Egyptian Journal of Occupational Medicine, 2023; 47 (1) : 51 - 64

THE TOXIC EFFECTS OF OCCUPATIONAL EXPOSURE TO HALOGENATED INHALATIONAL ANESTHETICS

By

Shalaby NM[1], ElRafey DS[2], Adel Hamoda MA[2], Mahmoud AR[1] and Sakr S[1]

[1]Department of Forensic Medicine and Clinical Toxicology, [2] Department of Community, Environmental and Occupational Medicine , Faculty of Medicine, Zagazig University, Egypt.

***Corresponding author**: Sakr S. **E-mail** : sasakr@medicine.zu.edu.eg*

***DOI:** 10.21608/ejom.2022.153564.1287*

***Submit Date:** 2022-08-02* ***Revise Date:** 2022-09-01* ***Accept Date:** 2022-09-05*

***Authors' contribution:** All authors contributed equally in this work.*

Abstract

Introduction: Contamination of operating theaters with the waste anesthetic gases (WAGs) is unavoidable. Halogenated anesthetics namely halothane, isoflurane, desflurane, and sevoflurane are the major constituents of WAGs. Medical personnel are exposed to lower WAGs concentrations than patients, yet their extended exposure over years magnifies the risk of WAGs-associated toxicity. **Aim of Work:** To investigate the possible toxic effects of exposure to the halogenated inhalational anesthetics on the general health, liver functions, oxidative parameters, and cognitive functions of occupationally exposed personnel, and to study the effect of exposure duration / years on such effects. **Materials and Methods:** The current study was conducted on 56 healthcare workers (HCW) (28 exposed and 28 non-exposed) who were subjected to a questionnaire, medical examination, liver function tests, oxidative stress analysis, and Montreal Cognitive Assessment (MOCA). **Results:** Clinical evaluation of both groups revealed a statistically significant increase in the frequency of headache, dizziness, and fatigue among the exposed group compared to the non-exposed. Also, a significant elevation in the mean values of aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, and malondialdehyde (MDA) levels, along with reduction in the total antioxidant capacity (TAC), attention, language, delayed recall, and total MOCA score were noticed among the exposed group compared to the non-exposed. A statistically significant positive correlation was found between the duration of exposure / years and levels of ALP, bilirubin, and MDA in serum, while a statistically significant negative correlation was detected between the exposure duration / years and TAC and total MOCA score as well, among the exposed group. **Conclusion and Recommendations:** Occupational exposure to inhalation halogenated anesthetics is associated with adverse health effects like headache, dizziness, fatigue, altered hepatic functions, impaired redox balance, and disturbed cognitive functions. In addition, exposure duration / years positively correlates with the hepatic dysfunction and lipid peroxidation and negatively with the TAC and total MOCA score in the occupationally exposed personnel. A central high-flow scavenging system and low leakage anesthesia machines are strongly required in all the operating theaters.

Key words: Halogenated anesthetics, Oxidative stress, Liver functions, Cognitive functions, Waste anesthetic gases (WAGs) and Exposure duration.

Introduction

Waste anesthetic gases (WAGs) are the halogenated anesthetics (halothane, isoflurane, desflurane, sevoflurane), and nitrous oxide (N2O) leaked from the systems in operating rooms or exhaled by patients in the recovery units. Consequently, healthcare workers (HCWs), especially anesthesiologists and nurses, are inevitably exposed to WAGs in each operation using the inhaled anesthetics (Gaya da Costa et al., 2021). Although exposure to such gases seems to be much lower among HCW than patient, it usually extends over years increasing the risk of health hazards in medical personnel (Al-Ashour et al., 2014). According to OSHA, more than 200,000 HCWs are potentially prone to WAGs in operating theaters, recovery rooms, as well as dental and veterinary clinics (OSHA, 2010).

In order to minimize the negative health hazards on occupationally exposed workers, the USA National Institute for Occupational Safety and Health (NIOSH) has settled the maximum 8-h time-weighted average of N2O concentration at 25 ppm and less than 2 ppm for all the halogenated anesthetics if used alone, or below 0.5 ppm when combined with N2O (NIOSH, 1977).

Healthcare workers, exposed to inhalational anesthetics, usually experience wide variety of adverse health effects like headache, anxiety, loss of appetite, impaired memory, and altered intellectual functions (Ozer et al., 2006). Furthermore, some halogenated anesthetics have been linked to the neurotoxic, nephrotoxic, hepatotoxic, and carcinogenic effects, as well as the impaired fertility among the exposed workers (Borayek et al., 2018). Although the underlying mechanism is not certainly clarified, some researchers ascribed these effects to the oxidative stress mechanism (Malekirad et al., 2005).

Halogenated anesthetics are metabolized in the liver via a metabolic pathway entailing cytochrome P-450 2E1 (CYP2E1), with production of toxic trifluoroacetylated metabolite (Siha et al., 2019). The severity of hepatotoxicity positively correlates with the degree of hepatic metabolism and the toxic metabolite production. One third of halothane is fully metabolizes in the liver with the highest incidence of hepatic toxicity, while a considerably less common incidence of

hepatotoxicity has been reported with sevoflurane, desflurane, and isoflurane due to limited hepatic metabolism (Safari et al., 2014).

The fluoride containing halogenated anesthetics; sevoflurane, desflurane, and isoflurane produce inorganic fluoride during metabolism (Lin et al. 2013). Over a long time of exposure, fluoride causes fat deposition in liver, disturbs protein expression, enhances oxidative damage, induces vacuolization and necrosis of hepatic cells, and finally impairs liver functions (Emara et al., 2020).

Results of epidemiological studies remain controversial. Although the extended exposure to low concentrations of WAGs has been connected to the different health hazards in HCW, some investigators still deny the relationship between the inhalational anesthetics and the development of adverse effects (Ebrahem and Shaltout, 2021).

Aim of Work

To investigate the possible toxic effects of exposure to the halogenated inhalational anesthetics on the general health, liver function, oxidative parameters, and cognitive functions of occupationally exposed personnel, and to study the effect of exposure duration / years on such effects.

Material and Methods

-Study design: It is a comparative cross-sectional study.

-Place and duration of the study: The study took place in operating theaters at Zagazig University Hospital; from 1st December 2021 to end of March 2022.

-Study sample:

Sample size: The sample size was calculated using Open Epi according to the mean of Aspartate aminotransferase (AST) among the non-exposed group (15.6±6 U/L) and the exposed group (11.8±4 U/L) (Prokes et al, 2009). So, at power of study 80% and CI 95%, the sample size was calculated to be 56 subjects (28 exposed and 28 non-exposed).

-Sample selection: was done using systematic random sample technique. The study population included two groups:

1-Exposed group with **Inclusion criteria** as follows: workers (anesthesiologists and nurses) who had been working for 6 h/day for 6 days/ week, over duration of 2 years or more in the operating theaters and recovery rooms. **Exclusion criteria:** workers of less than two years of exposure,

cardiac, hepatic, and renal diseases, neurodegenerative disorder, psychiatric disorders, surgery within the last 6 months, hypertension, diabetes, drug dependence, malignant tumors, and those who refuse to participate in the study.

2-Non-exposed group: Non-exposed subjects (doctors and nurses) were obtained from the outpatient clinics with no history of occupational exposure to anesthetic agents.

Study methods:

1-Questionnaire: All participants were subjected to a questionnaire including socio-demographic characteristics (age, marital status, special habits as smoking) and occupational history (types of anesthetics to which they are exposed, duration of exposure /hours/days/ years).

2- Clinical assessment: including medical, neurological, and psychiatric examination.

3- Investigations

Collection of blood samples: venous blood was collected from the studied group and transferred to the laboratory in special containers. Samples were centrifuged (4500× g, 5 min) immediately after they were drawn to separate serum, and then frozen at −20 °C for the subsequent analyses of:

A- Liver function tests: Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin were determined using kits of Biodiagnostic (Giza, Egypt) following the instructions of the manufacturer.

B- Oxidative stress indices in serum: the lipid peroxidation marker (MDA) was measured according to Ohkawa et al. (1979) method and the total antioxidant capacity (TAC) was determined according to the spectrophotometric method of Koracevic et al. (2001). Kits were obtained from Biodiagnostic (Giza, Egypt)

4- The Montreal Cognitive Assessment (MOCA): evaluates multiple domains of cognitive functioning, a cutoff score of 26 was used (25 or below indicating impairment) (Nasreddine et al., 2005).

Consent

All subjects were fully informed about the nature and objectives of this study and a written informed consent was taken from all the included subjects. All data were kept confidential and used only for the research purpose and no harm or risk was encountered for any of them.

Ethical Approval

This study was carried out within the ethics of The Scientific Ethical Committee of Faculty of Medicine, Zagazig University (Institutional Review Board).

Data Management

Data were analyzed using Statistical Package of Social Science (SPSS), software version 27.0 (SPSS Inc, 2020) **(**SPSS for windows, version 27.0. Chicago, SPSS Inc). Quantitative variables are reported as Means and SD, an independent t test and Mann Whitney test used for comparing two groups. Qualitative data were represented as frequencies and percentages, Chi-square test (χ^2) and fisher exact test were used for comparing groups. Pearson's correlation coefficient used for finding correlation between quantitative variables. The test results were considered significant when p-value <0.05 and highly significant if p <0.001. All p values were two-tailed.

Results

The study was conducted on 56 healthcare workers (29 doctors and 27 nurses) with mean age of 35.6 ± 6.12 years and sex distribution 20 females (35.7%) and 36 males (64.3%).

Table (1): Socio-demographic data of the studied groups.

Variables	Exposed (No=28)	Non-exposed (No =28)	Test	p
Age: Range	26 – 45	27 – 43	t	p
Mean ± SD	36.1± 6.46	35.3 ± 5.94	0.47	0.64
Duration of work (years): Range	2 – 20	2 – 18	MW	
Median	13	12	1.39	0.17
Mean ± SD	15.6 ± 7.94	14.5 ± 6.54		
Sex: Male No (%)	19 (67.9%)	17 (60.7%)	χ^2	
Female No (%)	9 (32.1%)	11 (39.3%)	0.31	0.58
Marital state: Married No (%)	18 (64.3%)	15 (53.6%)	χ^2	
Non married No (%)	10 (35.7%)	13 (46.4%)	0.66	0.42
Smoking: NO No (%)	20 (71.4%)	21 (75%)	χ^2	
Yes No (%)	8 (28.6%)	7 (25%)	0.09	0.76
Occupation: Doctor No (%)	15 (53.6%)	14 (50%)	χ^2	
Nurse No (%)	13 (46.4%)	14 (50%)	0.07	0.79

SD: Standard deviation t: Independent t test MW: Mann Whitney test χ^2: Chi square test

Both exposed and non-exposed groups were matched for age, sex, educational level, marital status, smoking, and occupation (Table 1).

Table (2): Health complaints among the studied group.

Health effects	Exposed (No = 28)		Non-exposed (No = 28)		p	OR (95% CI)
	Yes No (%)	NO No (%)	Yes No (%)	NO No (%)		
Headaches	25 (89.3%)	3 (10.7%)	15 (53.6%)	13 (46.4%)	**0.003***	**7.22 (1.77-29.55)**
Dizziness	23 (82.1%)	5 (17.9%)	16 (57.1%)	12 (42.9%)	**0.04***	**3.45 (1.02-11.72)**
Memory problems	22 (78.6%)	6 (21.4%)	20 (71.4%)	8 (28.6%)	0.54	1.47 (0.43-4.97)
Fatigue	26 (92.9%)	2 (17.1%)	19 (67.9%)	9 (32.1%)	**0.02***	**6.16 (1.19-31.82)**

Chi square & Fisher exact test OR: Odds ratio *: Statistically significant ($p<0.05$)

Table 2 showed a statistically significant increase in the frequency of physical symptoms like headache (OR=7.22), dizziness (OR=3.45) and fatigue (OR=6.16) among the exposed group compared to the non-exposed .

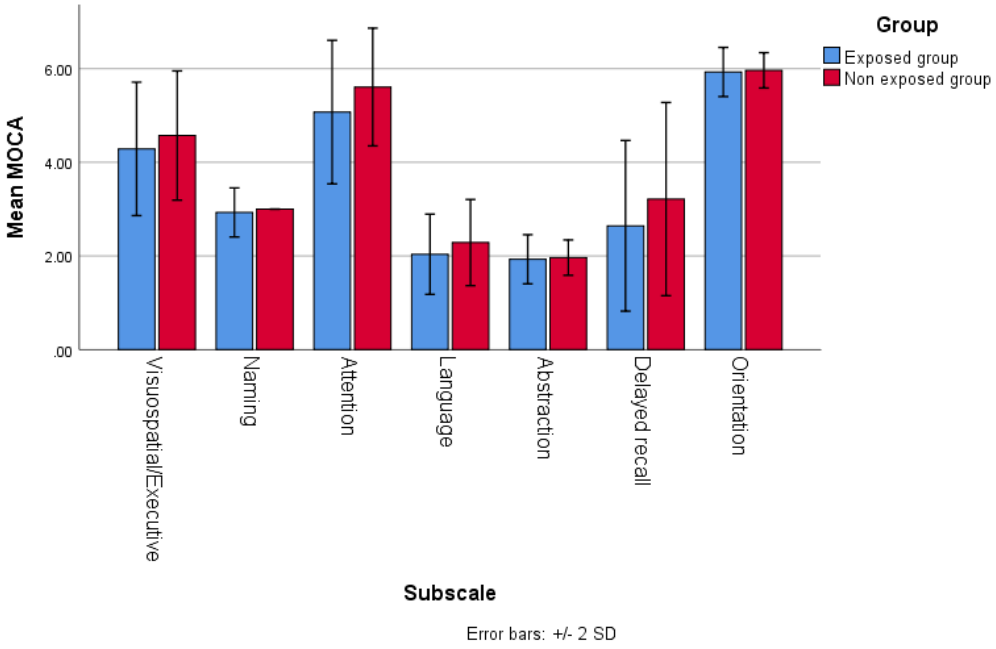
Table (3): Liver function tests and oxidative stress markers among the studied groups.

Variables		Exposed Mean ± SD	Non-exposed Mean ± SD	t	p
AST (IU/L)	Male	(No=19) 28.09 ±6.12	(No=17) 26.54 ±5.80	0.78	0.44
	Female	(No=9) 27.50 ±4.82	(No=11) 23.35 ±3.12	2.33	**0.03***
t		0.01	1.43		
p		0.99	0.17-		
ALT (IU/L)	Male	(No=19) 22.16 ±6.48	(No=17) 20.09 ±5.50	1.03	0.31
	Female	(No=9) 19.62±6.82	(No=11) 16.74 ±4.06	1.17	0.25
t		0.95	1.73		
p		0.35	0.09		
ALP (IU/L)	Male	(No=19) 90.55±13.25	(No=17) 70.54±12.08	4.71	**<0.001****
	Female	(No =9) 93.44±14.82	(No =11) 70.33±13.51	3.65	**0.002***
t		0.51	0.04		
p		0.61	0.97		
Total bilirubin (mg/dl)	Male	(No=19) 0.74±0.24	(No=17) 0.58±0.18	2.24	**0.03***
	Female	(No=9) 0.73±0.23	(No=11) 0.55±0.15	2.11	**0.04***
t		0.10	0.41		
p		0.92	0.69		
MDA (mmol /L)		(No=28) 68.98±15.25	(No=28) 57.04±13.90	3.06	**0.003***
TAC (mmol /L)		(No=28) 152.99±33.12	(No=28) 196.95±34.21	4.88	**<0.001****

AST: Aspartate aminotransferase ALT: Alanine aminotransferase ALP: Alkaline phosphatase
MDA: Malondialdehyde TAC: Total antioxidant capacity SD: Standard deviation
t: Independent t test *: Significant ($p<0.05$) **: Highly significant ($p<0.001$)

Table (3) showed a statistically significant increase in the mean values of AST levels among females of exposed group compared to the non-exposed one. In addition, the mean values of both ALP and bilirubin were found to be higher among the exposed group (male and female) compared to the non-exposed. As regards the oxidative stress indices, a statistically significant increase in lipid peroxidation marker (MDA) and reduction in TAC were detected in the exposed group when compared to the non-exposed one.

Figure (1): MOCA subscale among the studied groups.



Comparing MOCA score test results among the exposed and the non-exposed groups revealed that there was a statistically significant decrease in the mean values of attention (5.07±0.77 versus 5.61±0.63), language (2.04±0.43 versus 2.29±0.46) and delayed recall (2.64±0.91 versus3.21±1.03) as well as the total MOCA score (26.14±1.8 versus 27.75±1.43) among the exposed versus non-exposed group (Figure 1).

Table (4): Correlation between exposure duration and laboratory findings and MOCA score among the exposed group.

Variables	Duration of exposure/years	
	r	p
AST	0.24	0.11
ALT	0.22	0.13
ALP	0.46	**0.008***
Total bilirubin	0.38	**0.02***
MDA	0.39	**0.02***
TAC	-0.36	**0.03***
MOCA score	-0.51	**0.001***

AST: Aspartate aminotransferase ALT: Alanine aminotransferase ALP: Alkaline phosphatase MDA: Malondialdehyde TAC: Total antioxidant capacity MOCA score: Montreal Cognitive Assessment r: Pearson's correlation coefficient *: Statistically significant ($p<0.05$)

Table 4 showed a statistically significant positive correlation between the duration of exposure / years and ALP, bilirubin, and MDA levels and a statistically significant negative correlation between the duration of exposure / years and TAC and total MOCA score among the exposed group compared with the non-exposed one.

Discussion

When inhalation anesthetics are administered, minimal amounts of WAGs are elaborated into the environment of operating room. As a result, all staff becomes exposed to the leaked volatile compounds (AL-Rasheedi et al., 2021). A number of studies suggested a correlation between the chronic exposure to WAGs and the development of systemic toxicity in medical personnel (Byhahn et al., 2001).

There was a statistically significant increase in the frequency of headache, dizziness, and fatigue with non-significant change in the memory among the exposed studied personnel compared to the non-exposed ones (Table 2). This agreed with the results obtained by Shaker et al. (2011) from Egypt who revealed a statistically significant increase in headache and drowsiness among the exposed group compared to the control. Also, Aal et al. (2008) from Egypt and Deng et al. (2018) from China have reported a statistically significant increase in the frequency of symptoms like dizziness, irritability, headache, anxiety, decreased concentration, as well as the easy fatigability among the operating room personnel in comparison with the control. Interestingly, all manifestations have disappeared after leaving the workplace (Deng et al., 2018).

As regards liver function tests, results of the current work demonstrated higher levels of AST, ALP, and total bilirubin in the exposed group compared to the non-exposed (Table 3). These results are in line with Emara et al. (2020) from Egypt and Safari et al. (2014) from Iran who revealed elevated hepatic markers (AST, ALT, ALP, GGT) in subjects with repeated exposure to halogenated inhalational anesthesia. Emara et al. (2020) attributed the hepatotoxicity to the reduced hepatic blood flow and oxygenation caused by halogenated anesthetics.

Similarly, by comparing the operating room personnel exposed to halothane to the control group working in a bank, there was a significant increase in AST, ALT, ALP, and total bilirubin levels among medical personnel compared to the control group. Hepatic toxicity and altered liver biochemistry were linked to the aggressive generation of free radicals and lipid peroxidation (Prokes et al., 2009).

Also, the current study findings cope with the results of Casale et al. (2014) from Ghana in which occupational

exposure to low dose of anesthetic gases has resulted in increased hepatic parameter such as AST, ALT, GGT, and total bilirubin among the exposed workers compared to the non-exposed ones. Also, a study conducted by Ebrahem and Shaltout (2021) from Egypt had revealed a statistically significant increase in the mean values of ALT and AST among the exposed group compared to the control ones.

Halogenated anesthetics can initiate oxidative stress. When reactive oxygen species (ROS) are created faster than their elimination, an imbalance of redox status supervenes (Elgharabawy et al. 2018). Although ROS play a key role in maintaining normal cell function including cell signaling, excess ROS generation can negatively affect cell function (AL-Rasheedi et al., 2021).

Concerning the oxidative stress parameters, there was a statistically significant increase in malondialdehyde (MDA) levels and reduction in total antioxidant capacity (TAC) among the exposed group compared to the non-exposed (Table 3). These results are consistent with the study of Malekirad et al. (2005) from Iran who reported a significant increase in lipid peroxidation marker and reduction in antioxidant thiol groups in the staff exposed to halothane and N2O in the operating rooms for nine years. Also, Wrońska-Nofer et al. (2012) stated that chronic exposure to anesthesia induces oxidative damage and diminishes the antioxidant defense markers**.** Furthermore, in Turkish operating rooms, Türkan et al. (2005) indicated reduced glutathione peroxidase (GPX) and superoxide dismutase (SOD) levels among staff exposed to halothane, isoflurane, desflurane, enflurane, and sevoflurane.

In order to investigate the effect of halogenated anesthetics on cognitive function of HCWs, Montreal Cognitive Assessment (MOCA) score was applied to the studied groups. Results revealed a statistically significant reduction in attention, language, delayed recall, and total MOCA score in exposed subjects (Figure 1). Actually, the brain represents the prime target of inhalational anesthetics which work by magnifying the inhibitory function or reducing the excitatory transmission in brain nerve endings (Darkwa et al., 2017). Diminished synaptic density and dendritic numbers were noticed in subjects exposed to subclinical doses of halothane over a long-time span (Chen et al., 2022).

The cognitive functions like memory retrieval, consciousness, and coding are strictly related to the changes in functional network connections of

the brain. In healthy volunteers inhaled 2% and 1% sevoflurane, respectively, decreased brain network correlation was detected, especially the network connection between anterior and posterior cingulate gyrus and the secondary parietal cortex (Chen et al., 2022). Consistently, Ranft et al. (2016) reported the ability of sevoflurane to reduce the connection between the frontal lobe and thalamic cortex with impaired cognition functions.

The study of the effect of duration of exposure/years on the toxic effects of halogenated anesthetics has indicated a statistically significant positive correlation between the exposure duration and AST, ALP, and bilirubin, as well as MDA levels on one hand, and a negative correlation with TAC and total MOCA score on the other hand, among the exposed subjects (Table 4).

In support of our results, a highly significant increase in ALT, AST, and MDA levels and reduction in antioxidant enzymes levels has been found in personnel with more than 10 years of working experience compared to personnel who had less than 10 years of working experience (Jafari et al., 2018). Likewise, Ebrahem and Shaltout (2021) reported increased ALT and AST levels with the increased exposure duration to halogenated inhalational anesthesia and the highest values among the group of more than 20 years of exposure.

Conclusion and Recommendations:

Occupational exposure to halogenated anesthetics is associated with adverse health effects like headache, dizziness, and fatigue, altered hepatic functions, impaired redox balance, and disturbed cognitive function. Exposure duration positively correlates with altered hepatic function and lipid peroxidation, and negatively with the TAC and cognitive score. A central high-flow scavenging system and low leakage anesthesia machines are strongly required in all the operating theaters.

Conflict of Interest

Authors have declared that no conflict of interest exists.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Acknowledgement

The authors would like to acknowledge all the personnel who participated in this study.

References

1. Aal B, Galal A, and Manal A (2008): Genotoxic and Oxidative Stress Effects due to Occupational Exposure to Anesthetic Gases among Operating Room Personnel. Menoufia Med J; 21 (1): 2008.
2. Al-Ashour IAK, Abd-Ali DK, Fallah MA and Kteo IQ (2014): Effect of Inhaled Anesthetics Gases on Health Staff Health Status in Al-Najaf City. Int J Sci Technol Res; 3 (12): 383-8.
3. AL-Rasheedi KA, Alqasoumi AA and Emara, AM (2021): Effect of Inhaled Anaesthetics Gases on Cytokines and Oxidative Stress Alterations for the Staff Health Status in Hospitals. Int Arch Occup Environ Health; 94 (8): 1953–62. Doi:10.1007/s00420-021-01705-y
4. Borayek GE, Abou El-Magd SA, El-Gohary SS, El-Naggar AM and Hammouda MA (2018): Occupational Genotoxic Effects Among a Group of Nurses Exposed to Anesthetic Gases in Operating Rooms at Zagazig University Hospitals. Egypt J Occup Med; 42 (1): 105-22. Doi: 10.21608/ejom.2018.4942
5. Byhahn C, Wilke HJ and Westpphal K (2001): Occupational Exposure to Volatile Anaesthetics: Epidemiology and Approaches to Reducing the Problem. CNS Drugs; 15 (3):197-215. Doi: 10.2165/00023210-200115030-00004
6. Casale T, Caciari T, Rosati MV, Gioffrè PA, Schifano MP et al. (2014): Anesthetic Gases and Occupationally Exposed Workers. Environ Toxicol Pharmacol; 37(1): 267-74. Doi: 10.1016/j.etap.2013.12.003.
7. Chen X, Zheng X, Cai J, Yang X, Lin Y et al. (2022): Effect of Anesthetics on Functional Connectivity of Developing Brain. Front Hum Neurosci; 16:853816. Doi: 10.3389/fnhum.2022.853816.
8. Darkwa E, Djagbletey R, Ofosu-Appiah E, Owoo C, Sottie D et al. (2017): Knowledge of Anaesthesia Providers on Exposure to Inhalational Anaesthetic Agents in Ghana. Int J Biosci Med; 5: 21-34. Doi: 10.4236/jbm.2017.54003.
9. Deng HB, Li FX, Cai YH and Xu SY (2018): Waste Anesthetic Gas Exposure and Strategies for Solution. J Anesth; 32 (2): 269-82. Doi: 10.1007/s00540-018-2448-1.
10. Ebrahem NE and Shaltout ES (2021): Effect of Duration of Exposure to Anesthetic agents on Liver and Kidney Functions of Anesthesiologists. MJFMCT; 29 (2): 33-9.
11. Elgharabawy RM, Elgharbawy DM and Emara AM (2018): Activation of the Molecular and Functional Effects of Nrf2 against Chronic Iron Oxide Nanorod Overload-Induced Cardiotoxicity. Hum Exp Toxicol; 37(8): 870-85. Doi: 10.1177/0960327117741751
12. Emara A, Alrasheedi K, Aldubayan M, Alhowail A and Elgarabawy R (2020): Effect of Inhaled Waste Anaesthetic Gas on Glood and Liver Parameters among Hospital Staff. Hum Exp Toxicol; 39:1585–95. Doi:10.1177/0960327120938840
13. Gaya da Costa M, Kalmar AF and Struys MMRF (2021): Inhaled Anesthetics: Environmental Role, Occupational Risk, and Clinical Use. J Clin Med; 10 (6):1306. Doi:10.3390/jcm10061306
14. Jafari A, Jafari F and Mohebbi I (2018): Effects of Occupational Exposure to Trace Levels of Halogenated Anesthetics on the Liver, Kidney, and Oxidative Stress Parameters in Operating Room Personnel. Toxin Rev; 39 (3): 242-51. Doi:10.1080/15569543.2018.1498898
15. Koracevic D, Koracevic G, Djordjevic V, Andrejevic S and Cosic V (2001): Method for the Measurement of Antioxidant Activity in Human Fluids. J Clin Pathol; 54 (5): 356-61. Doi: 10.1136/jcp.54.5.356.
16. Lin H, Fan SZ, Chen HM, Cheng SJ, Chang HH et al. (2013): Changes in Biomarkers of Hepatic and Renal Function after Prolonged General Anesthesia for Oral Cancer Surgery: A Cohort Comparison Between Desflurane and Sevoflurane. J Dent Sci; 8 (4): 385–91. Doi: 10.1016/j.jds.2013.01.005
17. Malekirad AA, Ranjbar A, Rahzani K,

Kadkhodaee M, Rezaie A et al. (2005): Oxidative Stress in Operating Room Personnel: Occupational Exposure to Anesthetic Gases. Hum Exp Toxicol; 24 (11): 597–601. Doi: 10.1191/0960327105ht565oa

18. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V et al. (2005): The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool for Mild Cognitive Impairment. J Am Geriatr Soc; 53 (4): 695–9. Doi: 10.1111/j.1532-5415.2005.53221.x
19. NIOSH (National Institute for Occupational Safety and Health) (1977): Criteria for a recommended standard: occupational exposure to waste anesthetic gases and vapors. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH) Publication No. 77B140. Available at: https://www.cdc.gov/niosh/docs/77-140/default.html
20. Ohkawa H, Ohishi N, and Yagi K (1979): Assay for Lipid Peroxides in Animal Tissues by Thiobarbituric Acid Reaction. Anal Biochem; 95 (2): 351-8. Doi: 10.1016/0003-2697(79)90738-3.
21. OSHA (Occupational Safety and Health Administration) (2010): Anesthetic Gases: Guidelines for Workplace Exposures; OSHA: Washington, DC, USA. Available at: https://www.osha.gov/waste-anesthetic-gases/workplace-exposures-guidelines
22. Ozer M, Baris S, Karakaya D, Kocamanoglu S and Tur A (2006): Behavioral Effects of Chronic Exposure to Subanesthetic Concentrations of Halothane, Sevoflurane and Desflurane in Rats. Can J Anaesth; 53 (7): 653-8. Doi: 10.1007/BF03021623
23. Prokes B, Mikov I and Glavaski M (2009): The Effect of Occupational Exposure to Wasted Halothane on Liver Functions of Operating Room Personnel. Pol J Environ Stud; 18 (5): 893-9.
24. Ranft A, Golkowski D, Kiel T, Riedl V, Kohl P, et al. (2016): Neural Correlates of Sevoflurane-Induced Unconsciousness Identified by Simultaneous Functional Magnetic Resonance Imaging and Electroencephalography. Anesthesiology; 125 (5): 861–72. Doi: 10.1097/ALN.0000000000001322
25. Safari S, Motavaf M, Seyed Siamdoust S and Alavian S (2014): Hepatotoxicity of Halogenated Inhalational Anesthetics, Iran. Red Crescent Med J; 16 (9): e20153. Doi: 10.5812/ircmj.20153.
26. Shaker DA, Samir AM, Hagag HA, Abd El-Aal AA and Afify RA (2011): Cytogenetic Damage in Operating Room Nurses Exposed to Anesthetic Gases. Med J Cairo Univ; 79 (1): 237-44.
27. Siha MS, Farahat SA, Rashed LA and Helmy NM (2019): Study of Some Health Hazards among Operating Theater Personnel Due to Exposure to Anesthetic Gases (II). Egypt J Occup Med; 43 (3): 313-29
28. SPSS (Statistical Package for the Social Sciences) Inc (2020): SPSS for windows, version 27.0. Chicago, SPSS Inc. Available at:http://www.unimunester.de/imperia/md/content/ziv/service/software/spss/handbuecher/englisch/spss_brief_guide_27.0.pdf.)
29. Türkan H, Aydin A and Sayal A (2005): Effect of Volatile Anesthetics on Oxidative Stress due to Occupational Exposure. World J Surg; 29: 540–2. Doi: 10.1007/s00268-004-7658-z
30. Wrońska-Nofer T, Nofer JR and Jajte J (2012): Oxidative DNA Damage and Oxidative Stress in Subjects Occupationally Exposed to Nitrous Oxide (N2O). Mutat Res; 731(1-2): 58-63. Doi: 10.1016/j.mrfmmm.2011.10.010