Original Article

Volatile Organic Compounds as a Preventive Health Challenge in the Petrochemical Industries

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Abstract

Background: The aim of this study was to assess the effects of long-term exposure to VOCs on employees' clinical parameters in one of the main petroleum centers in Iran. **Methods:** In this case-control study, 80 operational and administrative employees with 8–15 years of work experience were considered as the case and control groups. Liver function was evaluated by measuring serum alanine transaminase (ALT) activity and lipid profile was measured. Gas chromatography-mass spectrometry (GC-MS) was used to analyze the VOCs levels at the workplace. **Results:** There were increased levels of serum ALT ($P = 0.003$), triglycerides ($P = 0.015$), total cholesterol ($P = 0.003$), and LDL-C ($P = 0.010$) among the operational staffs compared to the administrative staffs. Assessment of the relationship between worksite pollutants and ALT levels revealed that there were significant positive relationship between benzene ($r = 0.45$, $P = 0.004$) and styrene ($r = 0.37$, $P = 0.034$) with increased ALT concentrations. **Conclusions:** VOC exposure could be contributed to reduced liver function and impaired lipid profile. Therefore, proper preventive strategies seem to be necessary for reducing hazardous exposure.

Keywords: *Lipid profile, liver enzyme, petrochemical employees, volatile organic compounds*

Introduction

Volatile organic compounds (VOCs) are considered from both biogenic and anthropogenic sources, contained in a wide range of petroleum products such as fuel oils, solvents, and gasoline.[1,2] These chemical agents are classified into the organic compounds that have boiling point between 50°C and 260°C and among VOCs, the most commonly found are BTXS (benzene, toluene, xylenes, and styrene) and terpenes (limonene, α-pinene, etc.); main indoor carbonyl compounds include acetaldehyde and formaldehyde.[3]

VOCs considered as the most important health threats in petroleum industries.[4,5] Some amounts of the solvent vapors in the work environment can enter the lungs through inhaling air, and after passing through the pulmonary alveoli, enter the circulatory system, and exert a detrimental impact on different organs.[6,7] Some VOCs are associated with sick building syndrome (SBS) including irritation, headache, and fatigue while some of which are known as carcinogens (e.g. benzene).[8]

Liver considered as the main source of VOCs detoxification. It has been indicated that liver enzymes are increased during liver damages. In addition, epidemiological studies have confirmed the relation between liver damages, such as cholestasis, and chronic exposure to organic solvents in industrial workers.[2] For instance, Mohammadi *et al*. in a case-control study in 2010, measured the liver enzymes change in 163 subjects exposed to organic solvents in an auto manufacturing plant in Iran. Their data showed that serum alkaline phosphatase activity in the case group was significantly higher than that in the control group, indicating that exposure to non-permissible levels of a mixture of aromatic solvents can cause mild cholestatic hepatic dysfunction.[9]

In recent years, there has been a growing interest in the relationship between air pollutants and health in petroleum industries. Since VOCs are the most important health threats in petroleum industries, the main aim of this pilot study was to evaluate the effects of long-term exposure to VOCs on metabolic indices and liver function among petrochemical industry employees in one of the main petroleum centers in Iran.

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Methods

Studied population and sampling

This case-control study was performed in one of the main petrochemical companies in 2015. The cases were exposed to organic solvents from operational staff and controls were selected from administrative staff with no expose through a random sampling method in one of the main petrochemical companies, in the city of Mahshahr, located by the Persian Gulf, Iran. Operating staff routinely worked outdoor and were continuously exposed to direct oil products. Administrative staff worked indoor and their location was equipped with proper ventilation systems. Employees' Average work time was 40 hours per week. The inclusion criteria were male personnel with at least 8 years of working experience in stable position at petrochemical companies. Moreover, data about workers' age, weight, and height, body mass index (BMI), medical history, duration of employment, medications, and alcohol consumption were obtained through questionnaire and workers' medical records. We excluded the subjects with any medication use, alcohol consumption, regular smokers and those with background diseases such as hyperthyroidism and hepatorenal dysfunction based on their medical records. Written informed consent was obtained from all employees. From a total of 134 operational employees who were continuously exposed to the worksite pollutants, 40 subjects with work experience of 8–15 years, within the age range of 30–45 years and body mass index of 22 to 27 were randomly selected as the case group. As the controls, 40 men with the same characteristics were recruited from 157 administrative and non-operational employees. To accomplish lab measures, the blood sampling was performed at 8:00 a.m and 5 ml venous samples were collected from each worker, centrifuged, and then stored at –70°C for further analyses. Ethical approval of research protocol was confirmed by the Institute Ethical Review Board of Islamic Azad University, Shahreza Branch, Shahreza, Iran.

Biochemical tests

Serum biomarkers such as alanine aminotransferase (ALT) activity, as an index of liver function, serum fasting glucose, triglycerides, total cholesterol as well as low-density lipoprotein cholesterol (LDL-C) were measured based on commercial kits protocol (Pars Azmoon, Tehran, Iran) using autoanalyzer (Prestige 24i, Japan).

Sampling procedure of the workplace air

The sampling of the workplace air was performed according to the standard method of the National Institute for Occupational Safety and Health (NIOSH), 1501. Briefly, absorbent charcoal and individual sampling pump (calibrated by rotameter) with a flow rate of about 50–200 ml/min were used for the sampling procedure. At first, an activated carbon sorbent tube was encoded and the sampling process for each job lasted about 5–7 hours. To prevent saturation of the activated charcoal, two absorbent tubes were used, each lasted about 3 hours. We asked the workers to do their normal activities during the sampling process and avoid any actions that may result in losing the samples. After completing the sampling, the absorber tubes were located in plastic caps and frozen at –10°C.

VOCs analysis

VOCs, including benzene, toluene, styrene, acetone, xylene, n-hexane, and epichlorohydrin were quantitatively analyzed with a gas chromatograph (GC) (Varian, Inc CP3800, USA) equipped with a flame ionization detector (FID) and mass spectroscopy (MS), splitless injector, and capillary column (SGE code: 25 mm × 0.22 nm). Standards with a purity of 99% (GC grade) were purchased from Merck (Darmstadt, Germany). The carrier gas was helium. The oven temperature was programmed at 30°C for 12 minutes and increased to 180°C for 8 minutes and then, stopped at 180°C for 0.5 min. The injector temperature was set at 180°C, and the flow rate was 0.01–0.2 L/min. The VOCs were analyzed quantitatively using GC-FID and confirmed by gas chromatography-ion trap mass spectrometry. As shown in Table 1, calibration curves for VOCs were constructed using external standards, and the limits of detection (LOD) and limits of quantification (LOQ) were determined as S/N = 3 and S/N = 9, respectively, where S/N is the ratio of signal/noise.

The R-Squared (r^2) showed an acceptable calibration curve, which was linear in the defined range for each VOCs. The recovery and reproducibility of the VOCs are listed in Table 2. Recovery for the standards from the collection tube was measured from three replicate experiments,

Table 1: Linearity range and detection limits for GC-MS analyses

Volatile organic compounds	Range (ppm)	Linear equation	r^2	LOD (ppm)	LOQ (ppm)
Benzene	0.5-100	Y=752.3X-2920	0.99	0.006	0.02
Toluene	0.5-100	Y=532.7X-1317	0.99	0.045	0.15
n-Hexane	0.5-100	Y=520.1X-2978	0.99	0.015	0.05
Styrene	0.5-100	Y=6.987X-1.803	0.99	0.030	0.10
Acetone	0.5-100	Y=543.2X-1154	0.99	0.060	0.20
Xylene	0.5-100	Y=218.9X-6690	0.99	0.006	0.02
Epichlorohydrin	0.5-100	Y=532.3X-1325	0.99	0.006	0.02

LOD: limits of detection and LOQ: limits of quantification

using a standard gas containing 20–100 ng/tube of each compound. The average recoveries of all the VOCs range from 96 to 99%. The reproducibility expressed in terms of relative standard deviation (RSD) and was found in the range 3.5–5.7%.

Statistical analysis

For statistical analysis, the mean, standard deviation, and range were determined for quantitative data, and then, compared using student *t*-test (due to normal distribution of data). In order to adjust the confounding factors and to evaluate the relationship between exposure to the VOCs and change in biochemical indices precisely, we used the linear regression method (Pearson's correlation). All calculations were done using SPSS, version 16.0. *P* values less than 0.05 were considered statistically significant.

To determine the normality of variable distribution, KS test was applied.

Results

As indicated in Tables 1 and 2, the gas chromatography accordingly indicated the VOCs concentration in workplace with r^2 of 0.99 and effective LOD and LOQ. As shown in Table 3, no significant differences were observed in terms of demographic indices including age, BMI, height, weight, and work experience between the case and control groups.

Table 2: Summary of method validation data (standards)

Volatile organic compounds	Recovery (%)	Reproducibility (RSD; %)
Benzene	99	3.7
Toluene	97	4.8
n-Hexane	97	5.1
Styrene	96	3.5
Acetone	97	4.1
Xylene	96	5.5
Epichlorohydrin	98	5.7

Three different levels for each stock standard were prepared (approx. 20, 50 and 100 ng/tube) †Relative standard deviation (RSD) was obtained from three different tests for each VOCs

Results showed that workers exposed to the worksite pollutants had significantly elevated serum ALT ($P = 0.003$), serum triglyceride ($P = 0.015$), total cholesterol ($P = 0.003$), and LDL-C ($P = 0.010$) concentrations compared to their controls [Table 4].

Table 5 shows a significant increase in benzene ($P < 0.001$), toluene ($P < 0.001$), epichlorohydrin ($P < 0.001$), n-hexane ($P < 0.001$), styrene ($P < 0.001$), acetone ($P < 0.001$) and xylene ($P < 0.001$) within the surrounding area of the exposed workers, than those of unexposed employees. Significant correlation was found between serum ALT and styrene ($r = 0.370$, $P = 0.034$) and benzene levels ($r = 0.450$, $P = 0.004$) in the exposed workers [Table 6]. Another correlation was shown between Acetone and Glucose level ($r = 0.490$, $P = 0.001$). However, there was no significant correlation between VOCs concentrations and metabolic indices.

Discussion

In the present study, the association of exposure to VOCs with lipid profile and liver function among petrochemical industry employees was evaluated. In previous studies, it was shown that chemicals present in petroleum refining setting can adversely affect the liver function.[10,11] In this regard, our data showed that workers exposed to the worksite pollutants had significantly elevated ALT levels compared to the controls. The raised serum levels of ALT could be due to the release of this enzyme from the hepatocytes in response to stimuli of hepatocellular damage or cell death.[12] In accordance with these results, Akintonwa and Oladele (2003) reported a significant increase in serum activity of ALT and AST in workers of pump stations.[13] Likewise, Saadat and Ansari-Lari (2005) in a study on 56 workers of Shiraz pump stations, reported significantly elevated plasma levels of serum activity of ALT and AST in the exposed subjects as compared to the control group.[14] Egbuonu and Nkwaszema (2015) confirmed liver dysfunction in 64 petroleum workers. Their results showed a significant increase in liver function indices including ALT, AST, ALP, and gamma-glutamyl transpeptidase (GGT) in petroleum depot workers compared to their controls.[15] In a simillar study Wang and coworker reported that male

Table 3: Demographic characteristics of the studied participants

Groups	Variables	Length of exposure (year)	Body mass index (kg m^{-2})	Weight (kg)	Height (cm)	Age (year)
Operating staff (*n*=40)	Mean	12.4	25.5	79	175	36
	SD	1.1	1.1	5.6	4.8	2.3
	Minimum	9	22	69	162	33
	Maximum	14	26.9	92	190	43
Administrative staff (*n*=40)	Mean	11.6	26.6	79.2	176	36
	SD	1.8	9.3	5.6	5	2.6
	Minimum	8	23	65	166	32
	Maximum	15	27.2	86	185	43
P value†		0.19	0.45	0.99	0.30	0.48

†*P* values of less than 0.05 were considered statistically significant

Table 4: The serum biochemical parameters of the studied participants

Groups	Serum Variables	ALT (IU/L)	LDL-C (mg/dL)	Total Cholesterol (mg/dL)	Triglyceride (mg/dL)	Glucose (mg/dL)
Operating staff (*n*=40)	Mean	51.7	131	215.2	197	85.4
	SD	29.4	33.4	46.1	112.3	11.2
	Minimum	13	76	111	72	70
	Maximum	137	225	352	509	124
Administrative staff (*n*=40)	Mean	27	113	187.7	147	81.6
	SD	12	27	33.4	61.6	7.3
	Minimum	125	63	125	47	71
	Maximum	298	181	298	300	98
P value[†‖]		0.003	0.01	0.003	0.015	0.074

[†]Due to normal distribution of all variables, the unpaired two-samples *t*-test was used to compare the mean of two groups [‖]*P* values of less than 0.05 were considered statistically significant

Table 5: Comparing the workplace exposure to VOCs in both operating (cases) and administrative (controls) groups

Groups	Variables	Benzene (ppm)	Toluene (ppm)	n-Hexane (ppm)	Styrene (ppm)	Acetone (ppm)	Xylene (ppm)	Epichlorohydrin (ppm)
Operating staff (*n*=40)	Mean	1.03	5.60	0.40	3.48	6.35	8.19	0.52
	SD	1.40	13.66	0.29	10.75	11.47	22.20	0.83
	Minimum	0.09	ND[††]	ND	0.06	ND	ND	ND
	Maximum	5.91	46.11	0.94	63.32	56.29	78.66	4.60
Administrative staff (*n*=40)	Mean	0.18	0.21	0.09	0.24	0.48	0.04	0.05
	SD	0.14	0.55	0.17	1.33	0.57	0.09	0.07
	Minimum	0.03	ND	ND	ND	ND	ND	ND
	Maximum	0.56	3.37	0.77	8.46	2.23	0.58	0.36
P value[†‖]		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

[††]Not detected [‖]Due to normal distribution of all variables, the unpaired two-samples *t*-test was used to compare the mean of two groups [†]*P* values of less than 0.05 were considered statistically significant

Table 6: Correlation between VOCs levels at the worksite and serum biochemical parameters in the exposed workers

Volatile organic compounds	ALT (IU/L)		LDL-C (mg/dL)		Total Cholesterol (mg/dL)		Triglyceride (mg/dL)		Glucose (mg/dL)	
	r	*P*[†]	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Benzene	**0.450**	**0.004**	0.053	0.744	0.101	0.536	0.090	0.582	0.161	0.321
Toluene	0.054	0.739	0.092	0.572	0.117	0.471	0.170	0.293	0.135	0.406
n-Hexane	0.165	0.308	0.061	0.708	0.038	0.815	0.225	0.163	0.044	0.789
Styrene	**0.370**	**0.034**	0.198	0.221	0.054	0.739	0.204	0.206	0.054	0.739
Acetone	0.239	0.137	0.013	0.936	0.141	0.385	0.181	0.264	**0.490**	**0.001**
Xylene	0.177	0.275	0.181	0.264	0.174	0.283	0.140	0.388	0.103	0.528
Epichlorohydrin	0.123	0.449	0.053	0.746	0.121	0.465	0.107	0.512	0.237	0.141

[†]*P* values of less than 0.05 were considered statistically significant

mice which were exposed to various concentration of four different doses of VOCs mixture for consecutively 10 days at 2 h/day decreased significantly erythrocyte count (RBC), platelet (PLT) in peripheral blood in mice. While AST, ALT, and ALP increased significantly. Flow cytometry analysis also indicated that the number of splenic lymphocyte subpopulation cells decreased significantly. They over ally showed that inhalation of VOCs mixture affects liver and kidney function as well as some hematological parameters in mice.[16] In a more recent study, Beaudoin *et al*. showed the gestational effect of VOC exposure.

In the current study, a significant increase in serum triglycerides, total cholesterol, and LDL-C concentrations was observed in the exposed workers [Table 6]. The increased serum levels of these lipids could be attributed to decreased liver function, as mentioned earlier. Liver plays a crucial role in lipid metabolism. Thus, hepatocellular damage may lead to multiple dysfunctions such as impaired LDL secretion, alterations in β-oxidation, and pathways involved in the synthesis of fatty acids.[17]

VOCs are contained in a wide range of organic solvents and each component has unique toxic properties.[18] For instance, D'Andrea *et al*. (2014) studied the relationship between serum levels of benzene with liver enzymes in children following a flaring incident at the British Petroleum refinery in the Texas (USA). They observed that benzene-exposed children had remarkably higher levels of ALP, AST, and ALT compared with unexposed children. Their results

indicated that children exposed to benzene were at higher risk of developing hepatic disorders.[19] Furthermore, several studies have reported that high levels of xylene and toluene cause liver damage in humans.[9,20] The exact mechanism underlying liver dysfunction in exposure to VOCs is not clearly indicated yet. However, recently it has been shown that main pathogenic mechanisms responsible for liver dysfunction caused by VOC are: inflammation, dysfunction of cytochrome P450, mitochondrial dysfunction, and oxidative stress.[21]

We observed a significant correlation between serum ALT and styrene levels in the exposed workers. In agreement with our finding, Brodkin *et al*. (2001) showed a constant and linear relation between hepatic enzymes levels and environmental styrene.[22] In previous studies, the toxic effect of styrene on the liver of animal models has been reported.[23] Some of the styrene hepatotoxic effects are related to its transformation by hepatic enzymes. Styrene is metabolized in the liver and transformed into styrene oxide that is a toxic and potentially carcinogenic metabolite.[24] Styrene 7,8-oxide (SO), as a main metabolite of styrene, is known to reduce glutathione (GSH) levels both *in vivo* and *in vitro*.[25,26] Low levels of GSH were found related to increased lipid structure damage in the liver of rodents exposed sub-chronically either to styrene and/or SO.[27] In addition, Dare *et al*. (2004) reported that styrene and its metabolite, i.e., SO, can induce mitochondrial dysfunctions *in vitro*.[26] Also, Boccellino *et al*. (2003) have shown that SO induced a significant increase in caspase-3 activity, and stimulate apoptotic response in *vitro*.[25] According to the key role of the liver in glucose and lipid metabolism, the occurrence of apoptosis and mitochondria*l* dysfunctions could be associated with liver failure and lipid profile alterations in workers' blood. Taken together, our finding in line with previous study indicated that there is a close relationship between styrene levels in workplace and liver dysfunction.

In addition to styrene, a significant correlation was observed between ALT activity and benzene levels in the exposed workers. In the ambient area of the exposed workers, the benzene levels were about two times higher than threshold limit value–time-weighted average (TLV–TWA), as defined by American Conference of Governmental Industrial Hygienists.[28] The *in vivo* studies have shown that benzene can be a potential hepatotoxic agent.[29] This solvent can lead to decreased activity of antioxidants enzymes and occurrence of oxidative stress that can be defined as unbalance between the generation of reactive oxygen species (ROS) and the level of their consumption by antioxidants. This group of researchers showed that benzene intoxication increased the activities of liver enzymes (ALT, AST, and alkaline phosphatase) and the bilirubin level. Furthermore, benzene inhalation at 10, 30, and 50 ppm for 14 days in adult male rats enhanced NO production in both serum and liver.[29] In addition, Uzma *et al*. showed that there is a significant increasing in the concentration of benzene and its derivatives in both blood and urine were found in the workers compared with the controls. The levels of ROS and oxidized lipid were significantly elevated in the workers compared with the controls.[30] Other VOCs have been shown to induce DNA damage via oxidative stress.[31] Therefore, reduced antioxidant capacity of liver might be resulted in apoptosis of hepatocyte.[32,33] This potential mechanism could be related to the occurrence of liver dysfunction in subjects exposed to benzene.

Our study has several limitations, including the small number of participants that could, therefore, be regarded as a pilot study and also individuals' metabolic variations which could influence toxicity of VOCs.

Conclusions

The changes of specific liver enzyme, as well as serum lipid profile observed in operational employees in petrochemical company, indicate the harmful effects of VOCs, especially styrene and benzene, on the liver cells. Therefore, considering the known effects of these pollutants, proper safety and preventive strategies seem to be necessary for reducing staff exposure and prevention of complicated disease. In addition, further studies should be carried out on other routes and duration of exposure to demonstrate the exact effect of other chemical substances, which might also contribute to the health hazards in employees.

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Conflicts of interest

There are no conflicts of interest.

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