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Full Length Research Paper

Human kidney injury molecule-1 and interleukin-18 as predictive markers of nephrotoxicity in acute organophosphorus poisoned patients in Zagazig University hospitals

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Organophosphorus (OP) poisoning is a major common cause of mortality and morbidity in most countries. Some clinical cases developed renal injury after acute OP poisoning. The aim of our study is to evaluate the levels of kidney injury molecule-1(KIM-1) and interleukin -18(IL-18) in acute OP poisoned patients as early predictors of OP induced nephrotoxicity. Over a period of one year, the observational cross sectional study was conducted at the Poison Control Center, Zagazig University hospitals, Zagazig, Egypt. The study group consisted of 95 patients who fulfilled the inclusion criteria; the patients were categorized according to Peradeniya organophosphorus poisoning (POP) scale. The serum pseudocholine esterase enzyme (PChE), serum creatinine, urinary KIM-1 and IL-18 were assayed at 0, 12, 24 and 48 h after admission. There were progressive increases in the mean values of KIM-1 and IL-18 at different time intervals especially in severe poisoned patients compared to the increased levels of serum creatinine. The cutoff values of urinary KIM-1 and IL-18 that determined patients with potential AKI were 2.8 ng/ml creatinine (86.9% sensitivity, 94.6% specificity and 0.859% area under curve) and 59 pg/dl creatinine (90% sensitivity, 92% specificity and 0.946% area under curve), respectively. A positive correlation was observed between KIM-1 and IL-18 and serum creatinine. Moreover, KIM-1 is positively correlated with IL-18. Urinary KIM-1 and IL-18 may be considered as valid markers for prediction of acute kidney injury among acute OP poisoned patients.

Key words: Organophosphorus poisoning, IL-18, KIM-1, acute kidney injury.

INTRODUCTION

Pesticides include different groups of compounds such as insecticides, herbicides, fungicides. There are many active substances incorporated in several preparations of

pesticides used in agriculture. Synthesis of several organophosphorus (OP) compounds started since 1930 (Thunga et al., 2010). According to World Health

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Organization, there are 3 million cases of OP poisoning occurring every year, leading to more than 250,000 deaths. One million serious unintentional poisonings occur every year and other two million people are hospitalized for suicide attempts with pesticides (Banerjee et al., 2012; Reddy et al., 2016).

In developing countries, OP poisoning is considered as a major common problem. This is due to its easy availability and low-cost, so, it has become an agent of choice for suicide especially in rural areas (Banday et al., 2015). Exposure to it may occur through different means such as drinking, breathing or dermal exposure (King and Aaron, 2015).

Organophosphorus compounds act through irreversible inhibition of cholinesterase enzyme inducing massive accumulation of acetylcholine within the synaptic cleft. This leads to overstimulation of cholinergic receptors (nicotinic and muscarinic receptors) in the central and peripheral nervous system which occur by excess acetylcholine leading to manifestations of OP poisoning (Carey et al., 2013).

Clinically OP poisoning is characterized by acute cholinergic crisis which develops within a few minutes to hours after being exposed to it. This crisis manifests by the followings; bradycardia, hypotension, tachycardia, excess salivation/lacrimation, excessive sweating, nausea, vomiting, diarrhea, abdominal pain, fecal and urinary incontinence (Lotti and Moretto, 1995). Central nervous system manifestations include anxiety, restlessness, convulsion, miosis, insomnia, coma, Cheyne-Stokes breathing, respiratory and cardiovascular failure (Singh and Khurana, 2009; Peter et al., 2014).

The death rate could reach 40% even with proper treatment. The main cause of death is respiratory failure (Carey et al., 2013). Other complications related to OP poisoning are motor neuropathy, arrhythmia, pulmonary edema, pneumonia, pancreatitis, and renal failure (Lee et al., 2015).

Acute kidney injury (AKI) is a problem all over the world with different causes and manifestations. Severe adverse outcomes such as high morbidity, long hospital stays, high medical cost, a risk of long-term dialysis and even late mortality can occur as a result of misidentification or underestimation of this problem (Pakula and Skinner, 2015). Acute kidney injury diagnosis is based on an absolute or percentage elevation in the serum creatinine concentration over the baseline (Waikar and Bonventre, 2009). There are many novel biomarkers for early detection of AKI such as kidney injury molecule-1 (KIM-1) and interleukin-18 (IL-18) (Vanmassenhove et al., 2013).

Kidney injury molecule-1 (KIM-1) is an immunoglobulin (Ig) superfamily transmembrane receptor. It is up regulated and expressed specifically in injured proximal tubular cells to help the removal of necrotic and apoptotic debris. This expression can continue till complete recovery of the damaged cells occurs (Shao et al., 2014).

Thus, KIM-1 is considered as an ideal biomarker as well as a good predictor of prognosis for kidney injury (Ahmed and Hamed, 2015). Interleukin-18 (IL-18) is a proinflammatory cytokine with a molecular weight of 18 kDa. Renal tubular cell is one of the major sources of IL-18 production. It is up-regulated and increased in cases of AKI (Gavrić and Kališnik, 2016). Therefore, this study was conducted to evaluate the urinary KIM-1 and IL-18 levels in acute OP poisoned patients as early predictors of OP induced nephrotoxicity.

SUBJECTS AND METHODS

Study protocol

An observational cross sectional study was conducted in the Poison Control Centre, Zagazig University hospitals, Zagazig, Egypt. The study was done from January 2017 to January 2018. It was done on adult patients having a history of acute organophosphorus intoxication 24 h previously and diagnosed from full detailed history given by patient or relatives, pesticide containers, thorough clinical examination and measurement of plasma cholinesterase or pseudocholesterase enzyme level (PChE) at the time of admission. All patients were followed up during treatment.

Exclusion criteria

These include the followings:

- (1) Pre-existing renal impairment
- (2) Urinary tract infections (UTI) by urine analysis
- (3) History or suspicion of ingestion of other poisons concomitantly.
- (4) Other concomitant illness like cardiac, pulmonary and hypertension
- (5) Pregnant and paediatric patients.
- (6) Chronic exposure to OP.

The organophosphorus compounds were identified by the containers given by the patients or their relatives; they were chlorpyrifos in 93% cases, diazinon in 5% cases and parathion in 2% cases.

Study population

Out of 380 organophosphorus poisoned patients, 285 patients did not fulfil our criteria. 95 patients were enrolled; out of them there were 45 males and 50 females, with an average age of 18 to 50 years old. The patients were classified according to Peradeniya OP poisoning (POP) scale (Table 1) (Senanayake et al, 1993) into: (I) mild poisoned patients (n=45), (II) moderate poisoned patients (n=40) and (III) severe poisoned patients (n=10). According to POP scale, the following scores were given to the patients: a score of 0 to 3 is considered as mild poisoning, 4 to 7 as moderate poisoning and 8 to 11 as severe poisoning. Informed consents from patients were obtained.

All patients underwent decontamination and received the standard medical treatment for acute OP poisoning according to poison control centre protocol for management of OP poisoning (Eddleston and Clark, 2011). The patients were followed up till their final clinical outcome or hospital discharge.

Table 1. Peradeniya Organophosphorus Poisoning Scale (POP).

Parameter	Data	Scale
Pupil size	>2 mm	0
	<2 mm	1
	Pin point	2
Respiratory rate	<20/min	0
	>20/min	1
	>20/min with central cyanosis	2
Heart rate	>60/min	0
	41-60/min	1
	<40/min	2
Fasciculation	None	0
	Present, generalized or continuous	1
	Both generalized and continuous	2
Level of consciousness	Conscious and rationale	0
	Impaired response to verbal commands	1
	No response to verbal commands	2
Seizures	Absent	0
	Present	1

Source: Senanayake et al. (1993).

The medical protocol of treatment included administration of single dose of 1 g/kg of activated charcoal, atropinisation starting with 1-3 mg then doubling doses at every 5-10 min interval. Atropine given until disappearance of chest crepitation (abolishing of muscarinic signs) was added by removing nasopharyngeal secretions and oxygen inhalation. The symptomatic cases received Pralidoxime chloride (1 to 2 g) infused over 20 to 30 min followed by 0.5 g/h for 1-3 days up to 7 days. Patients that needed to be intubated were transferred to intensive care unit (ICU).

Data collection

Data were collected by study doctors in Poison Control Centre within Zagazig University hospitals. Blood and urine samples were collected at the time of admission (0 h) before beginning treatment; 12 h from admission (12thh) and daily thereafter for the next 2 days (24thh and 48th h) for estimation of serum PChE level, serum creatinine, urinary KIM-1 and IL-18, respectively. Serum samples used for the measurement of PChE levels were collected and centrifuged using Pchem Cholinesterase reagent kit (Adaltis S.R.I., Milano, Italy) by spectrophotometer (Optizen 3220 UV, Mecasys Co., Ltd, Korea) at 405 nm according to the manufacturer's instruction. The data were expressed by U/L and the baseline reference values were 3000-9000 U/L.

Serum creatinine was measured in serum samples according to the method of (Husdan and Rapoport, 1968). using a Dimension RxLauto analyzer (Siemens Healthcare Diagnostics Inc., Newark, DE, USA). The data were expressed as mg/dl and the base line reference values were 0.7-1.2 mg/dl. A fresh mid-stream urine samples were collected using disposable cups without

preservatives. The samples were immediately centrifuged, separated, and stored at -80°C until further analysis. Urinary KIM-1 and IL-18 were measured using enzyme-linked immunosorbent assay (ELISA) (MyBioSourceMBS700484, San Diego, California, USA) according to the manufacturer's instructions. The data were expressed by ng/ml and pg/dl, respectively. All analytical procedures were done in Poison Control Centre, Zagazig University hospitals laboratories, Zagazig, Egypt.

Statistical tests

Continuous variables were expressed as mean±SD and categorical variables were expressed as a number (percentage). Data were analysed using ANOVA. Least significant difference (LSD) was used for comparison in between groups. Distribution of categorical variables was compared using the Chi-square (χ^2) test. The Pearson correlation (*r*) was calculated to assess the correlation between serum creatinine and pseudocholeline esterase, urinary KIM-1 and IL-18. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values of urinary KIM-1 and urinary IL-18 with maximum sensitivity and specificity. *p* value <0.05 was considered statistically significant, *p* <0.001 was considered highly significant, and *p* ≥0.05 was considered non-significant.

RESULTS

This study included 95 patients with average age from 18 to 50 years. There were 63 patients (66.3%) with age

Table 2. Acute OP poisoning patients age distribution as a percentage.

Age range	No of patients	Percent
18-35y	63	66.3
36-50 y	32	33.7

Table 3. Demographic characteristics between acute OP poisoning studied groups using ANOVA and Chi-square statistical tests.

		Mean \pm SD	Range	F	p. value	
Age (29.8 \pm 10.8)	Mild	27.7 \pm 10.4	18-50	3.333	0.04*	
	Moderate	32.1 \pm 11.2	18-50			
	Sever	36.2 \pm 11.3	18-50			
Sex	Males (No. =45)		Females (No. = 50)		χ^2	p. value
	No.	%	No.	%		
Mild	20	44.4	25	50.0	2.3	0.317**
Moderate	18	40.0	22	44.0		
Sever	7	15.6	3	6.0		

Values are expressed as means \pm standard deviation (n= 95).

* Significant ($p < 0.05$).

** Non significant ($p > 0.05$)

%: percent

F: ANOVA test

χ^2 :Chi-square test.

range from 18-35 years old and 32 patients (33.7%) with age range from 36-50 years old (Table 2). The OP poisoning cases were classified according to POP scale as 45 patients (47.4%) of mild toxicity and 40 patients (42.1%) of moderate toxicity and 10 patients of severe toxicity (10.5%). There was no significant difference between different groups based on gender ($p > 0.05$). However, comparing the mean values of age with the severity of toxicity, there was a significant increase in the mean values of age associated with severe toxicity group ($p < 0.05$) (Table 3).

In this study, there was a significant difference in the mean values of PChE among the studied groups at different time interval of examinations (0, 12, 24 and 48 h). There was significant reduction in the mean values of PChE in all studied groups at 0 and 12 h at the time of admission followed by gradual increase in PChE levels in both mild and moderate groups at 24 and after 48 h of admission; this approximates the laboratory reference values. However, in severe group, the mean values of PChE showed significantly lower levels when compared with mild and moderate groups during and after 48 h of admission (Figure 1).

Regarding serum creatinine levels, there were gradual unnoticeable increases in the mean values of serum creatinine, where the levels were still within the normal

laboratory reference ranges at different time intervals in the studied groups. The highest levels were recorded at 48 h of admission compared to 0 h (time of admission). We also found that there were significant increases in the mean values of serum creatinine after 24 and 48 h in severe OP poisoned group compared to the mild and moderate groups ($p < 0.001$) (Table 4).

In comparing the mean values of urinary KIM-1 at different time intervals in different groups, its highest levels were recorded at 48 h at the time admission in all groups. The statistically significant increment was detected at 24 h in mild and moderate groups and at 0 and 12 h in severe group ($p < 0.001$). When different studied groups were compared with each other, we found significant differences in the mean values of urinary KIM-1 with the highest levels in the severe group ($p < 0.001$) (Table 4).

Meanwhile, the mean values of urinary IL-18 were compared with the time intervals among different studied groups; there were highly significant increases with the highest level at 48 h after admission in all groups. The significant increment was detected at 24 h in mild group and at 0 h in moderate and severe groups ($p < 0.001$). When different studied groups were compared with each other, we found significant differences in the mean values of urinary IL-18 with the highest levels in the severe

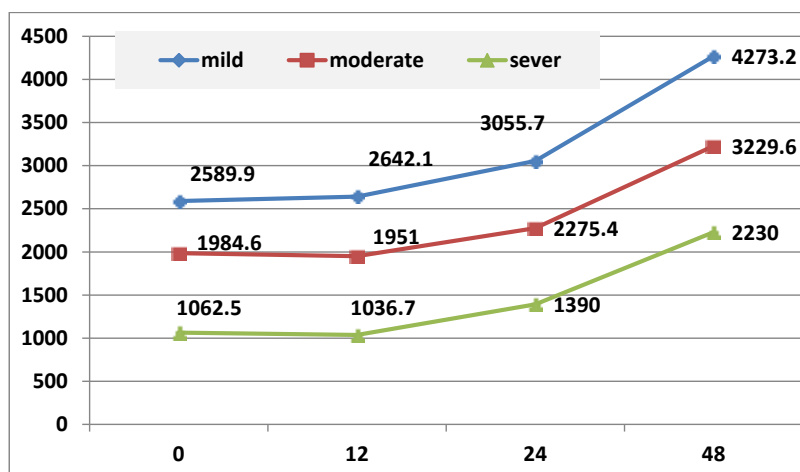


Figure 1. Pseudocholine esterase enzyme levels at different time intervals among the studied organophosphorus poisoning groups.

Table 4. Comparison between different time intervals from admission regarding serum creatinine, urinary KIM-1 and urinary IL-18 levels in acute organophosphorus poisoning studied groups.

Variable	Hour	Mild Mean \pm SD	Moderate Mean \pm SD	Sever Mean \pm SD	F	p.value
Serum (mg/dl) creatinine	0	0.551 \pm 0.03	0.62 \pm 0.07	0.61 \pm 0.06	15.562	<0.001**
	12	0.554 \pm 0.02	0.65 \pm 0.1	0.66 \pm 0.08	22.566	<0.001**
	24	0.61 \pm 0.1	0.68 \pm 0.1	0.83 \pm 0.07	20.158	<0.001**
	48	0.62 \pm 0.1	0.72 \pm 0.1	0.84 \pm 0.1	11.161	<0.001**
F		6.89	5.652	14.926		
p. value		<0.001**	0.001*	<0.001**		
KIM-1(ng/ml)	0	0.51 \pm 0.2	0.68 \pm 0.1	0.8 \pm 0.07	15.607	<0.001**
	12	0.52 \pm 0.2	0.72 \pm 0.2	2.2 \pm 0.8	95.788	<0.001**
	24	0.89 \pm 0.4	0.94 \pm 0.3	2.3 \pm 0.8	8.913	<0.001**
	48	0.94 \pm 0.4	1.3 \pm 0.09	2.8 \pm 0.7	16.54	<0.001**
F		4.454	10.775	14.409		
p. value		0.005*	<0.001**	<0.001**		
IL-18(pg/dl)	0	46.6 \pm 7.7	51.9 \pm 3.5	51.9 \pm 4.2	9.331	<0.001**
	12	49.6 \pm 2.9	54 \pm 7.8	58.3 \pm 2.9	24.513	<0.001**
	24	52.6 \pm 4.2	67.5 \pm 15.6	85.2 \pm 20.5	34.527	<0.001**
	48	60.8 \pm 12.9	67.5 \pm 17.6	86.9 \pm 19.6	11.386	<0.001**
F		29.848	15.004	17.535		
p. value		<0.001**	<0.001**	<0.001**		

Values are expressed as means \pm standard deviation (n= 95).

F: ANOVA test

* Significant (p< 0.05).

**Highly Significant (p< 0.001).

group (p<0.001) (Table 4).

Regarding the correlation between PChE levels, urinary KIM-1, urinary IL-18 and serum creatinine, PChE showed significant positive correlation with IL-18 and serum

creatinine. Meanwhile, it showed significant negative correlation with KIM-1. A significant positive correlation was recorded with both KIM-1 and IL-18 and serum creatinine. We also found that KIM-1 is positively

Table 5. Correlation Coefficient between pseudocholesterase enzyme levels, urinary KIM-1, urinary IL18 and serum creatinine in acute organophosphorus poisoning patients.

Variable	KIM-1 (ng/ml)		IL-18 (pg/dl)		PChE (U/L)	
	r	p. value	r	p. value	r	p. value
PChE (U/L)	-0.125	0.015*	0.006	0.908		
Serum creatinine (mg/dl)	0.758	<0.001**	0.755	<0.001**	-0.145	0.005*
IL-18 (pg/dl)	0.699	<0.001**			0.006	0.908

r: Pearson correlation

* Significant (p< 0.05).

**Highly Significant (p< 0.001).

Table 6. Validity and accuracy of urinary KIM-1 and IL-18 in prediction of AKI in acute organophosphorus poisoning patients.

	Cut-off	AUC	Sensitivity (%)	Specificity (%)	PPV	NPV	Accuracy	95% confidence interval		p. value
								Lower	Upper	
KIM-1 (ng/ml)	2.8	0.859	86.9	94.6	83.3	95.9	92.6		0.737	<0.001**
IL-18 (pg/dl)	59	0.946	90	92	75	97.2	91.6		0.902	<0.001**

%: percent

PPV: Positive predictive value.

NPV: Negative predictive value.

AUC: Area under the curve.

**Highly Significant (p< 0.001).

correlated with IL-18 (Table 5). The cut-off value of urinary KIM-1 that detected patients with AKI in OP poisoned cases was 2.8 ng/ml creatinine, (area under the curve) 0.859 AUC, 86.9% sensitivity, 94.6% specificity; the positive predictive value (PPV) was 83.3 and negative predictive value (NPV) was 95.9 (Table 6; Figure 2). While the cut-off value of urinary IL-18 was 59 pg/dl, 0.946AUC, 90% sensitivity, specificity 92%; the positive predictive value was 75 and negative predictive value was 97.2 (Table 6) and (Figure 3).

DISCUSSION

Organophosphorus (OP) compounds are usually used as pesticides and are considered the commonest poison-related morbidity and mortality in our country. In our hospital, OP poisoned patients constituted the majority of admissions and this motivated us to carry out the study. Multiple organs could be affected with OP poisoning leading to worsening of clinical presentations and/ or prognosis. Renal failure may be the cause of death in some OP cases (Agostini and Bianchin, 2003). Acute kidney injury (AKI) is a sudden unexpected and sustained reduction of kidney function with several aetiologies and clinical presentations (Bellomo et al., 2001).

Acute kidney injury was reported to be frequent in severe OP poisoning (Rubio et al., 2012). A study

recorded 6.17-fold higher risk of AKI among OP patients (Lee et al., 2015). Several hypotheses were proposed to explain the mechanism of AKI in OP patients, however it is unclear. An experimental study reported increase in oxidative stress, direct damage to the distal convoluted tubules, rhabdomyolysis and dehydration induced hypovolaemia (Agostini and Bianchin, 2003).

In our study, we wanted to find an association between acute OP poisoning and development of AKI within 48 h of exposure by detection of urinary KIM-1 and IL-18 as early predictors of AKI. A total of 95 patients were recruited for this study (45 males and 50 females). Majority of the patients were from rural area and their age ranged from 18 to 50 years; 66.3% were in the age group of 18-35 years (middle age). The OP poisoning severity was determined according to the POP scale from mild to severe; 47.4% of the patients were graded as mildly poisoned, with a POP score of 0-3, 42.1% of the patients were moderately poisoned (4-7) and 10.5% of the patients had severe grade of poisoning (8-11).

Our results are consistent with previous studies that used POP scale to detect OP severity among OP poisoned patients (Raikod et al., 2014; Dubey et al., 2016); they reported similar distribution of age (21-30 years) and sex (female gender) for majority of their patients. Previous studies recorded the majority of OP patients were young adults in the age group of 15-35 and 21-33 years, respectively (Khan et al., 2003; Ashray et

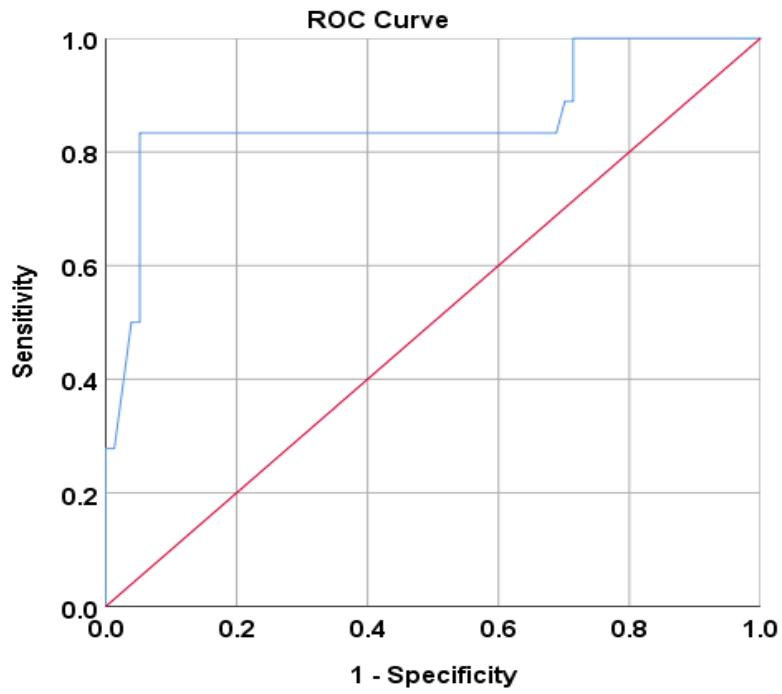


Figure 2. ROC curve to assess urinary KIM-1 as a predictor of acute kidney injury in acute organophosphorus poisoning patients

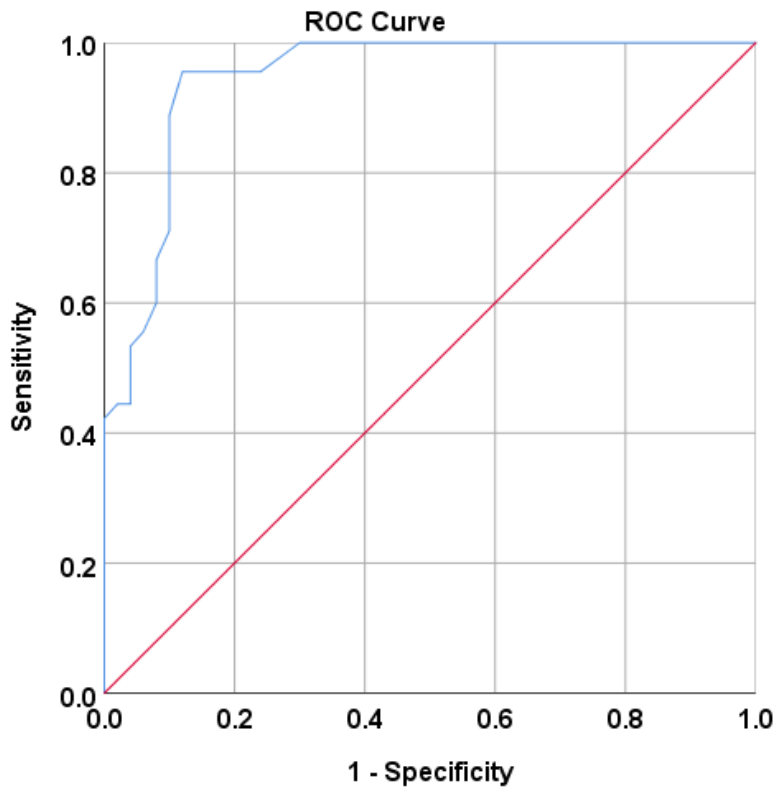


Figure 3. ROC curve to assess urinary IL-18 as a predictor of acute kidney injury in acute organophosphorus poisoning patients.

al., 2018). This age group may be attributed to the vulnerability of this age group to various emotional conflicts (Khan et al., 2003). The most dependable features for diagnosis of OP poisoning are history of exposure, miosis that has been considered a stronger indicator for OP poisoning and serum or red blood cells cholinesterase level estimation (Singh and Khurana, 2009).

In the current study, Pseudocholine esterase enzyme levels (PChE) mean values of studied groups showed lower levels in all groups at the time of admission (0 h) especially, with severe poisoned group. The mean values of PChE levels gradually increased at day two of admission; however in severe group the levels were still low. These results are in agreement with a study done by Prashant et al, on the serial measurements of serum acetylcholine esterase levels for OP poisoned cases. The study recorded gradual increment in PChE levels in moderate poisoned group while in severe poisoned group, the levels were low (Prashant et al., 2012).

Acetylcholine esterase enzyme is usually inhibited after OP poisoning resulting in increased acetylcholine in the synaptic junctions and disturbance of neurotransmission (Rovasio et al., 2011). This leads to marked reduction of both PChE and red blood cell cholinesterase activities that are considered indicators of OP excessive absorption (Prashant et al., 2012). It was suggested that PChE level could be helpful in predicting the length of ICU stay, prognosis (Prashant et al., 2012) and morbidity of OP poisoning (Ashray et al., 2018); this indicates its role in OP poisoning associated morbidity.

Our results demonstrated significant increase of serum creatinine after 24 and 48 h at the time of admission in severe group of OP poisoning compared to results of 0 and 12 h during admission. While in the mild and moderate groups of poisoning, the highest level was recorded at 48 h during admission. However during the follow up, we noticed that the levels of serum creatinine were still in the average laboratory reference ranges.

Moreover, the results of urinary KIM-1 and IL-18 showed statistically significant increase after 24 h in mild group, while in moderate and severe groups the high levels detection was earlier during admission especially, with IL-18 results. However, the severe group of OP poisoning was the most affected either with KIM-1 results or IL-18 results. Our results showed that KIM-1 and IL-18 revealed the potential development of AKI earlier than serum creatinine.

Clinically AKI was defined as sudden disruption of renal function depending on elevation of serum creatinine at a rate of ≥ 0.3 mg/dL from baseline and/ or reduction of urine output (< 0.5 mL/kg/h for more than six hours) through 48 h and staged as stage 1 injury (Mehta et al., 2007). However, it was demonstrated that about 80% of death rate increased in renal insult patients with variations of serum creatinine as little as 0.3 to 0.5 mg/dL

(Uchino et al., 2006).

Unfortunately, the traditional diagnostic serum creatinine has a limited role to be used as early predictor as its concentrations tended to be raised through 24-36 h after renal injury; if the glomerular filtration rate decreased, the half-life of serum creatinine increased from 4 h to 24-72 h and finally AKI in patients with fluid overload may be missed or delayed because the volume variations affect serum creatinine level (Liu et al., 2011). The detection and validation of new biomarkers for AKI has been progressed to replace or complement serum creatinine (Palevsky et al., 2013). These new markers could detect the little changes in renal function before serum creatinine rose (sub-clinical AKI) (Delanaye et al., 2014). The development of specific interventions made it possible to reverse AKI, if the type of injury could be diagnosed earlier (Ostermann and Joannidis, 2016).

Previous studies reported several available putative biomarkers and having the ability to provide an earlier diagnosis of AKI in humans such as KIM-1 (Han et al., 2002) and (IL-18) (Melnikov et al., 2001). Human KIM-1 is from structural trans- membrane glycoprotein (339 amino acid residues in length) with an N-terminal ectodomain and may not be detectable in normal kidney tissue or urine. However it is highly expressed after renal ischemic or toxic injury in humans and animals (Zhang et al., 2007).

Urinary KIM-1 was recorded to have very high sensitivity and specificity in urine samples and is stable in frozen urine samples (Ruangyuttikarn et al., 2013). In the urine of healthy individuals, the KIM-1 levels were recorded to be less than 1 ng/ml. However, its levels after ischemic renal injury were from 3-7 ng/ml. This started to elevate as early as 6 h and remained high for 48 h after the insult (Slocum et al., 2012).

KIM-1 has been recently recognized as a biomarker for renal injury by drug and food administration in preclinical studies of pharmacological agents (Vaidya et al., 2010). It could be used as a nephrotoxic biomarker in conditions of drug induced renal ischemia (Prozialeck et al., 2007). It was reported in an experimental study on induced renal disease that urinary KIM-1 represented the tubular KIM-1 expression (Shao et al., 2014).

Interleukin 18 is pro-inflammatory cytokine and is known as interferon-gamma inducing factor. It is produced by macrophage cells (monocyte) and bind to IL18 receptor to induce its action which is cell mediated immunity (Gami and Garovic, 2004). Previous studies reported that IL-18 is specific for renal tubules as its level increased with ischemic reperfusion injury (Faubel and Edelstein, 2005) and increased in AKI patients for being superior to serum creatinine in early detection (Jayaraman et al., 2014). Haase et al. (2008) attributed its increased levels for being non-specific marker that was associated with systemic inflammation rather than damage of renal tubules. IL-18 was detected as the best

predictor of the primary outcome due to deteriorated AKI or death (Arthur et al., 2014) and it could predict the deterioration of AKI when the diagnosis is based on serum creatinine (Koyner et al., 2012).

In the current study, the cut-off value of urinary KIM-1 for prediction of AKI was 2.8 ng/ml; with sensitivity of 86.9%, and specificity of 94.6%. While the cut-off value for urinary IL-18 was 59 pg/dl, with sensitivity of 90% and specificity of 92%. Wherefore, the patients with KIM-1 and IL-18 levels higher than the cut-off values were considered to have potential AKI. Previous studies on the prediction of AKI in different situations contrary to serum creatinine reported the efficiency of KIM-1 and IL-18 in early prediction of AKI before affecting serum creatinine or development of proteinuria (Liu et al., 2013; Qasem et al., 2014; Ahmed and Hamed, 2015; EL-Attar et al., 2017).

Conclusion

Urinary KIM-1 and IL-18 levels showed significant increase earlier than serum creatinine in acute OP poisoning. Urinary KIM-1 and IL-18, as non-invasive markers, were more specific in prediction of AKI in OP poisoned patients; this could be helpful in early ICU admission, prevention of renal insult and improvement of the patients.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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Full Length Research Paper

Influence of dry erase ink solvent mixtures on eye irritation

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Teaching is the process of imparting knowledge by teachers in learners. To enhance this, methods of presenting information visually to a full room of students at once are used. This includes writing on whiteboards written using whiteboard marker pens. Dry erase ink for whiteboard marker pen is composed of volatile solvent vehicle which easily vaporizes allowing the mark to dry on the surface of the whiteboard. Different manufactures use different solvents and different composition ratios in their ink brands. Different mixtures of VOCs have different irritation thresholds and potencies. This study sought to establish the components of vapour produced when different dry erase inks used in secondary schools in Nakuru County evaporate and compare their ability to elicit eye irritation on the teachers. The study design was repeated measures. Thirteen secondary schools which used whiteboards only in the classrooms were selected purposefully and the teachers in these schools were randomly selected; there were 224 respondents. Questionnaires were used to collect data on self-reported eye irritations while chromatography was used to identify the components of the vapours produced by the different brands of ink. The three ink brands used in the schools were found to contain acetone, ethanol, hexane and methanol. Inks 2 and 3 were found to have a more potent mixture than ink 1 (Odds ratio= 2.182; 95 C.I. =1.174-4.054). The study concludes that different ink solvent mixtures have different abilities to elicit eye irritation on persons exposed to their vapours ($\chi^2 =6.933$; $p=0.031$) and that methanol and acetone solvent mixture (found in ink 1) were the least potent eye irritants.

Key words: Dry erase, eye irritation, secondary schools, solvents mixture, teachers.

INTRODUCTION

Traditionally, school teachers write on chalkboards written using chalk. The chalk produces a lot of dust which accumulates on surfaces and the computer machines. This has made many schools to substitute the chalkboards with whiteboards. The whiteboards or dry-

erase boards came into use in the late 1980s. By the 1990s most of the class rooms were replaced with whiteboards instead of blackboards (Muttappallymyalil et al., 2016).

Dry erase ink for whiteboard marker pen is composed

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of volatile solvent vehicle, binder resin, fluorinated surfactant, non-fluorinated surfactant or surfactants, including the preferred cationic amide oxide, release agent and poly(oxyalkylene) substituted colorant (Carroll and Valenti, 2000). A solvent can be defined as a liquid that has the ability to dissolve, suspend or extract other materials, without chemical change to the material or solvent (Dick, 2006). The solvent easily vaporizes allowing the mark to dry on the surface of the whiteboard (Uhara et al., 2009). In the process, these volatile organic compounds (VOCs) are released into the air and can easily get into contact with the eyes and skin of the teachers. They can also be inhaled or ingested by both the teachers and students (Halverson, 2011). The solvents used include butanol, diacetone alcohol, ethanol, Isopropyl alcohol, Methyl isobutyl ketone and 2-butoxy-ethanol (Halverson, 2011). Toluene and xylene are also used as solvents (Conner, 2009).

Butanol causes irritation to the eyes, skin and throat. It also causes headache, drowsiness blurred vision, photophobia (abnormal visual intolerance to light), dermatitis, auditory nerve damage, hearing loss and central nervous system depression. Diacetone alcohol causes corneal damage and also irritates the eyes, skin, nose and throat. Ethanol causes lassitude (weakness, exhaustion), drowsiness, headache and is also an irritant to the eyes, skin and nose. Isopropyl alcohol (rubbing alcohol) may cause dizziness, headache and drowsiness as well as irritate the nose, eyes and throat. Methyl isobutyl ketone irritates the eyes, mucous membrane and the skin when it comes into contact with it. It may also cause headache, narcosis, dermatitis and coma if the exposure is high. Monobutyl ether (2-butoxy-ethanol) causes eyes, skin, nose and throat irritation, destruction of red blood cells, central nervous system depression, headache and vomiting. It may also result in blood in the urine (Halverson, 2011).

Health effects of xylene are determined by the dose, duration and route of exposure (ATSDR, 2007). Short-term exposure of people to high levels of xylene can cause irritation of the skin, eyes, nose, and throat, difficulty in breathing, impaired function of the lungs, delayed response to a visual stimulus, impaired memory, stomach discomfort and possible changes in the liver and kidneys. Both short and long-term exposure to high concentrations of xylene can also cause a number of effects on the nervous system, such as headaches, lack of muscle coordination, dizziness, confusion, and changes in one's sense of balance. It can also cause death (Kandyala et al., 2010). Low to moderate levels of toluene can cause tiredness, confusion, weakness, drunken- type actions, memory loss, nausea, and loss of appetite. Long-term exposure to toluene in the workplace may cause some hearing and color vision loss while repeatedly breathing in toluene may permanently damage the brain (ATSDR, 2015). Marker pen inks with

alcohol as a solvent are characterized with low odour unlike the toluene and xylene solvents which have strong odour (ATSDR, 2007). The manufacturers of the alcohol based marker pen inks label their products as non-toxic although they are irritants (ATSDR, 2015).

The irritants found in the schools as a workplace for the teachers can be controlled using the hierarchy or preferred order. This hierarchy suggests that the source should be eliminated if possible. This is the most effective control measure. Substitution is considered next where the source of irritant can be substituted with one that has no health effects. Isolation is the next considered where barriers or screens are installed for separating the teacher from a source of irritant. Administrative control can also be used which involves introduction of work practices that reduce the risk. These may include limiting the amount of time a teacher is exposed to the particular irritant. Personal protective equipment is considered when the other control methods fail. These may include the use of gloves, barriers and facemasks, to prevent contact with the irritant (Tyrer and Lee 1985; Quinlan and Bohle, 1998). It is therefore important to identify the solvents in the inks used in secondary schools and establish their potency in causing irritation on the eyes of the teachers. This can act as a guide in the selection of the most effective control method of the irritants in the different marker pens to ensure occupational safety of the secondary school teachers.

The objectives of the study were i) to identify the different brands of dry erase used in the secondary schools in Nakuru County in Kenya; ii) to establish the components of vapour produced by the different dry erase brands and iii) to compare the relative eye irritation potencies of the different brands of dry erase ink.

MATERIALS AND METHODS

The research design was repeated measure design. The study limited itself to the thirteen schools in Nakuru County in Kenya which used whiteboards in the classrooms only. Teachers in the selected schools were randomly and proportionately selected giving a total of 224 teachers. The observations were carried out at two different times. During the first time of the study, all the schools were doing their end term examination (July 2016) and therefore the teachers were not using the whiteboard marker pens because there was no teaching going on. The second observation was done during another term (February 2017) at a time when teaching was going on in all the selected schools. All the teachers were therefore using the whiteboard marker pen ink. The data on self-reported information on eye irritation of the teachers were collected using a questionnaire.

A sample of each ink brand was placed in an evacuated tube using a syringe. The ink was warmed in water bath at 60°C for 20 min to allow the headspace to reach equilibrium as used by Portari et al. (2008). The headspace vapours were then sucked using a syringe and dissolved in acetone, hexane and ethanol solvents. Chromatography was then carried out on these solutions using an Agilent technologies 7820A gas chromatography machine with a

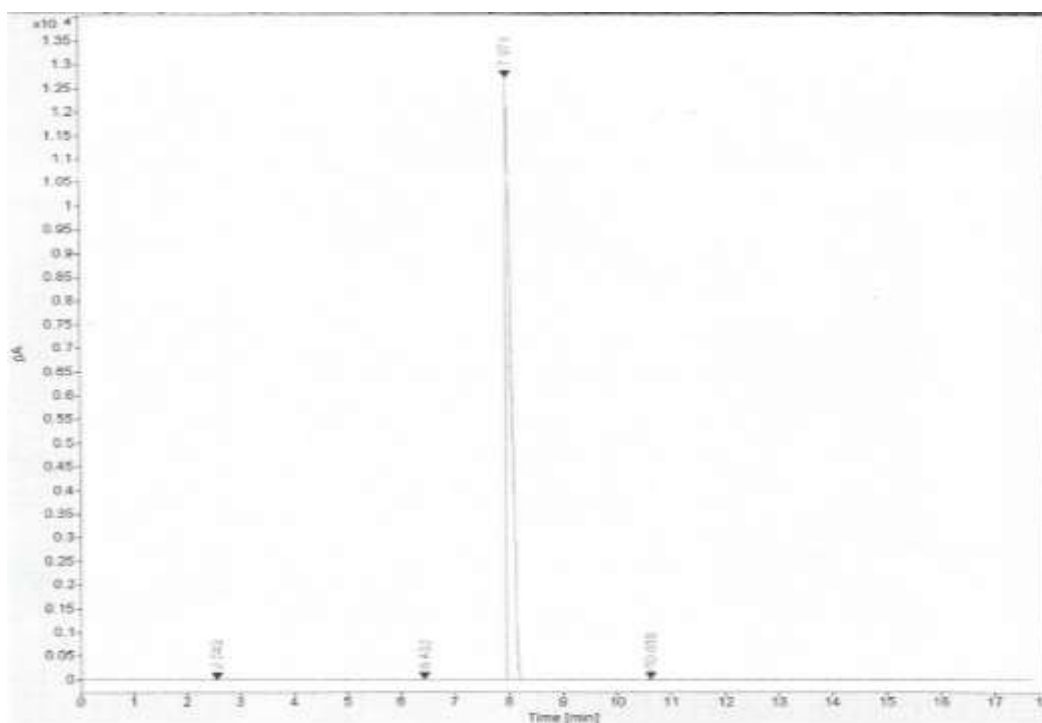


Figure 1. Ink 1 vapour in acetone.

DB 624 column of a length of 30 m, an internal diameter (ID) of 320 μm and a film thickness (DF) of 1.8 μm . The temperatures at the injection, detector and column were 250, 200 and 60 -150°C respectively. The airflow rates of oxygen, hydrogen and nitrogen were 400, 40 and 45 ml/min, respectively. The split ratio used was 100:1. The column temperature program started at 60.0°C for 2.00 min and was then ramped at 6.0°C per minute until 150°C was obtained. The area under the curve on the chromatogram of each of the components was used to determine the percentage composition of the components in the ink vapour.

Data were managed using SPSS (Version 23.0 for Windows) and analyzed using descriptive and inferential statistics. Tables and charts were used to represent data. One way ANOVA was used to compare the incidences of eye irritation of teachers who used the different brands of ink. Chi square was used to test the association between ink brands and eye irritation while ANOVA for repeated measures was used to compare the incidence of eye irritation of teachers during the different times of exposure. The Odds ratio was used to compare the ability of the different ink brands to cause eye irritation.

RESULTS AND DISCUSSION

Dry erase brands used in the secondary schools

The results show that there were three different brands of ink used in the secondary schools in Nakuru County. These were ink 1, ink 2 and ink 3. Seven schools used ink 1, three schools used ink 2 and the other schools

used ink 3.

Components of the ink vapour

The results indicate that the vapour from ink 1 had methanol and acetone. The vapour of ink 2 had acetone and hexane while the vapour of ink 3 had ethanol and hexane (Figures 1-13). These components easily evaporated from the ink when placed in a water bath at 60°C. This means that these components have a low boiling point and easily evaporate at the normal classroom temperature. Uhara et al. (2009), Cantú (2012) and Cantú (2015) say that when ink writings are exposed to the air, the solvents in them evaporate and this makes the writing to dry. In the process, they contaminate the classroom indoor air.

These result findings agree with research study carried out by Anderson and Anderson (2003) who carried out gas chromatography on emissions of felt pens and whiteboard cleaners. He found that they contained a mixture of alcohols, acetates and ketones. Castorina et al. (2016) measured emission rates of VOCs of different markers under controlled laboratory conditions and found that alcohols were the most highly emitted class of VOCs from dry erase markers.

The percentage composition of the components in the

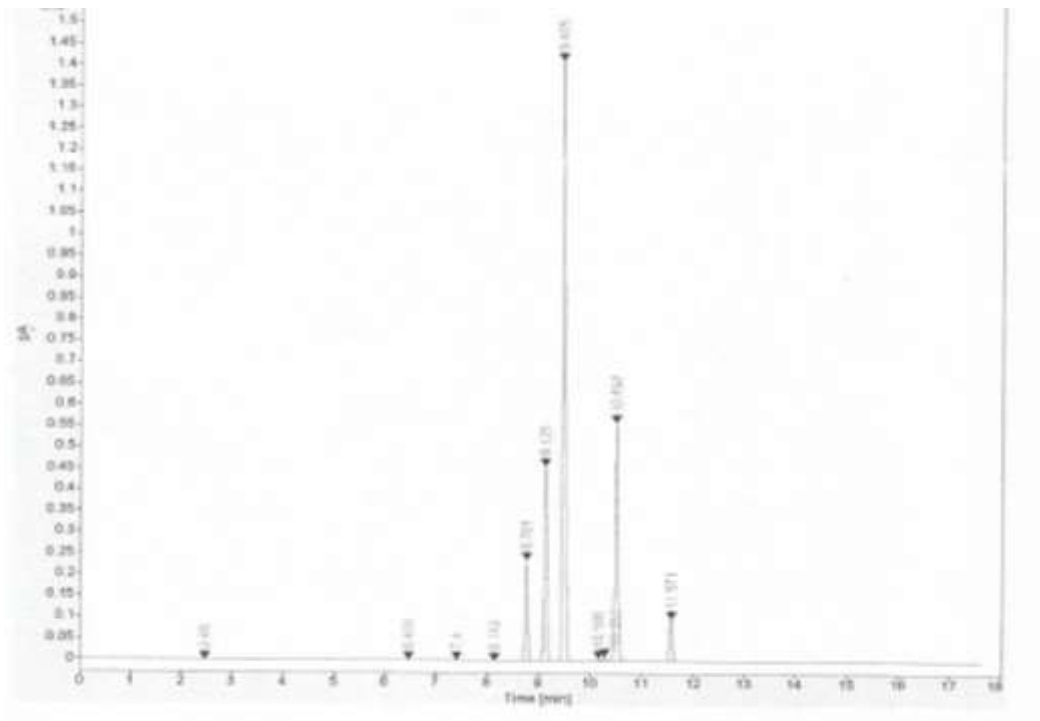


Figure 2. Ink 1 vapour in hexane.

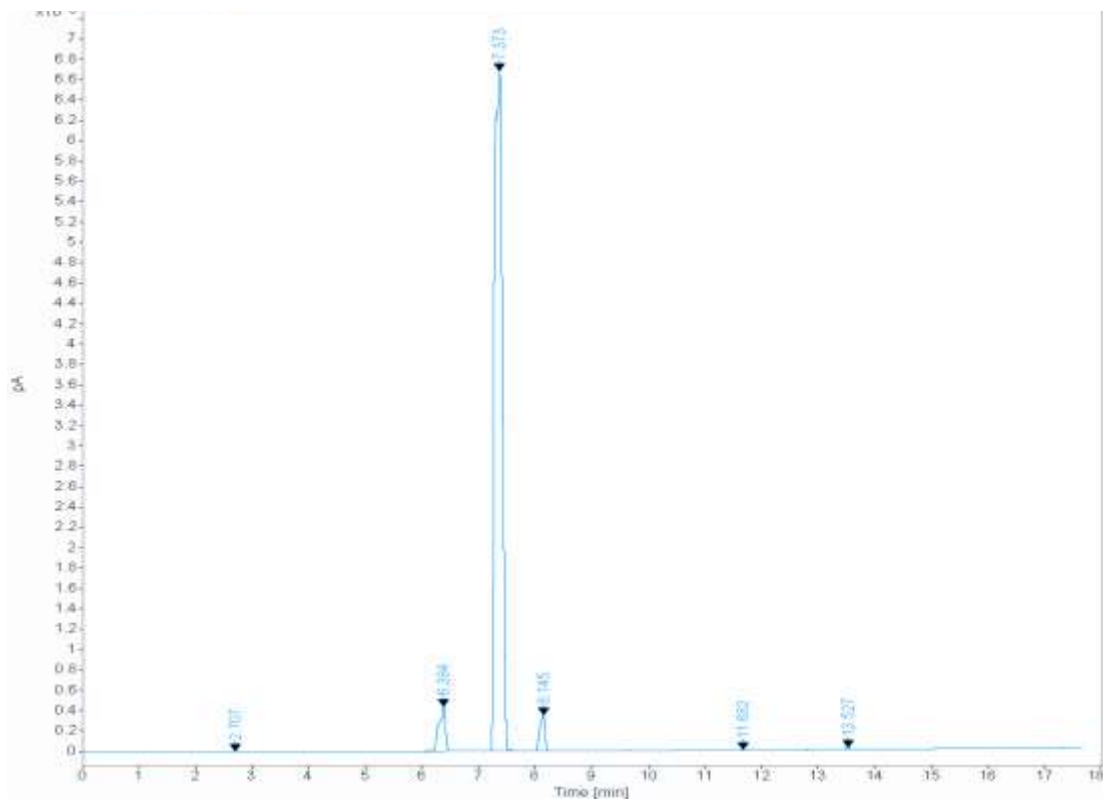


Figure 3. Ink 1 vapour in ethanol.

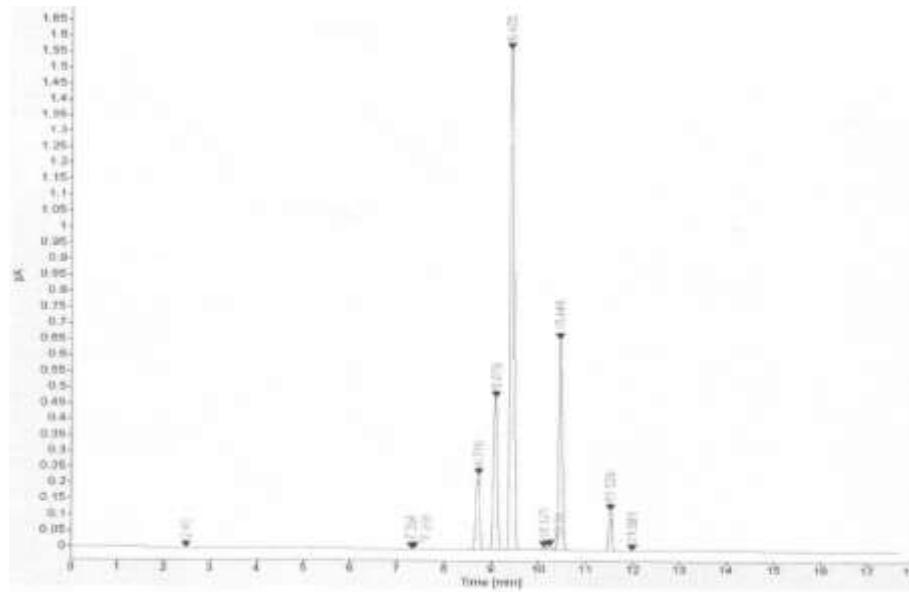


Figure 4. Hexane.

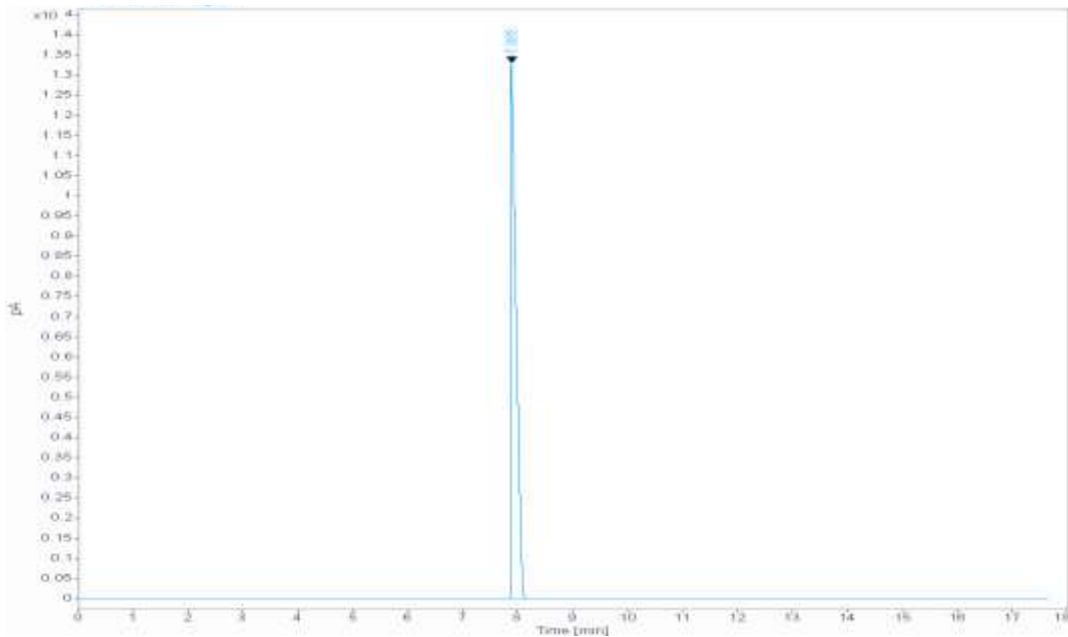


Figure 5. Acetone.

ink vapour was calculated based on the area under the curve for each component. The results indicate that the quantities of the different solvents in each of the ink were different with ink 1 having more methanol than acetone. Ink 2 had more acetone than hexane while ink 3 had a very high percentage of hexane (Table 1).

Influence of dry erase vapour on development of eye irritation

The incidence of eye irritation was higher among teacher when the marker pen ink was in use (27.1%) than when it was not in use (21.4%) (Figure 14). Whiteboard marker

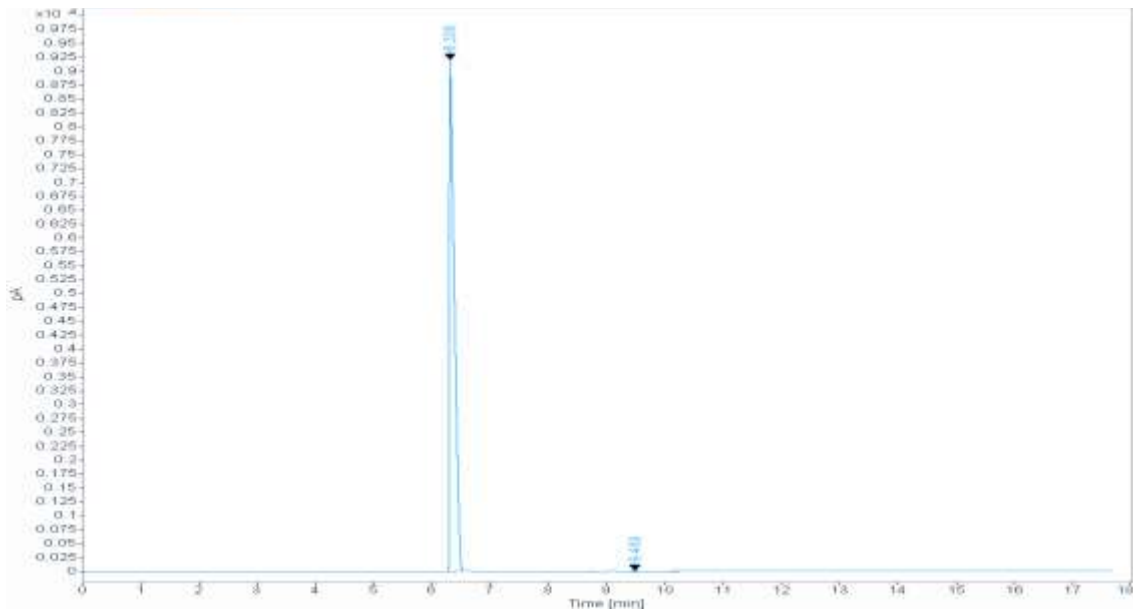


Figure 6. Methanol.

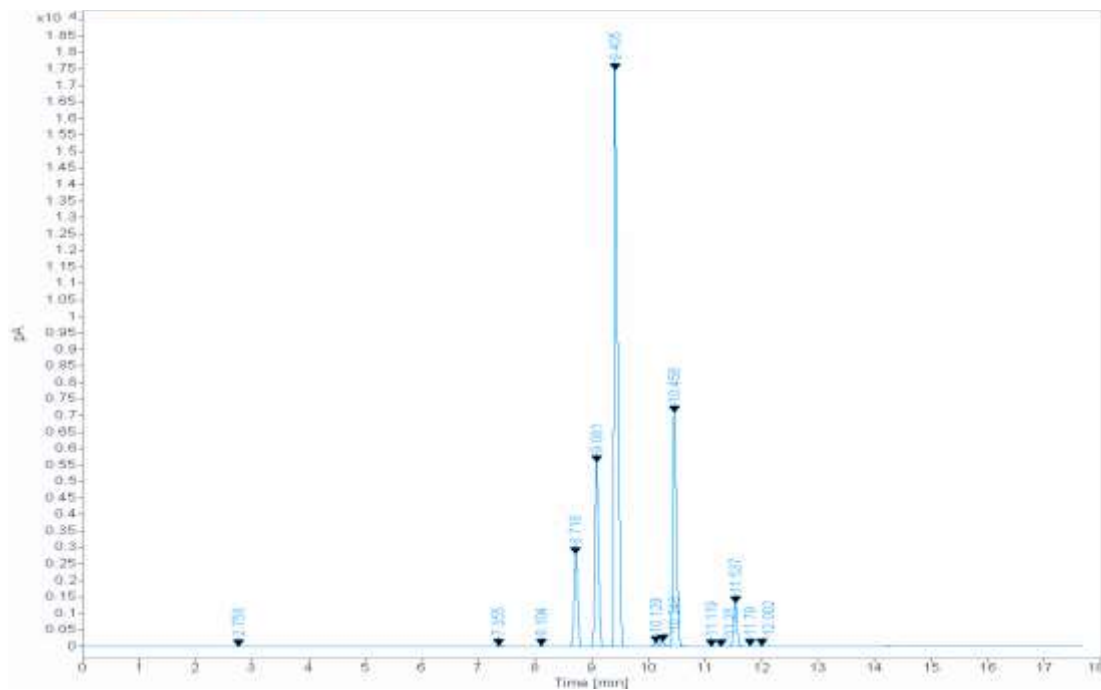


Figure 7. Ink 2 vapour in hexane.

pen ink was not used during July 2016 observation because the students were doing their end term examination. However, Whiteboard marker pen ink was in use during the February (2017) observation because teaching was going on in all the schools.

These findings agree with ATSDR (2015) who say that the components of dry erase ink are irritants. However, the difference in incidences of eye irritation between the different exposure status was not significant because seasonal factors acted as confounders ($p=0.164$) (Table

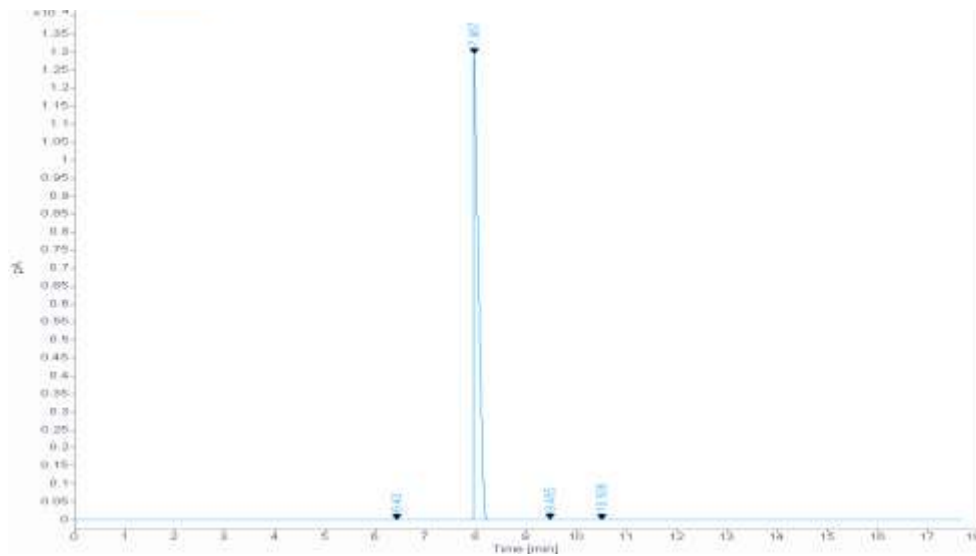


Figure 8. Ink 2 vapour in acetone.

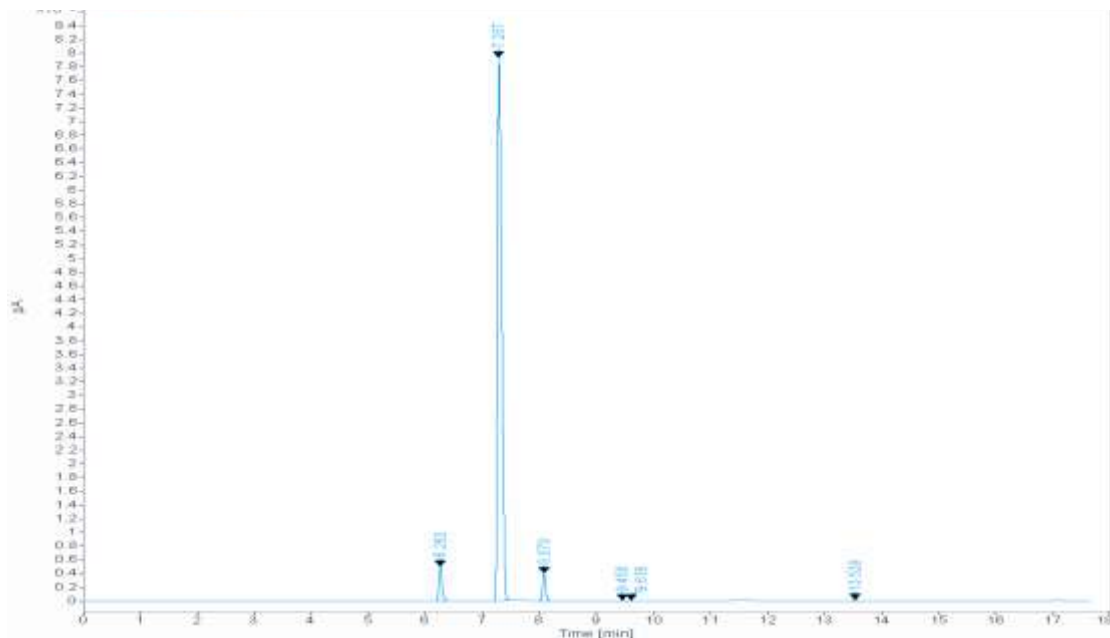


Figure 9. Ink 2 vapour in ethanol.

2).

When the incidences of eye irritation among the teachers who used the three different brands of whiteboard marker inks were compared, the difference was not significant during the non-exposure time of observation ($F=1.342$; $p=.265$) (Table 3).

The percentage incidence of eye irritation was different among the teachers who used different brands of

whiteboard marker pen inks during the time when the whiteboard marker pen inks were in use. Teachers who used ink 3 had the highest incidences of eye irritation while those who used ink 1 had the lowest incidences of eye irritation (Figure 15) Statistical testing showed that there was a significant association between the brand of ink and the development of eye irritation among the teachers during the use of the ink ($\chi^2=6.933$; $p=0.031$)

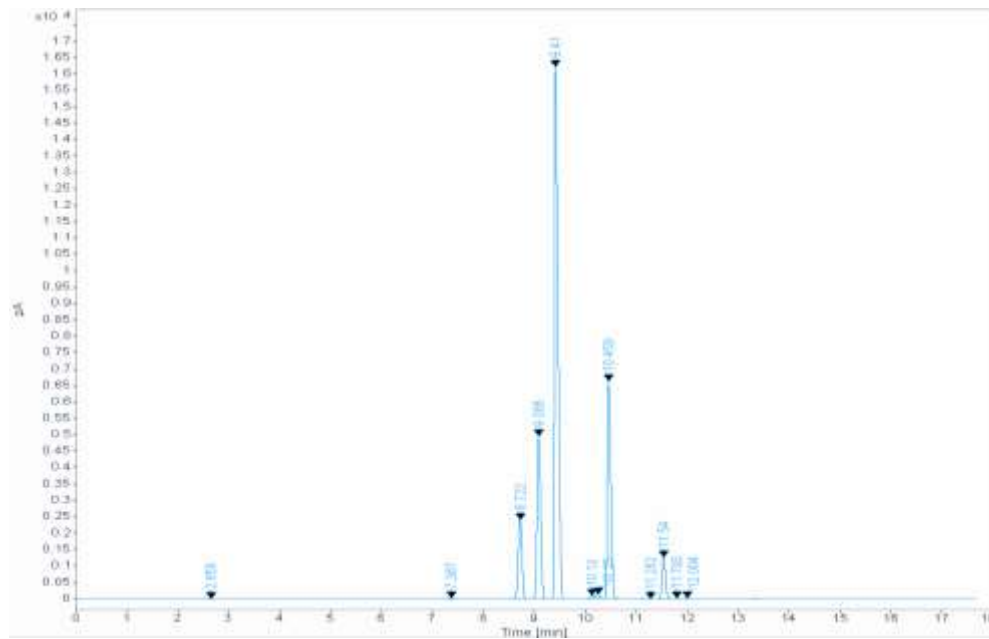


Figure 10. Ink 3 vapour in hexane.

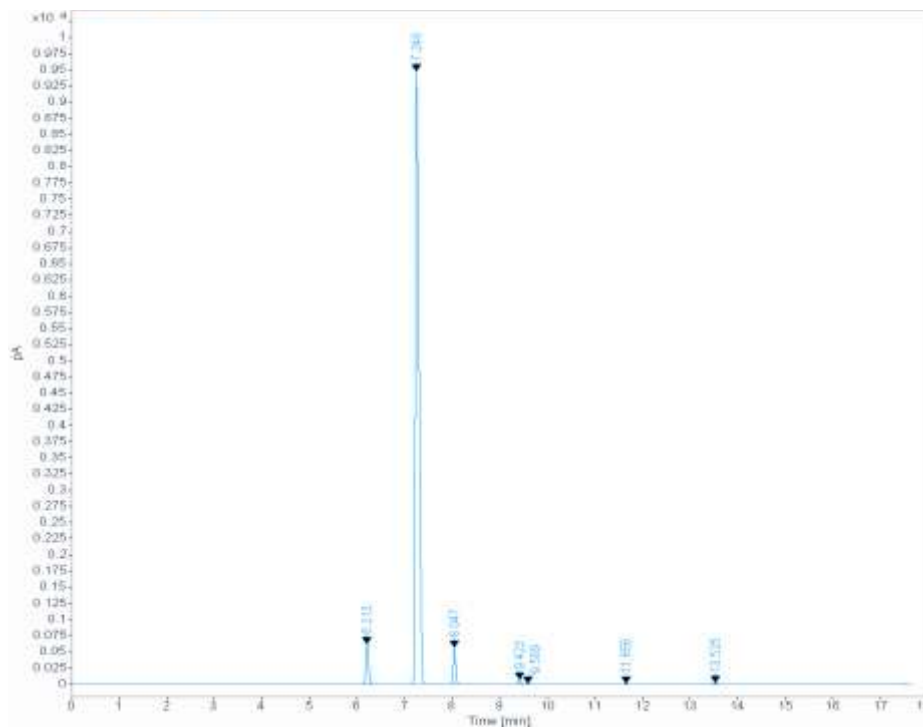


Figure 11. Ink 3 vapour in ethanol.

(Table 4).

Increase in incidence of eye irritation when the ink was in use and the existence of a significant difference in

incidences between the teachers who used different brands of ink is an indication that the whiteboard marker pen ink causes eye irritation. These findings agree with

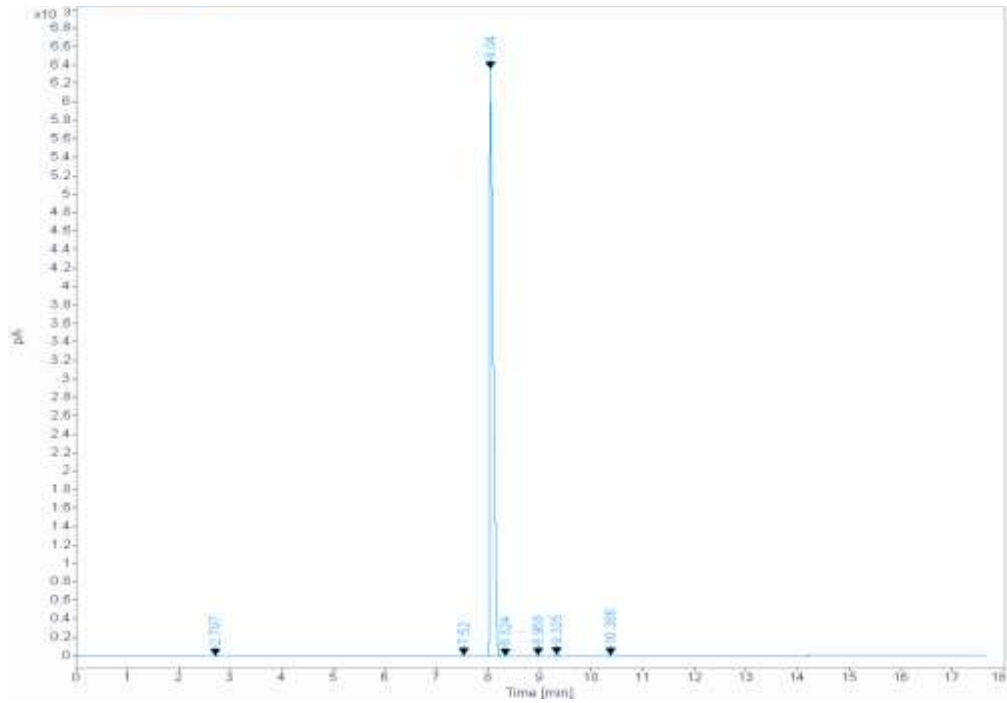


Figure 12. Ink3vapourinacetone.

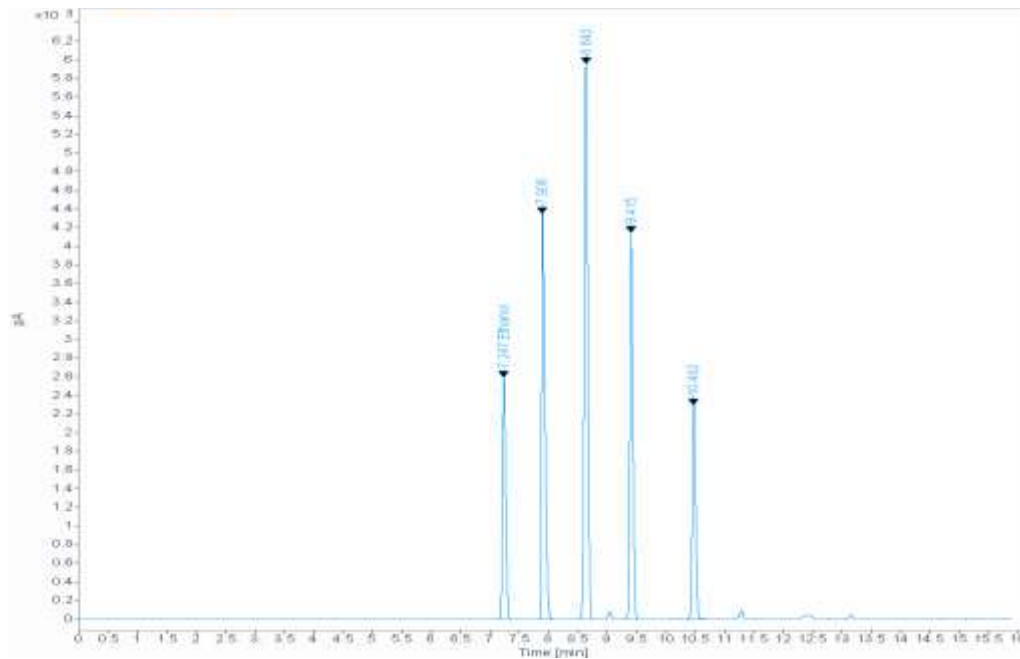


Figure 13. Ethanol and other solvents.

several authors (Mendicino, 2000; Maurer et al., 2001; Anderson and Anderson, 2003; Greenberg et al., 2003; Hathaway and Proctor, 2004; Agyeman and

Himmelberger, 2009; Halverson, 2011; Battersby, 2011; Roelofs and Do, 2012; ATSDR, 2015) who found the components of dry erase ink to be irritants.

Table 1. Percentage composition of ink vapour.

Solvent		Acetone	Hexane	Methanol	Ethanol	Total
% of solvent in the ink vapour	Ink1	40		57.9		97.9
	Ink2	50.1	49.9			100
	Ink3		73.8		26.2	100

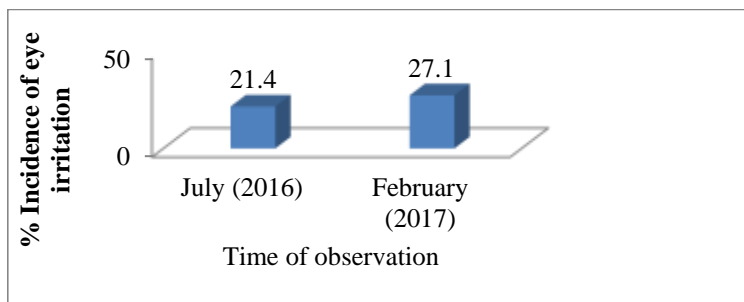


Figure 14. Influence of dry erase vapour on development of eye irritation.

Table 2. Comparison of incidences of eye irritation during exposure and non-exposure times of observation.

Source	Factor	Type III Sum of Squares	df	Mean Square	F	Sig.
Factor	Linear	0.369	1	0.369	1.955	0.164
Error(factor)	Linear	36.631	194	0.189		

Table 3. Incidences of eye irritation among teachers during non-exposure to ink.

Parameter	Sum of Squares	df	Mean Square	F	Sig.
Exposure and non-exposure times	0.436	2	0.218	1.342	0.265
Eye irritation incidences	19.483	120	0.162		
Total	19.919	122			

Post hoc test was carried out to establish which of the significantly different. The statistical test (one way ANOVA) showed that there was no significant difference between the ink 2(acetone and hexane) and 3(ethanol and hexane) ($p=0.435$) (Table 5).

The odds ratio of developing eye irritation by teachers using ink 2(acetone and hexane) and ink 3(ethanol and hexane) was compared with that of those who used ink 1(acetone and methanol) because ink 2 and 3 were found not to be significantly different. The results showed that the odds of developing eye irritation by a teacher using ink 2 or 3 was significantly higher than the odds of developing eye irritation by a teacher using ink

1(Odds ratio= 2.182 ; 95 C.I.=1.174-4.054) (Table 6).

The mixture of methanol and acetone had the lowest potency of eliciting eye irritation while those mixtures that had hexane had a high potency. This agree with Ernstgård et al. (2005) who did not find significant irritation from methanol vapour in their study on the disposition of methanol vapor in humans. Maurer et al. (2001) found that acetone is associated with mild irritation while Cometto-Muñiz et al. (2006) found that hexane vapour caused chemesthetic stimulation resulting in sharp eye irritation. Oh et al. (2013) found that dry eye syndrome, which is associated with ocular inflammation or eye irritation is more prevalent among those exposed

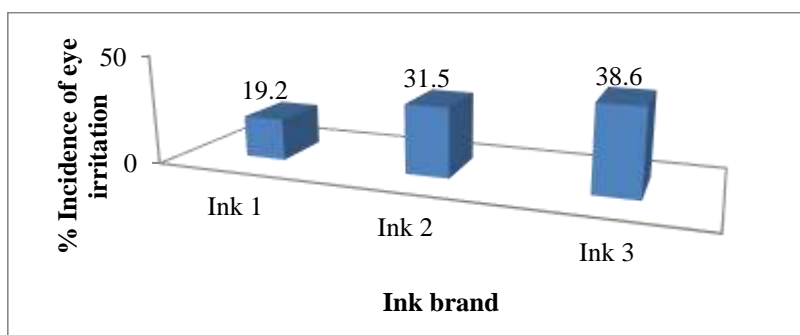


Figure 15. Incidences of eye irritation among teachers using different brands of dry erase ink.

Table 4. Association between ink brand and eye irritation.

Parameter	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	6.933	2	0.031
Likelihood Ratio	6.951	2	0.031
Linear-by-Linear Association	6.749	1	0.009
N of Valid Cases	221		

Table 5. Comparison of incidences of eye irritation between those who used ink 2 and ink 3.

Parameter	Sum of Squares	df	Mean Square	F	Sig.
Ink brand	0.140	1	0.140	0.613	0.435
Eye irritation incidence	26.185	115	0.228		
Total	26.325	116			

Table 6. Risk Estimate for those who use ink 2 or 3.

Parameter	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for inks for odds ratio test (ink 2 or ink 3 / ink 1)	2.182	1.174	4.054
For cohort whether eyes feel irritated = yes	1.778	1.114	2.837
For cohort whether eyes feel irritated = no	.815	.694	.957
N of Valid Cases	221		

to ethanol. Different VOCs also react differently with air and other pollutants in the indoor air resulting in different mixtures which have different health effects (EPA, 2018). Capello and Gaddi (2018) say that groups of VOCs are more potent irritants than the individual VOCs. A mixture is therefore different from the sum addition of its

components. The inks may therefore have shared some individual components (both ink 1 and ink 2 had acetone) but each had a different composition of VOCs in the mixture (ink 1 had acetone and methanol while ink 2 had acetone and hexane) explaining the differences in their ability to cause eye irritation. This means that teachers

who use the dry erase with methanol and acetone mixture are safer than their counterparts who use dry erase inks with hexane and acetone or hexane and ethanol mixtures. These findings also indicate that substitution method can be used to control these irritants. Substituting inks 2 and 3 with ink 1 can aid in the control of eye irritation.

Conclusion

The vapour from ink 1 had methanol and acetone, vapour of ink 2 had acetone and hexane while the vapour of ink 3 had ethanol and hexane. The different ink solvent mixtures have different abilities to elicit eye irritation on persons exposed to their vapours ($\chi^2 = 6.933$; $p = 0.031$) and that mixtures of ethanol and hexane as well as acetone and hexane were more potent eye irritants than the mixture of methanol and acetone (Odds ratio = 2.182; 95 C.I. = 1.174-4.054). Therefore substituting inks 2 and 3 with ink 1 would reduce the risk of eye irritation.

RECOMMENDATION

More research is required to establish the potency of other marker pen ink brands so that teachers can choose the marker pen ink brand that has the lowest potency to improve their occupational health and safety. The schools can meanwhile substitute the use of inks 2 and 3 with ink 1 to reduce the risk of eye irritation.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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