UNIVERSITI PUTRA MALAYSIA

EXPOSURE OF POLYCYCLIC AROMATIC HYDROCARBON ON POTENTIAL HEALTH RISKS AND GENOTOXICITY OUTCOMES AMONG PRIMARY SCHOOL CHILDREN IN THE VICINITY OF PETROCHEMICALS AREA

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

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July 2020

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Prolonged exposure to polycyclic aromatic hydrocarbons (PAHs) air pollutants may increase the risk of developing cancer and multiple acute respiratory health problems, especially children who live near heavy industries. Moreover, the air pollutants emitted from the industry had been frequently associated with genetic defects among children. This study aimed to evaluate the association of particulate PAHs exposure on potential genotoxicity among primary school children living close to the petrochemical industry and comparative group in Terengganu. A validated questionnaire on socio-demographic, dietary, health status, and personal exposure was distributed to randomly selected children. The indoor and outdoor samples of fine particulate matter ($PM_{2.5}$) bound to PAHs were collected on quartz fibre filters using a MiniVol portable air sampler, for 24h. The 16s priority PAHs concentration was quantified using Gas Chromatography-Mass Spectrometer. Source diagnostic ratio was applied to determine the source of PAHs emission. Meanwhile, the biomarker of PAHs exposure, which is urinary 1-hydroxypyrene (1-OHP), was determined by a High Performance-Liquid Chromatography, with fluorescence detector. The formation of micronucleus (Mn) and DNA damage in the buccal cell were evaluated using Micronucleus Assay and Comet Assay. The results showed that the outdoor total 16s priority PAHs concentration was higher (range between 7.18 to 67.72 ng/m^3) than the indoor environments (range between 3.45 to 63.22 ng/m^3). These concentrations were obviously higher at the exposed school as compared to the comparative schools. Based on the source diagnostic ratio, the PAHs of the exposed school are pyrogenic, which mainly originated from high combustion activities (vehicle and industrial emissions). Meanwhile, the urinary 1-OHP concentration was significantly higher among the exposed children than the comparative group (0.25 vs 0.14 µmol/mol-creatinine). The Mn frequency and DNA damage were also considerably higher among the exposed children as compared to the comparative group. Significant associations were observed between

environmental PAHs exposure with urinary 1-OHP, Mn frequency, and DNA damage. Children in the industrial area had 3 to 6 higher risk of DNA damage, and 2 to 7 times higher risk of chromosomal damage. According to the Incremental Lifetime Cancer Risk (ILCR) model, the average cancer risk for the exposed and comparative children was 9.95E-07 and 1.80E-07, respectively. The result from Multiple Linear Regression shows the concentration of total PAHs, the total carcinogenic PAHs, and open burning practice were the most significant factors associated with the Mn frequency and DNA damage in children, after controlling the possible confounders. This study reveals that the children who reside nearby the industry and frequent open burning were exposed to higher concentration air pollutants as compared to the comparative group. The higher exposure had increased the risk of genotoxic effect and cancer risk among a vulnerable group like children. This finding indicates that there is a need for industrial management to monitor and control emissions from industrial activity actively. Besides, it also assists the authorities in the formulation of strategic guidelines for air quality management at the primary school and establishing the safe level of air pollutants exposure in the microenvironment.

Keywords: Polycyclic aromatic hydrocarbon (PAHs), genotoxicity, children, petrochemical industry

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PENDEDAHAN POLISIKLIK AROMATIK HIDROKARBON TERHADAP POTENSI RISIKO KESIHATAN DAN KESAN GENOTOKSISITI DALAM KALANGAN PELAJAR SEKOLAH RENDAH BERDEKATAN DENGAN KAWASAN PETROKIMIA

Oleh

NOR ASHIKIN BINTI SOPIAN

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Pendedahan terhadap pencemar udara polisiklik aromatik hidrokarbon (PAHs) boleh meningkatkan risiko kanser dan pelbagai masalah kesihatan respiratori akut terutamanya kanak-kanak yang tinggal berdekatan dengan industri berat. Tambahan pula, pencemar udara dibebaskan dari kawasan industri kerap dikaitkan dengan kerosakan genetik dalam kalangan kanak-kanak. Kajian ini bertujuan untuk menilai hubungkait antara pendedahan partikulat PAHs ke atas potensi genotoksisiti dalam kalangan kanak-kanak sekolah rendah yang tinggal berdekatan industri petrokimia dan kawasan perbandingan di Terengganu. Borang soalselidik tervalidasi tentang sosiodemografik, permakanan, status kesihatan dan pendedahan individu telah diedarkan secara rawak kepada kanak-kanak. Sampel $PM_{2.5}$ (dalaman dan luaran), yang dikumpulkan di atas filter berfiber quartz dengan menggunakan pensampel udara mudah alih (MiniVol) selama 24 jam. Kepekatan 16 spesies PAHs telah dikuantifikasi menggunakan Kromatografi Gas Spektroskopi Jisim. Nisbah diagnostik telah digunakan untuk menentukan punca emisi PAHs. Manakala, biopenanda bagi pendedahan PAHs, iaitu urinari 1-hidroksipirena (1-OHP) telah dianalisa dengan Kromatografi Cecair Prestasi Tinggi, dengan pengesan fluorosen. Pembentukan mikronukleus dan kerosakan DNA telah dinilai dengan Asai Mikronukleus dan Asai Komet. Hasil menunjukkan kepekatan total PAHs luaran adalah lebih tinggi (julat antara 7.18 hingga 67.72 ng/m^3) berbanding persekitaran dalaman (julat antara 3.45 hingga 63.22 ng/m^3). Kepekatan total PAHs adalah lebih tinggi bagi sekolah terdedah berbanding sekolah perbandingan. Berdasarkan nisbah diagnostik, pencemaran PAHs di sekolah terdedah bersifat pirogenik, yang berpunca daripada aktiviti pembakaran bersuhu tinggi (emisi dari kenderaan dan industri). Manakala, kepekatan urinari 1-OHP secara signifikannya lebih tinggi dalam kalangan kanak-kanak di kawasan terdedah berbanding kumpulan perbandingan (0.25 vs 0.14 µmol/mol-kreatinin). Frekuensi Mn dan kerosakan

DNA secara signifikannya adalah lebih tinggi bagi kanak-kanak terdedah berbanding kumpulan perbandingan. Hubungkait yang signifikan turut diperhatikan antara kepekatan PAHs dengan urinari 1-OHP, frekuensi Mn dan kerosakan DNA. Kanak-kanak di kawasan industri mempunyai 3 hingga 6 kali risiko kerosakan DNA dan 2 hingga 7 kali risiko lebih tinggi kerosakan kromosom. Berdasarkan model Risiko Kanser Seumur Hidup (ILCR), purata risiko kanser bagi kanak-kanak terdedah dan kumpulan perbandingan adalah 9.95E-07 and 1.80E-07. Hasil daripada Regresi Linear Berganda menunjukkan kepekatan total PAHs, kepekatan total karsinogenik PAHs dan amalan pembakaran terbuka merupakan faktor yang paling signifikan berkait dengan frekuensi Mn dan kerosakan DNA, selepas mengawal faktor-faktor pembauran yang berkemungkinan. Kajian ini menunjukkan kanak-kanak yang tinggal berdekatan industri dan kekerapan pembakaran terbuka, adalah terdedah kepada kepekatan pencemar udara yang lebih tinggi berbanding kumpulan perbandingan. Pendedahan yang lebih tinggi meningkatkan risiko kesan genotoksik dan risiko kanser bagi kumpulan berisiko seperti kanak-kanak. Hasil kajian menunjukkan keperluan bagi pengurusan industri untuk memantau dan mengawal emisi dari aktiviti perindustrian secara lebih aktif. Di samping itu, ia dapat membantu pihak berwajib bagi menghasilkan garis panduan pengurusan kualiti udara di sekolah rendah dan mewujudkan paras selamat pendedahan pencemar udara dalam persekitaran mikro.

Kata kunci: Polisiklik aromatik hidrokarbon (PAHs), genotoksisiti, kanak-kanak, industri petrokimia

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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision.
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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LIST OF ABBREVIATIONS

>	More than
<	Less than
∑	Summation
µg/m^3	Microgram per meter cube
1-OHP	1-hydroxypyrene
ACP	Acenaphthene
ACY	Acenaphthylene
ADD	Average daily dose
ANOVA	Analysis of variance
ANT	Anthracene
AT	Averaging time
ATSDR	Agency for Toxic Substances and Disease Registry
BaA	Benz[a]anthracene
BaP	Benzo[a]pyrene
BaPeq	Benzo(a)pyrene equivalent concentration
BbF	Benzo[b]fluoranthene
BgP	Benzo[ghi]perylene
BkFe	Benz(k)fluoranthene
BMI	Body mass index
BW	Bodyweight
CA	Chromosomal aberration
CI	Confidence interval
CO	Carbon monoxide
CO_2	Carbon dioxide
CSF	Cancer slope factor
CYR	Chrysene
DALYs	Disability-adjusted life-years
DbA	Dibenz[a,h]anthracene
DNA	Deoxyribonucleic acid
DOE	Department of Environment
ED	Exposure duration
EDTA	Ethylenediaminetetraacetic acid
EF	Exposure frequency
EPA	Environmental Protection Agency
ETS	Exposure to tobacco smoke
FLA	Fluoranthene
FLU	Fluorene
GCMS	Gas chromatography-mass spectrophotometry
GDP	Growth Domestic Product
H	Hour
HCl	Hydrochloric acid
HI	Hazard index
HMW	Heavy molecular weight
HPLC	High-performance liquid chromatography
HQs	Hazard quotients
IARC	International Agency for Research on Cancer
IdP	Indeno[1,2,3-cd]pyrene

ILCR	Incremental lifetime cancer risk
IQR	Interquartile range
IR	Inhalation rate
IUR	Inhalation unit risk
ktoe	Kilo tonne of oil equivalent
L/min	Litre per minute
LADD	Lifetime average daily dose
LPG	liquid petroleum gas
LMA	Low melting agarose
LMW	Low molecular weight
M	Molar
Med	Median
Mn	Micronucleus
MOE	Ministry of Education in Malaysia
MOH	Ministry of Health Malaysia
m/z	mass-to-charge ratio
N	Total population
n	Number of samples
NAP	Naphthalene
ng/g	Nanogram per gram
ng/m^3	Nanogram per meter cube
NIOSH	National Institute of Occupational Safety and Health
nitro-PAHs	Nitroaromatic hydrocarbons
Nm	Nanometre
NO_2	Nitrogen dioxide
O_3	Ozone
oxo-PAHs	Oxygenated aromatic hydrocarbon
PAHs	Polycyclic aromatic hydrocarbon
PBS	Phosphate buffer solution
PHE	Phenanthrene
PM	Particulate matter
PM_{10}	Particulate matter with aerodynamic diameter below than 10 µm
$PM_{2.5}$	Particulate matter with aerodynamic diameter below than 2.5 µm
Ppb	Part per billion
ppm	Part per million
PR	Prevalence ratio
POR	Prevalence of odd ratio
PYRe	Pyrene
ROS	Reactive oxygen species
SCE	Sister chromatid exchanges
SD	Standard deviation
SO_2	Sulfur dioxide
TEF	Toxicity equivalent factor
TEQ	Toxicity equivalent to concentration
VOC	Volatile organic compound
WHO	World Health Organization
B	Standardize coefficient
χ^2	Chi-square

CHAPTER 1

INTRODUCTION

1.1 Study Background

Industrialization implies positive and vital economic development in one country. The excessive growth of large-scale industry contributes to numerous environmental problems, especially the abundant release of air pollutants. The petrochemical industries are the dominant contributor to anthropogenic air pollutions in petroleum-producing countries. It can emit a wide range of point source pollutants such as volatile organic compound, persistent organic pollutants, and combustion end product including particulate matter (PM), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) through plant's operation (Cetin et al., 2003; Nadal et al., 2009; Rovira et al., 2014; Ayuni et al., 2014; Zhao et al., 2015; Luo et al., 2018). Apart from that, mobile air pollutants from heavy traffic density around the petrochemical area may synergize pollutant concentration in the atmosphere (Nadal et al., 2011).

In petrochemical industries, most of the organic compounds were derived from the refining process, liquid petroleum gas (LPG) handling and leakage, and vehicular emission. Aliphatic hydrocarbon is the dominant VOCs emitted from the industry, followed by aromatic hydrocarbon and olefins (Vega et al., 2011). For instance, ethylene dichloride is the most abundant aliphatic hydrocarbon emitted from the petrochemical complex in Izmir, Turkey. This compound is a leaded gasoline additive used in the refinery process and intermediate product of the vinyl chloride process in the petrochemical complex (Cetin et al., 2003). Ethane, propane, n/i-pentane, toluene, and formaldehyde are commonly emitted from the oil refinery process (Vega et al., 2011). In another study by Luo et al. (2018), they characterized a high load of organic carbon composition (26.8%) in the air samples at a petrochemical city in Northern China. The ratio of organic carbon to elemental carbon (OC/EC) was 6.68, which was higher than the ratio found in megacities in China, indicating an increased contribution of secondary organic carbon in the atmosphere. Among the three groups of hydrocarbons, the aromatic hydrocarbon ranked the top concern as it is frequently associated with the incidence of carcinogenesis (Peluso et al., 2013; Thepanondh et al., 2011).

Exposure to the mixture of air pollutants may be significant for fence-line communities who live near to the industries, especially in terms of health effects (Nadal et al., 2009; Jalaludin et al., 2014; Vawda et al., 2014). Susceptible group populations, like children, are prone to get adverse health outcomes from air pollutant exposure due to their developing stage of biological and physical condition (World Health Organization, 2018). Scientific studies have demonstrated that the impact of inhalation particulate matter (PM) on human

health has been associated with physicochemical properties, the presence of inorganic pollutants and organic pollutants (Yang Razali et al., 2015; Yang et al., 2019; Oliveira et al., 2019). The severity of the health impacts of inhalation of PM is mainly attributed to inhalable particulates with an aerodynamic diameter of less than 2.5 µm. Because of their large specific surface, these particulates tend to be adsorbed by various organic substances, such as polycyclic aromatic hydrocarbons (PAHs), nitroaromatic hydrocarbons (nitro-PAHs), and oxygenated aromatic hydrocarbon (oxo-PAHs) (Oliveira et al., 2019).

Particle bounded polycyclic aromatic hydrocarbon (PAHs) is one of the highly lipophilic and pervasive harmful organic pollutants ubiquitously found in the environment, and eventually enter the human body through three main routes of inhalation, ingestion, and dermal absorption (Ali, 2019; Dai et al., 2019; Huang et al., 2019). They are widely distributed in the urban atmosphere due to vehicle exhaust, cigarette smoke, residential heating, and industry by incomplete combustion of organic matter or in processes using charcoal or petroleum derivatives (Genies et al., 2013). The inhalation particle-bounds PAHs are a major concern as it is commonly associated with the increase of cancer risk (Khan et al., 2015). In addition, the United States Environmental Protection Agency (USEPA) had listed seven carcinogenic PAHs compounds namely as benzo(a)anthracene, benzo(a)pyrene, benzo(b)fluoranthene, benzo(k)fluoranthene, chrysene, dibenzo(a,h) anthracene and indeno(1,2,3-cd)pyrene.

The severity of PAHs toxicity is strongly dependent on its molecular weight, as the compound with the heaviest weight tends to produce a more significant carcinogenicity response. Apart from that, the molecular weight and atmospheric condition will determine phase distribution in the atmosphere either in gas, particle gas, or particle phase. In other words, the most massive compound will be engulfed or adsorbed by the suspended particulate matter, which exhibits more significant health effects. Due to its severe toxicity, the study on PAHs is becoming viral worldwide, especially studies on atmospheric PAHs in high traffic cities and genotoxicity studies. Furthermore, the PAHs exposures among a susceptible group like children were also highlighted in previous literature (Busso, Carreras, and Amarillo., 2014; Fan et al., 2012; Jasso-pineda et al., 2015; Pelallo-Martínez., 2014; Ruchirawat et al., 2007).

Genetic toxicology study is a branch of science which provides precise information about risk effects of multiple exposures on the health to prevent health problem. Exposure to genotoxic substances like PAHs can cause oxidative stress, which then will lead to DNA damage and alter DNA replication. Disturbance in DNA replication may cause mutation and may lead to carcinogenic effects. The genetic material damage can be quantified with an application of a genotoxic biomarker. It can help in understanding the relative contribution of ambient air pollution as a risk factor for cancer. It also facilitates health risk assessments, especially under moderate or low air pollution (Hrelia et al., 2004; Suhaimi et al., 2015).

Biomarkers such as DNA, hemoglobin, albumin adducts, chromosome aberrations (CA), sister chromatid exchanges (SCE), micronuclei (MN), DNA fragmentation are frequently used to demonstrate the association between PAHs exposure and genotoxic effect at different levels (Neri et al., 2006). The buccal cell sampling is a valuable tool and less invasive to determine genetic damage in humans. It represents a preferred target population for early genotoxic events induced by carcinogen introduced via inhalation and ingestion (Holland et al., 2008; Ceppi et al., 2010; Bonassi et al., 2011; Muhamad Daud et al., 2018).

1.2 Problem Statement

Investigators have seen the petrochemical industry as the primary cause of industrial air pollution in petroleum-producing countries. Numerous epidemiological studies had documented the deterioration of air quality in school in the proximity of petrochemical industrial area, which then leads to significant acute respiratory health effect among the children (Rovira et al., 2014; Demirel et al., 2014; Godoi et al., 2013; Loyo-Berríos et al., 2007; Wichmann et al., 2008; Smargiassi et al., 2009). Anthropogenic emission from the industry also contributes to significant chronic health effects with an increasing number of carcinogenesis incidences and cancer mortality rate among neighbourhoods living in the vicinity of the complex (Liu et al., 2008; Lin et al., 2004; Pan et al., 1994; Sans et al., 1995; Yu et al., 2006).

The literature review showed that several studies in Malaysia find substantial evidence of industrial air pollution exposure associated with increased prevalence of respiratory symptoms, impairment of lung function, and inflammation of the airways among children living near the Kertih Petrochemical Industry (Ayuni et al., 2014; Ab Jamil et al., 2015; Suhaimi et al ., 2015; Suhaimi et al., 2017; Kamaruddin et al., 2019). Furthermore, the children living within 5km of the industry also had greater genotoxic risk, as indicated by a higher rate of chromosomal abnormalities (Muhamad Daud et al., 2018). These suggest that proximity to the petrochemical plant plays a significant role in worsening the children's health. Moreover, increasing proximity to the industrial zone and the busiest road could expose to a higher level of air pollution and, therefore, could elevate childhood cancer risk as studied by Seifi et al. (2019).

Children had been postulated as one of the most susceptible populations due to their physical and biological conditions, which are still under the developmental stage (WHO, 2018). Exposure to a highly polluted environment during their childhood time can alter lung development and lung function (Esposito et al., 2014). Besides, they usually spent the majority of their time outdoor (especially at times when PM concentrations are higher), and their active lifestyle can increase their breathing rate, which leads to a more significant inhalation dose of air pollutants (Sánchez-guerra et al., 2012). Mouth breathing is more frequent in children, which bypasses the filtering function of the nose and pull the air pollutants deeper through the respiratory tract, lung and goes to the bloodstream. As a result, the particle dose in the pulmonary region can be two to fourfold

higher among children than adults. Moreover, children are known to have a low capacity of metabolism as compared to the adult. Thus, inhalation of polluted air may increase the metabolism burden in their small body (Fan et al., 2012). Health effects encountered early in life will increase the risk of illness in the future for a child and lead to lifelong consequences (WHO, 2018).

The inhalation of particulate matter with several chemical compositions and size fraction is a global health concern, especially the respirable particle with more excellent capability to penetrate deeply into alveoli. Particle-bound PAHs are ubiquitously found in the environment, with carcinogenic and mutagenic properties (Iwegbu et al., 2019; Sulong et al., 2019; Oliveira et al., 2019; WHO, 2006). Agency for Toxic Substances and Disease Registry (ATSDR) had ranked the PAHs congener as top 9th out of 275 chemicals in a priority list of hazardous substances, due to the consequences effect for human exposure and its occurrence in the environment (ATSDR, 2020).

A study by Etchie et al. (2018) demonstrated a total of 49,500 DALYs per year as a burden of disease from the exposure to particulate PAHs. The exposure of annual PAHs concentration, 458 ± 246 ng/m^3 in Nagpur district of India, estimated about 55.1% of DALYs were due to cardiovascular impairment, lung cancer (23.1%), immunological impairments (18.0%), and reproductive abnormalities (0.4%). The higher estimation of DALYs signifies an urgency to quantify ambient particulate PAHs so that relevant mitigation measures can decrease the PAHs emission, mainly from high combustion activities (industrial and traffic emission).

It was found that inhalation of particulate bound PAHs had a significant effect on children's health (Murawski et al., 2020; Tang et al., 2019; Fan et al., 2012; Jasso-pineda et al., 2015; Busso et al., 2014; Pelallo-Martínez., 2014; Ruchirawat et al., 2007) and has been linked to the elevated risk of cancer (Sulong et., 2019, Othman et al., 2021). Numerous international studies also had monitored significant level of particulate PAHs emission at the petrochemical industrial area; however, the adverse health effect on the children live nearby the industry has not been well investigated yet (Quang et al., 2019; Yuan et al., 2015; Zhao et al., 2015; Zhao et al., 2014 Dong et al., 2009). Thus, these are the study justification that the genotoxic properties of petrochemical air pollutants may have a possibility to cause genetic material damage, which then may lead to cancer. The aid of cytogenetic biomarkers can investigate the damage of genetic material. A comprehensive assessment of the organic composition of particulate PAHs and the origin of emission is highly needed for a better environmental health mitigation approach.

1.3 Study Justification

In Malaysia, studies to determine levels of PAHs in ambient air had been conducted in early 1996 by Abas and Simoneit (1996), which strongly emphasized greater PAHs concentration emitted from biogenic and

anthropogenic sources during haze episodes. In the next years, studies on ambient PAHs mostly revolved around the source of PAHs identification and characterization, which mainly originated from biomass burning and vehicle emission at high traffic density and urban area (Sulong et al., 2019, Khan et al., 2015; Jamhari et al., 2014; Bahry et al., 2009; Omar et al., 2006; Abas et al., 2004; Okuda et al., 2002; Omar et al., 2002). The previous studies mainly emphasized the estimation of carcinogenic health risk assessment of PAHs exposure on the general population (Jamhari et al., 2014; Khan et al., 2015; Sulong et al., 2019).

With this countable information on the health impact of exposure to ambient PAHs, it gives limited knowledge and understanding of the chronic effect of children's exposure to PAHs. This study was, therefore, conducted to fill the knowledge gap on industrial-scale PAH emissions and health outcomes concerning genotoxic effects, prediction of cancer, and non-cancer risk among children living near the petrochemical industrial area. This research provided information on how long-term PAHs could affect temporary and permanent damage to children's DNA, leaving a gap for further studies on this matter. For a clearer picture of this present study, a conceptual framework is illustrated in Figure 1.1.

Reducing the health effects of outdoor air pollution is mostly beyond the individuals' control and requires action by public authorities. Therefore, the scientific finding on the characterization of air pollution could support the decision of policymakers for the implementation of mitigation policies to protect the public, especially on children's health. It is hoped that the research outcome will assist in the formulation of strategic guidelines for air quality management at the primary school and promulgation of the safe level PAHs in the microenvironment. The measurement of particulate PAHs in the school could serve as baseline data on microenvironment exposure near the industrial area. Further studies are warranted to explore the PAHs exposure at different environmental settings and an additional advanced biomarker to represent the related health outcomes. The finding can encourage the Malaysian government, especially the Department of Environment (DOE), to comprehensively monitor the PAHs parameter (particulate and gaseous) in the air quality stations, to improve air monitoring and data communication.

Apart from that, this research's findings can be used to raise environmental health awareness on the air pollution threat. The communities live nearby the industry might be continuously exposed to industrial air pollution, emissions from traffic, and open burning. Hence, the proactive actions to promote air pollution reduction in the surrounding schools shall start within the nearby community, school management organization, local and federal authorities to ensure the school environment is clean for the children.

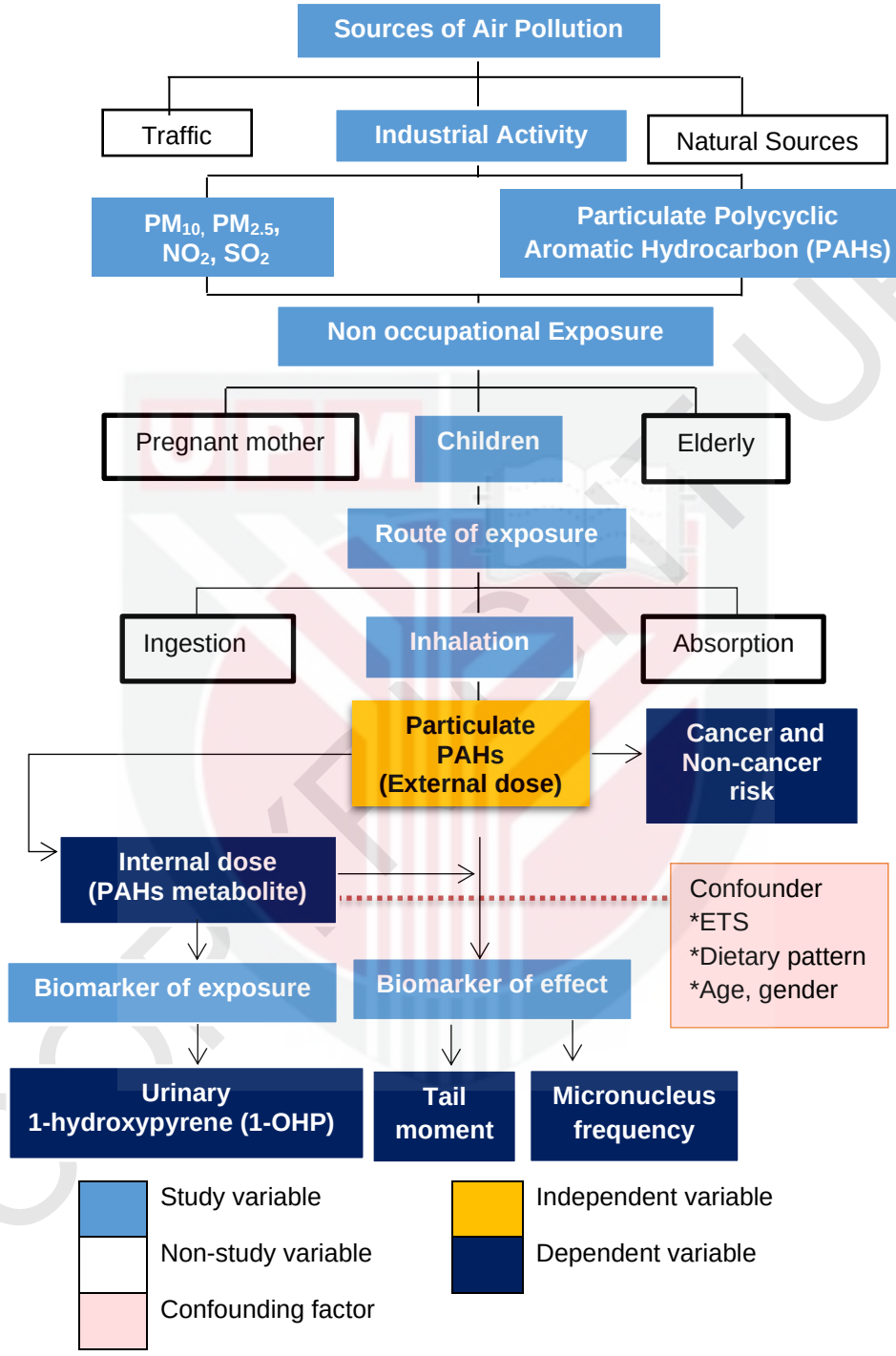

Figure 1.1 : Conceptual framework

1.4 Research Objective

1.4.1 General objective

To assess the distribution of particulate PAHs and their genotoxic potencies on buccal epithelial cells among primary school children living in the vicinity of the petrochemical area.

1.4.2 Specific objectives

i. To determine socio-demographic information, house condition, family background, and history of exposure among the school children living near the petrochemical industrial area and the comparative group
ii. To evaluate the concentration of indoor air pollutants and polycyclic aromatic hydrocarbons (PAHs) at the selected schools of industrial area and comparative area.
iii. To assess the human health risk assessment in terms of both carcinogenic and non-carcinogenic effects
iv. To compare the concentration urinary 1-hydroxypyrene (1-OHP) among primary school children living close to the petrochemical industry and comparative area
v. To compare the formation of micronucleus and intensity of DNA damage in buccal cells among primary school children living close to the petrochemical industry and comparative area
vi. To evaluate the association between exposure level of PAHs and level of genotoxicity (micronucleus frequency and DNA damage in buccal epithelial cells) among primary school children.
vii. To evaluate the association between exposure level of PAHs and remaining metabolite of PAHs; 1-OHP among primary school children living close to the petrochemical industry and comparative area
viii. To determine the selected risk factors associated with the concentration of urinary 1-OHP, formation of micronucleus, and DNA damage in buccal epithelial cells among primary school children

1.5 Research Hypothesis

i. The exposure level of indoor air pollutants and PAHs are significantly higher among primary school children in the exposed area as compared to the comparative group
ii. The risk associated with non-carcinogenic PAHs and lifetime cancer risk is higher among primary school children residing nearby the industrial area are higher than the comparative group
iii. There is a significant difference between the concentration of urinary 1-OHP among primary school children living close to the petrochemical industry and comparative area
iv. There is a significant difference between the formation of micronucleus and intensity of DNA damage among primary school children living close to the petrochemical industry and comparative area
v. There is a significant association between PAHs concentration and urinary 1-OHP
vi. There is a significant association between PAHs concentration and formation of micronucleus and intensity DNA damage in buccal epithelial cells among primary school children.
vii. There is a significant association between the selected risk factors and concentration of urinary 1-OHP, the formation of micronucleus, and DNA damage in buccal epithelial cells among primary school children

1.6 Research Questions

i. What are the exposure levels of indoor air pollutants and PAHs among the primary school children living near the petrochemical industry and comparative area?
ii. Is lifetime cancer risk among primary school children residing in the petrochemical industrial area is complying with the USEPA acceptable limit of PAHs exposure?
iii. Is there any significant difference between the concentration of urinary 1-OHP among primary school children living close to the petrochemical industry and comparative area?
iv. Is there any significant difference between the formation of micronucleus and the intensity of DNA damage among primary school children living close to the petrochemical industry and comparative area?
v. Is there any significant association between air pollutants concentration and the remaining metabolite of PAHs, 1-OHP?
vi. Is there any significant association between air pollutants concentration and micronucleus formation and intensity DNA damage in buccal epithelial cells among primary school children?
vii. Is there any significant association between the selected risk factor and concentration urinary 1-OHP, the formation of micronucleus, and DNA damage in buccal epithelial cells among primary school children?

1.7 Definition of Variables

1.7.1 Conceptual definition

a) $PM_{2.5}$

$PM_{2.5}$ is referring to fine particles with an aerodynamic size of less than 2.5 µm. This respirable particle tends to be deposited in the lower respiratory tract. It is usually emitted anthropogenically from motor vehicle emission, biomass burning, and coal combustion (Pui et al., 2014).

b) Polycyclic aromatic hydrocarbons (PAHs)

PAHs are organic compounds with multiple benzene rings fused and classified based on structural and physicochemical properties such as molecular weight, melting point, boiling point, and solubility. It has a wide distribution due to emissions from the pyrogenic and petrogenic sources. The pyrogenic sources usually dominate PAHs composition in an urban atmosphere, with vehicular emission as a significant contributor. It also can be contributed by the combustion of the domestic source (i.e., burning of coal, oil, gas, tobacco, and grilled cooking), agricultural emission (i.e., open burning), and industrial emission (petrochemical plant, incinerator, and coke production). The petrogenic emission solely comes from direct contamination, such as oil products' spillage (Jamhari et al., 2014). It exists in two phases; particulate and gaseous phases.

c) Urinary 1-OHP
1-hydroxypyrene is a metabolite that exclusively comes from the metabolism of pyrene, which is a joint compound present in the mixture of PAHs. Hence, this metabolite can be a surrogate marker of total PAHs exposure to assess multiple exposure routes. Besides, this metabolite is best to describe 24-hour cumulative exposure of PAHs.

d) Micronucleus

Micronucleus is derived from acentric chromosome fragments or whole chromosomes that fail to migrate to spindle poles during anaphase (Fenech, 2000). The presence of a small nucleus in the dividing cell provides a convenient indicator of genotoxicity due to chromosomal breakage and loss. Exfoliated epithelial cell collection from the buccal mucosa is reported as a minimally invasive method proposed since 1983 in indicating and determining the level of genetic damage due to inhalation and ingestion of xenobiotic substance (Nina Holland et al., 2008; Thomas et al., 2011).

e) DNA damage

Comet assay is a toxicology testing, which was first introduced by Ostling and Johanson (1984) in determining the level of DNA damage in a mammalian cell. It can be called a single cell gel electrophoresis assay (SCG or SCGE assay) and frequently assessed in lymphocytes and various types of cells (Liao et al., 2009). It is used as an indicator of genotoxicity.

1.7.2 Operational Definition

a) $PM_{2.5}$

The $PM_{2.5}$ was collected using low volume air samplers equipped with cyclone (Airmetrics Mini Vol) with a flow rate of 5 L/min through weighted quartz microfiber filters.

b) Polycyclic aromatic hydrocarbons (PAHs)

PAHs were determined from the filter paper containing $PM_{2.5}$. It required organic digestion before it can be analyzed using gas chromatography-mass spectrophotometry (GCMS). The PAHs concentration was quantified through an internal calibration standard containing a known concentration mixture of 16s PAHs congeners.

c) Urinary 1-OHP

The urinary 1-OHP was determined from the sample taken earliest in the morning. The sample was extracted and purified by using C-18 cartridges eluted in methanol, and later will be dried by nitrogen gas. The concentration of 1-OHP was determined using high-performance liquid chromatography (HPLC) with a fluorescence detector at two wavelengths; excitation wavelength at 281 nm and emission wavelength at 388 nm. The concentration of urinary 1-OHP was adjusted with creatinine concentration, and the final concentration was expressed in µmol/mol-creatinine.

d) Micronucleus (Mn)

Buccal mucosa cells were taken from the inside cheek of respondents using a sterile cytology brush. The cells were fixed onto two slides. The Mn frequency was be determined by counting the number of Mn that appear in 1000 cells per slide by using a light microscope with 1000 times magnification (Jyoti et al., 2012). It was used as an indicator of genotoxicity among children.

e) DNA damage

DNA damage of buccal epithelial cells was assessed using a Comet Assay. In general, there are six main steps involved in this assay; slide preparation and cell lysis, unwinding, electrophoresis, neutralization, DNA staining, and comet visualization. The treated buccal mucosa cells can be visualized under a fluorescent microscope. The level of DNA damage was expressed in the tail moment (a measure of tail length x measure of DNA in the tail); meanwhile, undamaged DNA is manifested in the comet head as DNA will remain tightly in the nucleoid of the cell (Liao et al., 2009). It was used as an indicator of genotoxicity among children.

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