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Volatile organic compounds (VOC), formaldehyde and nitrogen dioxide (NO_2) in schools in Johor Bahru, Malaysia: Associations with rhinitis, ocular, throat and dermal symptoms, headache and fatigue

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HIGHLIGHTS

- Xylene, formaldehyde and NO_2 in schools in Malaysia can be associated with fatigue among students.
- Formaldehyde and NO_2 in the classrooms can be associated with ocular symptoms.
- The indoor and outdoor levels of benzene were often above the EU standard for ambient air.

GRAPHICAL ABSTRACT

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ABSTRACT

This paper studied associations between volatile organic compounds (VOC), formaldehyde, nitrogen dioxide (NO_2) and carbon dioxide (CO_2) in schools in Malaysia and rhinitis, ocular, nasal and dermal symptoms, headache and fatigue among students. Pupils from eight randomly selected junior high schools in Johor Bahru, Malaysia (N = 462), participated (96%). VOC, formaldehyde and NO_2 were measured by diffusion sampling (one week) and VOC also by pumped air sampling during class. Associations were calculated by multi-level logistic regression adjusting for personal factors, the home environment and microbial compounds in the school dust. The prevalence of weekly rhinitis, ocular, throat and dermal symptoms were 18.8%, 11.6%, 15.6%, and 11.1%, respectively. Totally 20.6% had weekly headache and 22.1% fatigue. Indoor CO_2 were low (range 380–690 ppm). Indoor median NO_2 and formaldehyde concentrations over one week were 23 $\mu g/m^3$ and 2.0 $\mu g/m^3$, respectively. Median indoor concentration of toluene, ethylbenzene, xylene, and limonene over one week were 12.3, 1.6, 78.4 and 3.4 $\mu g/m^3$, respectively. For benzaldehyde, the mean indoor concentration was 2.0 $\mu g/m^3$ (median < 1 $\mu g/m^3$). Median indoor levels during class of benzene and cyclohexane were 4.6 and 3.7 $\mu g/m^3$, respectively. NO_2 was associated with ocular symptoms ($p < 0.001$) and fatigue ($p = 0.01$). Formaldehyde was associated with ocular ($p = 0.004$), throat symptoms ($p = 0.006$) and fatigue ($p = 0.001$). Xylene was associated with fatigue ($p < 0.001$) and benzaldehyde was associated with headache ($p = 0.03$). In conclusion, xylene, benzaldehyde, formaldehyde and NO_2

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in schools can be risk factors for ocular and throat symptoms and fatigue among students in Malaysia. The indoor and outdoor levels of benzene were often higher than the EU standard of 5 μg/m^3.

1. Introduction

Health problems caused by the indoor environment are of increasingly public health concern. The sick building syndrome (SBS) was defined by a WHO working group and include eye, nose and throat and facial skin symptoms, as well as headache, fatigue and nausea (WHO, 1983). Poor ventilation, volatile organic compounds (VOC), building dampness and mould can be associated with symptoms included in the SBS (Apter et al., 1994; Hodgson, 1995; Redlich et al., 1997; Norbäck, 2009; WHO, 2009; Sahlberg et al., 2010).

VOC have been measured in indoor environments for many decades and levels of indoor and outdoor VOC have been reviewed. For most, but not all VOC, the indoor concentrations are higher than outdoors, typically 2–5 times higher and for some compounds the indoor/outdoor ration (I(O ratio) is even higher (Cometto-Muniz and Abraham, 2015; Chikara et al., 2009). Mixtures of VOC has been used in experimental exposure chamber studies and exposure to a mixture of 22 common VOC during 2.75 h (TVOC exposure level 25 mg/m^3) has been demonstrated to cause eye and throat irritation, headache and drowsiness with no sign of adaptation (Hudnell et al., 1992).

During recent decade, a number of epidemiological studies on associations between levels of specific VOC and TVOC in homes have been published, mainly from Japan and China. One study from Osaka found that indoor concentration of limonene, tolualdehyde, 2-pentanone, tetrachloroethylene, n-decane n-heptane and TVOC were higher in homes where the subjects reported SBS (Nakayama and Morimoto, 2009). One study in newly built detached houses in Sapporo found that formaldehyde and alfa-pinene concentration in indoor air were higher in homes with SBS (Takeda et al., 2009). One larger study in newly built dwellings in six prefectures from northern to southern Japan found that formaldehyde, but not specific VOC or TVOC, were associated with SBS (Takigawa et al., 2010). One study from Dalian, China, found positive associations between 1,1,1-trichloroethane, xylene, butanol, methyl isobutyl ketone, and styrene concentrations in homes and current SBS (Guo et al., 2013). Another study from Taiwan found associations between TVOC and upper respiratory symptoms, dry throat and mucosal irritation (Lu et al., 2015). One study found positive associations between levels of ethylbenzene, trichloroethylene, xylene and TVOC in population-based samples of homes in France (Billonnet et al., 2011). In addition, two longitudinal SBS home studies have been published from Japan. One study in newly constructed homes in Okayama found associations between indoor levels of benzene and SBS (Takigawa et al., 2009). A larger study in newly built dwellings in six prefectures found that elevated levels of indoor aldehydes and aliphatic hydrocarbons were associated with SBS (Takigawa et al., 2012).

The school environment is an indoor environment where the students spend many hours per day. There are very few studies available on associations between indoor VOC in schools and SBS or rhinitis among students. One early longitudinal study from primary schools in mid-Sweden found associations between chronic SBS and total VOC concentration in the classrooms (Norbäck et al., 1990). One recent study among primary schools in six cities in France found associations between the level of formaldehyde in the schools and rhinoconjunctivitis (Annesi-Maesano et al., 2012). Finally, one study in four newly built or renovated elementary schools in Osaka city in Japan found a tendency of an increase of SBS among the students after renovation (Yura et al., 2005).

The indoor environment in schools can be influenced by outdoor air pollution, and nitrogen dioxide is commonly measured as a proxy variable for traffic air pollution. Associations between NO_2 levels in schools have been studied in two longitudinal studies in Taiyuan in northern China. In the first study (2004–2006), indoor NO_2 levels were associated with the prevalence of mucosal SBS at baseline and the symptoms improved when away from school (Zhang et al., 2011). In the second study (2010 − 2012) outdoor NO_2 was positively associated with new onset of skin, mucosal and general symptoms (Zhang et al., 2014). However, we found no previous study on association between indoor and outdoor VOC, formaldehyde or NO_2 in schools and sick building syndrome (SBS) among students in the tropics.

The main aim of the study was to investigate associations between rhinitis and other types of weekly SBS symptoms among junior high school students in Johor Bahru, Malaysia and levels of formaldehyde, NO_2, CO_2 and commonly detected VOC in the students' classrooms. The symptoms included mucosal symptoms (eye symptom, rhinitis, throat symptoms), general symptoms (headache and tiredness) and dermal symptoms (any weekly dermal symptom).

2. Material and methods

2.1. Study population

Totally eight out of 110 junior high schools were randomly selected in Johor Bahru, Malaysia in 2007. In each school, four classes of grade two students were randomly selected and 15 students were randomly selected in each class. The participation rate was 96%, a total of 462 pupils participated. All schools had a two shift system, one group was at school from 7 a.m. to 1 p.m. (our study group) and another afternoon shift was at school from 1 p.m.–7 p.m. (not participating in our study).We have previously published results on associations between fungal and bacterial exposure and asthmatic symptoms and airway infections among the students in these schools (Cai et al., 2011; Norbäck et al., 2014; Norbäck et al., 2016).

2.2. Ethics statement

The study proposal was approved by the Medical Research and Ethics Committee of the National University of Malaysia and all participants gave informed consent. We obtained written consent from the students. The students brought the questionnaire home to answer it together with their parents or guardians, but we got signatures only from the students. The Ethical Committee approved this procedure since the study only included questionnaire data. The study had permission from Johor State Health Department, the principals of the schools and the head teachers in each class.

2.3. Assessment of health data

We used a standardized questionnaire with questions on age, smoking, asthma, allergies and parental allergy/asthma. (Kim et al., 2005; Kim et al., 2011; Zhang et al., 2011; Mi et al., 2006). The questionnaire was given to the selected students by the class teachers and answered at home together with the parents. When the students returned the questionnaires, a school nurse went through the questionnaires during a face-to-face interview with each student to clarify any uncertainly in the answers. When answering the questionnaire, the student had no information on the results of our environment measurements in the classrooms. The questionnaire asked about the following symptoms: Eye irritation (one question), nasal catarrh or nasal congestion (two questions combined to rhinitis), dry throat or sore throat (two questions combined to any throat symptoms), headache (one question), tiredness (one question) and facial and hands rashes or itching (four questions combined to any dermal symptom). Each question had four alternative answers: Yes, everyday; Yes, 1–4 times per week; Yes, 1–3 times per month; and No, never. The recall period was 3 months. The questionnaires were answered the same week as the inspections and the measurements in the classrooms.

2.4. Building inspection and indoor climate

We inspected the buildings and the classrooms. Details on the type of construction and building materials, construction year of the building, type of ventilation system, and signs of building dampness or indoor mould were noted. Temperature (°C), Relative Humidity (RH, %) and concentration of CO_2 (ppm) were measured in all classrooms during class with Q-TrakTM IAQ monitor (TSI Incorporated, St. Paul, Minnesota, USA). The instruments recorded average values over 1 min and were regularly calibrated.

2.5. Sampling of chemical compounds in the schools

Indoor and outdoor VOC were sampled on charcoal tubes (Anasorb 747), the air sampling rate being 0.2 L/min during 4 h and by a charcoal diffusion sampler (ORSA 5) for 7 days. The charcoal tubes were desorbed by 2 mL and the diffusion samplers by 3 mL of carbon disulphide and analyzed for specific VOC by gas chromatography–mass spectrometry (GC–MS) in scan mode by a Hewlett Packard 5890 gas chromatograph equipped with a mass-selective detector (HP 5970) (GC–MS). In addition, the charcoal tube extracts were analyzed for benzene, cyklohexane and methylcyclohexane using selective ion monitoring (SIM). For each detected substance, a mass spectrum and a retention time were determined, and the concentration was quantified by external standards. Indoor and outdoor NO_2 was sampled by a diffusion sampler obtained from and analyzed by IVL Swedish Environmental Research Institute Ltd. (Gothenburg, Sweden), an accredited laboratory for this type of analysis. Indoor and outdoor formaldehyde was measured by SKC UME 100 sampler obtained from SKC (Eighty Four, PA, USA). The formaldehyde diffusion samplers were analyzed by liquid chromatography at the Department of Occupational Medicine, Örebro, Sweden. The sampling time was a continuous seven-day period (24 h/day) for each diffusion sampler. Indoor diffusion samplers were placed in the classrooms approximately 2 m above the floor, to keep them out of reach for the students. The outdoor samplers were placed 2.5–3.5 m above the ground, under a plastic cover to protect from rain.

2.6. Assessment of the home environment and microbial components in school dust

The general questionnaire included a number of questions about the home environment, including one question about environmental tobacco smoke (ETS) in the current home, graded at four levels; never, 1–3 times per month, 1–3 times per week, and daily exposure (coded 0–3) (Zhang et al., 2014). Moreover, there were four yes/no questions asked about any signs of dampness or indoor moulds during the last 12 months at home (water leakage, floor dampness, visible moulds, mould odour) (Norbäck et al., 1999). They were combined into one dampness mould variable. Finally, there was one question about indoor painting the last 12 months in the home (Wieslander et al., 1997). The statistical models included adjustments for these home environment factors.

2.7. Statistical methods

Correlations between different types of indoor exposures were analyzed by a rank correlation test (Kendal-Tau beta). Within- and between school buildings variability were evaluated using linear mixed models with a random intercept on the school level, using STATA version 13.0. Factor analysis was applied for two sets of indoor pollutants, using principal component analysis and rotated component matrix (varimax with Kaiser normalization). The first set consisted of VOC detected in at least one ten classrooms measured by diffusion sampling during one week. The second set consisted of CO_2 and VOC detected in at least one classroom measured by pumped air sampling during class.

Initially, we analyzed associations between the independent variables and symptoms by stepwise multiple logistic regression (forward Wald, $p < 0.10$ as inclusion criteria). The first set of models included indoor exposures (CO_2, NO_2, formaldehyde and VOC by diffusion sampling and pumped air sampling), personal factors (sex, race, current smoking, atopy, parental asthma/allergy) and home environment factors (ETS, dampness/mould, recent indoor painting). The inclusion criteria for indoor VOC were that the particular VOC should have been detected in at least 10 of the 32 classrooms with the particular sampling method. Significant exposure variables in the stepwise regression models were then entered in 3-level logistic regression models, together with all personal factors (sex, race, current smoking, atopy, parental asthma/allergy) and the home environment factors (ETS, dampness/mould, recent indoor painting), irrespectively if the personal or home environmental factors were significant or not. In our previous article we found associations between the total amount of dust in the classrooms and the concentration of endotoxin (a marker of gram-negative bacteria) and ergosterol (a marker of mould) in vacuumed classroom dust (Norbäck et al., 2016). Because of this observation, we created a second set of models with additional adjustment for these dust-related exposures in the classrooms. Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated using the Statistical Package for the Social Sciences (SPSS) 21.0 or STATA (version 13) (for multi-level logistic regression) with two-tailed tests and a 5% significance level.

3. Results

3.1. Personal characteristics and symptoms

The mean age was 14 year (range 14–16) and 52% of the students were girls. A total of 13.1% had doctor's diagnosed asthma and 21.1% reported pollen or furry pet allergy (atopy), 42.3% were Malays, 42.7% were Chinese and 15.0% were Indian. The prevalence of weekly SBS symptoms is found in Table 1.

Table 1
Prevalence of weekly ocular, rhinitis, throat and dermal symptoms, headache and fatigue among students ($N = 462$) from junior high schools in Johor Bahru, Malaysia.

Weekly symptoms the last 3 months	(%)
Ocular symptoms	
Dry eyes or itching in the eyes	11.6
Nose symptoms	
Runny nose	11.5
Nasal congestion	14.9
Any nose symptom (rhinitis)	18.8
Throat symptoms	
Dry throat	10.7
Sore throat	10.4
Any throat symptoms	15.6
Dermal symptoms	
Rash in the face	0.5
Itch in the face	2.2
Rash on the hands	3.1
Itch on the hands	7.6
Any dermal symptoms	11.1
General symptoms	
Headache	20.6
Fatigue	22.1

3.2. Descriptive data on the school environment

The mean age of the buildings was 16 years. The newest school was constructed in 2004 and the oldest in 1967. The school buildings were 2–4 storeys concrete buildings. The walls and ceilings in the classrooms were painted and the floors surface consisted of concrete without any paint or floor covering. The classrooms contained chairs and desks but no carpets or book shelves. All rooms had an electric fan in the ceiling. None of the buildings had air conditioning or mechanical ventilation. Each classroom had two windows, one on each side, with venetian blinds on both sides. The ambient air could enter though one window and exit through the other creating an efficient natural ventilation. During class, the doors were closed and the windows opened. The mean room temperature in the classrooms was 29 °C (range 27–31) and the mean outdoor temperature was 29 °C. The mean indoor relative air humidity was 70% (range 60–78), and the mean outdoor air humidity 73%) The average number of students in each classrooms was 45 the day we made the pumped air sampling (range 24–42). Five (16%) classrooms had signs of water leakage at the ceilings but none had indoor mould.

3.3. Descriptive data on chemical exposure

Data on CO_2, NO_2, formaldehyde and VOC are given in Table 2 and Table 3. The mean CO_2 concentration in the classrooms was 490 ppm (range 380–690), and 410 ppm outdoors. The levels of NO_2 was, on average, similar indoors and outdoors (mean I/O ratio 0.97). Formaldehyde levels were relatively low indoors and somewhat higher outdoors than indoors (mean I/O ratio 0.75). VOC compounds that could be detected in at least 10 classroom (31%) by diffusion sampling of the classrooms are presented in Table 2. Xylene and toluene was found in the highest concentrations indoors and outdoors. Levels of ethylbenzene, limonene and benzaldehyde were lower both indoors and outdoors. The mean indoor outdoor ratio was less than one for all compounds, indicating that the main source of the VOC were the outdoor environment. VOC compounds that could be detected in at least 10 classroom (31%) by the pumped air sampling during lectures are presented in Table 3. Xylene was the dominating compound indoors followed by benzene, toluene and cyclohexane. The same pattern was found for outdoor VOC. I/O ratio was below or equal to one for benzene, toluene and xylene indicating that the main source was the outdoor environment, while the I/O ratio were above one for cyclohexane and ethylbenzene indicated some indoor sources.

Some compounds were detected only in a few classrooms and were not included in the tables. Alkanes were detected by pumped air sampling in some classrooms at low concentrations. Among alkanes, n-octane was detected in five indoor samples (16%) (maximum 4.5 μg/m^3), n-nonane was detected in four samples (13%) (maximum 1.7 μg/m^3), n-decane was detected in 11 samples (34%) (maximum 2.8 μg/m^3)), n-undecane was detected in seven samples (22%) (maximum 1.6 μg/m^3) and n-dodecane was detected in two samples (6%) (maximum 2.3 μg/m^3). Moreover, some terpenes were detected in low concentrations indoors. Alpha-pinene (CAS 7785-26-4) was detected in two samples (6%) (maximum 7.0 μg/m^3), delta-3-carene (CAS 13466-78-9) was detected in three samples (9%) (maximum 12.9 μg/m^3) and longifolene (CAS 475-20-7) was detected in three samples (9%) (maximum 7.5 μg/m^3). Finally, octamethylcyclotetrasiloxane (CAS 556–67-2) was detected in two classroom (6%) (maximum 15.0 μg/m^3).

As a next step, correlations between different indoor exposures were analyzed. There were some correlations between indoor VOC detected by diffusion sampling, particularly for aromatic compounds and limonene (Kendal Tau beta 0.4–0.6). Similar correlations, especially for aromatic compounds, limonene, cyclohexane and chlorobenzene compounds were detected for pumped air sampling during lecture (Kendal Tau beta 0.3–0.6). There were no significant correlations between CO_2, NO_2 or formaldehyde and any of the measured VOC. Five compounds were measured by both diffusion sampling and pumped air sampling and were detected in a sufficient number of classrooms (at least 10 classrooms by one sampling method). There were no significant correlations between indoor VOC levels sampled by diffusion sampling and pumped air sampling for toluene, ethylbenzene, limonene or benzaldehyde but a borderline significance for correlation between xylene by diffusion sampling and pumped air sampling (Kendal Tau beta 0.23; $p = 0.06$). The ratio between toluene and xylene can be used to identify the sources of these compounds. The median of the indoor toluene/benzene ratio was 0.96 (IQR 0.83–1.24). The median of the outdoor toluene/benzene ratio was 0.97 (IQR 0.70–3.08).

For many compounds detected indoors, the variation between schools were much larger than the variation within schools, especially for the one week measurements by diffusion sampling. Some compounds, such as formaldehyde, para-dichlorobenzene and ethylbenzene during lectures had a similar variation between and within schools. A few compounds, such as xylene, cyclohexane and chlorobenzene during lectures and benzaldehyde by diffusion sampling had much larger variation within schools than between schools (Table 4). In addition, we calculated the median indoor exposure for each school (median of the four classrooms) and compared the range (min-max) of these medians with the range (min-max) of the outdoor concentrations. In most cases, the range of the indoor and the outdoor concentrations were similar. In a few cases (formaldehyde, xylene by pumped sampling and methylcyclohexane by pumped sampling) the range of the indoor concentrations were greater than the range of the outdoor concentrations.

Factor analysis of compounds measured during class identified four factors. The first factor consisted of the aromatic compounds benzene, toluene, ethylbenzene, and xylene. The second factor consisted of cyclohexane, methylcyclohexane and benzaldehyde. The third factor consisted of CO_2, chlorobenzene and dichlorobenzene. The fourth factor consisted of limonene, only. Factor analysis of compounds measured by diffusion sampling identified three factors. The first factor consisted of the aromatic compounds toluene, ethylbenzene, xylene and benzaldehyde. The second factor consisted of NO_2 and formaldehyde. The third factor consisted of benzaldehyde, only.

Table 2
Concentration of indoor and outdoor CO_2, NO_2, formaldehyde and VOC sampled by diffusion sampling (1 week) in junior high schools in Johor Bahru, Malaysia (32 classrooms in 8 schools).

Type of compound	Indoor ($N = 32$)				Outdoor ($N = 8$)				I/O ratio
	Median (IQR)	M	Max	DR (%)	Median (IQR)	M	Max	DR (%)	Median (IQR)
CO_2	512 (416–536)	492	689	100	394 (386–402)	440	410	100	1.25(1.05–1.35)
NO_2	23.2 (17.0–32.3)	24.3	41.7	100	20.3(16.9–26.9)	23.8	30.8	100	0.97(0.80–1.59)
Formaldehyde	2.0 (3.0–4.0)	4.2	18.0	100	4.0 (3.0–4.0)	5.5	6.0	100	0.75(0.54–1.00)
Toluene	12.3 (8.2–29.1)	17.5	38.3	100	18.1 (9.3–35.4)	17.6	52.2	100	0.82(0.68–1.07)
Ethylbenzene	1.6 (1.3–2.7)	1.9	3.8	97	2.8 (1.3–3.8)	1.9	6.9	88	0.87(0.36–1.17)
Xylene	78.4 (60.3–125)	85.4	141	100	141 (96.5–175)	86.7	183	100	0.61(0.43–0.87)
Limonene	3.4 (<1–10.1)	5.4	18.7	53	5.3 (<1–20.1)	5.4	26.6	50	NA
Benzaldehyde	<1 (<1–3.9)	2.0	13.3	41	<1 (<1 − <1)	2.7	9.3	38	NA

M = arithmetic mean IQR = interquartile range %DR = % above detection limit (1 μg/m^3) NA = not available DR = detection rate (%).

Table 3
Concentration of indoor and outdoor VOC by pumped air sampling (4-hours) in junior high schools in Johor Bahru, Malaysia (32 classrooms in 8 schools).

Compound (μg/m^3)	Indoor (N = 32)				Outdoor (N = 8)				I/O ratio
	Median (IQR)	M	Max	DR (%)	Median (IQR)	M	Max	DR (%)	Median (IQR)
Benzene	4.6 (2.0–12.4)	7.2	31.7	88	5.1 (1.0–5.1)	7.2	17.1	75	0.93 (0.78–1.07)
Toluene	4.3 (2.1–13.1)	7.0	28.4	88	6.7 (2.0–11.0)	6.5	17.1	88	0.82 (0.66–1.27)
Ethylbenzene	0.9 (<1–3.0)	1.6	9.1	53	0.8 (<1–2.3)	1.5	2.6	50	NA
Xylene	45.5 (27.6–112)	97.3	818	88	42.6 (28.2–42.6)	72.0	151	88	1.00 (0.92–1.67)
Cyclo-hexane	3.7 (2.6–6.7)	5.3	20.6	91	2.2 (1.6–4.2)	6.1	5.9	100	1.47 (0.91–2.90)
Metyl-cyclohexane	<1 (<1–4.5)	2.9	12.8	47	<1 (<1–1.0)	3.9	1.4	25	NA
Limonene	<1 (<1 –<1)	<1	2.6	9	<1 (<1 –<1)	<1	<1	0	NA
Benzaldehyde	<1 (<1 –<1)	<1	13.3	41	<1 (<1 –<1)	<1	<1	0	NA
Chlorobenzene	<1 (<1–1.9)	3.0	28.7	44	<1 (<1–1.4)	3.0	44.8	50	NA
Para-dichloro-benzene	<1 (<1–1.9)	1.6	13.1	47	<1 (<1–2.1)	1.6	52.1	25	NA

M = arithmetic mean IQR = interquartile range %DR = % above detection limit (1 μg/m^3) NA = not available DR = detection rate (%).

3.4. Symptoms in relation to concentrations of chemical compounds in classroom air

In the initial stepwise logistic regression models we included all exposure variables, personal factors (gender, ethnicity, current smoking, atopy, parental asthma/allergy) and the three home environment factors (recent indoor painting, dampness/mould and environmental tobacco smoke) (forward Wald, $p < 0.1$). Exposure variables that were significant in these models were entered into 3-level hierarchic models (student, classroom, school) including the personal factors and home environment factors mentioned above. Indoor NO_2 was associated with ocular symptoms ($p = 0.001$) and fatigue ($p = 0.01$). Indoor formaldehyde was associated with ocular symptoms ($p = 0.004$), throat symptoms ($p = 0.006$) and fatigue ($p = 0.003$). Indoor xylene measured by diffusion sampling was associated with fatigue only ($p < 0.001$). Moreover, there was an association between indoor benzaldehyde by diffusion sampling and headache ($p = 0.03$). Three negative associations were found. Ethylbenzene ($p = 0.03$) and metylcyclohexane ($p = 0.001$) by diffusion sampling were negatively associated with rhinitis and in addition there was a negative association between ethylbenzene by diffusion sampling and tiredness ($p = 0.03$) (Table 5). Similar results were obtained with additional adjustments for the total amount of classroom dust and the concentration of microbial components (endotoxin and ergosterol) in the vacuumed dust (Table 5).

Table 4
Variation within- and between buildings of air pollutants calculated from variance components (32 classrooms in 8 schools).

Sampling method	Type of compound	Variations between schools (%)	Variations within schools (%)
Continuous diffusion sampling during one week			
	NO_2	83	17
	Formaldehyde	51	49
	Toluene	96	4
	Ethylbenzene	86	14
	Xylene	86	14
	Limonene	88	12
	Benzaldehyde	11	89
Pumped air sampling during lecture			
	Benzene	79	21
	Toluene	78	22
	Ethylbenzene	52	48
	Xylene	26	74
	Cyclohexane	3	97
	Methylcyclohexane	64	36
	Benzaldehyde	63	27
	Chlorobenzene	31	69
	Para-dichlorobenzene	55	45

4. Discussion

Headache, fatigue and rhinitis and other SBS symptoms were common among the students and associated with indoor concentrations of chemical air pollutants. Indoor level of NO_2 was associated with ocular symptoms and tiredness and indoor formaldehyde was associated with ocular and throat symptoms and tiredness. Indoor benzaldehyde was associated with headache and indoor xylene was associated with tiredness. VOC and formaldehyde are usually considered to be emitted mainly from indoor sources. However, in our study performed in well ventilated schools in a tropical area, indoor and outdoor levels of VOCs were similar and in some cases slightly higher outdoors (I/O ratio < 1). Cyclohexane was the only VOC with a clear indoor source (I/O ratio 1.47). To our knowledge, this one of few studies on associations between rhinitis and SBS-symptoms and airborne chemicals in schools in a tropical area.

We measured air pollution by two methods, diffusion sampling and pumped air sampling. There were some discrepancy between indoor levels, variation between and within schools, and health associations when comparing data from the two sampling methods. This could be because the two methods reflect different pollution sources. The pumped sampling reflects the exposure during class, which is the most relevant exposure to study. The sources of air pollution during class can be the students, the indoor environment and the outdoor environment. One limitation of the pumped sampling is the short sampling time (day to day variation). Because of this we also used diffusion sampling for a longer period (7 days continuous 24 h sampling) to get a better average value. However, the disadvantage with this method is that most of the sampling time is in an empty classroom. Since the schools had a two shift system, the classrooms were occupied 12 h/day for 5 days (Monday–Friday) which corresponds to one third of the sampling time (7 days sampling).

We found health associations for indoor levels of two aldehydes, formaldehyde and benzaldehyde. The median levels of formaldehyde and benzaldehyde were higher outdoors than indoors, indicating mainly outdoor sources. It is well known that ozone and NO_2 have an important role in reactive indoor and outdoor chemistry where different aldehydes are formed (Weschler, 2001; Weschler et al., 2006). Such reactive chemistry is often the major source of free radicals and other short-lived reactive compounds in indoor environments (Weschler et al., 2006). The health significance of reactive indoor chemistry has been documented for terpene oxidation products (Rohr, 2013). One office study from USA found an association between outdoor levels of ozone and building-related symptom of SBS type and suggests that it is due to reactive indoor chemistry (Apte et al., 2008). Most studies on this issue are from a temperate climate and the health consequences of reactive air chemistry in the tropics have not been addressed. Traffic exhaust is nowadays a major source of NO_2. However, it has been demonstrated that oil palm plantations can lead to more nitrogen oxides and VOC in ambient airs as compared to rainforest, and that these compounds can increase the production of ground-level ozone (Hewitt et al., 2009). The southern part of peninsular Malaysia is covered with

Table 5
Final models (3-level hierarchic logistic regression) for associations between CO_2, NO_2, formaldehyde and VOC in classrooms and weekly symptoms among students ($N = 462$).

	OR (95% CI)[a]	p-Value	OR (95% CI)[b]	p-Value
Ocular symptoms				
NO_2	2.34 (1.40–3.90)	0.001	2.03 (1.08–3.79)	0.03
Formaldehyde	3.55 (1.51–8.38)	0.004	3.23 (1.11–9.40)	0.03
Xylene (pumped sampling)	1.21 (0.94–1.56)	0.13	1.20 (0.93–1.54)	0.16
Nose symptoms				
Ethylbenzene (diffusion sampling)	0.68 (0.48–0.96)	0.03	0.71 (0.51–0.99)	0.05
Methylcyclohexane (pumped sampling)	0.85 (0.77–0.94)	0.001	0.85 (0.96–0.94)	0.001
Throat symptoms				
Formaldehyde	2.85 (1.36–5.99)	0.006	2.33 (0.95–5.72)	0.07
Dermal symptoms				
No associations	NA	NA	NA	NA
Headache				
Benzaldehyde (diffusion sampling)	2.52 (1.09–5.81)	0.03	3.39 (1.34–7.63)	0.009
Fatigue				
NO_2	1.67 (1.12–2.47)	0.01	1.96 (1.11–3.48)	0.02
Formaldehyde	3.31 (1.52–7.24)	0.003	3.35 (1.33–8.42)	0.01
Ethylbenzene (diffusion sampling)	0.63 (0.45–0.96)	0.03	0.64 (0.42–0.99)	0.04
Xylene (diffusion sampling)	1.37 (1.22–1.55)	<0.001	1.41 (1.19–1.66)	<0.001
Xylene (pumped sampling)	0.80 (0.60–1.08)	0.13	0.78 (0.57–1.10)	0.16

(OR calculated for 10 μg/m^3 increase of NO_2).
(OR calculated for 10 μg/m^3 increase of formaldehyde).
(OR calculated for 100 μg/m^3 increase of xylene by pumped air sampling).
(OR calculated for 10 μg/m^3 increase of xylene by diffusion sampling).
(OR calculated for 1 μg/m^3 increase of ethylbenzene by diffusion sampling).
(OR calculated for 1 μg/m^3 increase of methylcyclohexane by pumped air sampling).
(OR calculated for 1 μg/m^3 increase of limonene by pumped air sampling).
(OR calculated for 10 μg/m^3 increase of benzaldehyde by diffusion sampling).
Analysis of associations were done for compounds detected in at least 10 classrooms.
[a] The models includes indoor exposure variables retained in a stepwise logistic regression model (forward regression Wald statistics, $p < 0.10$). These variables were entered in a 3-level hierarchic logistic regression model (pupil, classroom, school) including selected exposure variables and potential confounders (gender, ethnicity, smoking atopy, parental asthma/allergy, indoor painting last 12 months at home, dampness/moulds last 12 months at home, and environmental tobacco smoke (ETS) at home).
[b] These models included the same variables as in models a) but with additional adjustment for the total amount of dust in the classroom and the concentration of endotoxin and ergosterol in the vacuumed dust.

oil palm plantations and nowadays 13% of the total land area of Malaysia is oil palm plantations, as compared to 1% in 1974 (Hewitt et al., 2009). Our study did not specifically address the role of air pollutants linked to oil palm plantations or reactive air chemistry, and we did not measure indoor or outdoor ozone levels. However, there is a clear need for more detailed studies on this issue in tropical countries such as Malaysia.

The schools, classrooms and students were randomly selected from all secondary schools in Johor Bahru, Malaysia, and the response rate was high. All samples were analyzed after questionnaire data was completed, and all measurements were conducted the same week as the students answered the questionnaires. Johor Bahru is located in the tropics on the southern tip of the Malaysian peninsula with a similar climate every month. The constant climate makes the natural ventilation flow through the windows in the classrooms similar all year around. Most associations detected had a low p-value ($p < 0.01$ or less). Thus we conclude that the study was not seriously influenced by selection bias, information bias or multiple statistical testing. However, since it is a cross-sectional study we cannot draw conclusions on causality.

The indoor levels of CO_2 during class was between 380 and 690 ppm and always below the recommended limit of 1000 ppm (ASHRAE, 1999). This demonstrates that there was an efficient natural ventilation through the windows in all classrooms. We found no associations between CO_2 levels and any type of symptoms.

We found associations between indoor NO_2 levels and eye symptoms, throat symptoms and tiredness The median level of NO_2 was 23 μg/m^3 indoors and 20 μg/m^3 outdoor and exceeded the WHO guideline of 40 μg/m^3 (annual mean) (WHO, 2005) only in a few classrooms. None of the classrooms contained any combustion sources such as gas stoves or gas heaters. It is well known that NO_2 can react with water on indoor surfaces to form nitrous acid (HONO) which can induce eye symptoms (Rasmussen et al., 1995) and respiratory symptoms (Jarvis et al., 2005). The mechanism behind the health effects of HONO has been suggested to be formation of hydroxyl radicals (Gomez Alvarez et al., 2013). Since Malaysia is a tropical country with high air humidity formation of nitric acid could be one possible mechanism of our health findings concerning health associations for NO_2. NO_2 is also usually used as a proxy variable for traffic exhaust but in Malaysia NO and NO_2 can also be emitted from oil palm plantations (Hewitt et al., 2009).

We found an association between the indoor formaldehyde and ocular symptoms, throat symptoms and tiredness. The levels were well below the WHO air quality guideline for formaldehyde of 110 μg/m^3 (WHO, 2005). The mean outdoor levels (6.0 μg/m^3) were higher than the indoor levels (4.2 μg/m^3), suggesting that the main source of formaldehyde was the outdoor environment. This is in agreement with a previous school environment study from China, where formaldehyde levels were higher outdoors (5.8 μg/m^3) as compared to indoors (2.3 μg/m^3) (Zhao et al., 2008). Formaldehyde can be emitted from indoor sources but can also be formed at photochemical reactions in the outdoor air (Guo et al., 2004). We found no previous study on associations between formaldehyde levels in schools and SBS symptoms among students, but some previous studies have found association between formaldehyde levels in homes and SBS-symptoms (Sahlberg et al., 2013; Guo et al., 2013; Takigawa et al., 2010; Takigawa et al., 2012), but at much higher levels than in our school study. It could be speculated that the source of formaldehyde in our study could be reactive indoor or outdoor chemistry. Nitrogen dioxide is known to be involved in reactive chemistry with VOC causing formation of different aldehydes (Weschler, 2001; Weschler et al., 2006). The factor analysis revealed that NO_2 and formaldehyde were in the same factor. The sources of indoor and outdoor formaldehyde in Malaysia schools needs to be identified in more detailed studies.

Benzaldehyde is another aldehyde that can be formed from aromatic compounds in outdoor air by photochemical reactions during smog formation (Guo et al., 2004). We found an association between indoor benzaldehyde sampled by diffusion sampling and headache. In our study, the mean outdoor levels of benzaldehyde (2.7 μg/m^3) were somewhat higher than the mean indoor levels (2.0 μg/m^3) suggesting outdoor sources for this compound. Our outdoor levels if this compound were somewhat higher than reported from Hong Kong. They found 1 μg/m^3 of benzaldehyde in summer and 2 μg/m^3 in winter (Guo et al., 2004). Indoor sources of benzaldehyde includes decay of paper, and benzaldehyde levels in the range from 0.2–54 μg/m^3 has been measured in libraries and archives (Gibson et al., 2012). However, in our study the amount of paper in the classrooms were very limited. In Germany, a tentative indoor air quality standard of 20 μg/m^3 has been suggested to protect from unpleasant odour (Anonymous, 2010).

Benzene and toluene are found in traffic exhaust emissions, but can also come from indoor sources. The factor analysis found that all aromatic hydrocarbons (benzene, toluene, ethylbenzene and xylene) were in the same factor. The ratio between toluene/benzene can be sued to identify the sources of these compounds and is relatively constant for traffic air pollution in a certain area (Khoder, 2007). In our study, the indoor toluene/benzene ratio and the outdoor toluene/benzene ratio were similar on average, indicating that the main source of these two compounds is outdoor traffic exhausts. The median level of benzene was 4.6 μg/m^3 indoors and 5.1 μg/m^3 outdoors, and 50% of the indoor values and 50% of the outdoor levels exceeded the air quality standard for benzene of 5 μg/m^3 (annual average) by the European Union (European Commission, 2015). Maximum concentration was 31.7 μg/m^3 in one classroom. We found no previous studies on benzene in schools in Malaysia but one study measuring roadside benzene levels reported even higher outdoor levels (48 μg/m^3) in Kuala Lumpur (Lan and Binh, 2012). The median level of toluene during class was 4.3 μg/m^3 indoors and 6.7 μg/m^3 outdoors. Maximum concentration was 28.4 μg/m^3 in one classroom. We found no associations between benzene or toluene levels and any symptoms.

Ethylbenzene and xylene are two other aromatic compounds from traffic exhaust emissions as well as from indoor sources. Indoor levels of ethylbenzene were negatively associated with rhinitis and tiredness. Since the indoor levels were very low, the negative associations are most likely due to residual confounding with some other indoor exposure. The median level of ethylbenzene was 1.6 μg/m^3 indoors and 2.8 μg/m^3 outdoors as one week average but levels measured during lectures were even lower. Xylene was the aromatic compound found in the highest concentrations in the classrooms and indoor xylene measured by diffusion sampling was positively associated with fatigue. The median level was 78.4 μg/m^3 indoors and 141 μg/m^3 outdoors as one week average but levels during class were lower. We found no previous study on associations between exposure to xylene in schools and fatigue. However, one exposure chamber study found an increase of fatigue after exposure to m-xylene but at much higher levels (50 ppb for 2 h) (Ernstgård et al., 2002).

We found that indoor methylcyclohexane measured during class was negatively associated with rhinitis. We have no explanation to this negative association. The indoor mean concentration of this compound was 2.9 μg/m^3 indoors and 3.9 μg/m^3 outdoors. The factor analysis identified one factor consisting of cyclohexane, methylcyclohexane and benzaldehyde. Methylcyclohexane is found in consumer products (Sack and Steele, 1992) but can also be emitted from pathogenic bacteria associated with respiratory infections (Abd El Qader et al., 2015). In the large European AIRMEX study, the mean indoor levels of methylcyclohexane in public buildings/schools was the same as in our study (2.9 μg/m^3) but the outdoor levels were much lower (0.4 μg/m^3) (Geiss et al., 2011).

5. Conclusions

Indoor levels of xylene, formaldehyde, NO_2 and CO_2 in schools in Malaysia can be risk factors for ocular, throat symptoms and tiredness among the students. The indoor and outdoor levels of benzene were often higher than the current EU-standard of 5 μg/m^3. The associations between indoor levels of NO_2, formaldehyde and benzaldehyde and symptoms, despite relatively low concentrations of these compounds, indicate that reactive indoor chemistry could play a role. Outdoor sources seemed to be dominating for many of the VOCs. More detailed studies are needed on reactive chemistry in indoor and outdoor air in the tropics.

Conflict of interest

None of the authors declare any conflict of interest.

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