Volatile Organic Compounds Contribute to Airway Hyperresponsiveness

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Background: Volatile organic compounds (VOCs) in concentrations found in both the work and home environments may influence lung function. We investigated the prevalence of airway responsiveness in workers exposed to VOCs.

Methods: We used allergic skin tests, nonspecific airway hyperresponsiveness testing and questionnaires to study twenty exposed workers and twenty-seven control subjects. Atopy was defined as a reactor who showed >3+ response to one or more allergens on the skin prick tests. Airway hyperresponsiveness (BRindex) was defined as log [% fall of FEV1/log (last concentration of methacholine) +10].

Results: The VOC exposed workers, in comparison with the control subjects, tended to have a higher BRindex (1.19±0.07 vs. 1.15±0.08, respectively). Workers exposed to VOCs with atopy or smoker, as compared with the workers exposed to VOCs with non-atopy and who were non-smokers and the control subjects with non-atopy and who were non-smokers, had a significantly higher BRindex (1.20±0.05 vs. 1.14±0.06 vs. 1.10±0.03, respectively p<0.05). The BRindex was not correlated with atopy, the smoking status or the duration of VOC exposure.

Conclusions: These findings suggest that VOCs may act as a contributing factor of airway hyperresponsiveness in workers exposed to VOCs.

Key Words: Volatile organic compounds, Bronchial hyperreactivity

INTRODUCTION

Organic chemicals are ubiquitous indoors, where they are released from furnishings and equipment, construction materials and consumer and office products. Because these sources of organic chemicals are not always well ventilated, volatile organic compounds (VOC) are generated and trapped indoors and so this causes higher indoor levels than are found outdoors. Recently, there have been concerns raised about the adverse health effects of such exposure.

Hundreds of organic chemicals have been identified in indoor air. Although many of these agents are also released by outdoor sources such as chemical plants, these indoor sources have been shown to be responsible for the better part of a person’s exposures to most organic chemicals.

Despite the potential risks of the organic chemicals in indoor air, there have been few studies concerned with specific exposure-disease associations, largely because of the difficulty in characterizing the exposures and identifying the effects of complex mixtures of compounds in indoor and outdoor air. There have also been a few studies that have shown specific
exposure-disease associations in the occupational environment. The VOCs at concentrations found in both work and home environments may influence lung function and they are probably of importance as bronchial irritants\(^7\).

The aim of this study was to investigate airway hyperresponsiveness (AHR) in workers who were exposed to VOCs at one petrochemical plant in Korea.

**METHODS AND MATERIALS**

**Subjects**

The subjects consisted of twenty workers who were exposed to VOCs and twenty-seven non-exposed control subjects. The exposed workers were working at a petrochemical plant at the time of the study. The non-exposed control subjects were watched over the VOC factory. The exposed workers and non-exposed control subjects were randomly selected. The ambient air concentrations of VOCs were monitored as part of an epidemiological survey. The subject’s symptoms included cough, wheezing, shortness of breath, chest tightness, stuffiness, coryza and sneezing that occurred at work, during the evening or at night. All the subjects completed an interview about their clinical and occupational history. All subjects were free of respiratory infection at the time of the interview. None of the subjects took anti-histamine, cromolyn, theophylline or sympathomimetics within 72 hours of the challenge tests.

**Data collection**

A questionnaire for symptoms and medications was given and spirometry was performed for each subject. The skin prick tests and methacholine provocation tests were then done. Each subject was interviewed by trained field investigators by using a structured questionnaire. We obtained data on respiratory symptoms, a detailed work history that included previous employment, and the medical history that included the presence of atopy and the subject’s smoking habits.

Spirometry was performed with a SensorMedics 2200 spirometer (Cardiopulmonary care companyTM, Yorba Linda, California). Baseline measurements of vital capacity and FEV\(_1\) (forced expiratory volume in one second) were selected according to the American Thoracic Society criteria\(^8\) and reference values were taken from Choi et al.\(^9\).

Allergy skin prick tests were performed with nine common allergen extracts [Dermatophagoides farinae, Dermatophagoides pteronyssinus, aspergillus spp, alder, rye, mugwort, ragweed, Blatella germanica, cat tur and histamine (1 mg/mL, Bencard, Bradford UK) mixed with saline. The reactions were read 15 minutes later. When the wheal size was equal to or greater than that of histamine, it was read as 3+. Atopy was defined as a reactor who showed >3+ response to one or more allergens on the skin prick tests\(^10\).

Methacholine challenge tests were carried out by the method described by Chai et al. with some modifications\(^11\), and the results were expressed as the PC20 [defined as a provoking dose of methacholine causing a 20% fall in the FEV\(_1\)] in non-cumulative units. Nebulized methacholine dilutions varying from 0.075 to 25 mg/mL were administered. The FEV\(_1\) was measured 30, 60 and 90 seconds after nebulization until a 20% decrement in the FEV\(_1\) was demonstrated. The AHR was estimated as the concentration dose that provoked a 20 percent decrease of the FEV\(_1\). The PC20 level was obtained from the dose-response curve. The BRindex, as described by O’Connor et al.\(^12\) with some modifications\(^13\), was defined as log [(% fall of FEV\(_1\))/log (last concentration of methacholine) +10].

The ambient air concentrations of toluene, xylene and benzene were measured when manufacturing was taking place at the workplace\(^14\).

**Statistical analysis**

All the data was analyzed using SPSS version 10.0 for Windows. The data are expressed as mean standard deviation (SD). Statistical analysis was performed by the Mann–Whitney U test. Spearman’s correlations were used were appropriate. A \(p\)-value of <0.05 was considered significant.

**RESULTS**

The characteristics of the subjects are given in Table 1. The mean ambient air concentrations of VOCs were under the recommended levels (Table 2). The mean (SD) duration of exposure of workers to VOCs was 9.1±5.3 years. The mean duration of respiratory symptoms for the workers exposed to VOCs was 7.1±5.2 years.

**Atopy among workers exposed to VOCs and the control subjects**

Four of twenty workers and seven of twenty-seven control subjects had atopy. Differences for the prevalence of atopy were not noted between the workers exposed to VOCs and the control subjects.

**Airway hyperresponsiveness**

Four workers (20.0%) were shown to have respiratory symptoms. The VOC exposed workers, in comparison with the control subjects, tended to have a higher BRindex (1.19±0.07 vs. 1.15±0.08, respectively, Figure 1). There were no differences in the prevalence of nasal symptoms between the
Table 1. Clinical characteristics of the workers exposed to volatile organic compounds (VOC) and the controls

|                          | Workers exposed to VOC | Controls |
|--------------------------|------------------------|----------|
| Number                   | 20                     | 27       |
| Gender (male/female)     | 20/0                   | 23/4     |
| Age (year±SD)            | 39.2±5.7               | 35.9±10.3|
| Smoking                  |                        |          |
| (current/ex/none)        | 10/6/4                 | 9.6±8.5  |
| Pack-years               | 11.4±7.6               | 101.4±5.7|
| FVC (% pred.)           | 98.3±3.5               | 98.6±6.4 |
| FEV1 (% pred.)          | 100.3±4.3              | 98.2±6.6 |
| FEV1/FVC                | 101.3±6.6              | 98.2±5.6 |

All values are means±SD. FVC: Forced vital capacity, FEV1: Forced expiratory volume in one second.

Table 2. Ambient air concentrations of volatile organic compounds at the time of the study

| Chemical substance | Mean | Maximum | TLV–TWA* |
|--------------------|------|---------|----------|
| Toluene (ppm)      | 0.022| 111.1   | 100      |
| Xylene (ppm)       | 0.031| 31.0    | 10       |
| Benzene (ppm)      | 0.004| 5.2     | 10       |

*Threshold Limit Values–Time Weighted Average based on Threshold Limit Values and Biological Exposure Indices (ACGIH®).

Figure 1. BRindexs between the workers exposed to volatile organic compounds and the control subjects.

exposed workers and the control subjects. There were no differences of the BRindex between the atopy subjects and the non-atopy subjects (1.21±0.05 vs. 1.19±0.06, respectively), between the subjects with ≥10 year exposure and the subjects with <10 year exposure (1.16±0.07 vs. 1.19±0.09, respectively), and between the smokers and non smokers (1.17±0.05 vs. 1.16±0.04, respectively, Figure 2). The workers exposed to VOCs and with atopy or smoking (n=13), had a significantly higher BRindex (1.20±0.05 vs. 1.14±0.06 vs. 1.10±0.03, respectively, Figure 2) in comparison with the VOC workers (n=7) and the control subjects with non-atopy and who didn’t smoke (n=9).

Figure 2. BRindexs among the atopy or smoking group of workers exposed to volatile organic compounds (Group 1), the non-atopy and non-smoking group of workers (Group 2) exposed to volatile organic compounds and the control subjects.

Correlations between the BRindex and the clinical parameters
The BRindex was not correlated with atopy, the smoking status and the duration of VOC exposure.
DISCUSSION

These data showed that workers exposed to VOCs with atopy or that were smokers had a higher AHR in comparison to the non-atopy, non-smoking VOC exposed workers.

The relationship between allergens in the indoor environment and asthma has been extensively studied and recent studies have suggested the possibility of the role of chemical pollutants for the genesis of asthma in the occupational environment.

The organic chemicals found in indoor air can be grouped by their range of boiling points as volatile (0 to 240 °C), semivolatile (240 to 380 °C), and particulate (over 380 °C). The volatile and semivolatile organic chemicals are most relevant to human health. VOCs exist as vapors over the normal range of air temperature and pressures, whereas semivolatile organic chemicals are liquids or solids, but they also evaporate slowly.

Despite the potential risks of the organic chemicals in the work environment, few studies have shown specific disease–exposure associations.

VOCs at concentrations found in indoor air can be related to asthmatic symptoms. In this study, exposed workers with smoking or atopy had a higher BRindex, suggesting that smoking is an important additive factor to VOCs in relation to AHR. In some susceptible individuals, the development of respiratory hypersensitivity or the elicitation of asthmatic symptoms may also be related to the indiscriminate use of different household products and then this is followed by exposure to such compounds as diisocyanate, organic acid anhydrides, formaldehyde, styrene and hydroquinone. The VOC emissions from solvent-based paints might contribute to the development of respiratory symptoms and airway irritation.

There are probably some patients with an increased sensitivity to paint fumes who would derive a useful symptomatic benefit from using VOC-free paint. Some of the VOCs emitted by rape-seed oil have the potential to be allergens/irritants. In this study, there was no difference of AHR between the workers exposed to VOCs and the control subjects. Further, there was no AHR difference between the atopy and non-atopy workers exposed to VOC. The absence of AHR differences maybe due to the study population and the low VOC concentrations, as compared to the previous study of Ware et al. Further studies with larger subject pools are needed to clarify the relation between workers exposed to VOCs and the control subjects.

Although there were no differences of AHR between the workers exposed to VOCs with atopy and the workers exposed to VOCs with smoking and the control subjects, the workers with atopy or smoking showed increased AHR, suggesting that VOCs might contribute as an aggravating factor of AHR.

Exposure to chemical emissions from indoor paint is related to asthma, and some VOCs may cause inflammatory reactions in the airways. Significant relationships have been noted between nocturnal breathlessness and the presence of wall-to-wall carpets, and the indoor concentrations of CO₂, formaldehyde and VOCs. AHR is related to the indoor concentration of limonene, which is the most prevalent terpene.

Variability in the peak expiratory flow rates is related to two terpenes: alpha-pinene and delta-karen. This suggests that indoor VOCs and formaldehyde may cause asthma-like symptoms. The incidence of chronic respiratory symptoms is also positively associated with the concentrations of volatile organic compounds, considering that exposure to volatile organic compounds, including the emissions from chemical manufacturing plants, is associated with increased rates of chronic respiratory symptoms that are characteristic of reactive airways. For improving the management of asthma and to counteract the increasing frequency of asthma, the significance of the work environment can not be neglected.

However, because of the selection effects, the results of cross-sectional studies on respiratory symptoms in relation to occupational exposure to VOC emissions may be inconclusive. Despite the small size of the worker groups in this study, significant differences in the AHR of the workers exposed to VOCs with atopy or smoking were detected, and this suggests that VOCs may increase AHR. Further prospect studies with larger populations of workers should be done.

In the present study, any association between VOCs and AHR was not seen, but when this was adjusted for smoking or atopy, the association with VOC exposure was evident. Therefore, there is a need to decrease people’s exposure to VOCs and to improve the air supply in the work environment. Improved work environment can also be achieved by selecting proper building materials and paying close attention on the various options and choices when constructing a building. The emission of VOCs should be as low as reasonably achievable to minimize the asthma-related symptoms that are due to polluted air in the work environment.

In conclusion, this study indicated that the workers exposed to VOCs with atopy or that are smokers have increased AHR as compared to workers exposed to VOCs with non-atopy and that are non-smokers, in one Korean petrochemical plant. Therefore, volatile organic chemicals should be well ventilated during use in occupational and home environments to reduce
the occurrence of asthma-related symptoms.

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