



Volatile Organic Compounds and Nonspecific Conjunctivitis: A Population-Based Study

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ABSTRACT

Volatile Organic Compounds (VOCs) are present in both indoor and outdoor environments, and have the potential to adversely impact the health of all age groups of people that are exposed to them. This study examines and assesses the short-term effects of VOCs on nonspecific conjunctivitis. Data were collected from outpatient visits for nonspecific conjunctivitis in air-quality monitoring areas. Air quality data were collected from the Taiwan Environmental Protection Administration's air quality monitoring stations. To find the immediate and lag effects of VOCs, an area-specific, case-crossover analysis was performed and a meta-analysis with random effects was used to combine the area-specific results. The results show that toluene, m,p-xylene, o-xylene, propylene, and benzene had higher maximum incremental reactivity (MIR) values and concentrations in air than any of the other studied VOCs. These 5 VOCs also had the strongest short-term effects on outpatient visits for nonspecific conjunctivitis. The effect was strongest for toluene, and there was a 1.3% increase [95% confidence interval (CI), 0.4–2.2] for an interquartile range rise in concentration. The results showed no evident lag effects. This study, which combined and integrated VOC and ophthalmologic data to investigate associations between outpatient visits for nonspecific conjunctivitis and VOC levels, found that there was a correlation between these visits and the short-term effects of VOCs, suggesting possible causes for nonspecific conjunctivitis.

Keywords: Volatile organic compounds; Health effects; Nonspecific conjunctivitis.

INTRODUCTION

Volatile Organic Compounds (VOCs), which are released into the air mostly through the use of everyday products and materials, are present in both indoor and outdoor environments. They are of concern for the potential to adversely impact people's health. Because of their ubiquitous presence in the atmosphere and their impact on the environment and human health, VOCs are essential parameters for assessing the air quality in indoor and outdoor environments. Previous studies demonstrated that VOCs are associated with disorders of many body organs. Short-term health effects include eye and respiratory tract irritation, headaches, dizziness, visual disorders, and memory impairment. Long-term health effects are damage to liver, kidney, and central nervous system. And some are known to cause cancer in humans. (Rumchev *et al.*, 2007; Kampa

and Castanas, 2008; Zhou *et al.*, 2011; Ramirez *et al.*, 2012).

As a directly exposed part of the human body, the eyes are more susceptible to external stimulations such as air pollution. This is because the innervations in eyes are high in density and render them extremely sensitive to environmental changes (Tuominen, 2003). Furthermore, the eyes only have a thin layer of tear film to shield them from potentially damaging external influences and irritations (Wang, 2003). Air pollution exposure gives rise to not only ocular surface inflammation but also changes in cytology (Versura *et al.*, 1999; Saxena *et al.*, 2003; Novaes *et al.*, 2007). Previous studies have pointed out that exposure to VOCs can lead to ocular irritation and inflammation (Otto *et al.*, 1990; Wieslander *et al.*, 1999; Mølhav *et al.*, 2000).

Conjunctivitis is a commonly diagnosed ocular inflammation condition in ophthalmologic outpatient clinics and emergency rooms (Cohn and Kurtz, 1992; Lee *et al.*, 1994). Millions of ophthalmology outpatients are diagnosed with conjunctivitis every year, according to the data from the Bureau of National Health Insurance, Taiwan. These ocular disorders necessitate an exorbitant amount of medical expenditure and they have an adverse impact on people's daily activities, such as driving and work productivity.

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Moreover, eye drops including steroids used for treatment of air pollution-induced diseases occasionally cause severe side effects, such as cataracts and glaucoma, which can lead to permanent vision loss (Gerometta *et al.*, 2009). This study assesses the short-term effects of VOCs on the number of outpatient visits for nonspecific conjunctivitis in Taiwan between 2008 and 2010.

METHODS

Health Data

Data for ophthalmology outpatient visits between 2008 and 2010 were obtained from the National Health Insurance Research Database of Taiwan. In Taiwan, more than 99% of people are enrolled in the national health insurance program, and the Bureau of National Health Insurance has contracted with more than 90% of hospitals and clinics throughout the country (Chiang, 1997; Lu and Hsiao, 2003), making this database a valuable medical research resource. Outpatient visits for nonspecific conjunctivitis were selected according to the International Classification of Diseases, 9th revision (ICD-9), diagnostic codes. The following codes were included: 372.00 (nonspecific acute conjunctivitis), 372.10 (chronic conjunctivitis), 372.11 (simple chronic conjunctivitis), 372.20 (blepharconjunctivitis), 372.30 (other undefined conjunctivitis) and 372.39 (other conjunctivitis). We defined disorders of those ICD-9 codes as nonspecific conjunctivitis. The original data were further filtered with statistical software and only the data from ophthalmologists were used for calculation. Criteria for exclusion were: patients who visited either the same or another ophthalmologist more than once within 10 days and those for whom a diagnosis of conjunctival disorder was changed. Only outpatient visits with the aforementioned ICD-9 codes as the major diagnosis were included in this study.

Air Quality Data

Ambient air monitoring data are available from the Taiwan Environmental Protection Administration (EPA) monitoring stations. Air quality data between 2008 and 2010 were collected. A total of fifty-one VOCs were included in the analysis (Fig. 1), and the VOC measurements from monitoring stations were integrated into the daily point data. Temperature, rainfall, and relative humidity data were concurrently obtained from the monitoring stations. The data were retrieved from eight monitoring stations maintained by the Taiwan EPA: Ciaotou, Wanhua, Tucheng, Taisi, Tainan, Puzih, Xiaogang, and Chaozhou. The eight monitoring stations are located in three areas: North (Wanhua, and Tucheng), Yun-Chia-Nan (Taisi, Tainan and Puzhi), and Kao-Ping (Ciaotou, Xiaogang and Chaozhou) (Fig. 2).

Analytical Strategy

This study used a multi-area case–crossover design to investigate the association between daily VOC concentrations and the number of outpatient visits for nonspecific conjunctivitis according to the selected ICD-9 codes. Multi-station case–crossover analysis has been utilized to investigate the short-term effects of air pollutants on the

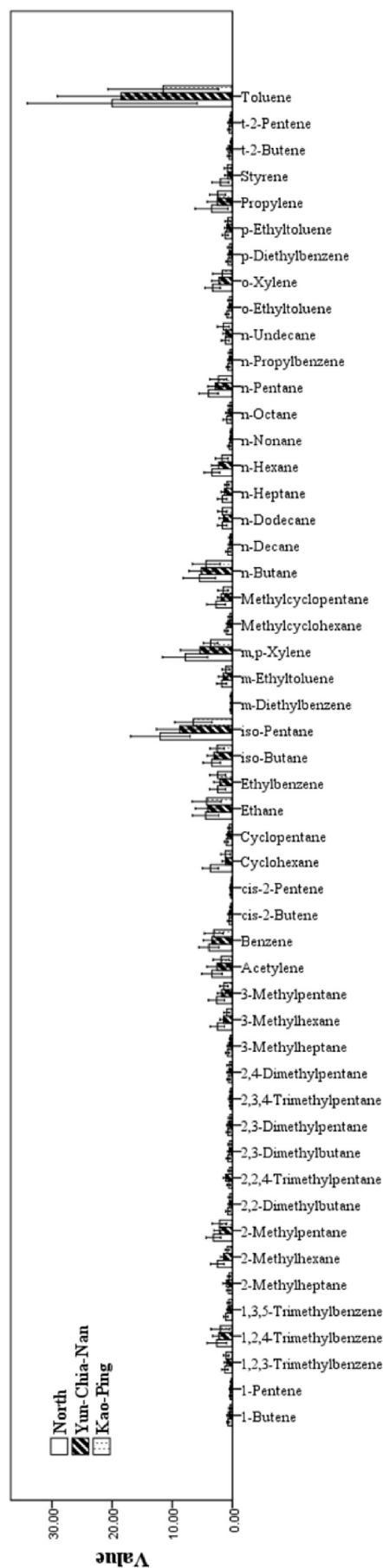


Fig. 1. Concentrations of volatile organic compounds for the 3 areas (Mean \pm SD), ppb.

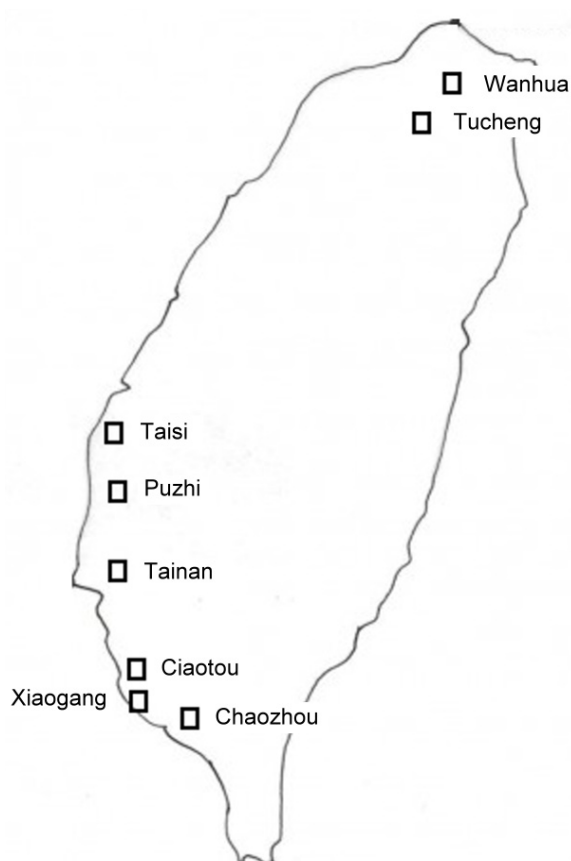


Fig. 2. Locations of eight EPA monitoring stations.

development of respiratory and ocular disorders (Maclure, 1991; Lin *et al.*, 2003; Barnett, 2005; Chang *et al.*, 2012). A case subject was regarded as a control person on days with no outpatient visits. This study selected the control days by matching the day of the visit with the day of the week in the same month and year. In addition, a case–crossover analysis was performed by matching every third day from the case day in the same month and year for a sensitivity analysis. In the analysis of every third day, the day-of-week variable was included in the regression model. Same-day mean temperature, rainfall, and relative humidity were used in the models to control the potential influence of weather conditions.

The effects from the same day up to 3 previous days were calculated by computing the moving averages as averages of exposure lags. For example, the 2-day moving average (lag 0–1) was computed as the mean of the same day and the previous day. The associations between air pollution and outpatient visits for nonspecific conjunctivitis were analyzed in each area separately. To estimate the average effect of all the areas, the area-specific results were combined using a random-effect meta-analysis (DerSimonian and Laird, 1986). The results are expressed as percentage increases in outpatient visits for an interquartile range (IQR) increase in exposure to each VOC component. The IQRs are the average of the three areas. A conditional logistic regression was used to analyze the data (SPSS18, IBM Corp., USA; Stata 11, StataCorp. LP, USA).

RESULTS

Characteristics of Subjects

The descriptive statistics for daily counts (mean and SD) of outpatient visits for nonspecific conjunctivitis in each of the three areas are listed in Table 1. Among the four age groups, the groups of patients younger than twenty years and older than sixty years had higher numbers of outpatient visits for nonspecific conjunctivitis, whereas the group of patients twenty to forty years old had the lowest number of visits. More female than male patients had outpatient visits for nonspecific conjunctivitis. The numbers of outpatient visits for nonspecific conjunctivitis were similar in all seasons. The characteristics of the distributions of the study population were similar for the three areas in this study.

VOCs

Fig. 1 presents the distributions of the daily mean concentrations of VOCs during the study period. The mean levels of VOCs varied across these three areas, and the degrees of variation were different among the various compounds. Among the three areas, the northern area had a higher VOC concentration in the air for most kinds of VOCs. The concentration of toluene was the highest among the fifty-one VOCs for all three areas. Ethane, butane, pentane, benzene, and xylene also had higher concentrations than those of the other VOCs. As for the weather factors, rainfall, temperature and relative humidity values were similar in all three areas.

VOCs and Nonspecific Conjunctivitis

Table 2 shows the combined results of the three areas for a single day and the moving averages for nonspecific conjunctivitis. Among the VOCs, toluene was most strongly associated with outpatient visits for nonspecific conjunctivitis, followed by m,p-xylene and o-xylene. Weaker associations were found for benzene and propylene. No significant associations between the other VOCs and nonspecific conjunctivitis were found for either single-day or moving averages. For the five VOCs with the most significant effects, associations were found for lag 0, and the association was strongest for lag 0 with a 1.3% rise (95% CI, 0.4–2.2) for a 14.6 ppb (parts per billion) increase in toluene. No statistically significant associations were found for the averages of lags longer than lag 0–1.

To obtain the average results of the three areas, a meta-analysis was conducted in conjunction with a random-effect. Table 2 also lists the p-values for homogeneity and significant heterogeneity (at a significance level of 0.05) among the results of the three air quality areas. This signifies that the study results of the impact of VOCs on eyes differ from area to area.

DISCUSSION

It has been shown that a favorable air-pollution–monitoring infrastructure combined with established public health data can provide valuable information for an examination of adverse health effects related to air pollution. A study in

Table 1. Descriptive statistics for daily counts of nonspecific conjunctivitis outpatient visits (mean \pm SD).

Characteristic	North ($\times 10^3$)	Yun-Chia-Nan ($\times 10^3$)	Kao-Ping ($\times 10^3$)
Age			
< 20 years	2.33 \pm 1.66	1.08 \pm 0.60	1.20 \pm 0.52
20–40 years	1.72 \pm 0.90	0.73 \pm 0.44	0.81 \pm 0.37
41–60 years	2.7 \pm 1.45	1.30 \pm 0.72	1.57 \pm 0.66
> 60 years	2.97 \pm 1.63	1.99 \pm 1.10	1.97 \pm 1.1
Sex			
Male	4.21 \pm 2.01	2.19 \pm 1.32	2.67 \pm 1.19
Female	5.50 \pm 2.63	2.91 \pm 1.62	2.88 \pm 1.20
Season			
Spring	2.42 \pm 1.10	1.14 \pm 0.57	1.43 \pm 0.48
Summer	2.42 \pm 1.12	1.33 \pm 0.46	1.42 \pm 0.57
Fall	2.44 \pm 1.13	1.32 \pm 0.45	1.44 \pm 0.52
Winter	2.43 \pm 1.12	1.32 \pm 0.48	1.26 \pm 0.62

Table 2. Percentage increase (95% CI) of outpatient visits for an IQR increase in air pollution: combined results across the three areas and p-value for homogeneity test.

VOCs	Percent (95% CI)	IQR	P-value for homogeneity
Toluene lag 0	1.3 (0.4 to 2.2)	14.64	0.23
Toluene lag 0–1	1.3 (0.1 to 2.5)	13.82	0.13
Toluene lag 0–2	1.4 (–0.3 to 3.1)	13.28	0.28
Toluene lag 0–3	1.4 (–0.5 to 3.3)	12.13	0.71
o-Xylene lag 0	0.9 (0.2 to 1.6)	9.12	0.18
o-Xylene lag 0–1	0.9 (–0.4 to 2.2)	8.98	0.008
o-Xylene lag 0–2	1.2 (–0.5 to 2.9)	7.61	0.18
o-Xylene lag 0–3	1.3 (–0.4 to 3.0)	6.87	0.31
m,p-Xylene lag 0	1.1 (0.4 to 1.8)	10.87	0.02
m,p-Xylene lag 0–1	1.2 (0.2 to 2.6)	9.56	0.002
m,p-Xylene lag 0–2	1.5 (–0.3 to 3.3)	7.14	0.12
m,p-Xylene lag 0–3	1.8 (–0.6 to 4.2)	7.10	0.17
Benzene lag 0	0.6 (0.2 to 1.0)	6.78	0.51
Benzene lag 0–1	0.9 (–0.3 to 2.1)	6.67	0.58
Benzene lag 0–2	1.2 (–0.6 to 3.0)	6.13	0.45
Benzene lag 0–3	1.5 (–0.9 to 3.9)	5.29	0.47
Propylene lag 0	0.4 (0.1 to 0.7)	11.87	0.13
Propylene lag 0–1	0.5 (–0.3 to 1.3)	9.22	0.09
Propylene lag 0–2	1.0 (–0.6 to 2.6)	7.97	0.19
Propylene lag 0–3	1.4 (–0.9 to 3.7)	7.12	0.13

Abbreviations: VOCs, volatile organic compounds, CI, confidence interval, IQR, interquartile range.

Taiwan suggested that exposure to high levels of PM_{2.5}, a proxy measure of PAHs, may be associated with an increased risk of death from breast cancer (Hung, 2012).

Exposure to VOCs can induce a wide range of acute and chronic health effects. A study was conducted to determine whether there was an excess number of adverse respiratory and ocular irritant health outcomes in a population who lived close to petrochemical manufacturing facilities. The results, which were statistically significant, showed that these residents had more acute symptoms (eye irritation, nausea, throat irritation, and odor perception) than those in a low-pollution area. But the concentration of VOCs was not mentioned in this study (Yang *et al.*, 1997).

The present study assessed the short-term effects of VOCs on outpatient visits for nonspecific conjunctivitis in three areas of Taiwan. The North, Yun-Chia-Nan, and Kao-

Ping areas are located in the northern, south central, and southern parts of Taiwan, respectively. They have different population densities, types of businesses, and traffic conditions. As a result, ocular health effects may differ; therefore, analysis was conducted in each area separately. To estimate an average effect of all areas, the area-specific results were combined using a meta-analysis.

Previous studies show that approximately 90% of rhinitis cases experience ocular symptoms at least 1 day per week, and some researchers suggest that conjunctival mucosa and respiratory mucosa react similarly to exogenous stimuli (Bielory *et al.*, 1997; Ono and Abelson, 2005). Respiratory morbidity and nonspecific conjunctivitis have been proved to be associated with similar groups of regulated air pollutants, including two or more of CO, NO₂, SO₂, O₃, and PM, but lag effects of air pollution were not found on

the eyes (Bedeschi et al., 2007; Chang et al., 2012). A study showed that VOCs had significant effects on asthma in children (Hwang, 2011). In our study, toluene, m,p-xylene, o-xylene, propylene, and benzene were found to have effects on ocular health. Therefore, it is possible that the respiratory tract and the eyes may have similar reactions to VOCs.

The exact mechanisms of the effects of VOCs on nonspecific conjunctivitis are not well known. The air concentrations of all 5 VOCs, toluene, m,p-xylene, o-xylene, propylene and benzene, related to nonspecific conjunctivitis in this study were higher than those of any of the other studied VOCs. It seems that concentration in air is an important factor for some VOC-induced effects on ocular health. Besides that, the MIR of VOCs seems to be another factor in VOC-induced nonspecific conjunctivitis. In this study, toluene, m,p-xylene, o-xylene, propylene and benzene had higher MIRs and concentrations in air, which means a higher potential for O₃ formation. And O₃ has been proved to be associated with nonspecific conjunctivitis (Chang et al., 2012). For VOCs with a high MIR but a low concentration in air, such as butene, pentene, and their isomers, and VOCs with a high concentration in air but a low MIR, such as butane, pentane, and their isomers, no effects on nonspecific conjunctivitis were found in this study. Ambient air monitoring data from the eight monitoring stations does not include both O₃ data and the VOC data at the same time; therefore, O₃ concentration was not used for calculations in this study.

Benzene had a high concentration in air but a low MIR; however, it had significant effects on nonspecific conjunctivitis in this study. Respiratory tract and ocular mucosa irritating properties of benzene may contribute to the high number of outpatient visits for nonspecific conjunctivitis. The other 4 VOCs, toluene, m,p-xylene, o-xylene, and propylene, also possess respiratory tract and ocular mucosa irritating chemical properties. Some VOCs with a high concentration in air may have a high O₃ formation capability relating to MIR or mucosa irritating properties or they may possess both factors.

Previous studies have proven the lag effects of air pollution on respiratory disorders. Associations between airway symptoms and air pollution appeared to increase or persist at longer lags (up to 5 days) (Bedeschi et al., 2007). A study in Copenhagen found a link between incident wheezing symptoms in infants and air pollution (PM₁₀, NO₂, CO) with a 3- to 4-day lag (Andersen et al., 2008). But no lag effect was found in studies investigating the effects of regulated air pollutants on ocular disorders (Bourcier et al., 2003; Chang et al., 2012). In this study, no lag effects results for VOCs on ocular disorders were similar to those for regulated air pollutants.

CONCLUSIONS

This study investigated the associations between outpatient visits for nonspecific conjunctivitis and VOC levels. Five VOCs, toluene, m,p-xylene, o-xylene, propylene and benzene, showed quantifiable effects on ocular health. No lag effects were found in this study. Further studies are needed

to investigate the mechanisms by which VOCs induce nonspecific conjunctivitis.

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