

## Research Paper

# The Oxidative Stress of Mercaptan Odorant Due to Occupational Exposure: Adverse Effects on the Cholinergic System



Rezvan Zendehtdel<sup>1</sup>, Shirin Seyed Ghoreyshi<sup>1\*</sup>, Fatemeh Rajabi<sup>1</sup>, Zohreh Amini<sup>2</sup>, Majid Mahdian Dehkordi<sup>2</sup>, Hakimeh Nouri Parkeštani<sup>2</sup>

1. Department of Occupational Health, Engineering and Safety, School of Public Health and Safety, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

2. Department of Research and Development, Chaharmahal & Bakhtiari Province Gas Company, Shahr-e-kord, Iran.



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### \* Corresponding author:

**Shirin Seyed Ghoreyshi, MD**

**Address:** College of Public Health, Shahid Beheshti University of Medical Sciences, Shahid Chamran Highway, Evin, Daneshjoo Square, Tehran, Iran.

**E-mail:** [shirin\\_s.ghoreyshi@yahoo.com](mailto:shirin_s.ghoreyshi@yahoo.com)

## ABSTRACT

**Background:** Tert-butyl mercaptan is one of the frequently used odorants derived from natural gases. It has been declared as a health hazard by the Occupational Safety and Health Administration (OSHA) in the USA. There is not much information available about the mercaptans long-term toxicity secondary to occupational exposure. This study was conducted to evaluate the oxidative stress caused by mercaptan odorant.

**Methods:** The inhalation exposure of 80 maintenance workers in a gas industry was evaluated, using NIOSH 2542 and samples analyzed by gas chromatography mass spectroscopy. Also, the administrative staff were selected as the unexposed workers with matching age and work experience compared to the exposed subjects. The lipid peroxidation and ferric reducing plasma ability (FRAP), was evaluated as oxidative stress biomarkers. The acetylcholinesterase activity was also assessed for the neurological risks.

**Results:** The tert-butyl mercaptan exposure was evaluated at average 0.01 ppm (0.005 to 0.15 ppm). There was oxidative stress in maintenance workers along with a significant increase in the lipid peroxidation, and a decrease in FRAP level ( $P=0.0001$ ). The acetyl cholinesterase activity was decreased in over half of the exposed subjects, and correlated significantly with the tert-butyl mercaptan level ( $r=-0.4$ ,  $P=0.026$ ).

**Conclusion:** There was a correlation between the inhibition of acetyl cholinesterase activity and the induction of oxidative stress. Based on the findings, the chronic occupational exposure to tert-butyl mercaptan was identified as a health hazard. Therefore, specific health care strategies should be developed to minimize the toxic effect of this chemical.

**Keywords:** Natural gas; Occupational exposure; Oil and gas industry; Oxidative stress; Sulfhydryl Compounds

## Introduction

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ercaptans are highly toxic, reactive, volatile, and corrosive gases. They are widely used in pharmaceuticals, pesticides [1], paper manufacturing, and in oil and gas refining industries [2]. Mer-

captans are natural gas odorants used primarily to alert about gas leaks. Tert-butyl mercaptan is a unique gas odorant, known for low odor threshold at the level of 0.1 part per billion (ppb). Natural gas odorants are utilized at a safe level for the public, but adding them to natural gas is a dilemma due to the level of exposure [3]. The occupational exposure to tert-butyl mercaptan has been iden-

tified as a health threat by the U.S. Occupational Safety and Health Administration (OSHA) provisions [4]. Irritation of eye and respiratory system [5] has been reported after exposure to tert-butyl mercaptan. Moreover, neural and mental symptoms have been reported due to exposure to this gas [6, 7]. A good example of the side effects is those reported due to an accident at Gulf South Natural Gas Pumping Station in Prichard, Alabama, USA, on July 27, 2012 [8]. The reported symptoms included nausea, headache, vomiting, inebriation, and agitated behavior in the subjects exposed to the gas [8].

Oxidative stress is responsible for the pathogenicity of various chronic diseases, such as neurodegenerative and chronic obstructive pulmonary disease (COPD) [9]. It is well known that oxidative stress occurs due to exposure to reactive oxygen species (ROS). This condition may also be caused by exposure to different physical agents, such as ionized radiation [10], heavy metals [11], organic solvents [12], and pesticides [13]. Furthermore, oxidative stress is a booster of the cholinergic effect secondary to tert-butyl mercaptan exposure. Organophosphates are metabolized to organic sulfides in the body [14] and related compounds, such as n-butyl mercaptan. They have inhibitory activity against acetyl cholinesterase [15] just like organophosphates. There are numerous reports on the oxidative stress as a toxic mechanism for the organophosphates' side effects [16]. Studies have shown that reduction of acetyl cholinesterase activity is the most toxic effect after exposure to organophosphates [17].

To date, limited research has been conducted on the long-term exposure of humans to tert-butyl mercaptan, which is categorized as a malodorous organo-sulphur chemical. There are various reports for the reactive oxygen species generation arising from exposure to organosulfur compounds [18]. Interestingly, some organosulphur compounds are believed to protect against reactive oxygen species [19]. However, the question remains that whether tert-butyl mercaptan plays a role in the oxidative stress or not, while the risk of its toxicity against human health has been investigated by limited studies [20]. This study was conducted specifically to investigate the oxidative stress and risk of cholinergic reaction secondary to the occupational exposure of people to tert-butyl mercaptan.

## Materials and Methods

### Study subjects

The maintenance workers of a natural gas company (n=80) were studied as the exposed population. Questionnaires about their demographic information, such

as work history, age, health condition, and smoking habits, were completed by the subjects. Eighty administrative subjects, who were not occupationally exposed to tert-butyl mercaptan or any other hazardous compounds, were matched with the exposed subjects, especially for their demographic parameters. All of the subjects had more than one year of work experience, and used the same diet for the breakfast and lunch that were provided by their employing institutions. In addition, they were asked not to use garlic for two weeks before their blood sampling. The subjects had no history of any diseases, based on their medical history. The study was approved by the Research Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.PHNS.REC.1397.55). At the end of their work shift, blood samples (5mL) were collected from each of the subjects and stored in a deep freezer until transferred to a medical laboratory for analyses.

### Occupational exposure assessment

The inhalation exposure to tert-butyl mercaptan was evaluated using gas chromatography mass spectroscopy (GC-Mass) method. The sampling was performed according to a NIOSH 2542 method [21]. Briefly, 25mm glass fiber filters with acrylic binder (SKC Company, Eighty Four, PA, USA), were impregnated with mercuric acetate before sampling. The air samples were prepared by an SKC pump, installed in the subjects' breathing zone for 8hr during their work shift. To prepare samples, tert-butyl mercaptan was desorbed by acidic solution from filters and was then extracted in dichloroethane, using liquid-liquid sample preparation. The Agilent 7890, GC-Mass combined with HP-5MS column (30m\* 0.25mm id, 0.25 $\mu$ m) and helium at the flow rate of 1mL/min were used to analyze the samples (Agilent Technologies, Inc.; USA).

The mass spectrometer was evaluated in electron impact mode (70eV) at a dwell time of 50 $\mu$ sec. Single ion monitoring (SIM) was selected in mass spectra for compound quantification in order to eliminate the matrix interference. The column was programmed at 0.3 $^{\circ}$ C/min and remained at 27 $^{\circ}$ C for 2 min and then switched to 150 $^{\circ}$ C at the rate of 50 $^{\circ}$ C/min, which stayed fixed for 5 min. The calibration curve was assessed between 5.3 and 180 $\mu$ g per sample at the limit of detection (LOD) of 0.86  $\mu$ g/sample. Two parameters were considered for the oxidative stress evaluation. Ferric reducing ability plasma (FRAP), as the antioxidant capacity, were evaluated. Plasma malondialdehyde (MDA), was estimated to represent the lipid peroxidation evaluation.

The MDA was assessed by high performance liquid chromatography (HPLC) equipped with an ultra-violet detector at 254nm [22]. For this assay, the plasma proteins were precipitated by HClO<sub>4</sub>. The HPLC system consisted of a Hitachi D-7000, with a Bondapak C-18 column (300 mm-4 mm I.D., 10 Åm). The chromatography was performed using a mobile phase of 30mM KH<sub>2</sub>PO<sub>4</sub> at pH4; methanol at the volume rate of 65:35% with the flow rate of 1ml/min. The calibration curve was evaluated, ranging from 1.09 µg/ml to 19.65 µg/ml with the LOD at 0.046. The FRAP was determined, using the method described by Benzie, et al. [23]. In this method, 2, 4, 6-tripyridyl-s-triazine (TPTZ) reacts with acetate buffer (pH 3.6) and FeCl<sub>3</sub>, and produced Fe<sup>++</sup> in blue color. The level of Fe<sup>++</sup> was determined by the spectrophotometer at 593nm. The acetyl cholinesterase activity was evaluated with human erythrocytes, using the Ellman method [24].

Acetylthio-choline iodide was selected as the substrate for the assessment of AChE activity. Quinidine (0.14mg/L) was used to eliminate butyryl choline esterase interference, in the blood samples for AChE activity measurement. Acetyl thio-choline iodide was used for this measurement as a substrate of acetylcholine esterase at the concentration of 75 mmol/L. Then, an indicator reagent (5, 5-dithiobis-2-nitrobenzoic acid; DTNB) was applied at the concentration of 0.127 mg/ml in phosphate buffer at pH 7.0. The acetyl cholinesterase activity was monitored at the absorbance level of 405 nm at 30 sec intervals every five minutes.

### Statistical analyses

The data were statistically analyzed, using SPSS software, v. 21, and the normality of variables was assessed, using Kolmogorov-Smirnov test. The parameter differences among the exposed subjects were determined, using student's t-test and Mann-Whitney U test based on the data distribution.

## Results

**Exposure to Tert-butyl Mercaptan:** The median exposure of the subjects to tert-butyl mercaptan was 0.01ppm (maximum=0.15 & minimum=0.005 ppm). The occupational exposure to the odorant was assessed in 10% of the administrative subjects. The results showed tert-butyl mercaptan was lower than the LOD in the unexposed group. The Mean±SD age of the workers were 37.3±6.5 years old with 10.9±5.9 years of work experience. The results indicated that the exposed and unexposed sub-

jects were fairly matched for their demographic characteristics (Table 1).

The maintenance subjects worked in the two groups of troubleshooting (n=42) and optimization tasks (n=38). In the first group, the workers fixed the leakage and changed filters and related elements. The second group arranged and installed gas regulators. The Mean±SD of the inhalation exposure to tert-butyl mercaptan was 0.02±0.04 ppm in the troubleshooting workers, and 0.014±0.016 ppm in the optimization task group (Figure 1). The results indicated that there were no significant differences for the occupational exposure to tert-butyl mercaptan between the troubleshooting and optimization task groups (P=0.14).

### Oxidative stress assessment

The results from the MDA evaluation indicated that there was a significant increase in the lipid peroxidation activities in the maintenance workers compared to that of the administrative staff (P=0.0001). The median level of MDA in the maintenance workers was 8.55µg/ml (range: 1.002 to 19.35 µg/ml). In the administrative staff, this parameter was 1.11 µg/ml (0.9 to 3.94 µg/ml). The FRAP level was significantly lower in the maintenance workers than in the control group (P=0.001), while the FRAP level was lower (0.44±0.520 µM) in the exposed than in the unexposed subjects (Table 2).

The results indicated that there was a significant relationship between the MDA level and the occupational exposure to tert-butyl mercaptan (P<0.05, r=0.488). However, there was no correlation among the age (P=0.564), work experience (P=0.646), and smoking habit (P=0.520), and the oxidative stress injuries documented between the two groups of workers.

### Acetyl cholinesterase activity evaluation

The data for the acetyl cholinesterase activity were not normally distributed. The median activity of acetylcholine esterase in the maintenance workers was 23.04 IU/L (min.=9.75 IU/L; max.=69.12 IU/L). There were significant reductions in the acetyl choline esterase activity between the exposed and unexposed subjects (P<0.02; Figure 2). There was negative correlation between the acetyl cholinesterase activity and the tert-butyl mercaptan exposure (r=-0.4, P=0.026), based on the Pearson's correlation test. Moreover, there was correlation between the inhibition of cholinergic activity and the induction of oxidative stress, as reflected by the MDA levels (Pearson's r=0.3; P=0.003).

**Table 1.** Characteristics of the studied groups

| Variables                                   | Mean±SD/Frequency |                      | P    |
|---|-------------------|----------------------|------|
|   | Maintenance Group | Administrative Group |      |
| Age   | 37.3 ±6.5         | 36.5±5.1             | 0.4  |
| Work experience                             | 10.9 ±5.9         | 9.4±5.5              | 0.1  |
| Smoking                                     | 9                 | 8                    | 0.08 |
| Inhalation exposure to tert-butyl mercaptan | 0.02±0.04         | 0.014±0.016          | 0.14 |

## Discussion

Tert-butyl mercaptan is a very volatile compound, mixed with the natural gas as an odorant to alert the consumer of gas leakage [25]. There is strong evidence in favor of routine health assessment for exposure to sulfur-containing compounds, such as hydrogen sulfide [26] and sulfur dioxide [27], in related occupations. However, little is known about the inhalation evaluation of such odorants. Determination of the occupational exposure of mercaptan in different industries may have an important role for health management of the workers. The current study investigated the occupational exposure to tert-butyl mercaptan via respiratory route in a population of workers employed by a gas industry. We also evaluated the neurological effects and symptoms of the oxidative stress in the maintenance workers at the same industry.

The inhalation exposure of workers to tert-butyl mercaptan ranged between 0.005 and 0.15 ppm in the maintenance workers of that gas industry. The time-weighted average (TWA) of tert-butyl mercaptan was 0.5 ppm, based on the OSHA's guidelines. The results demonstrated that exposure of the maintenance workers to tert-butyl mercaptan was lower than the occupational hazard standard. This was expected, since the maintenance employees worked on the gas transmission lines in the outdoors. It turned out that there was no significant difference between the troubleshooting staff and those involved in the optimization tasks for the exposure to the odorant gas.

Generally, in the gas industry, in the staff that optimized the transmission lines, gas leakage was the cause of their exposure. It appeared that the gas leakage was not so different between the two groups of workers that was why the inhalation exposure did not vary between the two groups of staff, i.e., troubleshooters versus the optimizers. This study was designed to evaluate the oxidative stress of tert-butyl mercaptan, by analyzing the ROS level as the reason for the adverse health effects [27]. There are contradictory reports on the ROS generation from sulfur-containing compounds. Hydrogen sulfide [28] and dimethyl sulfides [29] produce low ROS levels, while sulfur-containing pesticides have the potential to induce strong oxidative stress [30]. Sulfur mustard is known as an oxidating agent of proteins and lipids in the lung tissue [31].

This study evaluated the oxidative stress indices of FRAP and MDA levels and the oxidative properties of tert-butyl mercaptan in the subjects with the optimization and troubleshooting tasks in the gas industry. Based on the results, the tert-butyl mercaptan exposure in the studied occupations induced antioxidant defense. Also, the ROS generation was not influenced by such factors as age, work experience, and smoking, while tert-butyl mercaptan had its main effect on the oxidative stress. The negative correlation between acetyl cholinesterase activity and tert-butyl mercaptan ( $r=-0.4$ ,  $P=0.026$ ) suggests that by increasing odorant exposure, the enzyme activity decreased.

**Table 2.** The ferric reducing ability in the studied groups

| Groups         | FRAP Mean±SD ( $\mu$ M) |
|----------------|-------------------------|
| Maintenance    | 0.44±0.520              |
| Administrative | 0.48±0.048              |
| P              | 0.001                   |

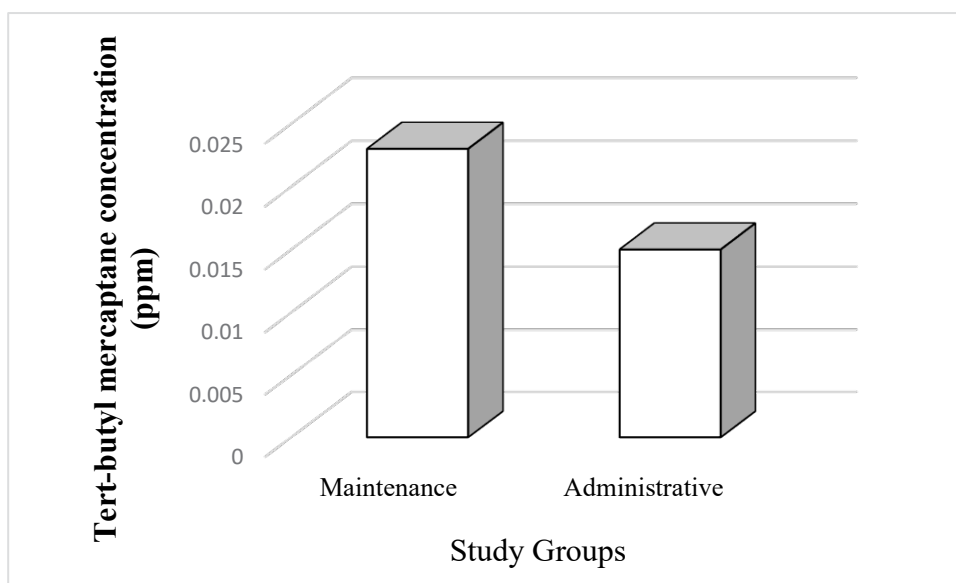


Figure 1. Occupational exposure to tert-butyl mercaptan between the groups

Some organosulphur components are derivatives of organophosphates [32]. However, evaluation of acetyl cholinesterase activity is a suitable marker for monitoring organophosphate exposure. The anticholinergic effect of organosulfur has been reported in another study earlier [33]. In the current study, there was a decrease in the cholinergic activity for the maintenance workers of the gas industry. There was a significant correlation between acetyl cholinesterase activity and tert-butyl mercaptan exposure, indicating the neurologic effect of this compound. It was found that cholinergic activity in the tert-butyl mercaptan exposure was increased. Based on these findings, acetyl cholinesterase activity is a relevant biological monitoring for gas odorant exposure.

The results confirmed the relationship between lipid peroxidation and acetyl cholinesterase activity. A previous study has also suggested correlation between acetyl cholinesterase activity and oxidative stress [34]. The basic level of acetyl cholinesterase activity was evaluated in unexposed subjects by 70% of the mean value. The results showed that acetyl cholinesterase activity was lower than the basic value in the 56.6 % of maintenance workers (24.5 IU/L). Moreover, the chance of a decrease in the acetylcholine esterase activity in exposed workers was two times higher than the unexposed groups.

**Limitation of the Study:** Low number of samples is a limitation of this study, which needs to be improved in future investigations.

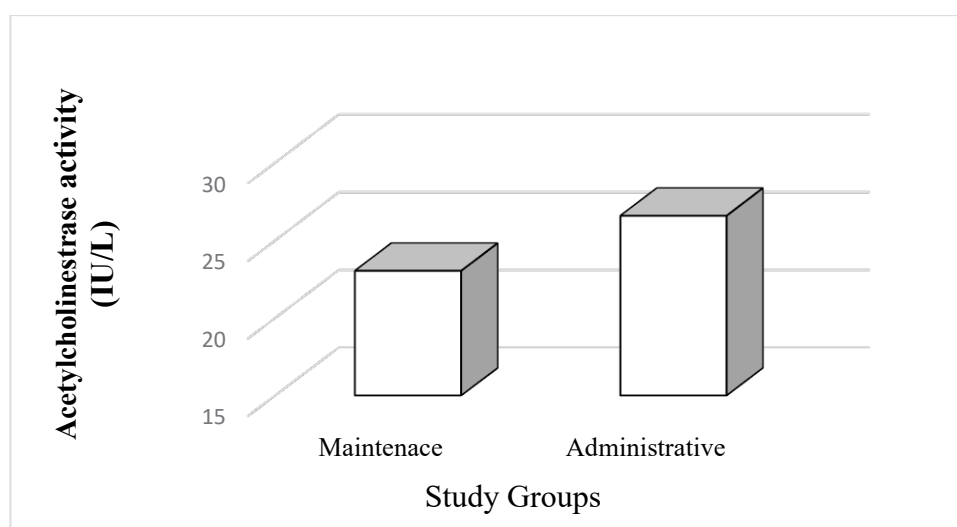


Figure 2. Acetyl choline esterase activity between the groups

**Recommendation for Future Studies:** Given the results, although the strong odor and irritation properties [35] of tert-butyl mercaptan is an important issue, the occupational health risk of mercaptan exposure should be paid ample attention. The assessment of butyryl cholinesterase activity and the adverse neurological effects are suggested in future studies.

## Conclusions

Based on the findings, there was a rise in the lipid peroxidation in the exposed subjects compared to those with administrative tasks. The ferric reducing level in maintenance workers, was low, while the ROS generation due to exposure to tert-butyl mercaptan was confirmed by our findings. Our data suggest that exposure to tert-butyl mercaptan leads to increased anticholinergic effects and oxidative stress. However; the relationship between lipid peroxidation and acetyl cholinesterase activity was highlighted. Finally, the health-risk evaluation of the workers due to exposure to tert-butyl mercaptan should be highly emphasized.

## Ethical Considerations

### Compliance with ethical guidelines

The study protocol was approved by Ethics Committee of Shaheed Beheshti University of Medical Science (IR.SBMU.PHNS.REC.1397.55).

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### Author's contributions

Supervision: Rezvan Zendehelel; Investigation, Data collection, and Data analysis: Shirin Seyed Ghoreyshi and Fatemeh Rajabi; Funding acquisition and Resources: Zohre Amini, Majid Mahdian Dehkordi and Hakime Nouri Parkes-tani; Writing – original draft, and Writing – review & editing: All authors. All authors approved the final version.

### Conflict of interest

The authors declared no conflict of interest.

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