

BIOMONITORING OF SEVOFLURANE EXPOSURE IN ANESTHESIOLOGIST

Firly Ratsmita¹ Muhammad Ilyas²

¹Departement of Community Medicine, Medical Faculty, University of Indonesia, Indonesia

²Occupational Environmental Health and Research Center IMERI FKUI, Indonesia

Correspondence Address: Firly Ratsmita

Email: firly.ratsmita@ui.ac.id

ABSTRACT

Sevoflurane is used by anesthetists for the induction and maintenance of general anesthesia. This causes the anesthetist to get daily exposures. This will be a potential hazard for exposed operating room personnel, especially anesthetists. The adverse health effects of sevoflurane as hepatotoxic, nephrotoxic and neurotoxic in the human body can be a risk for anaesthetists. Biological monitoring can be done by measuring the levels of sevoflurane and its metabolites or by looking at biomarkers for their effects on health effects. The aim of this study was to seek a literature review on the biomonitoring of sevoflurane exposure in anaesthetists. We searched the literature review using the PRISMA method in PubMed and Google scholar using the following keywords "occupational disease" "chronic effects" "anaesthetist" "sevoflurane exposure" "inorganic fluoride" "biomarkers" previously using the term MeSH and combined with Boolean "OR" and "AND". We obtain 75 articles taken from the database, excluded 35 articles, and selected 5 articles. The results of the review articles showed that there were health effects, especially on liver and kidney function in chronic exposure. Biological monitoring can be undertaken by detecting sevoflurane and its metabolites in the urine during work and function of the liver and kidneys. The evidence for biological monitoring as surveillance in anaesthesiologists remain inconsistent due to limited studies. We recommend to measure sevoflurane in ambient air using a hierarchy of controls, such as elimination, replacement, engineering, administrative and personal protective equipment. We need to undertaken environmental and biological monitoring in order to acquire a safe and healthy work environment.

Keywords: sevoflurane exposure, occupational health, anesthesiologist

INTRODUCTION

Prior to the invention of intravenous drug administration, the first anaesthetics (diethyl ether) were delivered through inhalation and used as a general anaesthetic by Long in the 1840s. Classification of inhaled anaesthetic drugs are ethers, alkanes, and gases. The drugs have an unconscious and immobile effect in patient. The pharmacokinetic of drugs relies on their physical properties. Most of the absorption of inhalation anaesthetics and the rate of elimination from the alveoli are determined by solubility in blood where the soluble substance has a faster rate than the less soluble substance. The effect of inhalation anaesthetics depends on the alveolar concentration not on the dose of the anesthetic absorbed. Wells first used nitrous oxide in 1844 for dental analgesia, and chloroform (trichloromethane) was

developed by Simpson in 1847 as a non-explosive alternative to ether. These medicines, of which only nitrous oxide is still commonly used, dominated the first century of anaesthesia. Ethers include diethyl ether, methoxy propane, vinyl ether, enflurane, methoxyflurane, isoflurane, sevoflurane, and desflurane (Hemmings and Egan, 2019).

Sevoflurane, a halogenated inhalational anaesthetic, used for the induction and maintenance of general anaesthesia in adult and paediatric patients that more than 20 years. The character of sevoflurane is volatile, non-flammable, non-irritant, and easy to provide, with low solubility profile and blood-to-gas partition coefficient (Brioni *et al.*, 2017).

Sevoflurane, a fluorinated methyl isopropyl ether has very poor blood solubility. Sevoflurane is a volatile anaesthetic with smells sweet and

minimally pungent that used during surgical procedures offers hypnosis, amnesia, analgesia, akinesia, and autonomic blockade. Sevoflurane causes modern agents with the least cerebral vasodilation, thus it is favourable in neurosurgical patients with elevated intracranial pressure (Edgington, Muco and Maani, 2007; Hemmings and Egan, 2019).

Inhaled anaesthetics can result in brain damage that can be a trigger the onset of Alzheimer's disease. It can be a potential risk factor for cognitive decline. Inhaled anaesthetics in human cell cultures cause amyloid β accumulation and cell death, suggesting a possible molecular mechanism of cognitive decline related to anaesthesia. The researchers found that more plaques were created by the transgenic mice exposed to inhalation anaesthetics (Kubota, 1992; İnan and Özköse Şatırlar, 2015).

Sevoflurane triggers health effects in high and low concentrations. Headache, fatigue, disorder coordination, liver and kidney disease are common symptoms that occur at high concentrations. Generally, chronic effects with small concentrations do not cause health problems. However, several study showed the relationship between the incidence of miscarriage, genetic mutations, and cancer among workers in the operating room. In addition, workers exposed to anaesthetic gases have an increased incidence of chronic

headaches, peripheral neuropathy, anemia, multiple sclerosis and depression (Dalagkozi *et al.*, 2018).

The main effects of sevoflurane exposures are nephrotoxic, hepatotoxic, and neurotoxic. The aim of this review is to provide an understanding to the specific biological monitoring and systemic health effect of sevoflurane exposure in anaesthesiologist.

METHOD

We undertook the literature searching strategies for answering the clinical question performed on December 14, 2020 with the PRISMA method that used electronic database in Google Scholar and PubMed. Keywords used were “chronic effect of sevoflurane for occupational disease” and “biomarker of sevoflurane exposure in anaesthesiologist” in google scholar. Keywords in PubMed has been used “occupational disease” “chronic effect” “anaesthesiologist” “sevoflurane exposure” “inorganic fluoride” “biomarker” which previously used the MeSH term and combined with Boolean operation “OR” and “AND”. Our goal was to find answers to the question 'What is the specificity of biological monitoring and health effect in anaesthesiologist with sevoflurane exposure.

Table 1. Searching strategy using database from PubMed and Google Scholar

Database	Keyword	Finding	Selected
Google scholar	chronic effect of sevoflurane for occupational disease	20	2
Google scholar	biomarker of sevoflurane exposure in anesthesiologist	20	2
Pubmed	Search (((occupational disease) OR chronic effect)) AND anesthesiologist) AND (((sevoflurane exposure) OR inorganic fluoride) OR inorganic fluoride[MeSH Terms]) OR biomarker) OR biomarker[MeSH Terms])	35	1

The inclusion criteria of this searching strategy were research in anaesthesiologist, occupational exposure, biomonitoring, full text article available. The exclusion criteria of this article were inaccessible articles. We

critical appraisal article according to the systematic review, observational study, and case study. The authors concluded that this literature review did not require approval by the Ethics Committee.

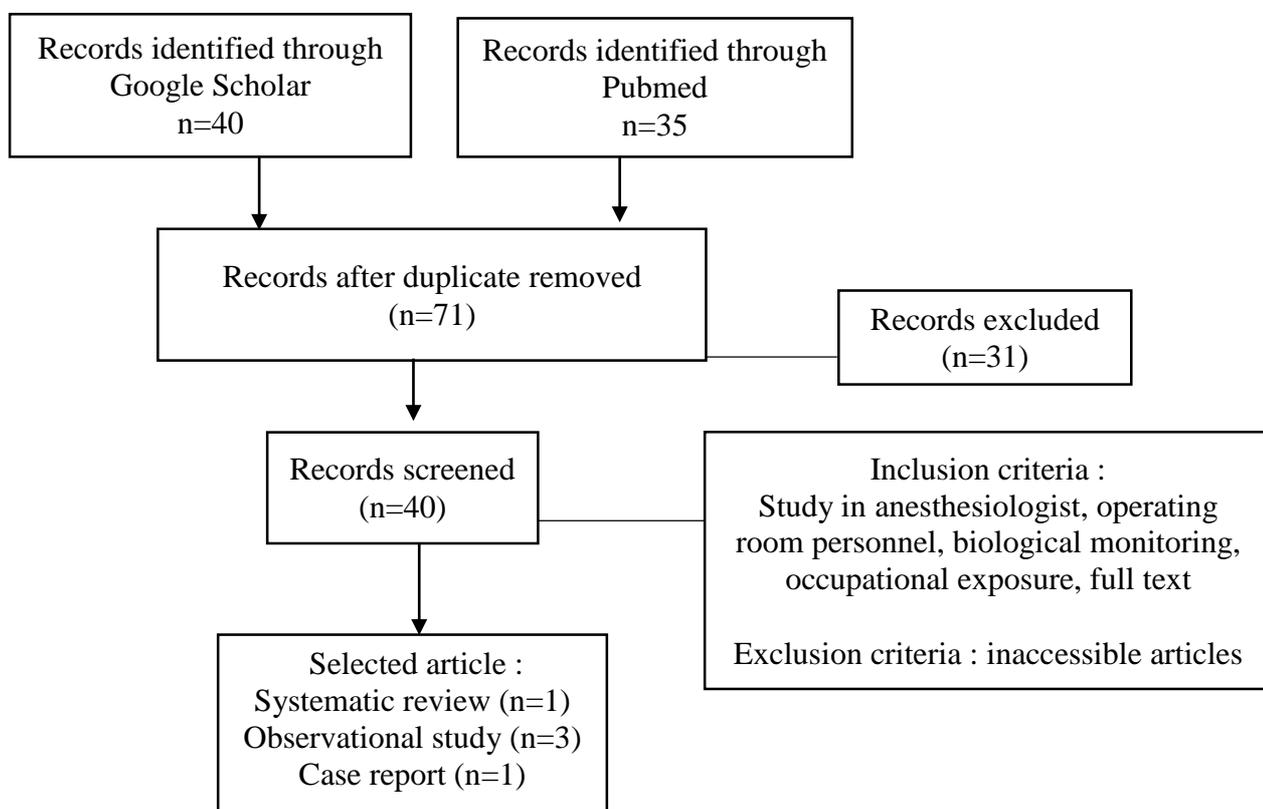


Diagram 1. Searching diagram on finding literatures

RESULT

A total of 75 articles were initially retrieved from online database. A total of 31 articles (41 %) were excluded because did not relate to the aims of study. The study was explained about the other inhaled

anaesthetic agent without sevoflurane. We eliminated the article from abstract. Then, we screened the 40 article that have inclusion criteria like study in anaesthesiologist, operating room personnel, biological monitoring, occupational exposure, and full text.

Table 2. Critical appraisal systematic review

Appraisal question	Answer
What was the issue PICO in the systematic review?	What is the impact of occupational exposure to volatile anesthetics exposure and the best health surveillance for exposed personnel?
F- Is it doubtful that important and substantial studies have been missed?	Unclear, because only use 2 database, in the Medline and Cochrane Library databases.

A- Are the criteria used to select articles appropriate?	Unclear, inclusion study just only depend on title, language, and population like anesthetists, surgeons, nurses and auxiliary personnel
A- Do the included studies have good validity to answer the questions posed?	Unclear, because no specific information or resume of validation the study in this review
T- Do have similar results from one study to another?	Yes
What is the results?	Evidence of the adverse effects on exposed workers of volatile anesthetics is contradictory since there is no evidence of adverse effects when the level of the monitoring environment is held below the legal threshold values. It is still very few reliable details exist in this systematic analysis and may involve reviewing and revising surveillance guidelines and procedures for exposed employees. No clinical signs or biomarkers have been established as appropriate for the use of exposed workers in surveillance.

A systematic review containing seventeen studies on the impact of sevoflurane was conducted by Molina Aragonés *et al.*, 2016 to address their concern about the effect of occupational exposure to volatile anaesthetics and the best of health monitoring for exposed staff? They found that sevoflurane exposure, depend on the dose, can adversely affect the liver and kidney. Some authors said that sevoflurane can make a DNA damage when the sevoflurane exposure in workplace above 4 ppm and no impact of DNA when the sevoflurane exposure under 0,5 ppm. They believe if the air monitoring level under of 2 ppm would be the safety workplace. The effect of the currently used volatile anaesthetic on the population exposed has been routinely studied and very few reliable data have been collected. Therefore, review surveillance guidelines and procedures for exposed employees is unclear. No clinical sign or biomarker has

been established as appropriate for use in surveillance in exposed staff (Molina Aragonés *et al.*, 2016).

The other research involved anaesthesiologists in 52 operating room workers who had been randomly chosen for at least one year of exposure as a case group and fifty two administrative staff as a control group. The measure of outcome was concentrations of nitrous oxide, isoflurane, and sevoflurane in urine sampling that had taken in morning shift/ at least three hours of exposure in operating room. Liver and kidney function are calculated by mean levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, alpha-glutathione-s-transferase, and serum levels of kidney injury molecules-1, creatinine, and calcium (Neghab *et al.*, 2020).

In the result of this study showed that the non exposed group have lower risk

than the exposed group in aspartate aminotransferase (p value 0.04), alanine aminotransferase (p value 0.01), gamma glutamyl transferase (p value 0,003), alpha

glutathione s-transferase (p value 0.04), serum creatinine (p value 0.03), kidney injury molecule (p value 0.003), calcium (p value <0.001) (Neghab *et al.*, 2020) .

Table 3. Critical appraisal observational study

Articles	study design	Number of subject	Randomiza	Similarity treatment	Blinding	Domain	Deteminan	Measurement of outcome	Result	Level of evidence
Toxic Responses Of The Liver And Kidneys Following Occupational Exposure To Anesthetic Gases	case control	52 exposed and 52 unexposed group	Yes	Yes	Unclear	Population at risk in exposed group (operating room personnel)	yes, as in practice (exposure/risk factor)	Yes, urinary and blood sample use the same equipment	Exposed group have a higher risk to renal and liver function than unexposed group	3b
Biomonitoring occupational sevoflurane exposure at low levels by urinary	Observational study	Individual sevoflurane exposure	Unclear	Yes	Unclear	Population at risk	Yes, as in practice (exposure/	Yes, the passive air sampling device Radiello, and assaying Sev-	In this research, the exposure biomarker (urinary sevoflurane and hexafluoroisopropanol)	3b
Articles	Study design	Number of subject	Randomiza	Similarity treatment	Blinding	Domain	Deteminan	Measurement of outcome	Result	Level of evidence
sevoflurane and hexafluoroisopropanol		was measured in 100 health care operators					risk factor	U and HFIP concentration s. The environmental levels of sevoflurane in workplace	used to assess occupational exposure to sevoflurane has been found to	

		(physicians, anaesthetists, instrumentalists and nurses) at five hospitals							were also tracked	correspond with the anaesthetic levels measured in the air.	
Urinary sevoflurane and hexafluoroisopropanol as biomarkers of low-level occupational exposure to sevoflurane	Observational study	A group of 36 subjects (13 male, 23 female) occupationally exposed to volatile anaesthetics in paediatric operating	unclear	yes	unclear	Population at risk	Yes, as in practice (exposure/risk factor)	Yes, Individual passive sampler cartridges and urinary morning post-shift urine samples were collected. GC-MS method is used to quantitate environmental sevoflurane, urinary sevoflurane and total urinary HFIP. Breathing	Correlation between breathing area sevoflurane and total urinary HFIP with $r=0,749$ p value <0.0005 ; correlation between breathing area sevoflurane and urinary sevoflurane with $r=0.835$ p value $p<0.0005$	3b	
Articles	Study design	Number of subject	Randomiza	Similarity treatment	Blinding	Domain	Deteminan	Measurement of ourcome	Result	Level of evidence	
		rooms was studied in a 2-week survey						zone sevoflurane. Levels of concentration were expressed in parts per million, and			

analyte urine concentration were expressed in micrograms per liter of urine and in milligrams per liter of urine (for sevoflurane and HFIP)

In order to evaluate and analyze the best biomarker of exposure to sevoflurane, Maria et al have examined the relationship of sevoflurane levels with urinary concentration or hexafluoroisopropanol (HFIP) with the corresponding biological equivalent exposure limit values. The measure applied to 100 healthcare in operating room in five hospitals in north-eastern Italy who were exposed to sevoflurane by passive air sampling in breathing zone personnel and by assessing the levels of Sev-U (sevoflurane-urine) and HFIP in urine sampling obtained at the end of shift work in operating room (Scapellato *et al.*, 2014).

Gas chromatography-mass spectrometry was used for their research. They reported very low levels in personal exposure, typically under 0.5 ppm (mean 0.116 ppm; range 0.007–0.940 ppm), as a result. The concentrations of sevoflurane (Sev-U) and HFIP from urine sampling were between 0.1-17.28 mg/L and 5-550

mg/L, respectively. There was a statistically important association between the two biomarkers and workplace exposure levels (Sev-U, $r=0.49$; HFIP, $r=0.52$), but there was an abnormal distribution of value. Sevoflurane in urine (Sev-U values) appears to be affected at the end of the shift as a peak value of exposure, while HFIP on the day before. In conclusion, both Sev-U and HFIP are suitable biomarkers to determine the exposure of sevoflurane in this analysis (Scapellato *et al.*, 2014).

Antonio et al studied in 36 subjects (13 male, 23 female) occupationally exposed to volatile anaesthetics in paediatric operating rooms in a 2-week survey. The objective of the study is to quantify environmental sevoflurane, urinary sevoflurane and total urinary HFIP, using a previously mentioned GC-MS technique such as Maria et al (Accorsi *et al.*, 2005).

Table 3. Critical appraisal for case studies

Appraisal questions	Answer
Does the research answer the problem clearly?	Yes. Responding to anesthetic gas exposure as a potential risk of Parkinson's Disease (PD)
Is the study design appropriate for answering research questions??	Yes. The results of hexafluoroisopropanol was 483.4 µg/liter (over the 465 µg/liter threshold) in May 2007 and 535.6 µg/liter on next week.

Are the background and subject criteria related to the population to be referenced?	Yes, The subject has worked as a anesthesiologist for 30 years, exposing nitrous oxide for 22 years and sevoflurane for 23 years.
Is the researcher's perspective clearly explained??	Yes. Differential diagnosis is also considered. Sevoflurane has been shown to increase TNF-alpha and beta-amyloid development by activating caspases and apoptotic cascades, which are the key characteristics of PD that activation of caspases and apoptotic cascade
Is the data collection method clear??	Unclear Beginning with the individual evaluation (clinical, laboratory and electrophysiology) and the workplace obtained by individual samples of anesthetist in general hospitals in Veneto from 1990 to 1999.
Do the methods for analyzing data have good validity and are reliable? Are there any quality control measures??	unclear. The excessive exposure to the subject's anesthetic gases may have exacerbated parkinson's disease, given the limited evidence from human studies and sufficient evidence from laboratory studies.
Was the analysis repeated by more than one researcher to ensure reliability?	Unclear. The research was carried out by a team. No repeat and no repetition
Are the results credible, and if so, are they relevant to the practitioner?	Unclear Due to insufficient data from human studies
Are the conclusions drawn justified by the results?	Yes. To the results, the conclusion was appropriate .
Can the study findings be used in different practitioners?	Yes, at least for the personnel in the operating room

Sevoflurane concentration levels in the breathing zone were expressed in ppm and analyte urine concentrations were expressed in mcg dan mg per litre of urine (sevoflurane and HFIP). There was a correlation between sevoflurane breathing area and total urinary HFIP with a p-value of $r=0.749 < 0.0005$; correlation between sevoflurane breathing area and urinary sevoflurane with a p-value of $r=0.835 < 0.00055$ (Accorsi *et al.*, 2005).

A case was underwent by an anaesthesiologist, 59 years old, and 23 years exposed to sevoflurane. The absence

of family history of Parkinson's disease or tremors, mood disorders, a bronchial asthma and high blood pressure (use drug like beta blocker or calcium channel blocker) are not likely to lead to a non-occupational disease. There is no history of chemicals, rural living or use of water contaminated with pesticides. The patient is a smoker and a moderate drinker, but in theory that practices protect him from the disease of Parkinson (Mastrangelo *et al.*, 2013).

This case report want to know about how an anesthetic gasses are relatively

rarely associated with Parkinson's disease in several epidemiological studies. However, exposure in workplace to inhaled gases (nitrous oxide, halothane, isoflurane, levoflurane) with the risk of Parkinson's disease have been related by a number of recent mechanistic studies. It confirmed the assumption of an association between anaesthetic gas exposure and Parkinson's disease risk with a little evidence (Mastrangelo *et al.*, 2013).

DISCUSSION

Sevoflurane is the first choice of inhaled gases for general anaesthesia because it has a more rapid of induction, lower effect of airway irritation, respiratory depression, and arrhythmia potential than the other anaesthetic gases. Sevoflurane is often combined with other anesthetic gases for example nitrous oxide for analgesic effects and desflurane for maintenance of anaesthesia. According to some literature, health effect of sevoflurane can be a nephrotoxin and hepatotoxicity because of chronic exposure in occupational health. The neurotoxicity of sevoflurane is unclear because there have not a specific effect of sevoflurane exposure but some researcher believe that sevoflurane has be a trigger effect to β accumulation like in Alzheimer's disease. In the case study, Parkinson's disease as multifactorial causes have a limited correlation with sevoflurane exposure since the level of HFIP above a normal reference. It remains unclear because limited evidence said that sevoflurane triggers a Parkinson's disease

Formation of free radicals was one of the effects induced by long-term exposure to sevoflurane. It is necessary to preserve antioxidants by taking antioxidant supplements in order to resolve this problem. Pathogenic processes associated with cancer, degeneration disease, cardiovascular disease, which are the responsibility of free radicals, must also be prevented and may boost the immune function of anaesthesia workers who are

directly, especially in epidemiology study (Mastrangelo *et al.*, 2013).

Sevoflurane will be around 2-5 percent metabolism to a metabolite, fluoroacetic acid in the liver by a particular enzyme of cytochrome P450 (2E1). This particular metabolite has been discovered to alter microsomal liver proteins. subsequently function as hapten, activating antigens for an immune-mediated antibody response. With acyl halides attached to liver proteins, the antibody will react to hapten. In several case, like paediatric anaesthesiologists who were regularly exposed to halothane, the same autoantibodies were identified, indicating that these CYP2E1 antibodies do not have a pathogenic function. Although this response was unusual due to the low percentage of metabolized sevoflurane, but it still has health effect risk (Edgington, Muco and Maani, 2007; Hemmings and Egan, 2019).

Waste anaesthetic gases can cause health effect in anaesthesiologists that have chronic exposure, such as DNA damage and increased micronucleus. In addition, oxidative stress is often correlated with anaesthetic gas waste since it causes lipid peroxidation, DNA oxidative damage, and antioxidant protection system damage in such a way that genotoxicity and mutagenicity in anaesthesiologists. However, low occupational exposure to sevoflurane did not show a major impact on the peripheral blood lymphocytes of operating room workers, but further research in the long-term are warranted (Lucio *et al.*, 2018; zhimin ji *et al.*, 2020). long term exposed inhaled anaesthesia (Türkan, Aydin and Sayal, 2005).

Sevoflurane induced apoptosis and elevated levels of the level-site amyloid precursor protein-cleaving enzyme and $A\beta$. In exchange, Sevoflurane stimulated caspase, which raised the levels of amyloid precursor protein and $A\beta$ at the enzyme breakdown site. Further apoptosis is caused by the rise in $A\beta$ levels (Dong *et al.*, 2009).

Minor injury is characterized by a small increase in aminotransferase serum activity, while fulminant hepatic failure is associated with a substantial increase in liver enzyme activity and bilirubin levels, resulting in extreme liver necrosis. The study showed that some liver function biomarkers in the non-exposed group were lower than in the exposed group, especially aspartateaminotransferase, alanine aminotransferase, and gamma glutathione S transferase (Neghab *et al.*, 2020).

There are two suspected mechanisms for the potential nephrotoxic activity of sevoflurane. The metabolite, fluoroacetic acid, which has shown nephrotoxicity as well as hepatotoxicity, is the first element. The second is compound A's formation. Compound A is another fluorinated substance formed by an exothermic reaction between the absorbents of sevoflurane and carbon dioxide used in anesthetic delivery systems, which in animal studies can reportedly trigger mild and reversible injury. The theoretical risk of nephrotoxicity caused by compound A in humans can be time-dependent on dosage and exposure (Edgington, Muco and Maani, 2007).

Compound A (fluoromethyl-2,2-difluoro-1-[trifluoromethyl] vinyl ether) is the result of the metabolism of sevoflurane, formed by its interaction with carbon monoxide absorbents. The mechanism leading to renal toxicity is still debated, with the renal cysteine conjugate β -lyase pathway (involved in compound A biotransformation). Human beings may be less prone to compound A renal toxicity than rats if this pathway is responsible. Human studies have shown that long exposures (8 hours) to sevoflurane and low fresh gas flow rates can lead to substantial output of compound A. A low risk of biochemical changes in kidney injury occurs when the flow is low from sevoflurane administration (Hemmings and Egan, 2018).

As far as their demographic characteristics concerned, no major

variations between the revealed and referent subjects were noted. Furthermore, none of the studied subjects had a history of hepatotoxic and/or nephrotoxic that caused by material exposure. The result was that the biomarker of renal function in the exposed group was significantly different from the non-exposed group, particularly in the serum creatinine, kidney injury molecule-1, and calcium (Neghab *et al.*, 2020).

Recommended exposure limit values of 2 ppm have been recommended by NIOSH for all halogenated agents, including sevoflurane and 25 ppm for nitrous oxide. While biological exposure indices levels were not calculated for these anaesthetic gases by ACGIH and 3.6 $\mu\text{g/l}$ for sevoflurane, respectively, based on the NIOSH exposure limit of 2 ppm (Hoerauf *et al.*, 1996, 1999; Neghab *et al.*, 2020).

The degree of exposure to sevoflurane depends on a variety of parameters, including the absence or existence of sufficient ventilation and scavenging systems in the operating room, the form of operation, the extent of anaesthesia face mask leaks during anaesthetic gas administration, cylindrical leakage, whether gas leakage from the anaesthetic machine is regularly verified or not. In this case, dangerous working practices such as triggering the flow of anaesthetic gas before applying a mask to the patient's face or closing the flow of anaesthetic gas after removing a face mask and improperly fitting face masks also play an important role (Neghab *et al.*, 2020).

Accorsi *et al.*, 2005 examined operating room workers post-shift urine by gas chromatography-mass spectrometry coupled. Subjects' levels of urinary anaesthetic gases ranged from 0.4 to 1415.9 $\mu\text{g/l}$ for nitrous oxide, 0.0 to 36 $\mu\text{g/l}$ for isoflurane, and 0.0 to 46 $\mu\text{g/l}$ for sevoflurane. Similarly, the concentration of anaesthetic gases in the urine of forty workers was measured by Al-Ghanem *et al.* The mean urinary concentrations of nitrous oxide, isoflurane and sevoflurane were

respectively 1234, 3.75 and 4.3 µg/l (Hoerauf *et al.*, 1999).

At the beginning of an operating room shift or a work shift, operating room personnel exposed to sevoflurane during the previous work day had accumulated high HFIP values in their urine, indicating that 24 hours was not sufficient for HFIP elimination. As for Sev-U, our findings indicate that peaks of exposure in the end operating room session is especially influenced by this biomarker (2.8 h). The study showed there were a statistically significant correlation between sevoflurane urine and HFIP. The variation factor can be influenced by the biological factors, which tends to be greater even at minimal exposure (with sevoflurane exposure under 1 ppm), as well as by the presence of a group of subjects with low Sev-U but relatively high HFIP levels, presumably as exposure from the day before due exposure from the previous day (Scapellato *et al.*, 2014).

Based on the results of this analysis, the measured urinary biomarker concentrations according to the workplace exposure in 2 and 0.5 ppm were 318 and 131 mg/L for metabolite of sevoflurane (lower 95 % CL: 133 and 72 mg/L respectively) and 3.7 and 2.1 mg/L for sevoflurane urine (lower 95 % CL: 2.0 and 1.4 mg/L respectively). The biological equivalent concentrations of Imbriani *et al* for urinary HFIP were 488 and 160 mg/L, according to safe value of NIOSH exposure for airborne sevoflurane of 2 and 0.5 ppm, which some researchers proposed as a particular measure of occupational exposure to sevoflurane. Different HFIP values of 800 mg/L and 2772.7 mg/L for exposure to sevoflurane at 2 ppm. At the end of the operating session, the other study had substantial peak levels of sevoflurane exposure; the values were slightly lower (1.9 and 1.3 mg/L for 2 and 0.5 ppm environmental sevoflurane exposure, respectively) (Scapellato *et al.*, 2014).

Sevoflurane exposure to HFIP was more stable, with a longer half-life than the

urinary sevoflurane biomarker (2.8 and 19 hours, respectively, for sevoflurane and HFIP). However, this value indicates several factors that can affect sevoflurane metabolism such as smoking, alcohol consumption and genetic metabolic polymorphisms. HFIP is produced from the metabolism of the CYP2E1 enzyme, where its function can be established by smoking and alcohol habits (Scapellato *et al.*, 2014).

In addition to monitoring, according to a study conducted by Jenifer *et al.*, environmental monitoring with multi-capillary column-ion mobility spectrometry (MCC-IMS) method is also needed. There was a higher risk of turbulent flow compared to laminar flow in the operating room (Herzog-Niescery *et al.*, 2015; Kunze *et al.*, 2015; Neisi *et al.*, 2019).

Due to the hazards posed by sevoflurane, it is possible to undertake a risk assessment, thus possible threats to health conditions can be anticipated. Exposure to anaesthetic gases in the workplace damage operating room personnel. Health care and environmental control, such as anaesthesia equipment maintenance, breathing system efficacy and anaesthetic gas removal procedures, and regular staff training are also highly recommended (Dehghani *et al.*, 2020).

In order to develop an effective workplace, monitoring of occupational hazards for anaesthetists who are exposed on a daily basis is important to minimize risks and generates a successful anaesthesiology practice. This will result in less absenteeism, better patient care, and better improvement of the anaesthesiologist's quality of life (Hoerauf *et al.*, 1999; Volquind *et al.*, 2013).

CONCLUSION

Sevoflurane is an inhalational anaesthetic agent that is used to induce and maintain the patient under anaesthesia during surgery. Health effects of sevoflurane as hepatotoxic, nephrotoxic and neurotoxic in the human body pose as a

health risk for anaesthesiologist. We need to environmental and biological monitoring to create a safe and healthy workplace. We need more data to discover about a specific monitoring to supervise each anaesthesiologist that has sevoflurane exposure.

REFERENCE

- Accorsi, A. *et al.* (2005) 'Urinary sevoflurane and hexafluoroisopropanol as biomarkers of low-level occupational exposure to sevoflurane', *International Archives of Occupational and Environmental Health*, 78(5), pp. 369–378. doi: 10.1007/s00420-004-0580-8.
- Brioni, J. D. *et al.* (2017) 'A clinical review of inhalation anesthesia with sevoflurane: from early research to emerging topics', *Journal of Anesthesia*, 31(5), pp. 764–778. doi: 10.1007/s00540-017-2375-6.
- Dalagkozi, P. *et al.* (2018) 'The Effects of Exposure of Health Care Professionals to Volatile Anesthetic Gases', in. doi: 10.1007/978-3-319-70548-4_574.
- Dehghani, F. *et al.* (2020) 'Probabilistic health risk assessment of occupational exposure to isoflurane and sevoflurane in the operating room', *Ecotoxicology and Environmental Safety*, 207(May 2020), p. 111270. doi: 10.1016/j.ecoenv.2020.111270.
- Dong, Y. *et al.* (2009) 'The common inhalational anesthetic sevoflurane induces apoptosis and increases β -amyloid protein levels', *Archives of Neurology*. doi: 10.1001/archneurol.2009.48.
- Edgington, T. L., Muco, E. and Maani, C. V. (2007) 'Sevoflurane - StatPearls - NCBI Bookshelf', *xPharm: The Comprehensive Pharmacology Reference*, pp. 1–4.
- Hemmings, H. C. and Egan, T. D. (2018) *Pharmacology and physiology for anesthesia: Foundations and clinical application, Pharmacology and Physiology for Anesthesia: Foundations and Clinical Application*. doi: 10.1016/C2014-0-04139-1.
- Hemmings, H. C. and Egan, T. D. (2019) *Pharmacology and Physiology for Anesthesia_ Foundations and Clinical Application-Elsevier (2018).pdf*.
- Herzog-Niescery, J. *et al.* (2015) 'Occupational chronic sevoflurane exposure in the everyday reality of the anesthesia workplace', *Anesthesia and Analgesia*, 121(6), pp. 1519–1528. doi: 10.1213/ANE.0000000000001015.
- Hoerauf, K. H. *et al.* (1996) 'Occupational exposure to sevoflurane and nitrous oxide in operating room personnel', *International Archives of Occupational and Environmental Health*, 69(2), pp. 134–138. doi: 10.1007/s004200050127.
- Hoerauf, K. H. *et al.* (1999) 'Occupational exposure to sevoflurane during sedation of adult patients', *International Archives of Occupational and Environmental Health*, 72(3), pp. 174–177. doi: 10.1007/s004200050357.
- İnan, G. and Özköse Şatırlar, Z. (2015) 'Alzheimer disease and anesthesia', *Turkish Journal of Medical Sciences*. doi: 10.3906/sag-1407-40.
- Kubota, Y. (1992) 'Comparative Study of Sevoflurane with Other Inhalation Agents', (Table 3), pp. 118–124.
- Kunze, N. *et al.* (2015) 'Multi-capillary column-ion mobility spectrometry (MCC-IMS) as a new method for the quantification of occupational exposure to sevoflurane in anaesthesia workplaces: An observational feasibility study', *Journal of Occupational Medicine*

- and *Toxicology*. doi: 10.1186/s12995-015-0056-7.
- Lucio, L. M. C. *et al.* (2018) 'Occupational hazards, DNA damage, and oxidative stress on exposure to waste anesthetic gases', *Brazilian Journal of Anesthesiology*. doi: 10.1016/j.bjan.2017.05.001.
- Mastrangelo, G. *et al.* (2013) 'Exposure to anesthetic gases and Parkinson's disease: A case report', *BMC Neurology*, 13. doi: 10.1186/1471-2377-13-194.
- Molina Aragonés, J. M. *et al.* (2016) 'Occupational exposure to volatile anaesthetics: A systematic review', *Occupational Medicine*, 66(3), pp. 202–207. doi: 10.1093/occmed/kqv193.
- Neghab, M. *et al.* (2020) 'Toxic responses of the liver and kidneys following occupational exposure to anesthetic gases', *EXCLI Journal*, 19, pp. 418–429. doi: 10.17179/excli2019-1911.
- Neisi, A. *et al.* (2019) 'Investigation of health risk assessment sevoflurane on indoor air quality in the operation room in Ahvaz city, Iran', *Toxin Reviews*. doi: 10.1080/15569543.2018.1434796.
- Scapellato, M. L. *et al.* (2014) 'Biomonitoring occupational sevoflurane exposure at low levels by urinary sevoflurane and hexafluoroisopropanol', *Toxicology Letters*, 231(2), pp. 154–160. doi: 10.1016/j.toxlet.2014.10.018.
- Türkan, H., Aydin, A. and Sayal, A. (2005) 'Effect of volatile anesthetics on oxidative stress due to occupational exposure', *World Journal of Surgery*. doi: 10.1007/s00268-004-7658-z.
- Volquind, D. *et al.* (2013) 'Occupational Hazards and Diseases Related to the Practice of Anesthesiology', *Revista Brasileira de Anestesiologia*, 63(2), pp. 227–232. doi: 10.1016/S0034-7094(13)70221-6.
- Zhimin ji, Wanjun Wu, Fan zhou, Junfang Hu, Qiuping Xu, Weibin Yang, Xueyong Peng, Xinguo Wang, Cheng Zhang, L. L. (2020) 'Effects of Sevoflurane Exposure on Apoptosis and Cell Cycle of Peripheral Blood Lymphocytes, and Immunologic Function', *BMC Anesthesiology*. Available at: <https://doi.org/10.21203/rs.3.rs-139150/v1>.