UNIVERSITI PUTRA MALAYSIA

ASSOCIATION BETWEEN INDUSTRIAL AIR POLLUTANT EXPOSURE AND CYSTEINYL LEUKOTRIENES LEVEL AMONG SCHOOL CHILDREN IN KEMAMAN, MALAYSIA

NUR FASEEHA BINTI SUHAIMI

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By

NUR FASEEHA BINTI SUHAIMI

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

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Chairman : Associate Professor Juliana Jalaludin, PhD
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Industrial activities contribute to atmospheric pollution either directly or through background concentrations. The effects of industrial air pollution are pernicious especially to children due to their developing respiratory system. Although associations between short term and long term exposure to air pollutants with various health effects have been observed, their connections are complex and difficult to be explained. This study aims to determine the association between industrial air pollutants (PM_{10}, $PM_{2.5}$, NO_2, SO_2) exposure on cysteinyl leukotrienes (CysLTs) level among school children in Kemaman district. Secretion of CysLTs as inflammatory mediator was explored in this study to understand the connection between exposure to air pollutants and the concentration of CysLTs secreted to indicate the magnitude of exposure. A cross-sectional comparative study was conducted at selected primary schools in Kemaman with respondents chosen among those who fulfilled the inclusion criteria. Exposed schools were determined from those located within 5 km radius from an industrial area, whereas comparative schools were determined from those located more than 5 km radius from an industrial area with less traffic. Questionnaires adapted from American Thoracic Society and International Study of Asthma and Allergies in Childhood were used to determine respiratory symptoms, history of exposure and demographic background. Special equipment were used for exposure monitoring of the air pollutants in schools and residences. CysLTs were measured as biomarker of mediator following inflammation by using ELISA. Comparison between the two areas showed significant differences were found between cough, phlegm and wheezing. Exposed group's exposures to PM_{10}, $PM_{2.5}$, SO_2 and NO_2 in schools and residences were significantly higher than comparative group's exposures. Exposed group's CysLTs level was also higher than comparative group's CysLTs level with significant difference. Cough was revealed to have a significant association with all air pollutants measured in the schools, also SO_2 and NO_2 in residences. Phlegm was only significantly associated with SO_2 in schools, whereas wheezing was significantly associated with PM_{10}, SO_2 and NO_2 in schools. CysLTs had significant associations with PM_{10}, $PM_{2.5}$, SO_2 and NO_2 in schools, also with $PM_{2.5}$, SO_2 and NO_2 in residences. Results from Multiple Linear Regression shows that the most significant factors associated with level of CysLTs are

SO_2 in schools, $PM_{2.5}$ and NO_2 in residences, whereas results from Multiple Logistic Regression shows the most significant predictors of CysLTs concentration are SO_2 in schools, $PM_{2.5}$ in residences, and distance of residences from factory. On the whole, school children exposed to higher concentration of industrial air pollutants may potentially increase their level of CysLTs. The findings provide fundamental aspects relevant to future interventions to healthy children living near an industrial area from the environmental scope.

Keywords: PM_{10}, $PM_{2.5}$, SO_2, NO_2, Cysteinyl Leukotrienes

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Master Sains

HUBUNGAN ANTARA PENDEDAHAN TERHADAP PENCEMAR UDARA INDUSTRI DAN PARAS CYSTEINYL LEUKOTRIENES KANAK-KANAK SEKOLAH RENDAH DI KEMAMAN, MALAYSIA

Oleh

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Jun 2016

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Aktiviti perindustrian menyumbang kepada pencemaran udara sama ada secara langsung atau melalui kepekatan persekitaran. Kesan-kesan pencemaran udara perindustrian adalah memudaratkan terutamanya kepada kanak-kanak. Walaupun hubungan antara pendedahan jangka pendek dan panjang terhadap pencemar udara dengan pelbagai kesan kesihatan telah dilihat, hubungan mereka adalah kompleks dan sukar untuk dijelaskan. Kajian ini bertujuan untuk mengetahui hubungan antara pendedahan terhadap pencemaran udara perindustrian (PM_{10}, $PM_{2.5}$, NO_2, SO_2) ke atas paras cysteinyl leukotrienes (CysLTs) dalam kalangan kanak-kanak sekolah rendah di Kemaman, Terengganu. Rembesan CysLTs sebagai pengantara keradangan telah diterokai dalam kajian ini untuk memahami hubungan antara pendedahan kepada pencemaran udara dan kepekatan CysLTs yang dirembeskan untuk menunjukkan magnitud pendedahan. Satu kajian perbandingan keratan rentas telah dijalankan di sekolah-sekolah rendah terpilih di Kemaman dengan responden dipilih dalam kalangan kanak-kanak yang memenuhi kriteria pemasukan. Sekolah terdedah ditentukan daripada sekolah yang terletak dalam 5 km dari kawasan industri, manakala sekolah perbandingan ditentukan daripada sekolah yang terletak lebih daripada 5 km dari kawasan perindustrian dengan trafik yang sedikit. Soal selidik yang diadaptasi daripada American Thoracic Society dan International Study of Asthma and Allergies in Childhood telah digunakan untuk menentukan simptom pernafasan, sejarah pendedahan dan latar belakang demografi. Peralatan khas telah digunakan untuk memantau pendedahan pencemaran udara di sekolah-sekolah dan kediaman. CysLTs telah diukur dengan menggunakan ELISA sebagai penanda bio pengantara berikutan keradangan. Perbandingan antara kedua-dua kawasan menunjukkan perbezaan yang signifikan ditemui antara batuk, kahak dan nafas berdehit. Pendedahakan kumpulan terdedah kepada PM_{10}, $PM_{2.5}$, SO_2 dan NO_2 di sekolah dan kediaman adalah lebih tinggi daripada pendedahan kumpulan perbandingan. Paras CysLTs kumpulan terdedah juga lebih tinggi daripada paras CysLTs kumpulan perbandingan dengan perbezaan yang ketara. Batuk yang didapati mempunyai hubungan yang signifikan dengan semua bahan pencemar udara yang diukur di sekolah, juga SO_2 dan NO_2 di kediaman. Kahak hanya mempunyai perkaitan ketara hanya dengan SO_2 di sekolah, manakala nafas

berdehit mempunyai berkaitan ketara dengan PM_{10}, SO_2 dan NO_2 di sekolah. CysLTs mempunyai perkaitan yang signifikan dengan PM_{10}, $PM_{2.5}$, SO_2 dan NO_2 di sekolah, juga dengan $PM_{2.5}$, SO_2 dan NO_2 di kediaman. Hasil daripada Regresi Linear Berganda menunjukkan faktor paling signifikan yang dikaitkan dengan paras CysLTs ialah SO_2 di sekolah, $PM_{2.5}$ dan NO_2 di kediaman, manakala hasil daripada Regresi Logistik Berganda menunjukkan faktor paling signifikan yang dikaitkan dengan paras CysLTs ialah SO_2 di sekolah, $PM_{2.5}$ di kediaman, dan jarak kediaman dari kilang. Secara keseluruhannya, kanak-kanak sekolah rendah yang terdedah kepada kepekatan pencemar udara industri yang lebih tinggi berpotensi untuk meningkatkan paras CysLTs mereka. Dari skop persekitaran, hasil kajian ini menyediakan aspek asas berkaitan dengan intervensi pada masa hadapan kepada kanak-kanak sihat yang tinggal berhampiran kawasan perindustrian.

Kata Kunci: PM_{10}, $PM_{2.5}$, SO_2, NO_2, Cysteinyl Leukotrienes

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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This is to confirm that:

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<	Less Than
>	More Than
≥	At Least
5-HPETE	5-hydroperoxyeicosatetraenoic Scid
5-LO	5-lipoxygenase
8-OHdG	8-hydroxy-2'-deoxyguanosine
8-oxodG	8-Oxo-2'-deoxyguanosine
$\mu g/m^3$	Microgram per Metre Cube
ABC	ATP-binding Cassette
ATS	American Thoracic Society
B	Regression Coefficient
CC16	Clara Cell Protein
CDC	Centres for Disease Control and Prevention
CI	Confidence Interval
CO	Carbon Monoxide
CO_2	Carbon Dioxide
COPD	Chronic Obstructive Pulmonary Disorder
CysLTR1	Cysteinyl Leukotriene Receptor 1
CysLTR2	Cysteinyl Leukotriene Receptor 2
CysLTs	Cysteinyl Leukotrienes
DOSH	Department of Occupational Safety and Health
ELISA	Enzyme-Linked Immunosorbent Assay
GPCRs	G-protein-Coupled Receptors
HRP	Avidin-Horseradish Peroxidase
IAQ	Indoor Air Quality
IL-10	Interleukin 10
IL-12p40	Interleukin 12p40
IL-6	Interleukin 6
IL-8	Interleukin 8
IQR	Interquartile Range
ISAAC	International Study of Asthma and Allergies in Childhood

km	Kilometre
L/min	Litre per minute
LTA_4	Leukotriene A_4
LTB_4	Leukotriene B_4
LTC_4	Leukotriene C_4
LTC_4S	Leukotriene C_4 Synthase
LTD_4	Leukotriene D_4
LTE_4	Leukotriene E_4
m	Metre
MAAQS	Malaysia Ambient Air Quality Standard
MAPI	Malaysian Air Pollution Index
MCE	Mixed Cellulose Esters
mL	Millilitre
MOE	Ministry of Education
ng/mL	Nanogram per millilitre
NIOSH	National Institute for Occupational Safety and Health
NO	Nitric Oxide
NO_2	Nitrogen Dioxide
NO_x	Oxides of Nitrogen
O_2	Oxygen
O_3	Ozone
OD	Optical Density
pg/mL	Picogram per Millilitre
PM_{10}	Particulate Matter with up to 10 Micrometres Aerodynamic Diameter
PM_4	Particulate Matter with up to 4 Micrometres Aerodynamic Diameter
$PM_{2.5}$	Particulate Matter with up to 2.5 Micrometres Aerodynamic Diameter
PM_1	Particulate Matter with up to 1 Micrometre Aerodynamic Diameter
ppb	Parts per Billion
ppm	Parts per Million
PR	Prevalence Ratio
PVC	Poly Vinyl Chloride
SD	Standard Deviation
SE	Standard Error
SO_2	Sulphur Dioxide

SPSS	Statistical Package for Social Science
TATIUC	TATI University College
TNF-α	Tumour Necrosis Factor Alpha
UPM	Universiti Putra Malaysia
UPSR	*Ujian Penilaian Sekolah Rendah* (Primary School Assessment Test)
URTI	Upper Respiratory Tract Illnesses
USEPA	United States Environmental Protection Agency

CHAPTER 1

INTRODUCTION

1.1 Background

Malaysia is a developing country and is aiming towards establishing a developed nation by year 2020. One of the ways to achieve the 2020 nation is by focusing on the economic growth especially industrialisation, which generates more income to the country. The technologies in industries located in Malaysia are less advanced when compared with the technologies in industries located in developed countries. Many of the industries in Malaysia are receiving technologies transferred from those developed countries due to looser legislation and environmental controls. Furthermore, Malaysia is rich with natural resources that can generate profits in a long run such as oil and gas industry. It also has a large number of small-scale industries apart from the sprouting technology-based industries. Industrialisation is a key to a growing and profitable economy, thus it is bringing people out of poverty. However, it is also bringing up a health issue regarding adverse health effects through the release of malodourous air pollutants.

Air pollutants come from various sources and they can be divided into several categories: particulate matter and gases, primary and secondary, indoor and outdoor. Particulate matter comes in numerous sizes, compositions, and differ in what compounds are attached to them, also produced by many sources. Two common groups of particulate matter include particulate matter with up to 10 micrometres aerodynamic diameter (PM_{10}) and particulate matter with up to 2.5 micrometres aerodynamic diameter ($PM_{2.5}$), two parameters which will be the first and second air pollutants of interest for this study. As for gases, examples of such pollutants include carbon monoxide (CO), sulphur dioxide (SO_2) and oxides of nitrogen (NOx). SO_2 is the third air pollutant of interest for this study. It is formed when sulphur or compounds that contain sulphur are burned in air. A primary pollutant is an air pollutant that is emitted directly from a source, either a stationary source or a primary source. Meanwhile, a secondary pollutant is not directly emitted as a primary pollutant, but forms when primary pollutants react in the atmosphere (Ismail, 1996). An example of a secondary pollutant is nitrogen dioxide (NO_2), which is formed when nitrogen oxide (NO) combines with oxygen (O_2) in the air. NO_2 is the fourth air pollutant of interest for this study.

The health effects of air pollutants were first observed after the massive smog episodes in Meuse Valley, Belgium in 1930 (Nemery, Hoet & Nemmar, 2001) and had awakened people about this issue since the London smog episode in December 1952 (Bell, Davis & Fletcher, 2008). Today, various studies are still continuous on the harmful health effects of air pollutants. Air quality is an important issue in human health because man could only last a few minutes without air. Thus, inhaling polluted air can cause adverse acute or chronic health effects. These air pollutants could affect the lungs and respiratory system, aside from being taken up by the blood and pumped all around the body. Exposure to the air pollutants may initially cause throat irritation and breathing difficulty, whereas severe health problems could be developed at the later stage particularly for the high risk group. This group include children and the elderly, people with respiratory diseases such as asthma, chronic obstructive pulmonary disorder (COPD), cystic fibrosis and pneumonia who have shown to be particularly vulnerable to the effects of air pollutants (Clark *et al.*, 2010; Delfino, Staimer & Gillen, 2006). People who live near an industrial area, who are highly exposed to air pollution due to the economic growth and urbanisation that is going around the area are also considered as high-risk group. Moreover, there are also road transportation vehicles such as diesel-powered lorries which contribute to the air pollution in the ambient air near an industrial area.

Although associations between short term and long term exposure to air pollutants with various health effects have been observed (Vattanasit *et al.*, 2014; Dobreva *et al.*, 2013), their connections are complex and difficult to be explained. Depending on the size of the pollutants, some of them could deposit anywhere along the respiratory tract or penetrate deep in the gas exchange region. The deposition of particulate matter for example, could trigger inflammatory responses via oxidative and toxic compound imported (Vattanasit *et al.*, 2014) on their surface, which will cause alveolar activation and acute inflammation (Hiraiwa & van Eeden, 2013). Furthermore, it also activates the production of biological markers, also known as biomarkers, which can be detected in biological fluids, as proposed for this study. The biomarkers released further aggravate the defence mechanisms in the airways, which include local and systemic inflammation.

Air pollution is not the only source that is upsetting respiratory health. In countries with four seasons, climate change may also pose allergic reactions, thus affects respiratory health. Other major contributors include tobacco smoke, humidifier, age of housing units, socioeconomic factors, sensitising agents (Vandenplas, 2011), allergens, moisture or mould, and endotoxin (Mendell, 2007). As for the levels of the air pollution emitted by industrial areas, the values depend on the season and weather in that area. The goal of this study is to get the baseline data on industrial air pollutants exposure level among school children living near an industrial area in Kemaman and to study the association of air pollutants exposure with the respiratory health among the school children living near an industrial area in Kemaman.

1.2 Problem Statement

The exposure levels to industrial air pollutants in developing countries are usually higher than that in developed countries. The air pollution control in developed countries is stricter, and resident areas are usually far from industries. Malaysia is one of the developing countries, which is not exceptional to have air pollution problems. Unfortunately, Ministry of Health Malaysia did not publicly release information on the statistics of people with respiratory symptoms, who are affected by air pollution in both state and national level each year. Therefore, it is hard to say whether air pollution problem has improved, worsened or remained the same over the past few years. During dry season, when the weather is dry and hot, the air quality is quite poor that leads to forest fire outbreak in certain areas. The prevalence of respiratory problems are statistically significant with PM_{10}, $PM_{2.5}$, SO_2 and NO_2 concentrations (Labelle, Brand, Buteau, & Smargiassi, 2015; Nazariah, Juliana & Abdah, 2013; Dobreva *et al.*, 2013; Clark *et al.*, 2010).

Epidemiological studies have discovered that exposure to high concentrations of air pollutants contribute to many serious respiratory conditions. According to a Harvard study, about 60,000 mortality cases are estimated annually from exposure to particulate air pollution (Morgan, 2003). Diseases of the respiratory system ranked the third (11.84%) among the top ten principal causes of hospitalisation in both government and private hospitals in Malaysia (Health Facts 2015, 2015). They are also the second (18.19%) among the top ten principal causes of death in government hospitals in Malaysia (Health Facts 2015, 2015). Two studies reported the association between PM_{10}, $PM_{2.5}$, SO_2 and NO_2 concentrations, and respiratory symptoms among primary school children who live near an industrial area (Ayuni, Juliana & Ibrahim, 2014; Ithnin *et al.*, 2013). They have demonstrated PM_{10}, $PM_{2.5}$, SO_2 and NO_2 concentrations may increase risk of getting respiratory symptoms.

Traffic and industrial air pollution have long been recognised as the crucial external causes of respiratory problems (Latif *et al.*, 2011; Azmi, Latif, Ismail, Juneng & Jemain, 2010). The problem is expected to grow in the coming years with the desire of local and foreign investors in Malaysia to achieve the establishment of Malaysia as an advanced industrialised nation by the year 2020. The federal government began setting standards for ambient air quality to protect citizens. These industrial activities are strictly regulated under the Environmental Quality Act 1974, which includes restriction on pollution of the atmosphere (Environmental Quality Act 1974, 2006). Industrial and residential areas are usually separated, but air pollutants from these industrial activities travel over long distances to the surrounding areas. Therefore, industrial activities contribute to atmospheric pollution and poor air quality either directly or through background concentrations. Even though the industries in Malaysia are incomparable to the Western standards in term of industrial production and capacity, Malaysians should still be concerned on the cumulative impacts of air pollution that these industries could generate.

Children are particularly vulnerable due to their respiratory organ systems that are still growing, besides inhaling a larger volume of air per body weight. Since they inhale more air per seconds than adults do, they inhale more air pollutants as well, if present. Children are at risk of exposure because there are residential areas and schools near the industrial areas, which provide point source of industrial air pollutants. With other factors such as poor ventilation and wind speed, it is a concern that outdoor air pollutants from industrial activities penetrate indoors, thus causing indoor air pollution in neighbouring buildings.

Besides that, medical services and medicines to attend respiratory problems require money. Malaysians are considered fortunate to have access to medical services and medicines at the minimum price of RM1 at government clinics and hospitals. Since specific environmental factors are known to induce respiratory illness, attention and early intervention to these environmental conditions could greatly help in reducing these respiratory problems among primary school children. For this study, the target environmental factor is industrial air pollutants released by factories and plants in Kemaman.

Biomarkers have been utilised within clinical research studies of asthma to classify samples of the population for further study. Some of the biomarkers have been validated to be used as asthma biomarkers; most of the new biomarkers are still emerging with ambiguous applicability and lack of standardisation.

On the other hand, cysteinyl leukotrienes (CysLTs) were found to play a role in the pathophysiology of allergic inflammation of the upper and lower airways (Ogawa and Calhoun, 2006). Induced sputum is selected in sampling the CysLTs from the airway due its efficiency in yielding significant protein and cells for analysis compared to other samples, such as urine, serum or saliva. The administration of CysLTs in airway inflammation study is also relatively new in Malaysia.

1.3 Study Justification

Air pollution is a significant health problem in Malaysia. Malaysians experience haze quite a few times in a year, and air pollution problem to those who live in urban areas or near industrial areas. Release of gases from industries that produce chemicals, plastics, automobiles and many other products has created industrial pollution (Morgan, 2003). The target group for this study were school children living near an industrial area in Kemaman. Meanwhile, the target pollutants were PM_{10}, $PM_{2.5}$, SO_2 and NO_2. Short term exposure to these pollutants may cause respiratory problems such as cough and chest tightness. On the other hand, long term exposure to these pollutants remains largely unknown and thus, leaving a gap for more studies to be conducted on this matter.

With wind speed, outdoor air pollutants could travel over long distances to the surrounding areas. These pollutants then penetrate indoors, thus causing indoor air pollution in adjacent buildings such as schools and houses. It is a concern that the school children living near an industrial area is having constant exposure to industrial air pollutants. Therefore, this concern had initiated a study to be conducted among community living nearby an industrial area to know how exposures to industrial air pollutants could affect the respiratory health among the children. To easily understand the concept of the research that is proposed in this study, think of air pollutants as foreign particles that are trying to invade human. If human's immune system works well, inflammation will attempt to remove them. This can be proven by detection of inflammatory protein. In order to study the magnitude of exposure to air pollutants, the researcher examined the relationship between airway inflammation biomarkers and air pollutants. A better figurative representation of this study is as shown in **Figure 1**.

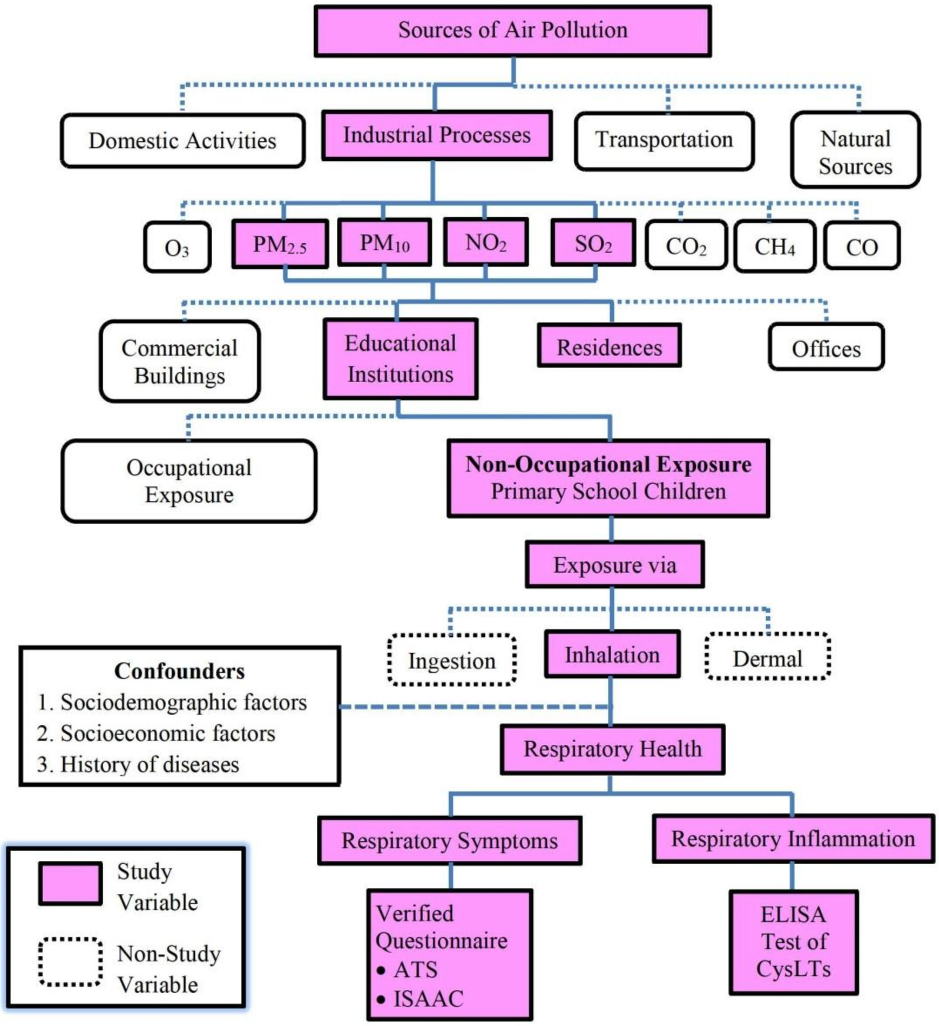

Figure 1: Conceptual Framework

This research focused on the exposure of school and residence to sources of air pollutants from industrial facilities, traffic, and indoor environment among school children by using selected airway inflammation biomarker, cysLTs that is induced by sputum. CysLTs comprise of LTC_4, LTD_4, LTE_4 (Kanaoka and Boyce, 2004). Leukotriene plays an important role in the early and late responses to bronchoconstriction and airway remodelling (Hallstrand and Henderson, 2010). Their overproduction causes inflammation in asthma and allergic rhinitis. CysLTs are biomarkers of effect for this study, which means they show any measurable biochemical or other variation in an organism, that can be recognised as associated with an established or possible health problem, depending on the magnitude of exposure (Committee on Human Biomonitoring for Environmental Toxicants, 2006).

To date, the previous research findings for leukotrienes are inchoate compared to other biomarkers such as sputum eosinophilia because its discovery as an airway inflammation biomarker is quite recent. Biomarkers can provide evidence of human exposure to a pollutant. Inflammation is the first responder of immune response to infection or injury in the body. Inflammation is detected by an increased concentration of biomarkers in the human body.

This is a preliminary study in Malaysia to use sputum cysLTs as a biomarker of mediator following inflammation to assess the airway inflammation among the healthy school children living near an industrial area. This study carried out the whole procedure of exposure assessment of school children living near an industrial area from the assessment of ambient exposure to industrial air pollutants at schools, survey and laboratory analysis of biomarker samples to statistical data analysis before risk characterisation can be made.

The outcomes can be used to increase awareness to the community living near an industrial area about the hazards that they are facing from constant exposure to industrial air pollution; it is also to educate parents and publics about the susceptibility of children's respiratory health as a part of the prevention effort. It is hoped that parents or guardians will be more attentive towards the health implications that their children are facing when they are exposed to industrial air pollutants. Moreover, this study suggests actions that the parents, guardians and school managements could take to ensure that the schools and residences are providing clean environments for the school children. As for the other researchers, there are still more gaps of understanding in the mechanisms of airways inflammation pertinent to exposure to air pollutants. Therefore, there should be rooms for improvements to be made from the findings of this study.

1.4 Study Objectives

1.4.1 General Objective

To determine the relationship between the magnitude of exposure to air pollutants (PM_{10}, $PM_{2.5}$, SO_2 and NO_2) and respiratory inflammation among school children living near the industrial area of Kemaman, Terengganu.

1.4.2 Specific Objectives

1. To determine sociodemographic and socioeconomic information, house condition and location, and family background among the respondents.
2. To compare the reported respiratory symptoms among the respondents in exposed area and comparative area.
3. To compare the concentrations of air pollutants (PM_{10}, $PM_{2.5}$, SO_2 and NO_2) inside respondents' classrooms and residences in exposed area and comparative area.

4. To compare the levels of CysLTs among the respondents in exposed area and comparative area.
5. To determine the association between the concentrations of air pollutants (PM_{10}, $PM_{2.5}$, SO_2 and NO_2) and respiratory symptoms among the respondents.
6. To determine the association between the concentrations of air pollutants (PM_{10}, $PM_{2.5}$, SO_2 and NO_2) and levels of CysLTs among the respondents.
7. To determine the association between the reported respiratory symptoms and levels of CysLTs among the respondents.
8. To determine the association between the concentrations of air pollutants (PM_{10}, $PM_{2.5}$, SO_2 and NO_2) and air pollutant sources at residences among the respondents.
9. To determine the association between the levels of CysLTs and air pollutant sources at residences among the respondents.
10. To determine the correlation between the concentrations of air pollutants (PM_{10}, $PM_{2.5}$, SO_2 and NO_2) and levels of CysLTs among the respondents.
11. To determine the factor(s) that are significantly associated to the respiratory symptoms after controlling the confounders.
12. To determine the factor(s) that are significantly associated to the levels of CysLTs after controlling the confounders.

1.5 Study Hypotheses

1. There is a significant difference between sociodemographic and socioeconomic information, house condition and location, and family background among the respondents.
2. There is a significant difference between the reported respiratory symptoms among the respondents in exposed area and comparative area.
3. There is a significant difference between the concentrations of air pollutants (PM_{10}, $PM_{2.5}$, SO_2 and NO_2) inside respondents' classrooms and residences in exposed area and comparative area.
4. There is a significant difference between the levels of CysLTs among the respondents in exposed area and comparative area.
5. There is a significant association between the concentrations of air pollutants (PM_{10}, $PM_{2.5}$, SO_2 and NO_2) and respiratory symptoms among the respondents.
6. There is a significant association between the concentrations of air pollutants (PM_{10}, $PM_{2.5}$, SO_2 and NO_2) and levels of CysLTs among the respondents.
7. There is a significant correlation between the concentrations of air pollutants (PM_{10}, $PM_{2.5}$, SO_2 and NO_2) and the levels of CysLTs among the respondents.
8. There is a significant association between the concentrations of air pollutants (PM_{10}, $PM_{2.5}$, SO_2 and NO_2) and air pollutant sources at residences among the respondents.
9. There is a significant association between the levels of CysLTs and air pollutant sources at residences among the respondents.

1.6 Definition of Variables

1.6.1 Conceptual Definitions

1. Primary School

Primary school in Malaysia is a school for children of 12 years old and below. Certain primary schools also include kindergartens in the same school compound. The Ministry of Education (MOE) Malaysia sets a comprehensive schooling system of primary school education in public schools. Under the national education system, each child who reaches the age of six on the first day of January of the current school year is required to undergo the 6-year compulsory primary education at primary schools (Malaysia Education Blueprint 2013-2025: Preschool to Post-Secondary Education, 2013). Most primary schools are public schools, which are either government schools or government-aided schools. Government schools include public-funded national schools or locally known as *Sekolah Kebangsaan*, whereas government-aided schools include public-funded national-type schools or locally known as *Sekolah Jenis Kebangsaan* (Malaysia Education Blueprint 2013-2025: Preschool to Post-Secondary Education, 2013).

2. Industrial Area

Industrial area is an area that is zoned for the purpose of industrial development within a town-planning scheme for various industries and productions (Guidelines for Siting and Zoning of Industry and Residential Area, 2012). These areas are frequently constructed outside of high populated areas or residential neighbourhoods, and are easily accessible via road or sea transportation systems. Besides, industrial areas are often governed by regulations and standards in relation to noise levels, water and air pollution, which are created to improve and monitor industries. Large variety of businesses ranging from light manufacturing industries to heavy petrochemical industries could be found in industrial areas. Industrial areas are often located near populated areas in many developing countries include Malaysia (Guidelines for Siting and Zoning of Industry and Residential Area, 2012).

3. Particulate Matter 10 (PM_{10})

PM_{10} is particulate matter with an aerodynamic diameter of 10 micrometres or less (0.0004 inches or one-seventh the width of a human hair). Particulate matter can be directly emitted or can be formed in the atmosphere when gaseous pollutants such as SO_2 and NOx react to form fine particles (Morgan, 2003). Malaysian Ambient Air Quality Standard mention that the national air quality standard for PM_{10} is 50 $\mu g/m^3$ (measured as an annual mean) and 150 $\mu g/m^3$ (measured as a daily concentration) (Malaysian Ambient Air Quality Guidelines, 2015).

4. Particulate Matter 2.5 ($PM_{2.5}$)

$PM_{2.5}$ is particulate matter with an aerodynamic diameter of 2.5 micrometres or less (approximately one-thirtieth the average width of a human hair). Because of their small size, fine particles can lodge deeply into the lungs (Morgan, 2003). Malaysian Ambient Air Quality Standard mention that the national air quality standard for $PM_{2.5}$ is 35 $\mu g/m^3$

(measured as an annual mean) and 75 µg/m^3 (measured as a daily concentration) (Malaysian Ambient Air Quality Guidelines, 2015).

5. Sulphur Dioxide (SO_2)

Sulphur dioxide belongs to a family of highly reactive gases called "oxides of sulphur". Fossil fuel combustion at power plants and other industries, also burning of high sulphur containing fuels by non-road equipment contribute as sources of SO_2 emissions (Morgan, 2003). Malaysian Ambient Air Quality Standard mention that the national air quality standard for SO_2 is 0.04 ppm or 40 ppb (measured as an annual arithmetic mean concentration) and 0.13 ppm or 130 ppb (measured as a daily concentration) (Malaysian Ambient Air Quality Guidelines, 2015).

6. Nitrogen Dioxide (NO_2)

Nitrogen dioxide belongs to a family of highly reactive gases called nitrogen oxides (NOx). These gases form when fuel is burned at high temperatures, and come principally from motor vehicle exhaust and stationary sources such as electric utilities and industrial boilers (Morgan, 2003). Malaysian Ambient Air Quality Standard mention that the national air quality standard for NO_2 is 0.04 ppm or 40 ppb (measured as an annual arithmetic mean concentration) and 0.17 ppm or 170 ppb (measured as a daily concentration) (Malaysian Ambient Air Quality Guidelines, 2015).

7. Respiratory Health Symptoms

Respiratory health symptom is a wide term that can be used to refer to a series of conditions that affect the respiratory system in the human body (Lloyd III, 2013). There are several types of respiratory diseases with different severity of each type that can affect human. Some of the symptoms last only for a few days with no medical treatment needed. Meanwhile, some of the symptoms may prolong without appropriate medical treatment.

8. Cough

Cough is a forceful release of air from the lungs that can be heard. Coughs can be either acute or chronic. Acute coughs typically begin suddenly and are often due to a cold or sinus infection. They usually last no longer than 4 weeks. Conversely, cough that lasts more than 4 weeks in children younger than 14 years of age or more than 8 weeks in adolescents and adults 14 years of age and older is considered to be chronic (Schmit *et al*., 2013).

9. Phlegm

Phlegm is a sticky mucous that is abnormally excreted in large quantities from the respiratory tract. It is produced from chest first thing in the morning or anytime during the day or night (Phlegm, 2007).

10. Wheezing

Wheezing is a whistling sound produced during breathing, usually on expiration or breathing out. Whistling noise is heard during breathing when the airways are narrowed or compressed as a result of inflammation (Bass, 2009).

11. Chest Tightness

Chest tightness includes any type of pain that occurs between our upper belly area and our lower neck (Chen, 2014). Chest tightness is also known as chest discomfort. It is a symptom of several diseases, which sometimes require medical attention as it may be life threatening.

12. Airways Inflammation

Airways inflammation is defined by infiltration of the airway by inflammatory cells which contribute to elevated levels of inflammatory biomarkers, mediators and procontractile stimulants (Khan, 2013). Such inflammatory biomarkers include cytokines and chemokines (Khan, 2013). When foreign particles such as allergens and air pollutants are entering the respiratory tract, immune system will take place to cause a local antibody activation.

13. Cysteinyl Leukotrienes (CysLTs)

CysLTs are a family of inflammatory lipid mediators of inflammation. The parent CysLT, LTC_4, is synthesised from arachidonic acid by various cells of innate immune system, which include mast cells, eosinophils, basophils, and macrophages, and is converted to the potent constrictor LTD_4 and the stable metabolite, LTE_4 (Laidlaw and Boyce, 2012). They are generated following exposure to allergens, proinflammatory cytokines, and other types of receptor-dependent stimuli (Theron *et al*., 2014).

14. Primary School Children

Primary school children in Malaysia are those children who go to primary schools for their compulsory primary education. If they are enrolled in public schools, they spend 6 years in primary schools. Their ages are between 6 to 12 years old according to month of birth, or 7 to 12 years old according to year of birth.

1.6.2 Operational Definitions

1. Primary Schools near an Industrial Area

Industrial area refers to an area that is zoned for the purpose of industrial development within a town-planning scheme for various industries and productions. Any primary school located within a radius of 5 km from this area was considered as primary schools near an industrial area. Therefore, primary schools located within 5 km radius from the closest boundary of Teluk Kalong Industrial Area and Kertih Petrochemical Plant were selected for this study.

2. Particulate Matter (PM_{10} and $PM_{2.5}$)

PM_{10} and $PM_{2.5}$ in schools were measured by using TSI DustTrak^{TM} DRX Aerosol Monitor 8534, which is based on light scattering principle. It uses a sheath air system that isolates the aerosol in the optic chamber to keep the optics clean for improved reliability and low maintenance. This instrument can detect aerosol concentration range between 0.001 to 150 mg/m^3. Therefore, it can simultaneously measure both mass and size fraction concentration corresponding to PM_{10}, PM_4, $PM_{2.5}$ and PM_1. Meanwhile, PM_{10} and $PM_{2.5}$ in residences were measured by using Gilian Personal Air Sampler, which is based on gravimetric principle.

3. Sulphur Dioxide (SO_2) and Nitrogen Dioxide (NO_2)

SO_2 and NO_2 were measured by using LaMotte Model BD Air Sampling Pump 1949, which uses absorption method with the LaMotte Air Pollution Test Equipment. This portable air sampling pump was used along with Sulphur Dioxide in Air Test Kit 7714 and Nitrogen Dioxide in Air Test Kit 7690 in which the portable vacuum pump draws precise volumes of air through an absorbing reagent in a special bubbling tube called impinger at a constant flow rate between 0 and 2.0 L/min in 0.1 increment regulated by a flow meter. After few treatments with Sulphur Dioxide Reagents and Nitrogen Dioxide Reagents, the resulting colour reaction were measured in an octet comparator for results in parts per million (ppm).

4. Respiratory Health Symptoms

The prevalence of respiratory health symptoms was determined from the questionnaires adapted from International Study of Asthma and Allergies in Childhood (ISAAC) and American Thoracic Society (ATS). These questionnaires assessed distinctions in the prevalence of respiratory symptoms at the population level and their causes by questioning responsible adults. In this study, the respiratory symptoms of interest were cough, phlegm, wheezing and chest tightness.

5. Cough

The occurrence of cough experienced by the school children was identified from the standardised questionnaires adapted from ISAAC and ATS for children. The questionnaires were filled in by parents or guardians. Certain parents or guardians were also interviewed at their residences about the occurrence of cough experienced by the respondents.

6. Phlegm

The occurrence of phlegm experienced by the school children was identified from the standardised questionnaires adapted from ISAAC and ATS for children. The questionnaires were filled in by parents or guardians. Certain parents or guardians were also interviewed at their residences about the occurrence of phlegm experienced by the respondents.

7. Wheezing

The occurrence of wheezing experienced by the school children was identified from the standardised questionnaires adapted from ISAAC and ATS for children. The questionnaires were filled in by parents or guardians. Certain parents or guardians were also interviewed at their residences about the occurrence of wheezing experienced by the respondents.

8. Chest Tightness

The occurrence of chest tightness experienced by the school children was identified from the standardised questionnaires adapted from ISAAC and ATS for children. The questionnaires were filled in by parents or guardians. Certain parents or guardians were also interviewed at their residences about the occurrence of chest tightness experienced by the respondents.

9. Airways Inflammation

Airways inflammation was identified by the concentration of selected airway inflammation biomarkers, which are CysLTs. Measurement of airway inflammation biomarkers can assist in the diagnosis of airway inflammation due to exposure to air pollutants indoors and outdoors.

10. Cysteinyl Leukotrienes (CysLTs)

The concentration of CysLTs in the sputum samples was measured by using CysLTs ELISA kit for Cysteinyl Leukotriene Receptor 1 (CysLTR1). This gene encodes a member of the G-protein coupled receptor 1 family. The encoded protein is a receptor for cysteinyl leukotrienes, and is involved in mediating bronchoconstriction via activation of a phosphatidylinositol-calcium second messenger system (CYSLTR1 Gene, n.d.). The test principle applied in the kit is sandwich enzyme immunoassay. The sensitivity of CysLTs ELISA kit was determined by calculating the mean of independent assays. Meanwhile, the specificity of this ELISA kit is for detection of Cysteinyl Leukotriene Receptor 1 (CysLTR1). The concentration of Cysteinyl Leukotriene Receptor 1 (CysLTR1) in the sputum samples was determined by comparing the optical density of the samples to the standard curve.

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