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Biological Monitoring of Occupational Exposure to Isoflurane by Measurement of Isoflurane Exhaled Breath

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The relationship between isoflurane environmental concentrations in operating rooms and the corresponding isoflurane concentration in the exhaled air of the operating personnel at the end of the exposure has been investigated. Isoflurane was retained in an adsorbent cartridge and after thermal desorption the concentration was estimated by gas chromatography. Significant correlation between environmental and exhaled air isoflurane concentrations allowed the establishment of a biological exposure index and biological exposure limits corresponding to proposed atmospheric threshold values.
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INTRODUCTION

Isoflurane (forane, 2-chloro-2,2,2-trifluoroethyl difluoromethyl ether, CAS no. 26675-46-7 mol.wt 184.5) is a widely used halogenated anaesthetic agent and there are numerous studies on its metabolism, partition coefficients between tissues and fluids and adverse effects.[1–5] All these aspects have been studied mostly in experimental animals or in patients receiving anaesthesia. There is also interest in it as a possible occupational hazard to medical personnel. Spontaneous abortion and liver damage have been mentioned as principal[6–8] toxic effects.

There are inherent difficulties in carrying out personal sampling in operating theatres, where the maintenance of sterile conditions and the minimum of interference with work are essential. Under such conditions diffusive samplers, which do not require sampling pumps, offer a convenient way of sampling. Rather than solvent desorption techniques, thermal desorption methods offer higher sensitivity through the avoidance of sample dilution.

Biological monitoring, as a complement to environmental assessment, has roused enormous interest in the search for biological indices of occupational exposure. Among the methods of biological monitoring, the analysis of exhaled breath has the advantage of non-invasiveness, which makes it well accepted by workers. Moreover, compounds are analysed directly, thus eliminating interferences from non-occupational factors. Additionally, isoflurane is mostly eliminated by exhalation.[2,9]

For the evaluation of isoflurane in air and in exhaled breath, thermal desorption–gas chromatography techniques were developed and validated.[10–12] The exhaled isoflurane is trapped in a solid adsorbent for chromatographic analysis. The method is not affected by water vapour condensation.[11]

The aim of this study was to propose a biological index of exposure based on the relationship between personal exposure to isoflurane in the operating theatre and its concentration in exhaled air.

EXPERIMENTAL

The study involved a total of 167 personal samples collected from anaesthetists, surgeons and nurses during their routine work in 13 surgical theatres in a Spanish hospital. The concentration of isoflurane in air was monitored continuously throughout exposure and exhaled air was sampled after exposure.

Isoflurane ambient concentrations

Isoflurane exposure was determined by using diffusive monitors attached to clothing within the breathing zone. The diffusive samplers were standard stainless-steel tubes for an ATD50 thermal desorption system (Perkin Elmer). The tubes were packed with 150 mg of conditioned Chromosorb 106.[10] Before use, and during storage, the tubes were protected with storage caps; when used, a diffusion cap was fitted to allow controlled exposure to the environment. The monitors were continuously exposed in the breathing zone for the whole operation periods.

All diffusive samplers were desorbed by means of the ATD system, directly connected to a Perkin-Elmer

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Table 1. Experimental conditions for thermal desorption and gas chromatography

Thermal desorption parameters	
Carrier gas	N_2 (68.95 kPa, 10 psi)
Desorption	Two stages
Oven temperature	240°C
Cold trap:	
lower temperature	–30°C
upper temperature	240°C
Heated transfer line	100°C
Gas chromatographic parameters	
Stationary phase	Free Fatty Acid Phase
Film thickness	0.3 μm
Column length	25 m
Column inner diameter	0.2 mm
Detector temperature	70°C
Detection	Flame ionization

8700 gas chromatograph by a heated transfer line. Operating conditions are summarized in Table 1.

The performance of this kind of sampler has been evaluated and validated. The sampler was found to collect isoflurane efficiently for up to 8 h at an uptake rate of 0.45 ml min^{-1}.[10,13]

Isoflurane in exhaled breath

The portable system used to take exhaled air samples has already been described.[14] It consists of a Haldane-Priestley aluminium tube modified to concentrate aliquots of end-expired (alveolar) air, from one or more exhalations, in a solid adsorbent for chromatographic analysis.

Samples of exhaled air were obtained by having the subject take two or three deep breaths, inhaling and holding their breath for 10–15 s, then exhaling into the aluminium tube of the sampler until all air was expelled. Isoflurane from end-exhaled air was retained in an adsorbent cartridge. A servomotor-driven gas syringe of 50 ml capacity alternately drew in from the aluminium tube and through the adsorbent metallic tube, standard for the ATD50 thermal desorption system. The tube was packed with 200 mg of 20/40 mesh Chromosorb 106 and was sealed at the end of the procedure for transport and storage.

The total volume of end-expired air that passed through the adsorbent tube was 1 l, representing five 200-ml aliquots for each of the five consecutive expirations. In all subjects, exhaled breath samples were collected 10 min after the end of exposure in an area separated from the site of exposure.

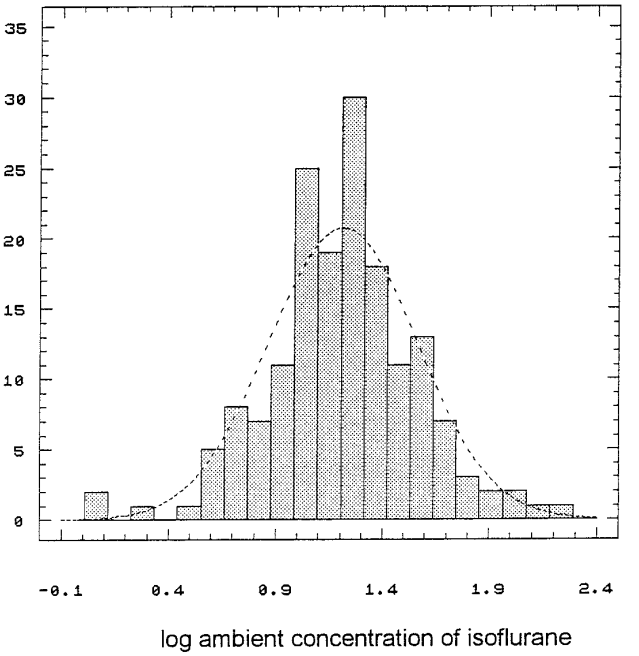

Figure 1. Log-normal distribution for the time-weighted average of the environmental concentration of isoflurane. Number of exposed subjects is expressed on ordinate axis.

All samples of exhaled breath air were desorbed following the same procedure as in the preceding section. Operating conditions are given in Table 1.

RESULTS AND DISCUSSION

Isoflurane in the operating rooms was always detectable. The distribution of the personal levels of isoflurane exposure for all theatre staff is shown in Fig. 1. Data were best fitted to a log-normal distribution. This type of distribution has been shown for other pollutants.[15,16]

Isoflurane concentrations ranged from 1.14 to 157.23 mg m^{-3} (Table 2). The results are similar to those obtained in other studies[17] but higher than those found in several Canadian hospitals,[18,19] where the arithmetic means ranged from 1.8 to 22.3 mg m^{-3}.

The percentage of biotransformation for isoflurane is only 0.2%,[2,4] so the best possibility for its biological monitoring is to measure the unchanged substance.

In order to obtain information about the sampling strategy, preliminary study was carried out under several exposure conditions (varying both isoflurane ambient concentration and exposure times). Alveolar air samples were taken at different times after exposure,

Table 2. Statistical parameters of the distribution of the time-weighted average of the environmental concentration and the exhaled air concentration of isoflurane

Environmental isoflurane concentration (mg m^{-3})		Exhaled air isoflurane concentration (mg m^{-3})	
Median value	16.62	Median value	3.03
Geometric mean	16.23	Geometric mean	2.85
Geometric standard deviation	2.23	Geometric standard deviation	2.51
Range	1.14–157.23	Range	0.15–26.09

the first sample being collected 10 min after the end of the exposure. Personal samples in the breathing zone were also taken for each sampled subject. Isoflurane concentrations and exposure times ranged from 8.4 to 157.2 mg m^{-3} and from 75 to 360 min, respectively, in order to study elimination through exhalation after different levels of exposure.

Elimination profiles of the exposition situations studied are shown in Fig. 2. After high exposure, initial exhalation concentrations were higher than after low exposure. In both cases, elimination profiles were similar to those found in anaesthetized patients[1,3] as well as to those obtained for other organic solvents that were mainly eliminated by the respiratory route (percloroethylene, for instance).[20–22]

Figure 3 shows the distribution of measured levels of isoflurane in exhaled breath air. Exhaled air isoflurane concentrations ranged, with a log-normal distribution, from 0.15 to 26.09 mg m^{-3} with a geometric mean of 2.85 mg m^{-3}.

A close relationship was found between the log of exposure dose, expressed as time-weighted average exposure multiplied by exposure time (D, mg m^{-3} min), and the concentration in the exhaled air (CAE, mg m^{-3}) ($r = 0.79$, $p = 0.0001$), as can be seen in Fig. 4. The linear regression line fits the following equation

$$\log CAE = 0.025 + 0.77 \log D$$

The regression line does not start from the origin of the Cartesian coordinate, as has been shown for isoflurane and halothane in urine.[17,23] This indicates that some isoflurane retained previously was not completely cleared during the resting period. This view was confirmed by the presence of isoflurane in samples of exhaled air taken 16 h after exposure.

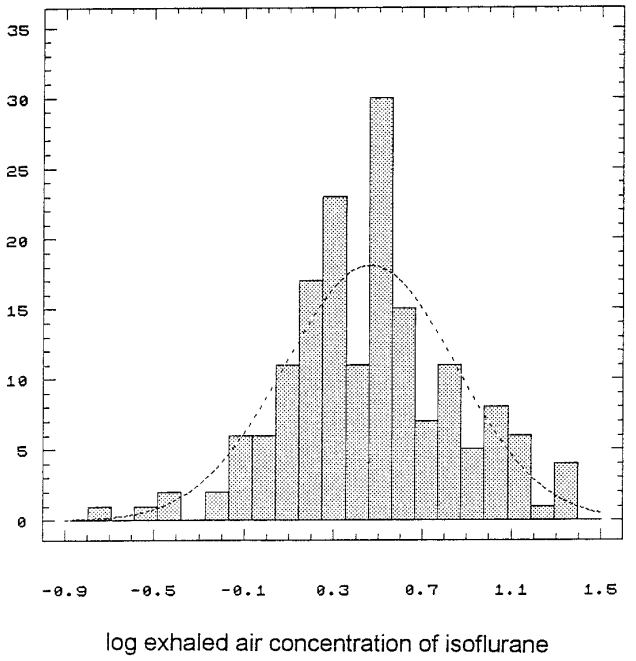

Figure 3. Log-normal distribution of exhaled air concentration of isoflurane for the population sampled. Number of exposed subjects is expressed on ordinate axis.

The limit value of 2 ppm was recommended by NIOSH for all halogenated agents.[24] This standard was given in 1977, when isoflurane was not yet in use.

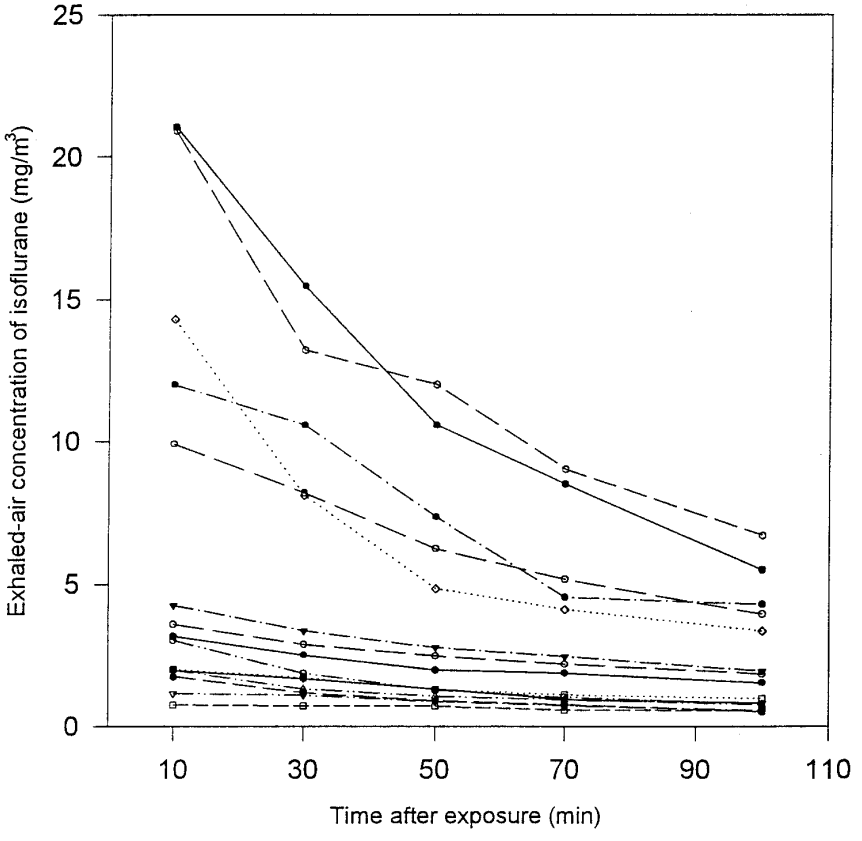

Figure 2. Elimination profiles of the volunteer exposures to isoflurane.

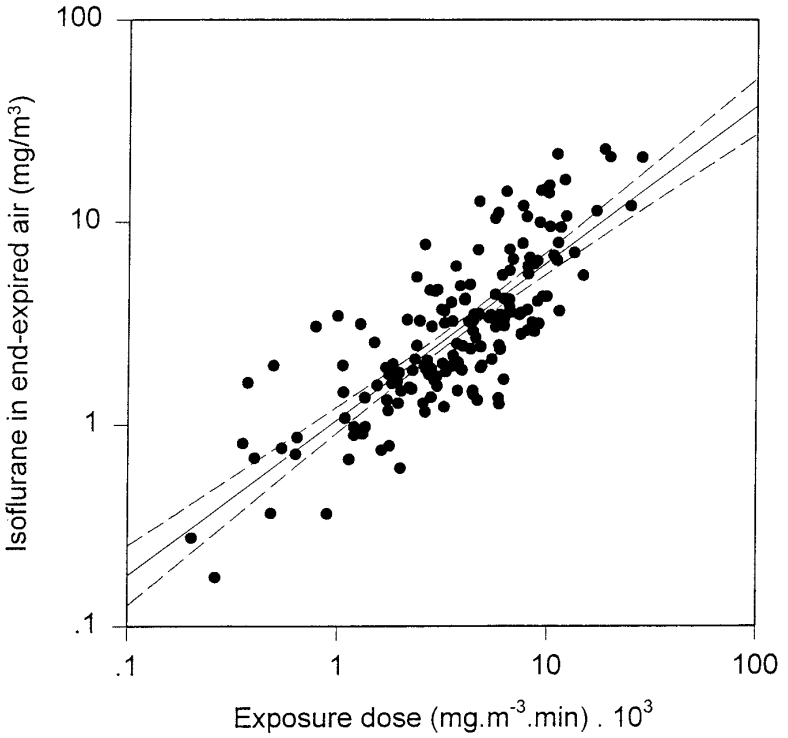

Figure 4. Relationship between exposure dose, expressed as time-weighted average multipled by exposure time, and exhaled air concentrations of isoflurane. Broken lines give 95% confidence intervals for the population value of the slope of the regression line.

More recently, the Swiss exposure standard for isoflurane and enflurane was set at a value of 10 ppm.[25]

The good correlation obtained allows the biological exposure limits to be calculated for both environmental limits. The biological index is 4.4 mg m^{-3} for an 8 h exposure to 2 ppm and 13.6 mg m^{-3} for exposure to 10 ppm. These biological exposure limits are the corresponding 95% lower confidence limits of the regression line.

The proposed method can be performed easily and quickly and could also be applied for another volatile liquid anaesthetic, desflurane, the use of which is currently increasing. Obviously, the exhaled air collection must always be performed with the same methodology and sampling strategy.

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