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Probabilistic health risk assessment of occupational exposure to isoflurane and sevoflurane in the operating room

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ABSTRACT

Risk assessment is an important tool in predicting the possible risk to health. It heightens awareness by estimating the probability of adverse health effects in humans who are exposed to chemicals in the course of their work. Therefore, the present work aims to determine the occupational exposure of operating room staff to the volatile anesthetic gases, isoflurane and sevoflurane, and estimates non-cancer risk using the United States Environmental Protection Agency method. Air samples from the breathing zone of staff members were collected using the Occupational Safety and Health Administration Method 103 and analyzed using gas chromatography-mass spectroscopy. The results indicate that the measured concentrations of isoflurane and sevoflurane are below the National Institute of Occupational Safety and Health standard (2 ppm) for technicians and nurses, but not for anesthesiologists and surgeons. Moreover, the estimated non-cancer risk due to isoflurane is above the acceptable value for anesthesiologists (but acceptable for other occupational categories). A sensitivity analysis indicates that exposure time has the most effect on calculated risk (53.4%). Occupational exposure to anesthetic gases may endanger the health of operating room personnel. Therefore, control measures, such as daily testing of anesthetic devices, ensuring the effectiveness of ventilation systems, advanced scavenging methods, and regular training of staff are highly recommended.

1. Introduction

Although total intravenous anesthesia has become popular in recent years, inhaled halogenated anesthetic agents remain a preferred option for the induction and maintenance of general anesthesia in operating rooms. Isoflurane, a fluorinated ether, is one of the most popular, commonly-used volatile anesthetic gases (Checkai, 2014). Another widely-used anesthetic agent is sevoflurane, a polyfluorinated methyl isopropyl ether; its low liquid/gas partition coefficient ensures rapid and predictable anesthesia and recovery, compared to intravenously-administered anesthetics (Haufroid et al., 2000; Hirai et al., 2019). The extensive use of these two halogenated gases is due to their favorable pharmacokinetic characteristics. Not only are they tissue inert, with predictable hemodynamic effects, they also have desirable physical properties such as colorlessness, non-flammability, high stability, and non-explosiveness (Tankó et al., 2014; Kishikawa et al., 2018; Neghab et al., 2020).

Despite technological advances, the leakage of anesthetic gases into the atmosphere of the operating room remains a concern. There are several potential sources, which can be classified into two main categories: fugitive gases that leak from equipment; and gases that are eliminated by the patient's respiratory system into the ambient environment (Newcomer and Chopra, 2019). Poor connections between the various components of the anesthetic equipment, such as the Y-connector, the vaporizer, the manual breathing bag, the CO_2 absorber, and common lines are potential sources of leakage (Zare Sakhvidi et al.,

Abbreviations: C, Concentration; AT, Average Lifetime; RfC, Inhalation Reference Concentration; HQ, Hazard Quotient; OR, Operating Room; ET, Exposure Time; EF, Exposure Frequency; EC, Exposure Concentration; ED, Exposure Duration; US EPA, US Environmental Protection Agency; LOAEL, Lowest Observed Adverse Effect Level; ACGIH, American Conference of Governmental Industrial Hygienists; OSHA, Occupational Safety and Health Administration; NIOSH, National Institute of Occupational Safety and Health; TLV, Threshold Limit Value; REL, Recommended Exposure Limit; NOAEL, No Observed Adverse Effect Level.

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2013; Shouroki et al., 2019). However, a more significant problem is that gas can escape between the patient's respiratory tract and the equipment that secures the airway during the delivery of anesthesia. In practice, the greatest potential source of anesthetic gas emission is the patient's mouth. Tankó et al. (2014) found that during intracerebral surgery, large amounts of evaporated sevoflurane were emitted through the patient's mouth, and were found in the anesthetist's breathing zone. The quantity of emitted gas is influenced by the type of device, notably the laryngeal mask airway and endotracheal tubes. For example, Herzog-Niescery et al. (2015) showed that the use of a laryngeal mask airway increased exposure to sevoflurane, compared to endotracheal tubes.

Acute exposure to high concentrations of isoflurane and sevoflurane has been reported to cause central nervous system disorders such as fatigue, headache, dizziness, and attention deficit (McGregor, 2000; Summer et al., 2003; Sárkány et al., 2016). Long-term exposure to waste anesthetics is associated with genotoxicity, spontaneous abortions, congenital abnormalities and infertility (Byhahn et al., 2001; Smith, 2010; Chaoul et al., 2015). Furthermore, the risk of renal and hepatic disease has been found to be higher among personnel who are exposed to isoflurane in operating rooms (Byhahn et al., 2001; Smith, 2010; Chaoul et al., 2015).

Despite the implementation of numerous control measures (e.g., effective ventilation, scavenger systems, and avoiding leakage) to minimize exposure to anesthetic gases, they remain a threat to the health of operating room staff (Tankó et al., 2014). In this context, a health risk assessment is an important tool in predicting the possible risk to medical workers. The health risk assessment process predicts the probability of adverse health effects in humans who are exposed to certain chemicals in the course of their work. The overall assessment is broken down into the following four stages: hazard identification; dose–response evaluation; exposure assessment; and risk determination (Gul and Ak, 2018). It is based on the quantitative determination of exposure and dose-response data, which can be obtained from the United States Environmental Protection Agency (US EPA). The combination of exposure level and dose-response data can be used to estimate the specific risk for a given compound (Omidi et al., 2019).

Various approaches can be used to estimate the health risk of chemicals. The typical, deterministic analysis is based on giving a fixed value to input variables in a risk equation; as it assigns a fixed value to input variables, it results in a fixed value output. This conservative approach is complicated by the fact that many input variables cannot be treated as single-point values. A more sophisticated method assigns a range of values to input variables, however, this leads to multiple risk estimates (Saha et al., 2017). In order to address this complexity, a probabilistic approach has become popular, and is widely-used for risk assessment (Jiang et al., 2015; Tong et al., 2019).

Anesthetic gases (in particular, isoflurane and sevoflurane) are known to be toxic, and all operating room staff are exposed to them. It is important to determine the level of these gases in the breathing zone of personnel and estimate the health risk. Therefore, the purpose of the present work is to quantitatively determine the occupational exposure of operating room staff to isoflurane and sevoflurane (the two main anesthetic gases found in the breathing zone) and, subsequently, determine the non-cancer risk of these compounds.

2. Materials and methods

2.1. Sample

The study was carried out in 2019. The sample for this cross-sectional study consisted of staff working in 10 operating rooms at the two leading teaching hospitals in Iran. A total of 50 people participated. This included 10 surgeons and their assistants, eight surgical nurses, eight anesthesiologists, and 24 operating room technicians. Waste gases can escape into the environment from various components of the anesthesia delivery system. Some of the main sources of potential leakage include connections in the breathing circuit, tank valves, defects in the rubber and plastic tubing, and the mouth of the patient (due to improperly inflated tracheal tube and laryngeal mask airway cuffs). An overview of an operating room, the location of staff, and exposure sources is presented in Fig. 1.

2.2. Sampling protocol

Fig. 1 shows some sources of anesthetic gas emissions. However, it should be noted that this figure does not show every possible source. Many parameters affect the level of anesthetic gas emissions in the operating room. Various other factors, such as the type of surgery, the number of surgeries performed per day, the ventilation system, and the condition of equipment are relevant. Moreover, the distribution of gases in different parts of the room may vary. In this study, we assume that the concentration of anesthetic gases is different in different parts of the theatre.

Following Occupational Safety and Health Administration (OSHA) Method 103 (Jafari et al., 2018), we attached a calibrated sampling pump to a member of staff during surgery. Their level of exposure to anesthetic gases (isoflurane and sevoflurane) was evaluated from 120 air samples that were gathered from the breathing zone during their shift. All samples were collected using a calibrated Pocket Pump TOUCH (20–500 mL/min, SKC, Inc.) at the recommended flow rate of 0.05 L/min, equipped with glass tubes packed with two sections of (140/70 mg) Anasorb 747 (SKC cat. no. 226-81A). To determine actual exposure and control break-through volume, three samples were collected at different times during the shift. After sampling, the tubes were immediately sealed with plastic end caps to prevent any gas escaping from the sorbent. The collected samples were then brought to the instrumental lab, and stored in a refrigerator prior to analysis. A schematic diagram of the setup used to sample the gases collected in this study is shown in Fig. 2.

2.3. Sample pretreatment and analysis

The collected samples of isoflurane and sevoflurane were transferred to extraction vials. Extraction was performed using 1.0 mL carbon disulfide (99.5%) (Merck Inc., Germany). For complete extraction, samples were exposed to ultrasonic waves for 30 min. After desorption, 1.0 μL of extracted sample was analyzed by GC-MS (CP-3800 gas chromatograph, and Saturn 2200 mass spectrometer, Varian Technologies Japan Inc., Japan) equipped with a CP-Sil 8 CB Varian capillary column (length 30 m, inner diameter 0.25 mm). Helium was used as a carrier gas, at a flow rate of 1 mL/min. The oven temperature was set at 45 °C for 4 min, then increased at a rate of 30 °C/min, to 150 °C/min for 1 min.

2.4. Non-cancer risk assessment

The framework for the health risk assessment is shown in Fig. 3. The isoflurane inhalation reference concentration (RfC) was determined using the method specified by the US EPA (US EPA, 2009; Persad and Cooper, 2008; Cui et al., 2020). Accordingly, the value was estimated from the lowest-observed-adverse-effect level (LOAEL). Findings from human studies (Beckman et al., 2006) have determined that, for 40 min of inhalation exposure, the LOAEL value for isoflurane is 1000 ppm (7546.01 mg/m^3). The RfC was calculated using Eq. (1):

$$RfC = \frac{LOAEL}{UF} \quad (1)$$

Where LOAEL is the lowest-observed-adverse-effect level, and UF is an uncertainty factor. Uncertainty factors include inter-human variability, intraspecies differences, subchronic-to-chronic studies, the use of LOAEL rather than the no-observed-adverse-effect level (NOAEL), database

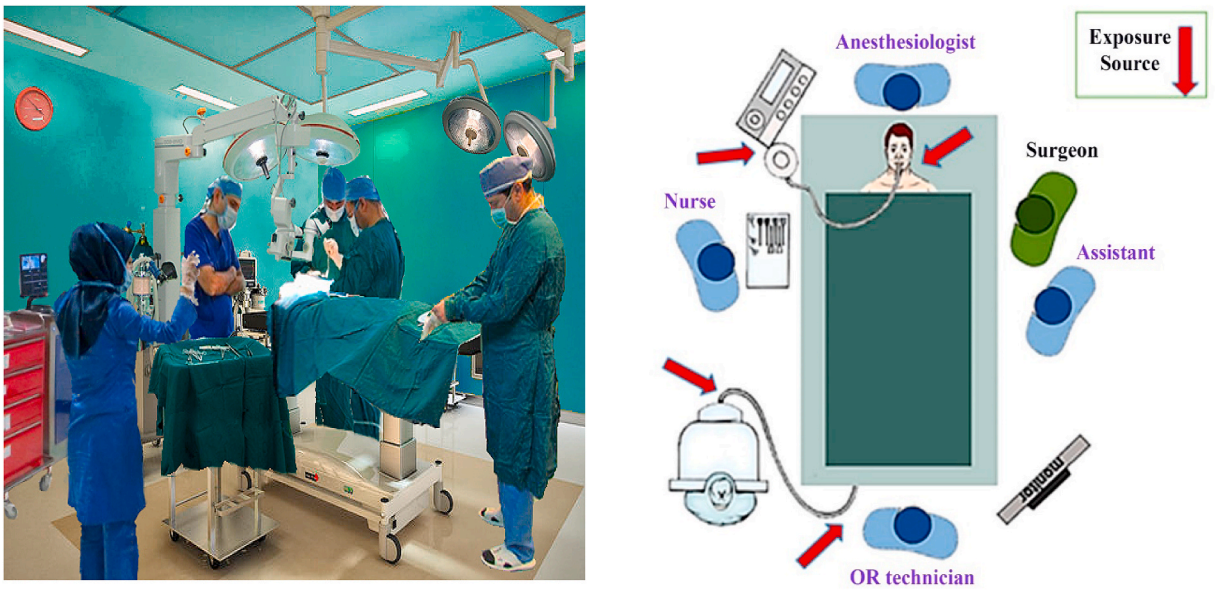


Fig. 1. A view of an operating room showing the location of staff members, and sources of exposure to anesthetic gases.

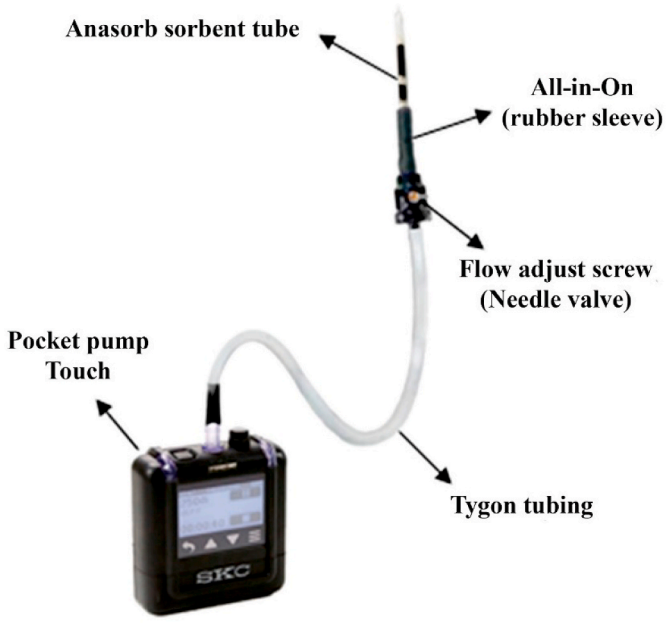


Fig. 2. Schematic diagram of the setup used to sample anesthetic gases from the breathing zone of operating room staff.

constraints, study type, and the point of departure (Persad and Cooper, 2008). Here, we adopt × 3 UF (the use of LOAEL rather than the no-observed-adverse-effect level (NOAEL), inter-human variability, and subchronic-to-chronic studies) for isoflurane. Therefore, the calculated RfC for isoflurane was 7.546.

According to EPA guide, the reference dose (RfD) is used to estimate non-cancer risk for chemicals that enter the body through the oral route. Anesthetic gases enter the body through inhalation; therefore, the use of the RfD to calculate non-cancer risk is not recommended. The EPA recommends equation (2) to derive the RfC from the RfD.

Therefore, the calculated reference dose (RfD) for sevoflurane (1.07 mg/kg/day) (Neisi et al., 2019) was applied to derive the RfC (3.745 mg/m^3), using Eq. (2):

$$RfC(mg/m^3) = RfD(mg/kg/day) \times 70(kg)/20(m^3/day) \quad (2)$$

Exposure concentration (EC) through the inhalation route was calculated using Eq. (3) (US EPA, 2009):

$$EC = (C \times ET \times ED \times EF)/AT \quad (3)$$

Where EC represents the exposure concentration (mg/m^3), C denotes the concentration of anesthetic gases in the breathing zone of operating room staff (mg/m^3), ET indicates the exposure time (hours day^{-1}), ED denotes the exposure duration (years), EF indicates the exposure frequency (days $year^{-1}$), and AT denotes the average lifetime (hours).

Table 1 shows the variables used to conduct the non-cancer risk assessment. Hazard quotients (HQ) related to exposure to anesthetic gases were computed using Eq. (4) (Fallahzadeh et al., 2018):

$$HQ = \frac{EC}{Rfc} \quad (4)$$

Where HQ is the hazard quotient, EC is the exposure concentration, and RfC is the inhalation reference concentration.

2.5. Sensitivity analysis

Using single-point values for each variable leads to uncertainties that can either underestimate or overestimate risk. To address this issue, we used a Monte Carlo simulation (Wu et al., 2011). Monte Carlo simulation is an established tool for evaluating health risks based on variability in input variables. The distribution of input variables is determined and randomly-selected variables are used multiple times in the health risk equation. The performance of the model is expressed as a distribution function. The method can also be used for a sensitivity analysis (Miri et al., 2018). The latter helps researchers understand which variables have the greatest effect on predicted health risks. In the present study, the Crystal Ball tool (version 11.1.1.1, Oracle, Inc., USA) was used in the sensitivity analysis, and the simulation was run 10,000 times.

3. Results and discussion

3.1. The concentration of measured anesthetic gases

Collecting air samples from the breathing zone of staff is considered

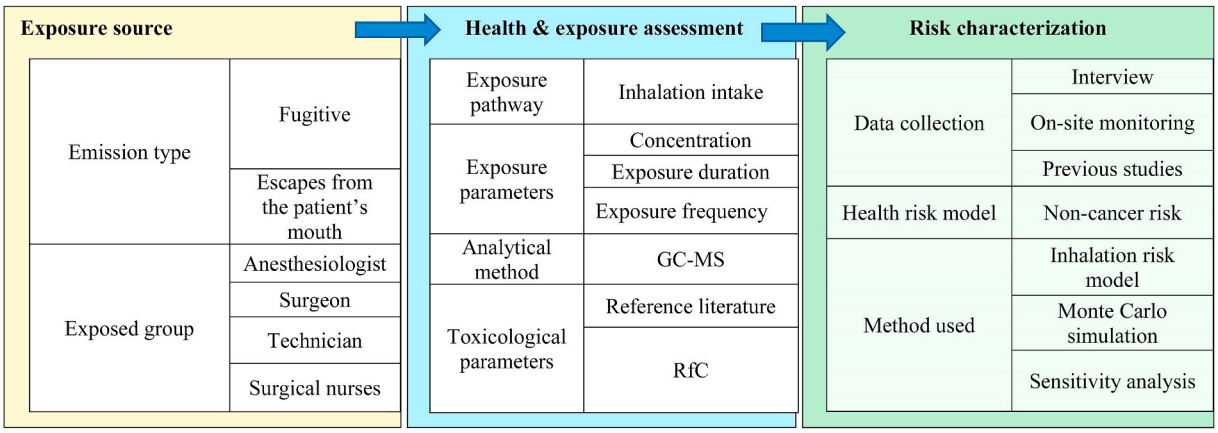


Fig. 3. The research framework used for the health risk assessment of operating room staff.

Table 1
Variables used to calculate non-cancer risk.

Parameter	Definition	Unit	Value	Basis	Reference
C	Concentration of anesthetic gases	mg m^{-3}	See Table 2	Sampling	
ET	Exposure time	hours day^{-1} (working hours)	6 for surgeons and 8 for other occupational groups	Questionnaire	
EF	Exposure frequency	days $year^{-1}$	230 ± 10	Questionnaire	
ED	Exposure duration	years	30	Questionnaire	
AT	Average lifetime	hours	165600	Lifetime in years (30 years × 230 days/year × 24 h/day)	US EPA (2009)
RfC	Inhalation reference	mg m^{-3}	7.546 for isoflurane and 3.745 for sevoflurane	Beckman et al. (2006), Neisi et al. (2020) using the US EPA methodology	Beckman et al. (2006), Neisi et al. (2020)
HQ	Hazard Quotient (Non-cancer risk)	–	To be calculated		

Table 2
The concentration of isoflurane and sevoflurane in the breathing zone of operating room (OR) staff.

OR personnel (n = 50)	Isoflurane (mg/m^3) ± SD	Sevoflurane (mg/m^3) ± SD
Surgeon (n = 10)	19.02 ± 0.75	2.78 ± 0.14
Surgical nurses (n = 8)	4.53 ± 0.08	1.64 ± 0.05
Anesthesiologist (n = 8)	21.13 ± 0.56	5.65 ± 0.13
Technician (n = 24)	14.94 ± 0.81	2.62 ± 0.15

to be the best way to measure personal exposure to volatile compounds. Table 2 presents concentrations of isoflurane and sevoflurane in the breathing zone of operating room staff. The highest concentrations were found for anesthesiologists, and the reported values are comparable with the results of the study conducted by Tankó et al. (2009).

The National Institute of Occupational Safety and Health (NIOSH) recommends a maximum exposure level of 2 ppm for halogenated anesthetic gases such as isoflurane and sevoflurane (Al-Ghanem et al., 2008; Tankó et al., 2014). The American Conference of Governmental Industrial Hygienists (ACGIH) has also suggested a threshold limit of 5 ppm for isoflurane (ACGIH Hygienists, 2020). Our study found that concentrations of the two gases were significantly different. In particular, the concentration of sevoflurane was below recommended limits in all investigated groups.

There are several possible reasons for this difference. One of the most important is the cost of the two gases. Sevoflurane is more expensive than isoflurane and often only used in special cases. At the same time, it has unique properties, such as a more rapid change in anesthetic depth, a non-pungent odor, and it does not cause respiratory irritability. It is particularly suitable for mask induction in pediatrics and adults. Another factor is the age of the patient, which affects the amount of gas used. Consequently, the selected gas is a function of the type of surgery and the condition of the patient, and the price of the gas.

The second important finding is that isoflurane exposure among anesthesiologists and surgeons exceeded recommended levels (Fig. 4). Anesthesiologists spend more time with patients (before, during, and after surgery) than other occupational groups. Staff are exposed to anesthetic gases as the patient exhales, in particular, in the operating room environment (Tankó et al., 2009). Minimum concentrations were obtained for surgical nurses. This is not surprising as this group is usually least-exposed to anesthetic gases.

Several studies have examined personal exposure to anesthetic gases in operating rooms. Both Accorsi et al. (2005) and Scapellato et al. (2014) found that the level of exposure to sevoflurane was significantly correlated with job title. They also reported that operating room technicians had the highest exposure to sevoflurane. However, the latter

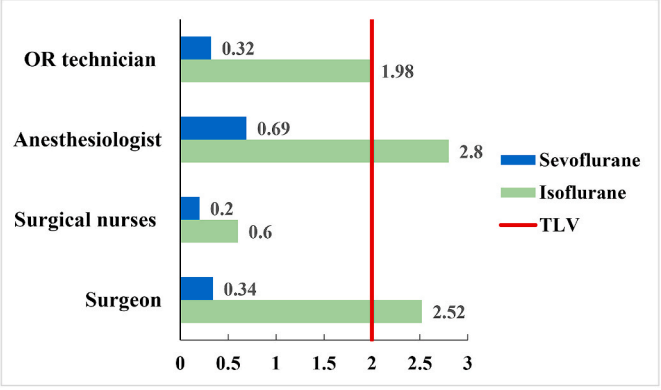


Fig. 4. Comparison of isoflurane and sevoflurane concentrations (ppm) for different occupational groups showing suggested threshold limit values (TLVs).

finding was not confirmed in the present study. Moreover, we found that exposure to isoflurane and sevoflurane was highest for anesthesiologists, which is likely to be due to the time they spend working in close proximity to patients and equipment. Finally, another study conducted by Jafari et al. (2018) found no significant differences in isoflurane concentration among different occupational groups.

3.2. Non-carcinogenic risk assessment

The present work evaluated the non-cancer risk of occupational exposure to anesthetic gases using the hazard quotient (HQ). It should be noted that in cases where the HQ is above 1, there is the potential for adverse health effects (Dehghani et al., 2018).

The HQ was calculated from the exposure concentration (Table 3), and these data were used in the non-cancer risk assessment. Table 4 shows 95th quartile HQ values for isoflurane and sevoflurane for the different occupational groups (surgeons, surgical nurses, anesthesiologists, and technicians) as a heat map. These analyses found that the calculated HQ for isoflurane and sevoflurane, in almost all occupational groups, was below one (Table 4 and Fig. 5). As noted above, the exception was anesthesiologists, and this finding indicates that there are potential adverse health effects (notably, a decrease in cognitive function). Anesthesiologists were followed by technicians and surgeons. Here again, the calculated risk was lowest for surgical nurses; the calculated values are acceptable and there appears to be little reason to be concerned about this group. Nevertheless, there is clearly a need to implement appropriate measures to control the level of exposure to isoflurane in the other studied groups.

Interestingly, both the concentration and the estimated non-cancer risk due to exposure to sevoflurane were remarkably lower than permissible values for all investigated occupations. Possible reasons for this finding are discussed above. A review of the literature highlights that very few studies have assessed the risk to health of exposure to anesthetic gases. One example is Neisi et al. (2019), who assessed non-cancer risk due to occupational exposure to sevoflurane in the operating rooms of three teaching hospitals. Their results revealed that calculated non-cancer risks were below the permissible limit, and comparable with our findings. Similarly, Afra et al. (2019) investigated the health risk arising from exposure to isoflurane in the operating rooms of two leading teaching hospitals in Abadan. Although they found that concentrations of isoflurane were above NIOSH recommended exposure limits, estimated non-cancer risks were below one.

However, their method was not the same as the one used in the present work. In particular, the latter authors used RfD as the reference dose in the risk assessment, but RfD is used to assess the risk of substances entering the body through the oral route, and not for inhalation exposure. The quality of the data is another key factor in estimating RfC. In the present work, isoflurane RfC was estimated using human LOAEL based on US EPA guidelines (Persad and Cooper, 2008), and was equal to 3.745 mg/m^3.

The results of the present work suggest that occupational exposure to anesthetic gases may endanger the health of operating room personnel. Therefore, we highly recommend that control measures, such as daily testing of anesthetic devices, ensuring the effectiveness of ventilation systems, the use of advanced scavenging methods, and regular staff training, are implemented.

Table 3
Exposure concentrations (EC) through the inhalation route for isoflurane and sevoflurane (mg/m3).

Occupational group	Isoflurane		Sevoflurane	
	Mean ± SD	95th	Mean ± SD	95th
Surgeon	4.72 ± 0.53	5.64	0.70 ± 0.08	0.83
Surgical nurses	1.51 ± 0.13	1.72	0.55 ± 0.05	0.63
Anesthesiologist	7.05 ± 0.63	8.10	1.88 ± 0.16	2.16
Technician	4.98 ± 0.48	5.81	0.88 ± 0.09	1.03

3.3. Sensitivity analysis

The sensitivity analysis evaluated the variables with the most influence on estimated non-cancer risk. Fig. 6 presents the results of the sensitivity analysis of isoflurane and sevoflurane exposure for anesthesiologists. As Fig. 6 indicates, exposure time (ET) had the most effect on calculated risk in both cases (53.4% and 49.4% for exposure to isoflurane and sevoflurane, respectively). Exposure frequency and exposure duration were the second and third most influential variables. These findings show that reducing exposure time significantly reduces non-cancer risk.

4. Limitations and further studies

The present study has some limitations. First, the type of surgery may affect exposure to anesthetic gases, which was not considered in this work. Second, our study was conducted in two teaching hospitals, which may not be representative of all hospitals. Therefore, we recommend that further studies should investigate the type of surgery on the emission of anesthetic gases in the operating room environment with larger samples.

5. Conclusion

The present work investigated occupational exposure to anesthetic gases (isoflurane and sevoflurane), and non-cancer risk in the operating rooms of two teaching hospitals in Iran. Exposure for all of the studied occupational groups (except anesthesiologists and surgeons) were below the NIOSH recommended exposure limit (2 ppm). Moreover, non-cancer risks due to occupational exposure to isoflurane and sevoflurane were acceptable (HQ $<$ 1) for all occupational groups except anesthesiologists.

However, the calculated non-cancer risk for anesthesiologists due to isoflurane exposure was 1.07, which is higher than the acceptable level. Although the obtained results suggest that occupational exposure to anesthetic gases in all measured occupations (except anesthesiologists) was below the acceptable level, long-term exposure to anesthetic gases may endanger the health of operating room personnel. Given the limitations of our study, and inter-human variability, the implementation of control measures is of great importance. Therefore, we highly recommend the implementation of administrative and technical controls, such as ongoing testing of anesthetic machines for leaks, regular checks of ventilation systems using advanced scavenging techniques, and periodic training of staff.

Authorship statement

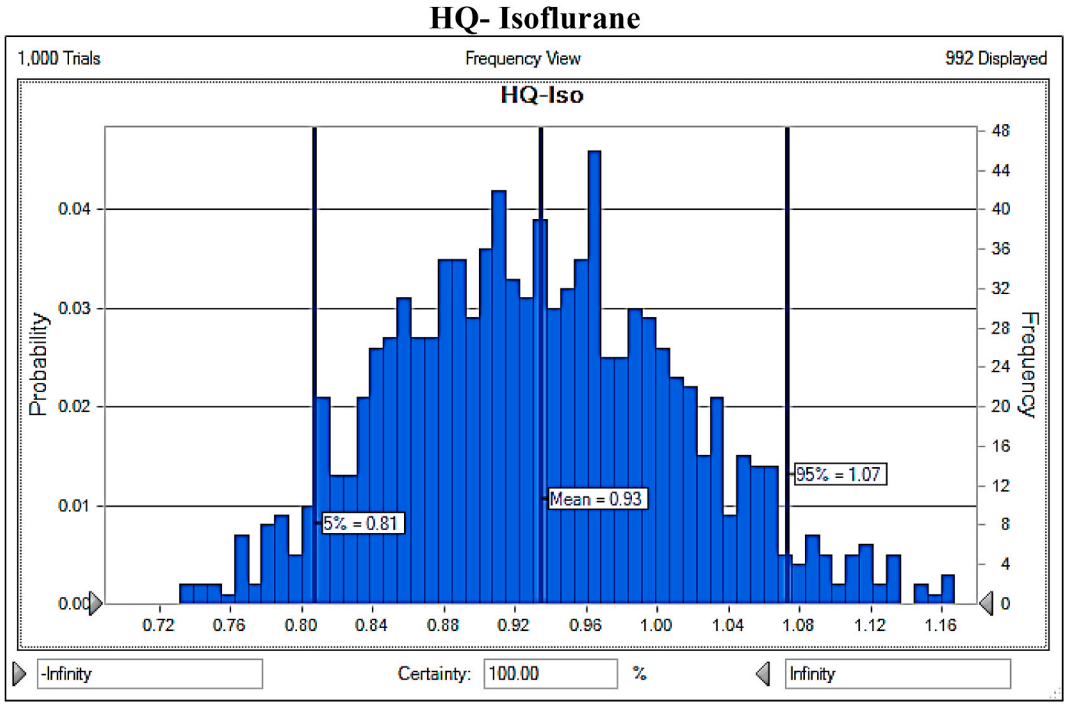
All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the Journal of Ecotoxicology and Environmental Safety.

Author contributions

Fatemeh Dehghani, Investigation, Formal analysis, Writing - original draft. Mojtaba Kamalinia, Supervision, Conceptualization, Methodology, Writing - review & editing. Fariborz Omidi, Methodology, Data curation, Writing - review & editing. Reza Ali Fallahzadeh, Software (Monte Carlo simulation).

Table 4
Non-cancer risk (HQ) values for occupational exposure to isoflurane and sevoflurane.

Occupational group	Surgical nurse		Surgeon		Technician		Anesthesiologist	
	Mean ± SD	95th	Mean ± SD	95th	Mean ± SD	95th	Mean ± SD	95th
Isoflurane	0.20±0.02	0.23	0.63±0.07	0.75	0.66±0.06	0.77	0.93±0.08	1.07
Sevoflurane	0.15±0.01	0.17	0.19±0.02	0.22	0.23±0.02	0.27	0.50±0.04	0.58
Good			moderate				serious	



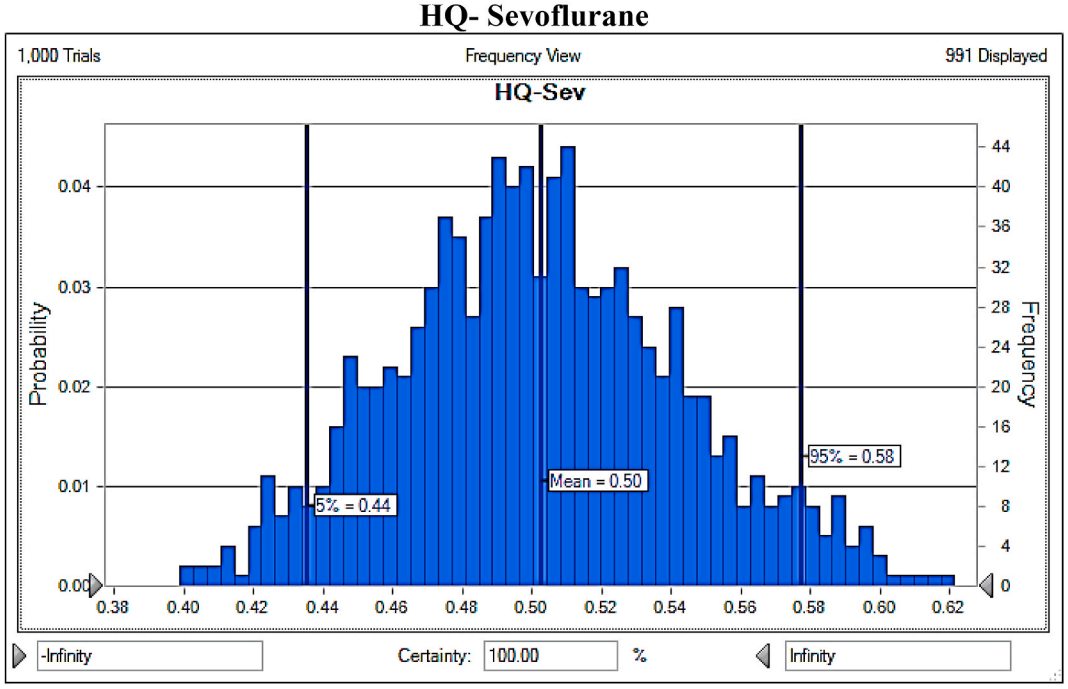


Fig. 5. The results of non-cancer risk (HQ) due to exposure with isoflurane and sevoflurane in anesthesiologist.

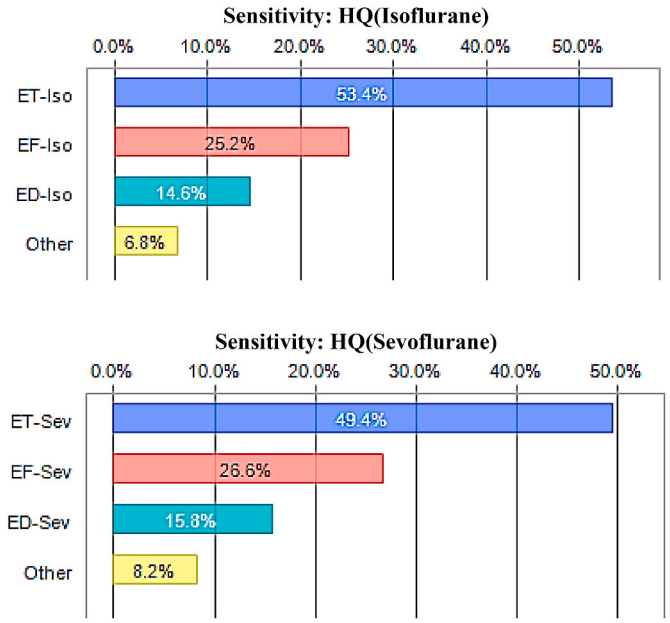


Fig. 6. The results of sensitivity analysis due to exposure with isoflurane and sevoflurane in anesthesiologists.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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