Pertanika J. Sci. & Technol. 27 (2): 589 - 600 (2019)

SCIENCE & TECHNOLOGY

Journal homepage: http://www.pertanika.upm.edu.my/

FeNO as a Biomarker for Airway Inflammation Due to Exposure to Air Pollutants among School Children Nearby Industrial Areas in Terengganu

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ABSTRACT

Exposure to industrial air pollutants is a public health concern particularly in children due to their immaturity of respiratory systems. The distance between their school and home from the industrial area will elevate the risk of airway inflammation among children. This study aims to determine the exposure of Industrial Air Pollutants (PM_{10}, $PM_{2.5}$, NO_2, SO_2, and VOCs) and its association with airway inflammation (FeNO) among primary school children in industrial and non- industrial areas in Kemaman, Terengganu. A cross-sectional comparative study was conducted among Malay primary school children in Kemaman, Terengganu. A validated questionnaire was randomly distributed to children to get the background information, respiratory symptoms and exposure history of the children. The assessment of indoor air quality was carried out in each primary school and home using indoor air monitoring equipment. Fractional exhaled nitric oxide (FeNO) was measured using an NIOX MINO device. The results showed a significant difference between concentrations of PM_{10}, $PM_{2.5}$, NO_2, SO_2, and VOCs in different classrooms from selected schools and homes of exposed and comparative groups, $P<0.05$. Statistical analysis revealed that the FeNO level was significantly higher among the exposed group compared to the comparative group

ARTICLE INFO

Article history:
Received: 03 December 2018
Accepted: 30 January 2019
Published: 25 April 2019

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ISSN: 0128-7680
e-ISSN: 2231-8526

(Z= -9.442, p= 0.001). The research suggests that the exposure to industrial air pollutants will increase the risk of getting respiratory inflammation among primary school children living near industrial areas.

Keywords: FeNO, NO_2, PM_{10}, $PM_{2.5}$, respiratory inflammation, SO_2, VOCs,

INTRODUCTION

Airway inflammation is a complex response of the immune system to a threat such as allergens, irritants and infectious agents in the respiratory tract. Numerous of respiratory diseases such as cystic fibrosis, bronchiectasis, chronic bronchitis and asthma are associated with airway inflammation (Alving & Malinovshi, 2010). FeNO is defined as a non-invasive, well-tolerated, and reproducible marker of airway inflammation (Dweik et al., 2011). This online and direct method will be done to measure airway inflammation, and is usually used in asthma patients. It makes asthma monitoring and treatment easier to be conducted routinely in a clinical practice (Yates, 2001).

Exposure to air pollution is a public health concern especially among children as their respiratory system is still not fully developed. Generally children are more vulnerable to the health effects of air pollution than adults as they inhale and exhale more air in proportion to their weight. In addition, children might be more likely to be affected by inflammation by air pollutants, as they have high physical activity and ventilation rate as well as smaller diameter of airways which contributes to greater inhalation dose of air pollutant (Sánchez-Guerra et al., 2012). Thus, the evaluation of airway inflammation in children is vital to understand the underlying mechanisms of respiratory illnesses and preventing children from getting the diseases.

This study was conducted to determine the association between particulate matter of less than 10 micrometers (PM_{10}) and 2.5 micrometers aerodynamic diameter ($PM_{2.5}$), nitrogen dioxide (NO_2), sulphur dioxide (SO_2), and volatile organic compounds (VOCs) with airway inflammation (FeNO) among primary school children in industrial areas in Kemaman, Terengganu due to recent expansion and development of industrial activities, which are petrochemical, iron and steel industries that have the potential to contribute adverse effects to community health especially children. Besides, there are significant findings of association between industrial air pollutants with the prevalence of airway inflammation by previous studies (Noor Hassim & Jalaludin, 2014). The importance of this study will either indirectly or directly help to increase the awareness of the community regarding the risk of exposure towards industrial air pollutants, which can later cause airway inflammation. This is also expected to provide supportive information or data to help developers or any related agencies to prepare a better development plan or control measure if there is a threat towards people nearby industrial areas.

MATERIALS AND METHODS

Study Design and Location

A cross sectional comparative study was conducted among male and female primary school children with the aim to determine the airway inflammation (FeNO) among primary school children in primary schools located near the industrial area under the exposures of PM_{10} $PM_{2.5}$, NO_2, SO_2, and VOCs. The parameter involved in airway inflammation was FeNO level. Exposed schools (E1, E2, E3) were schools located within 5 km radius to the nearest boundary of an industrial site, whereas comparative Schools (C1, C2) were located more than 5 km radius from the nearest boundary of an industrial site with less traffic.

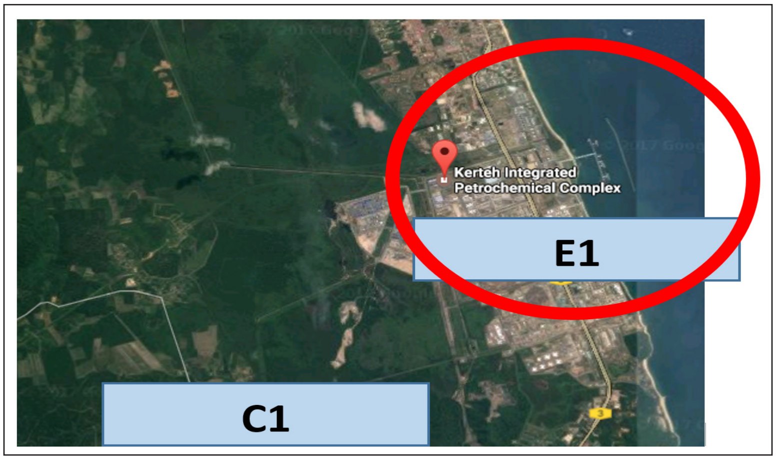

Figure 1. Study locations (E1) and (C1) within and outside a 5 km radius from industrial areas in Kemaman, Terengganu
Source: Image generated by Google Maps, 2015

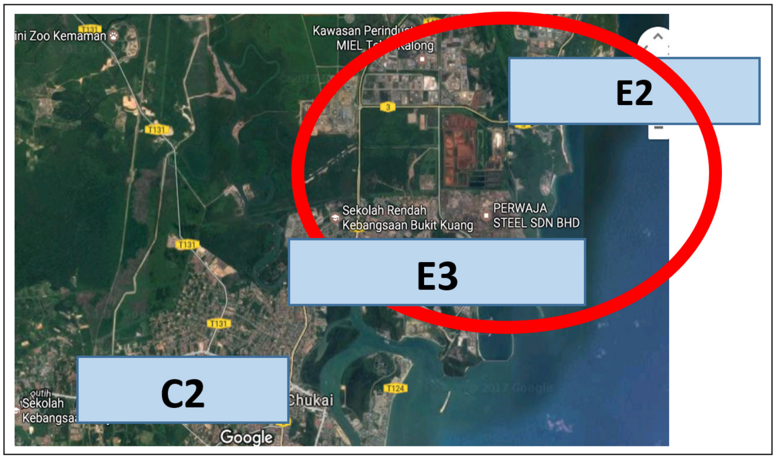

Figure 2. Study locations (E1), (E2) and (C2) within and outside a 5 km radius from industrial areas in Kemaman ,Terengganu
Source: Image generated by Google Maps, 2015

Study Sample

A total of 204 primary school children aged 11 years old were selected from five primary schools located in Kemaman, Terengganu. Exposed populations were selected among boys and girls who attended primary school located within a 5 km radius of the industrial area and for comparative group was selected among boys and girls who attended primary school located outside the 5 km radius from the industrial area in Kemaman. Random sampling method was employed to recruit the respondents with several inclusive criteria; only primary school children aged 11 years old, healthy, Malay, and free from any respiratory diseases. The name list of children was obtained from the teachers. The list of schools was obtained from the Ministry of Education before being divided into two groups; exposed and comparative group.

Monitoring in School and Residences

The measurement of indoor air quality was carried out in primary school using indoor air monitoring equipment. The air sampling was conducted for at least 5 or 6 hours during primary school normal activities and 24 hours in homes. There were 5 primary schools and 162 residences selected for the study. The indoor air monitoring equipment used were DustTrak DRX Aerosol Monitor 8534, Air Sampling Pump, PbbRAE Portable VOC Monitor (pbbRAE 3000), LaMotte Air Sampling Pump, Q-TrakPlus Model 8554 Monitor and TSI Velocicalc Plus Model 8386. The equipment were placed at a height of 0.6 to 1.5 metres above the floor, to simulate the location of breathing zone and was not closer than 1 metre to a door, window and wall. Whenever possible, all the equipment were placed at the back of the classroom to ensure no sound disruption from equipment during learning sessions and to avoid the children from being distracted by them. Meanwhile, the measurements in residences were performed by Gillian Air Sampling Pumps. This pump comprises a filter membrane cassette for $PM_{2.5}$ and PM_{10}, portable air sampling pump and cyclone. Using the volumetric flow control method, the pump under a fully charged battery draws ambient air at 1.7 litre/minute for to 24 hours. The filter paper used was Poly Vinyl Chloride (PVC) filters. The method used was in accordance with MDHS 14/3.

Fractional Exhaled Nitric Oxide (FeNO)

The respondents from each study group were recruited randomly to undergo a single-breath FeNO analysis. This FeNO measurement was done concurrently during measurements of indoor air pollutant. Exhaled nitric oxide (eNO) was measured online following the guidelines adopted from ATS/ERS using chemo-luminescence analyser Niox. (Aerocrine, Inc., Stockholm, Sweden). The measurement was carried out at least one hour after heavy physical activity (if any) while consumption of nitrate-rich food and caffeine among respondents was discouraged. The test began with each respondent required to stand up quietly and comfortably. First, the respondent's nose was clipped, and the respondent was required to fully expel air from the lungs by doing a full exhalation through the mouth, after which the respondent inserted the mouthpiece of the NIOX system and inhaled NO-free air calmly to the total lung capacity over a period of 2-3 seconds. The respondent then exhaled steadily for 6 seconds, maintaining a constant air speed in which the machine will emit a continuous humming sound if they were breathing correctly. Each of the respondent was provided with a disposable mouthpiece. As an error prevention measure in maintaining constant air speed while exhaling the air, a visual display of how strong the respondent is exhaling during the test was displayed on the screen of a computer. The visual display was shown to them so that they can control the speed of the air that was being exhaled. However, no repetition of analysis was made among the preschool children. The measured value of 20 ppb or more was indicated as occurrence of eosinophilic inflammation causing less likely of responsiveness to corticosteroids in children less than 12 years old (ATS/ERS, 2005).

Statistical Analysis

Statistical analysis was performed using SPSS version 20.0. Mann-Whitney U test and Chi square test were employed to determine the association and differences between indoor air pollutant concentrations and the FeNO level. The multiple regression test was performed to identify the main factors that influenced the FeNO levels of the children.

RESULTS AND DISCUSSION

The study was conducted to determine the associations of exposure to industrial air pollutants (PM_{10}, $PM_{2.5}$, NO_2, SO_2, and VOCs) with FeNO among primary school children in Kemaman, Terengganu. There were 48 boys (47.1%) and 54 girls (52.9%) from exposed area and 54 boys (52.9%) and 48 girls (47.1%) from comparative area who took part in this study. The children underwent the airway inflammation test for indicating the FeNO levels which was done concurrently with indoor air monitoring in schools.

Table 1
Concentration of air pollutants in schools

Variables	Exposed Group	Comparative Group	Z-value	p-value
	Median (IQR)	Median (IQR)		
PM_{10} (µg/m³)	116.00 (39.00)	53.00 (24.00)	-11.333	**<0.001***
$PM_{2.5}$ (µg/m³)	94.00 (39.00)	48.00 (22.00)	-11.762	**<0.001***
SO_2 (µg/m³)	331.46 (100.49)	123.79 (129.60)	-12.344	<0.001*
NO_2 (µg/m³)	220.04 (56.61)	22.60 (22.45)	-12.357	**<0.001***
VOCs (ppm)	0.25 (0.53)	0.07 (0.32)	-3.168	<0.001*

Note. N = 204, Mann-Whitney U test; *Significant at p<0.05

Table 2
Concentration of air pollutants in residences

Variables	Exposed Group	Comparative Group	Z-value	p-value
	Median (IQR)	Median (IQR)		
PM_{10} (μg/m^3)	90.00 (55.00)	63.00 (25.00)	-4.870	**<0.001***
$PM_{2.5}$ (μg/m^3)	70.00 (36.00)	51.00 (16.00)	-4.455	**<0.001***
SO_2 (μg/m^3)	165.14(83.12)	41.95 (83.00)	-10.223	<0.001*
NO_2 (μg/m^3)	165.50 (39.66)	57.60 (57.80)	-10.109	**<0.001***
VOCs (ppm)	0.71 (4.21)	0.04 (0.58)	-3.840	<0.001*

Note. N = 162, Mann-Whitney U test; *Significant at p<0.05

Tables 1 and 2 show the concentration of air pollutants in schools and residences between exposed and comparative areas. The concentrations of PM_{10}, $PM_{2.5}$, NO_2, and SO_2 were monitored based on the Malaysian Air Quality Guidelines (Ambient Standards) at a threshold of 150 μg/m^3, 75 μg/m^3, 75 μg/m^3, and 105 μg/m^3 for 24 hours average. It was concluded that the exposure of the exposed group from the concentrations of $PM_{2.5}$, NO_2, and SO_2 in schools and residences were higher compared to the comparative group and the Malaysian standard. The concentrations of VOCs were monitored based on the Industrial Code of Practice (ICOP), in which the recommended threshold level of TVOC should not exceed 3 ppm over an 8 hour time weighted average airborne concentration (DOSH, 2010). Both VOCs concentration in the exposed and comparative areas in this study were within the recommended levels.

Table 3
Comparison of FeNO level among respondents between two groups

Variables	Exposed Group (n= 102)	Comparative Group (n=102)	Z-value	p-value
	Median(IQR)	Median (IQR)		
FeNO (ppb)	21.00 (6.75)	12.00 (5.25)	- 9.442	0.001*

Note. N = 204, Mann-Whitney U test; *Significant at p<0.05.

Based on Table 3, the results showed that the FeNO levels were significantly higher among the exposed group compared to the comparative group (Z= -9.442, p= 0.001). The mean (S.D) for the exposed group [21.57(6.7O)] was higher compared to the comparative group [12.80(3.95)]. According to the study conducted by Noor Hassim and Jalaludin (2014), the results showed a significant difference between the FeNO levels with the study groups (exposed and comparative) with p-value of 0.001. The mean for FeNO values among those who were in the exposed area (11.43 ppb) was higher than those in the comparative area (8.17 ppb). Similarly, Yusoff et al. (2016) also reported a significant difference in FeNO values among school children of studied and comparative groups at p<0.001, suggesting that the school location might have influenced the FeNO levels among study respondents. The results could be due to the higher degree of exposure experienced by those in the exposed area as compared to those in the comparative area (Ayuni et al., 2014). Another study conducted by Aida et al. (2014) revealed that the mean concentrations of FeNO at both areas (urban =11.3 ppb, rural=9.5 ppb) were lower than the standards (20 ppb to 35 ppb for children) based on the ATS clinical practice guidelines for interpretation of FeNO. At a low FeNO value (<20 ppb), eosinophilic airway inflammation is unlikely to happen; whereas at a high FeNO (>20) level, eosinophilic airway is more likely to happen. Besides, several factors such as individual and environmental were highly related to the increase of FeNO values and they are needed to be investigated further in the multivariate analysis (Franklin, 2007). Individual factors influencing FeNO levels among children are gender, active lifestyle, nitrate-rich diet, airway calibre, any infectious disease, and medication while for environmental factors can be described as exposure to tobacco smoke and environmental pollutants such as SO_x and NO_x (ATS/ERS, 2005; Boqqs & Dokmeci, 2012). Thus, the findings support the hypothesis that the FeNO levels of the primary school in exposed areas are significantly higher than the primary school in the comparative area.

Table 4
The association of exposure between industrial air pollutants concentration in schools and FeNO levels among study groups

Variables	**FeNO**		**χ2**	**p-value**	**PR**	**95% CI**
	Unlikely (<20 ppb) Total (%)	**Present (≥20ppb) Total (%)**				
PM_{10}						
High (≥87 µg/m³)	62 (30.40)	40 (19.61)	7.84	0.001*	0.32	0.16-0.62
Low (<87 µg/m³)	42 (20.58)	60 (29.41)				
$PM_{2.5}$						
(≥81 µg/m³)	65 (31.86)	29 (14.22)	12.44	0.001*	0.17	0.08-0.35
(<81 µg/m³)	49 (24.02)	61 (29.90)				
NO_2						
(≥170 µg/m³)	68 (33.33)	28 (13.73)	10.82	0.043*	2.93*	1.02-8.45
(< 170µg/m³)	48 (23.53)	60 (29.41)				
SO_2						
(≥243 µg/m³)	72 (35.29)	30 (14.71)	25.68	0.005*	4.64*	1.56- 13.81
(< 243µg/m³)	31 (15.20)	71 (34.80)				
VOCs						
(≥ 0.084ppm)	48 (23.53)	60 (29.41)	18.70	0.001*	0.11	0.05-0.23
(< 0.084ppm)	70 (34.31)	26 (12.74)				

Note. N= 204, Chi- Square Test; *Significant at p< 0.05; Significant PR at 95% CI>1

Table 4 shows the association between the industrial air pollutant concentrations of PM_{10}, $PM_{2.5}$, NO_2, SO_2, and VOCs with airway FeNO values among exposed and comparative groups. Based on the median value, the level of PM_{10} concentration in schools was categorised into two groups; high level (≥ 87 µg m^{-3}) and low level (< 87 µg m^{-3}), PM $_{2.5}$ concentration; high level (≥ 81 µg m^{-3}) and low level (< 81 µg m^{-3}), NO_2 concentration; high level (≥ 170 µg m^{-3}) and low level (< 170 µg m^{-3}), $S0_2$ concentration; high level (≥ 243 µg m^{-3}) and low level (< 243 µg m^{-3}) and VOCs concentration; high level (≥ 0.084 ppm) and low level (< 0.084 ppm).

Based on Table 4, there was a significant association found between NO_2 and SO_2 with the FeNO value as p< 0.005. The children who were exposed to a high concentration of NO_2 were 2 times more likely to have a higher FeNO level (PR= 2.93, 95% CI=1.02-8.45) while the children who were exposed to a high concentration of SO_2 were 4 times more likely to have a higher FeNO level (PR= 4.64, 95% CI=1.56-13.81), depicting higher airway inflammation.

Table 5
The association of exposure between industrial air pollutant concentrations in residences and FeNO levels among study groups

Variables	FeNO		χ2	p-value	PR	95% CI
	Unlikely (<20 ppb) Total (%)	Present (≥20ppb) Total (%)				
PM_{10}						
High (≥ 74 µg/m^3)	40 (24.69)	42 (25.93)	11.78	0.001*	0.317	0.16-0.62
Low (< 74 µg/m^3)	60 (37.04)	20 (12.34)				
$PM_{2.5}$						
(≥ 61 µg/m^3)	39 (24.07)	49 (30.25)	24.72	0.001*	**5.024***	**2.58- 9.79**
(< 61 µg/m^3)	61 (37.65)	13 (8.03)				
NO_2						
(≥59 µg/m^3)	27 (16.67)	48 (29.63)	39.13	0.001*	**5.497***	**3.02-10.01**
(< 59µg/m^3)	73 (45.06)	14 (8.64)				
SO_2						
(≥84 µg/m^3)	33 (20.37)	48 (29.63)	30.21	0.001*	**4.598***	**2.55- 8.30**
(< 84µg/m^3)	67 (41.36)	14 (8.64)				
VOCs						
(≥0.070ppm)	16 (9.87)	60 (37.04)	5.800	0.016*	0.400	0.16-0.85
(<0.070ppm)	75 (46.30)	11 (6.79)				

Note. N= 162, Chi- Square Test; *Significant at p< 0.05; Significant PR at 95% CI>1

Table 5 shows the association of exposure between industrial air pollutant concentrations in residences and the FeNO levels among study groups. Based on the median value, the level of PM_{10} concentration in residences were categorised into two groups; high level

(≥74 µgm^{-3}) and low level (<74 µgm^{-3}), $PM_{2.5}$ concentration; high level (≥61 µgm^{-3}) and low level (<61 µgm^{-3}), NO_2 concentration; high level (≥59 µgm^{-3}) and low level (<59 µgm^{-3}), SO_2 concentration; high level (≥84 µgm^{-3}) and low level (<84 µgm^{-3}) and VOCs concentration; high level (≥0.070 ppm) and low level (<0.070 ppm).

Based on Table 5, children who were exposed to high industrial air pollutants in residences had high FeNO levels [PM_{10} (25.93%), $PM_{2.5}$ (30.25%), NO_2 (29.63%), SO_2 (29.63%), and VOCs (37.04%)]. As shown in Table 5, there was a significant association found between $PM_{2.5}$, NO_2, and SO_2 with the FeNO value as $p< 0.005$. The children who were exposed to high concentrations of $PM_{2.5}$ were 5 times more likely to have higher FeNO levels (PR= 5.024, 95% CI=2.58- 9.79). The children who were exposed to high concentrations of NO_2 were 5 times more likely to have higher FeNO levels (PR= 5.497, 95% CI=3.02- 10.01) while the children who were exposed to high concentration of SO_2 were 4 times more likely to have higher FeNO levels (PR= 4.598, 95% CI=2.55- 8.30), depicting higher airway inflammation.

Previous local studies had shown that the concentrations of indoor air pollutants in schools and residences nearby the industrial area were higher compared to the comparative group (Jamil et al., 2015; Suhaimi et al., 2016). A local study by Aziz et al. (2014) found that only NO_2 showed a significant association with the elevated levels of FeNO ($p<0.05$) in rural areas. However, the exposure to NO_2 in this study was lower in both areas based on the measurements carried out. When the data of these two study areas were combined, the results showed a significant association between NO_2 and FeNO. However, the relationship was not strong (coefficient of 1). This result may be related to individual susceptibility (nutrition status and genetics) instead of pollutant exposure (Stefania et al., 2012). Franklin et al. (2007) previously explained that the FeNO value in children increased until the age of 13. Thus, the findings support the hypothesis that there is a significant association of industrial air pollutant concentrations between FeNO levels in schools and residences.

Table 6
Multiple linear regressions for association between PM_{10}, $PM_{2.5}$, SO_2, NO_2 and VOCs in school with airway inflammation after controlling the confounders

Independent Variable	B (SE)	p-value	PR	95% CI
Constant	-0.76 (0.23)	0.001	0.47	
PM_{10} (µg/m^3)	1.67 (1.31)	0.203	5.30	0.41- 69.26
$PM_{2.5}$ (µg/m^3)	-1.54 (1.07)	0.151	0.21	0.03- 1.76
NO_2 (µg/m^3)	1.11 (0.49)	0.023	3.02*	1.16- 7.82
SO_2 (µg/m^3)	0.54(0.74)	0.466	1.72	0.40- 7.39
VOCs (ppm)	0.50 (0.54)	0.326	1.66	0.57- 4.80

Note. N=204, Method = Stepwise; *Significant at $p<0.05$; Adjusted R^2 = 0.42795%; CI= 95% Confidence Interval; B= Regression Coefficient; S.E= Standard Error

It is known that air pollutants in schools and residences are influenced by different activities; indoors or outdoors. Table 6 shows five variables to represent factors at schools which were significantly associated with airway inflammation among school children when they were statistically analysed at univariate level. Statistical analysis showed that NO_2 was the most significant factor in schools that influenced airway inflammation among primary school children. There was a significant direct linear relationship between NO_2 in schools and FeNO levels ($p<0.05$). With an increase of 1 µg/m^3 in NO_2 in schools, FeNO levels among school children increased by 0.001%. A study in the Netherlands found that changes in NO_2 concentrations were associated with evidences of acute airway inflammation (FeNO value) and impaired lung function (Strak et al., 2012). These findings were consistent with findings of Noor Hassim and Jalaludin (2014) whereby indoor NO_2 was found to have stronger associations with FeNO levels than $PM_{2.5}$. Other than that, a study done in London by Kharitonov et al. (1994) revealed that the level of FeNO increased in atopic patients than in non-atopic asthma patients. In another study in Italy conducted by Van den Toorn et al. (2001) on randomised clinical trial evaluating two groups of asthmatic children; one of them was assessed for FeNO measurements. After six months of follow- ups, they found that there was a significant reduction of FeNO levels, asthma exacerbation and clinical symptoms in the FeNO group after 6 months of therapy. Based on the study, it revealed that FeNO was potentially capable in evaluating the role of airways inflammation.

CONCLUSION

In summary, the research indicates that children exposed to industrial air pollutants might have increased risk of getting airway inflammation. This study also suggests that exposure and specific explanation about the risk of getting airway inflammation due to poor air quality inside classrooms and residences should be given to the public, primary school management, and parents. Further studies are required to confirm the observed association between industrial air pollutant concentrations and respiratory health among primary school children in the industrial and non- industrial areas. Thus, FeNO can be suggested as a non- invasive biomarker for airway inflammation among children.

ETHICAL CONCERN

Ethical approvals for this study were obtained from the Research Ethics Committee of Universiti Putra Malaysia (Reference no. FPSK EXP15 P148). The objectives of this study were explained to the parents in getting their approval from them in order for their children to be the respondents for this study. All respondents participated on a voluntary basis and may leave at any time without penalty. All the information obtained remains confidential.

ACKNOWLEDGEMENT

The authors would like to express their deepest appreciation to the respondents, their parents and guardians, management of the schools and staff of FMHS UPM for providing supportive valuable information for them to conduct this study successfully. This article was written as a part for a research project funded by the Ministry of Education, Malaysia (project code: 04-01-14-1449FR).

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