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Human Sputum Interleukin-6 by Exposure to PM₁₀ among Bus Drivers in Klang Valley

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Abstract: Epidemiologic evidences suggest a positive association between elevated levels of Particulate Matter (PM) pollution and respiratory illness including acute and chronic lung diseases and respiratory symptoms. This study aimed to investigate the association between particulate matter 10 (PM₁₀) and induction of inflammatory mediators; Interleukin-6 (IL-6). A total of 56 bus drivers as exposed group and 56 administrative staff as comparative group in Klang Valley were involved in this study. Exposure of PM₁₀ was measured using Dust Trak Aerosol Monitor while ELISA technique was used for the analysis of IL-6. Questionnaire adapted from American Thoracic Society (ATS) was used to collect information on respondent's socio-economic status, working history, and respiratory symptoms. The results of socioeconomic status were showed that there were no significant differences found between the groups. The exposure level of PM₁₀ were significantly higher among the bus drivers ($t = 7.57$, $p < 0.001$) than to comparative group which the PM₁₀ was almost 4 times higher in bus drivers. Similarly, the concentrations of IL-6 were also found significantly higher among bus drivers with ($z = -2.28$, $p < 0.05$). A positive correlation was observed between the PM₁₀ and IL-6 among the exposed and the comparative group of the present study. Moreover, prevalence of respiratory symptoms among the bus drivers was significantly higher compared the administrative staff. In conclusion, the bus drivers have higher level of IL-6 and at higher risk for respiratory symptoms compared to comparative group due to the exposure to PM₁₀.

Key words: PM₁₀, IL-6, respiratory symptoms, bus driver

INTRODUCTION

There is a growing global concern on the negative health effects on human due to the elevated level of air pollution. Air pollution is identified as a major environmental and health problem by most of the developed and developing countries (Brunekreef and Holgate, 2002; Pope, 2000). Generally, people live in larger cities became a victim of this problem. They are highly exposed to air pollution due to the effect of rapid urbanization, which directly and indirectly affects the quality of urban air (Sydbom *et al.*, 2001). Air pollutants are substance in the air that can cause harm to humans and the environment. They may be natural or man-made and they are in the form of solid particles, liquid droplets or gases. Pollutants in the air are divided into various groups, including particulate matter, volatile organic compounds, endotoxin, metal, toxic gaseous and halogen compounds (Environmental Protection Agency

U.S.E.P.A., 2003). Among these pollutants, elevated concentration of particulate matters which is a complex mixture of small particles and liquid droplets was identified as the main contributor of the acute and chronic respiratory and cardiovascular diseases (Dockery, 2001; Donaldson *et al.*, 2005; Pérez *et al.*, 2007). Particulate matters can be categorized into coarse (PM₁₀), fine (PM_{2.5}) and ultrafine particles (UFP). The categories of particulate matter with a diameter less than 10 µm but greater than 2.5 µm are known as Particulate Matter 10 micron fraction (PM₁₀), a diameter less than 2.5 but greater than 0.1 µm is known as Particulate Matter 2.5 micron fraction (PM_{2.5}) and particles with a diameter of less than 0.1 µm are considered as the ultrafine particles (UFP). The size distinction is important as the particle size reflects in part, the penetration potential into the respiratory tract (Muller *et al.*, 2002; Churg *et al.*, 2002).

PM₁₀ are mostly composed of combustion-derived, carbon-centered particles with associated hydrocarbons

and metals. A number of the components of PM_{10} have been hypothesized to drive the toxicological effects in human body. The increases in PM_{10} concentration in ambient air were associated with attacks of airways disease and deaths from cardiovascular and respiratory causes (Atkinson *et al.*, 2001). Diesel-powered vehicles and engines become the main contributor of particulate matter in the urban air. Because the mass of particulate exhaust emission from diesel engines is generally about a factor of ten times greater than that of gasoline engines therefore, there has been more focus on the effects of diesel exhaust emission than gasoline emission (Sawyer and Johnson, 1995). Diesel engines also produce submicron soot particles per traveled distance is over 10 times greater than petrol engines and over 100 times higher than petrol engines fitted with catalytic converters (Zweidinger *et al.*, 1990).

Most of the studies done in recent years discovered that air pollution highly affect the human respiratory system. During inhalation the particulate matters are brought deeply into the lungs and are deposited in the alveolar sacs. The deposition of this particles, later provoke an inflammatory response, increased cytokines production and lung tumor (Oberdorster *et al.*, 2000; Nordenhäll *et al.*, 2000). The IL-6 is a multifunctional cytokine produced by a variety of cell types and is considered to contribute to the initiation and extension of the inflammatory process (Peters *et al.*, 1997). It exerts its many activities through the interaction with specific receptors which were expressed on the surface of target cells. The biologic activities of IL-6 include the stimulation of B- and T-cell growth and differentiation, production of acute-phase proteins, multilineage hematopoiesis, osteoclast formation, maturation of megakaryocytes and platelet production (Turgeon, 1996). IL-6 also plays a critical role in pulmonary inflammation and injury induced by exposure to environmental air pollutants. IL-6 deficiency was found to be associated with attenuated inflammation and injury in the lung. It has been proven by many previous studies that the exposure to PM_{10} induced the production of IL-6 (Pérez *et al.*, 2007; Brunekreef and Forsberg, 2005; Becker *et al.*, 2005). These studies were conducted to study the relationship between ambient air PM_{10} and lung health. They found that particulate matters were interacted with Alveolar Macrophages (AM) and airway epithelial cells.

A high and direct exposure of the particles normally correlated to areas with more traffic, crowded population and industrial areas. The particulate matter that has been produced by the diesel exhaust vehicles is a major contributor to urban air pollution (Environmental Protection Agencies U.S.E.P.A, 2003; Mulli *et al.*, 2002).

People are exposed to vehicular exhaust and air pollution in the air they breathe everyday. In Malaysia, the main source of particulate matter is automotive exhaust. Heavy diesel engines, buses, and trucks contribute approximately 50-60% of the traffic emission in the urban areas. According to Afroz *et al.* (2003), emissions from mobile source contribute to at least 50-75% of the total air pollution. Therefore, workers involved in transportation industry were highly exposed to the particulate matter where the workplace is also a site of exposure to the combustion derived PM_{10} . Moreover, air pollution due to the particulate matter inside the vehicles is relatively higher than the air pollution outside the vehicles. It has been identified that, the air pollution inside vehicles especially the commercial vehicle is 10 times higher than outside the vehicles (Marla, 1999). In consequence, commercial vehicles drivers such as bus drivers are at higher risk for being exposed to PM_{10} and higher risk in getting lung disease due to the inhalation of particulate matter from the diesel waste (Mukherjee *et al.*, 2003).

This present study aims to determine the relationship between Particulate Matter (PM_{10}) and IL-6 among the public bus drivers in Klang Valley. Due to the nature of the job, bus drivers were among the risk group being exposed to highly polluted air. Everyday, the bus drivers were exposed to a mixture of air pollutant from the diesel exhaust particles during their work time (Ye *et al.*, 1999).

MATERIALS AND METHODS

This is a cross sectional comparative study which was conducted at a commercial bus company that gives their services of public bus transportation in most areas in Klang Valley in 2008. The study population consists of 56 bus drivers who are exposed to relatively higher level of particulate matter and the comparative subjects were administration staffs working in office environment where the levels of exposure to particulate matter is relatively lower. The respondents were chosen randomly through the name list provided by the management. They were all male, nonsmokers, were between 20 to 50 years old, Malaysian nationality and without the history of chronic lung and respiratory diseases. All of the respondents were participated in PM_{10} exposure measurement and analysis of sputum IL-6 concentration. Questionnaires adapted from American Thoracic Society were used to obtain background information about the respondents. The questionnaire consists of variables such as socioeconomic status, working history, personal and family history of disease, status of workplace environment and usage of PPE (personal protective equipments).

Exposure assessment: For each respondent, the exposure level of PM₁₀ was measured for eight hours. DustTrak Aerosol Monitor was used to measure the particle concentrations of PM₁₀. DustTrak provided information on the concentration of an aerosol changes for different processes over time. During the exposure measurement, the instrument was placed within the driving zone of the bus drivers and working zone of the administrative staffs. For the measurement among the administrative staffs, DustTrak was placed away from the direct sources of PM₁₀ such as photocopy machine, printer and vacuum cleaner to avoid higher particles exposure from direct sources.

Measurement of human sputum IL-6: This study involves the use of sputum to detect human IL-6. The concentrations of IL-6 were analyzed using Enzyme-Linked Immunosorbent Assay (ELISA) according to the manufacturer's instruction. Sputum induction was performed by inhalation of isotonic saline solution (NaCl 0.9%) and the aerosols were produced by ultrasonic nebulizer. The sputum samples that collected from the respondents were ultracentrifuge for 90 min at 25100 rpm at 4°C. The supernatants were kept under -80°C until the samples were analyzed. Initially, 96 wells which were coated with capture antibody were added with supernatants. The IL-6 concentration was quantified after incubation with detection anti-body. The concentrations of IL-6 were compared with a standard curve for IL-6. The sputum samples were undergoing human sputum IL-6 analysis in the Chemical Pathological Laboratory, Department of Pathology, Universiti Putra Malaysia.

Statistical analysis: Data obtained from this study were analyzed using statistical software, Statistical Packages for Social Sciences (SPSS, version 13). Analysis was carried out using this software at different level. The normality test that used was, Kolmogorov Smirnov with a Lilliefors Significance level ($p < 0.05$) to identify of normal distribution. Univariate, bivariate and multivariate tests were used to analyze the variables of this study. The univariate statistical analysis were performed to determine the descriptive data on socio-economic information of the respondents including age, height, weight, and duration of work and education level of respondents. On the other hand, bivariate analysis (t-test) were performed to compare mean differences for

quantitative variables of this study and compare the current respiratory status of the respondents. Pearson correlation tests were conducted to determine the relationship between the exposure level of PM₁₀ and IL-6 level and to determine the relationship between the duration of work and IL-6.

Study ethics: The present study obtained approval from the Committee of Ethics of Faculty of Medicine and Health Sciences, Universiti Putra Malaysia. Permission to conduct this study was also obtained from the commercial bus company and the management of the administrative staffs. Respondents were explained about the purpose of this study and respondent's written consents were obtained prior to conduct the study. The privacy of information that were gathered were protected during all phase of study. Confidentiality was maintained at all times. Sputum sample was collected from the respondents after getting the respondent's permission.

RESULTS

Socio-demographic information: Result showed no significant differences observed between the exposed and comparative group in terms of age, height, weight, and duration of work (Table 1). The mean of age for the study group was 38.41 ± 4.87 years and for the comparative group was 37.02 ± 4.81 years. The median and inter-quartile range of working experience (years) for the exposed group were 5.50 ± 5.00 years while for the comparative group were 5.00 ± 4.50 years (Table 2).

Comparison of IL-6 level: Normality test with Kolmogorov Smirnov analysis were performed and the concentration of IL-6 was found not normally distributed. Therefore, Mann-Whitney U test was performed to compare the mean of concentration between exposed and comparative group. The results obtained showed, there was a significant difference was observed with z-value of -2.28 ($p < 0.05$). The median and interquartile range for

Table 1: Socio-economic characteristic of respondents

Variables	Study group	Comparative group	t-value	p-value
	(N = 56)			
Age (Years)	38.41±4.87	37.02±4.81	1.52	0.131
Height (cm)	167.23±6.50	168.89±6.44	-1.34	0.183
Weight (kg)	72.33±11.38	69.85±6.25	1.43	0.156

Values are expressed as Mean±SD

Table 2: Comparison of work experience and concentration of IL-6 among the respondents

Variables	^a Exposed group	^a Comparative group	z-value	p-value
	(Median±IQR)			
Working experience (Years)	5.50±5.00	5.00±4.50	-0.59	0.555
IL-6 level (pg m ⁻¹)	6.86±4.73	5.44±4.06	-2.28	<0.05*

*Significant at $p < 0.05$. ^a: N = 56

Table 3: Comparison of personal exposure level to PM₁₀

Variables	Study group (N = 56)	Comparative group	t-value	p-value
PM ₁₀ (mg m ⁻³)	0.095±0.064	0.028±0.014	7.57	<0.001**

Values are expressed as Mean±SD **Significant at p<0.001

Table 4: Comparison of respiratory disease symptoms among the respondents

Variables		Exposed n (%)	Comparative n (%)	χ ² value	p-value	Odds ratio	CI 95%
Cough	Yes	12 (85.7)	1 (14.3)	12.94	0.002*	15.80a	1.53-7.43
	No	44 (46.7)	52 (53.3)				
Phlegm	Yes	17 (90.0)	1 (10.0)	19.08	p<0.001*	23.25a	1.49-7.39
	No	39 (43.6)	52 (56.4)				
Chest Tightness	Yes	4 (80.0)	1 (20.0)	4.80	0.091	6.07	1.61-7.50
	No	52 (50.0)	52 (50.0)				
Wheezing	Yes	2 (75.0)	0 (25.0)	5.00	0.082	6.94	1.63-7.53
	No	54 (50.4)	53 (49.6)				

*Significant at p<0.05, a Significant at OR = 1, 95% CI

Table 5: Correlation between exposure to PM₁₀ and biomarkers among respondent

	Exposed group (n = 56)		Comparative group (n = 56)	
Exposure to PM ₁₀	r	p	r	p
IL-6	0.568	<0.001**	0.347	<0.01*

*Significant at p<0.05, **Significant at p<0.001

exposed and comparative groups were 6.86±4.73 (range: 2.314-47.355) and 5.44±4.06 (range: 0.75-24.5), respectively (Table 2). This indicates that the probability of the comparative group to get lung diseases is less than the bus drivers. Particle concentration in the ambient air highly influenced cytokine binding for all condition.

Comparison of personal exposure level of PM₁₀: In the present study, the mean of exposure level of PM₁₀ of the bus drivers was 0.095±0.064 mg m⁻³ while the comparative group was 0.028±0.014 mg m⁻³ (Table 3). This showed that the personal exposure level to PM₁₀ among bus drivers was almost four times higher than the administrative staffs.

Comparison of respiratory prevalence symptoms among the respondents: The respiratory symptoms studied in this present study were cough, phlegm, chest tightness and wheezing. Prevalence of respiratory symptoms among the respondents was collected from questionnaire adapted from ATS. The result from statistical analysis reveals that the prevalence of respiratory symptoms in exposed group was significantly higher compared to comparative group for cough and phlegm (Table 4). On the other hand, there is no significant difference in the prevalence of respiratory symptoms between two groups for chest tightness and wheezing. Prevalence of respiratory symptoms among bus drivers was significantly higher for cough (χ² = 12.94, p<0.01, OR = 15.80) compared to comparative group. Prevalence of phlegm among bus drivers also significantly higher with (χ² = 19.08, p<0.001, OR = 23.25) (Table 4).

Correlation between exposure level to PM₁₀ level and IL-6 concentration: Spearman Correlation test was performed to determine the relationship between PM₁₀ level and IL-6 concentration. According to the test performed, there was a significant correlation were found between exposure level of PM₁₀ and concentration of IL-6 among the exposed (r = 0.568, p<0.001) and comparative group (r = 0.347, p<0.01) (Table 5). This clearly showed that the level of PM₁₀ influenced the concentration of IL-6 among of the study respondents.

DISCUSSION

Socio demographic of respondents: Age was considered as important factor in present study as to understand the susceptibility to air pollutant-induced lung disease. In order to control the aging effects, the present study restricted to the respondents aged 20-50 years. The mean height of the study group was 167.23±6.50 m and mean height of the comparative group was 168.89±6.44 m. On the other hand, the mean weight was 72.33±11.38 and 69.85±6.25 kg, respectively among the study group and the comparative group.

From the result of this study, there were no significant differences found for duration of work between the groups. This is very important as the duration of work may influence the risk of getting lung diseases and respiratory symptoms. In line with this, Jones *et al.* (2006) found that the respiratory symptoms among the bus drivers were higher due to the increased duration of work. The results obtained in present study are in accordance with those reported by Bigert (2007) where the elevated cardiovascular diseases were observed among the bus drivers with longer duration of work (years).

Comparison of IL-6 level: Generally, the concentrations of IL-6 were found to be elevated among group that exposed to higher level of diesel exhaust particles

(Veranth *et al.*, 2008). In line with this, Mazzarella *et al.* (2007) suggested that the biological effects of Diesel Exhaust Particles (DEP) have negative effects on the human lung. The author also found that there was increased in the level of IL-6 in human lung after the exposure to diesel exhaust particles. This increased in IL-6 level is due to macrophages activity in human epithelial cells that exposed to diesel exhaust particles. As human exposed to PM especially of the DE, the macrophages in the epithelial lining will be activated for a clearance mechanism to eliminate the DE particle (Steenberg *et al.*, 2003). A variety of evidence is available with regards the exposure to DEP and IL-6. An increased in sputum IL-6 was reported by Nordenhäll *et al.* (2000) together with other biomarkers exposed to diesel exhaust particles.

The increased in the level of IL-6 was correlated with effects on the human airways. On the other hand, Turgeon (1996) well demonstrates the role of the proinflammatory cytokine IL-6 in pulmonary inflammation and injury induced by exposure to environmental air pollutants. This study also summarizes that IL-6 plays a critical role in the inflammatory response and injury in the lungs of mice following exposure to environmental air pollutants. These findings, well supports the results of the present study where the level of IL-6 among the bus drivers were higher compared to the comparative group due to the higher exposure to UFP among bus drivers.

Comparison of personal exposure level of PM₁₀: In a study in Prague, Czech Republic, the exposure level of bus drivers was reported higher than the matching control of administrative workers. The mean personal exposure to PM₁₀ of the bus drivers was 38.9 ± 8.2 while the mean level of controls was 24.1 ± 6.5 . Location with denser traffic always related to higher level of air pollution particularly PM₁₀. They are mainly produced by incomplete combustion of diesel engines. A similar observation was found by Fang *et al.* (2008) which the mean ambient PM₁₀ level in an area abutting highway was 0.108 mg m^{-3} . This is also consistent with the previous investigation in Helsinki Metropolitan area, showing a significant higher exposure to PM₁₀ in high traffic area (Aarnio *et al.*, 2008). The main objective of the author was to analyze and evaluate PM₁₀ pollution in Helsinki Metropolitan area. Out of six areas where the measurements were done, two of them were urban traffic area. The mean PM₁₀ concentration in these two area were 0.097 mg m^{-3} and 0.137 mg m^{-3} , respectively for the area of Toolo and Vallila (Aarnio *et al.*, 2008).

On the other hand the mean personal exposure level of comparative group of the present study was

0.027 mg m^{-3} . In addition, a study done by Lee *et al.* (2002) in Hong Kong to determine the inter-comparison of air pollutants concentration in different indoor environments in Hong Kong. According to the results of air pollutants, he found that the average PM₁₀ level of office environment was less than 0.050 mg m^{-3} . According to Environmental Protecting Agencies U.S. E.P.A (2005) exposure to the indoor air pollutants inside buses will lead to adverse health effect include acute and chronic effects. The large fraction of combustion from the diesel engines which can be found inside buses are particulate matters (PM₁₀, PM_{2.5} and UFP), nitrogen dioxide, carbon monoxide and volatile organic compounds (VOCs). Acute health effects will appear after a single, high dose exposure or repeated exposures, include irritation of the eyes, nose, and throat, headaches, dizziness, fatigue, cough, phlegm and runny nose. Meanwhile, long term health effects will occurred only after long or repeated periods of exposure and it will cause respiratory diseases, immune systems disorder and even cancer. Numerous studies have been done and found that the exposure level of indoor PM₁₀ is relatively higher compared to the outdoor exposure.

Comparison of respiratory disease symptoms among the respondents: As shown in the results, the risk of the bus drivers to develop cough was almost thirteen times higher, phlegm was almost twenty times higher than the risk of the comparative group to develop these respiratory symptoms. The increased in air pollution due to the increased in combustion from industrial, commercial and personal activities have associated with a wide range of effects, both short-term and long-term on human health. Many epidemiological studies have demonstrated a strong association between exposure to particulate matter and respiratory symptoms. This includes the increased hospitalization for respiratory disease and increased incidence of respiratory symptoms, including coughing, wheezing, difficulty breathing and phlegm production. Furthermore, it is reported that workers exposed to diesel exhaust have an increased prevalence of cough, itching, burning, watering eyes, difficult breathing, chest tightness and wheeze. They also added that particulate component is important in the cytokine response induced by air pollution. According to Mukherjee *et al.* (2003) the workers involved in transportation such as commercial bus drivers are at higher risk to develop lung disease. This is due to the inhalation of particulate matter from the diesel waste.

This is well described in the study conducted by Joad *et al.* (2007) aimed to study the literatures associated with air pollutants and respiratory symptoms

including cough and wheeze. In conclusion, they found that the exposure to particulate matter and other mixed pollutants increase the episodes of cough compared to wheeze. On the other hand, wheezing was increased with exposure to irritant gases. Qian *et al.* (2004) reported that there were positive association between the long term exposure to ambient air pollutants and respiratory symptoms and illness prevalence among children in four district cluster. The study examine the association between ambient air pollutant mixtures including PM_{2.5}, PM₁₀, total suspended particles (TSP), SO₂ and NOx and six respiratory symptoms namely cough, phlegm, cough with phlegm, wheeze, asthma and bronchitis. As describe in their result, the higher concentration of ambient air pollutant were observed in the Cluster 4. In addition, the prevalence of the six respiratory symptoms was reported significantly higher in the Cluster 4. These findings are consistent with the outcome of the present study.

Correlation between exposure level to PM₁₀ level and IL-6 concentration: Experimental human exposure studies which been carried out using exposure chamber also demonstrated, elevated level of PM exposure provoked biomarkers concentration. Human induced sputum study conducted using two groups of non-smoker subjects, where a group was exposed to Diesel Exhaust (DE) and the control group was exposed to normal air. The results have shown an increase in the concentration of IL-6 in the sputum of the subjects who were exposed to DE than the subjects exposed to normal air (Nordenhäll *et al.* 2000). It is reported the circulating levels of IL-6 were elevated in subjects exposed to high levels of PM₁₀ during an episode of acute air pollution. They found that the cytokine induced a systemic response that have an important role in the pathogenesis of the cardiopulmonary adverse health effects associated with atmospheric pollution.

The elevated level of the cytokine in this study such as IL-6 provoked the production proinflammatory acute phase proteins and stimulation of the bone marrow. Similar conclusion also reported by Becker *et al.* (2005) whose research was conducted to understand the relationship between ambient air Particulate Matter (PM) and lung health. Their particulate matter parameters were PM₁₀ and PM_{2.5} while the biomarkers were IL-6, IL-8 and TNF. These particulate matters were interacted with Alveolar Macrophages (AM) and airway epithelial cells *in vitro* and the production of these biomarkers were observed. As a result, these particles provoked production of these cytokines. Moreover, the present study also supported by the evidence found in the study conducted by Soukup and Becker (2001). Their research

was focused on the soluble and insoluble particulate matter namely water soluble PM₁₀, insoluble PM₁₀, soluble PM_{2.5} and insoluble PM_{2.5} and the effects on the cytokine production of AM. It was observed that the exposed AM produces more IL-6. Specifically, insoluble PM₁₀ produces more IL-6 compared to other particles. Finding of the current study also supported by Monn and Becker (1999) investigated the stimulation of human and rat AM by urban air particles. They concluded that the inhaled particles, with a mass median aerodynamic diameter <10 µm could provoked more inflammatory effects compared to larger particles. They found that this range of particles could reach the lower respiratory tract where they are phagocytized by AM and produced proinflammatory cytokines. Finally, they reported that the exposure to PM₁₀ induces the production IL-6.

CONCLUSIONS

There should be no doubt to the danger of particulate matter exposure which can lead to the adverse human respiratory health. The present study revealed that the significantly higher concentration of biomarker and prevalence of cough and phlegm among the bus drivers in Klang Valley, were mainly contributed by the higher levels of personal exposure to Particulate Matter (PM₁₀). In addition there were significant relationship observed for the level of PM₁₀ and concentration of IL-6 which described the dose response relationship between the particulate and biomarker. Moreover, prevalence of respiratory symptoms among bus drivers is significantly higher than the comparative group. All these findings well describe that the diesel exhaust PM₁₀ is the main source of air pollution exposed by the bus drivers and they are the most vulnerable group of this PM₁₀ exposure. Thus, more control measures has to be taken to control the exposure and increase their health status. The current study only found the relationship of PM₁₀ exposure and IL-6, so more intense studies should be carried out in the future to increase and widen the knowledge of particulate exposures and the relationship of biomarkers. In addition, future studies should include more variables in their study including other pollutants and biomarkers.

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