were, then, used to identify respiratory (chronic cough, wheezing, phlegm, bronchitis, etc) conditions.

Pulmonary Function Tests (PFTs)

Pulmonary function tests, including Vital Capacity (VC), Forced Vital Capacity (FVC), Forced Expiratory Volume in the first second (FEV_1) and Peak Expiratory Flow (PEF), followed guidelines given by the ATS (1979)[14] and measured with a portable calibrated vitalograph spirometer (Vitalograph-COMPACT, Buckingham-England) on site. The spirometer was calibrated twice a day with a 1-liter syringe in accordance to the standard protocol for the instrument used. To investigate the cross-shift changes and in order to differentiate between possible acute and chronic effects of exposure to formaldehyde, PFTs were measured at the beginning (preshift) and at the end of first working day of the week (postshift).

Measurement of atmospheric concentrations of formaldehyde

Seven samples from the ambient air of 7 workshops at which workers were exposed to formaldehyde and 1 sample from the ambient air of the office areas, where referent subjects were working in, were taken, using two impingers in series each containing 20 ml of 1% sodium bisulfite solution, as the absorbing medium, connected to a calibrated SKC standard air sampling pump (model 224-44EX) at a flow rate of 1 lit/min. The sampling time for each sample was 40 min. One field blank sample was also taken at each workshop. Thereafter, samples were transferred to the laboratory according to the protocol recommended in NIOSH method 3500[15]. Chromtropic and concentrated sulfuric acids were, then, added to each sample and the solutions were analyzed for formaldehyde using visible absorption spectrometry technique at 580 nm by Unicam UV/Vis Spectrophotometer (model 8625).

Smoking habits

Smoking individuals were arbitrary classified into two subgroups i.e. light smokers (those consuming 4 or less cigarettes per day) and heavy smokers (those consuming more than 4 cigarettes per day).

Data analysis and statistical procedures

The data were statistically analyzed using student's *t*-test and χ^2 or Fisher's test, where applicable (with a preset probability of $p<0.05$). Equality of variances was examined by Leven test. Normal distribution of parameters was evaluated by Kolmogrov-Smirnov test. As referent subjects were symptom free, and the prevalence of most respiratory symptoms among them was zero, this did not allow a statistical analysis to be performed to calculate the odds ratio of respiratory symptoms among exposed individuals. To overcome this difficulty, hypothetical, non significant, value of 0.5 artificially added to the prevalence rates of symptoms among referent subjects[16] to enable a statistical analysis. Furthermore, using multiple linear analyses, the simultaneous effects of confounding variables such as smoking, age, weight, height, etc, on the changes in the parameters of pulmonary function were evaluated. Similarly, association between years of exposure and possible changes in PFTs was investigated by linear regression analysis. Statistical tests were conducted using SPSS software (version 11.5).

Results

Table 1 presents demographic characteristics, smoking habits of both exposed and non-exposed groups and formaldehyde concentration in the ambient air of workshops. Although non-exposed individuals were, on average, slightly older than exposed subjects, neither this difference nor the differences noted between other variables were statistically significant. Mean value of

Table 1. Demographic characteristics, smoking habits and ambient air concentrations of formaldehyde

Parameter	Non-exposed (n=24)	Exposed (n=70)	*p*-value
Age (yr) (mean ± SD)*	40.0 ± 8.2	38.2 ± 8.4	0.351
Weight (kg) (mean ± SD)*	74.3 ± 8.9	74.94 ± 10.5	0.773
Height (cm) (mean ± SD)*	172.1 ± 6.5	172.7 ± 6.8	0.705
Duration of exposure or employment (yr) (mean ± SD)*	14.5 ± 8.1	13.2 ± 7.8	0.482
Marital status†			
Single	2.0 (8.3%)	1.0 (1.4%)	
Married	22.0 (91.7%)	69.0 (98.6%)	0.159
Education†			
Under diploma	5.0 (20.8%)	20.0 (28.6%)	0.595
Diploma and higher	19.0 (79.2%)	50.0 (71.4%)	
Smoking†			
Yes	6.0 (25.0%)	17.0 (24.3%)	
No	18.0 (75.0%)	53.0 (75.7%)	1.0
Severity of smoking†			
Light (4 cigarettes or less per day)	4.0 (66.7%)	7.0 (41.2%)	
Heavy (More than 4 cigarettes per day)	2.0 (33.3%)	10.0 (58.8%)	0.371
Formaldehyde concentration (ppm) (mean ± SD)	N/D‡	0.78 ± 0.40††	-

*Independent sample *t*-test, †χ^2 or fisher's exact test, ‡Non-Detectable, ††n=7.

Table 2. Frequency (%) of respiratory symptoms in exposed and non-exposed subjects

Symptoms	Non-exposed (n=24)	Exposed (n=70)	Odds ratio	p-value*
Cough	0.5 (0.02%)	14 (20.0%)	12.57	0.018
Phlegm	0.5 (0.02%)	20 (28.6%)	19.90	0.001
Productive cough	0.5 (0.02%)	5 (7.1%)	3.70	0.324
Wheezing	2 (8.3%)	34 (48.6%)	10.38	0.001
Dyspnea	0.5 (0.02%)	13 (18.6%)	4.11	0.034
Chest tightness	0.5 (0.02%)	37 (52.9%)	54.85	0.001
Episodes of chest illness associated with cold	1 (4.1%)	24 (34.3%)	12.00	0.003

*χ^2 or Fisher's test.

Table 3. Percentage predicted lung function for exposed (preshift and postshift) and non-exposed workers

Parameter†	Non-exposed (n=24)	Exposed (preshift) (n=70)	Exposed (postshift) (n=70)	p-value‡
VC (mean ± SD)	99.3 ± 21.0	77.9 ± 12.0*	69.1 ± 13.6*	0.001
FVC (mean ± SD)	100.5 ± 14.5	86.6 ± 14.5*	76.8 ± 13.8*	0.001
FEV_1 (mean ± SD)	98.8 ± 14.6	86.6 ± 14.4*	76.1 ± 13.5*	0.001
FEV_1 /FVC (mean ± SD)	98.8 ± 5.3	100.2 ± 8.8	99.0 ± 8.4	0.089
PEF (mean ± SD)	89.8 ± 31.2	90.9 ± 15.9	77.0 ± 21.6*	0.001

†% predicted lung function = %observed/predicted,
*Independent sample t-test ($p<0.025$) (significantly different from the corresponding values for non-exposed group),
‡Paired t-test comparison of PFTs in exposed subjects (preshift vs postshift).

atmospheric formaldehyde concentration for exposed workers was found to be 0.78 ppm (SD=0.4). However, it was not detectable in the working place of non-exposed individuals.

Table 2 illustrates the frequency of respiratory symptoms among exposed and non-exposed subjects. As shown, exposed workers had significantly higher prevalence rates of cough, phlegm, wheezing, dyspnea, chest tightness and episodes of chest illness associated with cold. The results showed that occurrence chance of cough (OR=12.57), phlegm (OR=19.90), productive cough (OR=3.70), wheezing (OR=10.38), dyspnea (OR=4.11), chest tightness (OR=54.85) and episodes of chest illness associated with cold symptoms (OR=12.0) were significantly higher in exposed subjects than in their non-exposed counterparts.

The parameters of pulmonary function were also measured for both groups. Predicted percentages of VC, FVC, FEV_1, FEV_1/FVC ratio and PEF are presented in Table 3. As shown, most parameters of pulmonary function were significantly lower in both preshift and postshift measurements for exposed subjects as compared with those of their non-exposed counterparts.

Additionally, Table 3 exhibits the results of preshift and postshift lung function tests for exposed individuals. As seen, VC, FVC, FEV_1 and PEF parameters decreased significantly after exposure.

Association between exposure to formaldehyde and changes in the parameters of pulmonary function is shown in Table 4. Multiple linear regression analysis, including independent variables of age, weight, height, severity of smoking and exposure to formaldehyde in the model showed that after adjusting for confounders, there was statistically significant associations between exposure to formaldehyde with VC, FVC and FEV_1 values; in that, there was a general tendency for these values to become smaller as estimated cumulative exposure increased.

Table 4. Association between exposure to formaldehyde and changes in the parameters of pulmonary function

Parameter (dependent variable)	Regression coefficient β	p-value*
VC	–21.43	0.001
FVC	–13.88	0.001
FEV_1	–12.23	0.001

*Multiple linear regression.

Table 5 displays the effects of each year of exposure to formaldehyde on the parameters of pulmonary function. As seen, each year of exposure caused 0.1 unit decrement in VC, 0.43 unit in FVC, 0.375 unit in FEV_1, 0.1 unit in FEV_1/FVC ratio and 0.28 in PEF. These decrements reached statistical significance for FVC and FEV_1.

Table 5. Relationship between length of exposure (yr) to formaldehyde and changes in the parameters of pulmonary function

Parameter (dependent variable)	Regression coefficient β	*p*-value*
VC	–0.1	0.315
FVC	–0.43	0.02
FEV_1	–0.375	0.035
FEV_1 /FVC	–0.1	0.225
PEF	–0.28	0.2

*Linear regression analysis.

Discussion

The main purpose of this study was to investigate the respiratory effects, if any, of long term occupational exposure to formaldehyde. Exposed and referent participants had similar socioeconomic and demographic characteristics as they were from the same industry with almost identical age, weight, annual income, length of employment, ethnic background and smoking habits. Additionally, none of the subjects had past medical or family history of chronic respiratory illnesses.

Given the above and the fact that atmospheric concentration of formaldehyde exceeded the short term exposure limit (TLV-STEL) of 0.3 ppm[17] indicate that a significantly increased prevalence rate of respiratory symptoms as well as significant decrements in the parameters of pulmonary functions may well be explained by occupational exposure to formaldehyde.

Prevalence rates of respiratory symptoms such as cough, phlegm, productive cough, wheezing, dyspnea, chest tightness and episodes of chest illness associated with cold in exposed subjects were significantly higher than those of referent group. These findings are similar to the results of some other studies[4, 9, 18]. In accordance with these findings, National Institute of Occupational Safety and Health (NIOSH) has also reported that respiratory symptoms such as wheezing and chest tightness among formaldehyde exposed workers were common[18].

The findings of this study indicated that in addition to the acute partially reversible effects, long term occupational exposure to formaldehyde resulted in significant irreversible decrements in some parameters of pulmonary function such as VC, FVC and FEV_1.

As pointed out earlier, the studies conducted to evaluate the respiratory effects of formaldehyde have yielded conflicting results. For instance, Main and Hogan failed to demonstrate any significant decrease in PFTs attributable to formaldehyde exposure[9].

In contrast, Alexandersson *et al*., as cited in IPCS 89[4], demonstrated acute reversible decrements in PFTs which is in full agreement with the results of the present study. Similarly, Erdem *et al*. in a study on 35 workers exposed to 1.70 ppm of formaldehyde observed that changes in lung functions in exposed smokers and non-smokers were not significant ($p>0.05$). However, changes were found to be significantly higher in exposed smokers as compared to non-exposed smokers ($p<0.05$)[6]. They reported qualitatively similar decreases in VC, FVC and FEV_1 to our observations.

To the best of authors' knowledge, the distinction between possible acute and chronic effects of formaldehyde exposure in comparison with an appropriate referent group have not been examined by others. In this study, in order to differentiate between these effects, the parameters of pulmonary functions were measured before and after exposure. As shown in Table 3, exposure to formaldehyde was associated with significant reductions in most parameters of pulmonary functions. After exposure, these effects were more prominent. Interestingly, partial recovery of the lung functional capacities was noted as evidenced by a better performance in PFTs preshift values. Worth noting, despite this partial recovery, the difference between exposed and referent subjects remained statistically significant. These findings demonstrated that exposure to formaldehyde in addition to acute partially reversible effects induced chronic irreversible functional impairments of the lungs. The results of spirometry in this study showed that apart from FEV_1, vital capacity (VC) also significantly decreased in formaldehyde exposed subjects. This observation may indicate that exposure to formaldehyde is associated with restrictive pulmonary disorders. While the axact physiological reasons for this observation at present remain unexplained, it has to be noted that similar findings have been reported by others[6].

The possible respiratory effects of long term occupational exposure to formaldehyde in the absence of potential confounders have rarely been investigated. To control the role of important confounders, using multiple linear regression analysis, independent variables of age, weight, height, smoking habits and exposure to formaldehyde were included in the models. Regression analysis showed that significant associations exist between exposure to formaldehyde and VC, FVC and FEV_1 values.

Conclusions

In conclusion, the findings of this study provide circumstantial evidence in favor of the proposition that occupational exposure to formaldehyde is associated with respiratory symptoms and functional impairments (acute partially reversible and chronic irreversible effects) of the lungs. Therefore, engineering control measures such as local exhaust and general ventilation and personal protective devices are essential to protect the workers from developing more severe chronic respiratory diseases and to prevent respiratory impairments in recently employed workers before occurrence of any respiratory complications.

However, due to the subjective nature of the respiratory symptoms, the possibility of information bias (misclassification bias) should not be overlooked. Even though, the fact that both groups were interviewed by the same person and identical means (standard respiratory questionnaire) was used to evaluate the prevalence of respiratory symptoms in both groups indicate that the possible error (misclassification bias) would be non-differential. This type of error which is inherent to this type of study is unavoidable. However, nondifferential misclassification tends to bias the association toward the null hypothesis[19] (absence of any difference between the study groups).

Therefore, further studies with larger sample sizes, higher ambient concentrations of formaldehyde and longer duration of exposure and follow up in both male and female workers are strongly recommended to confirm the findings of this study and to determine more thoroughly the nature of functional impairments of the lungs.

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