

Halothane Biotransformation in Anesthetists

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Serum bromide levels were measured in 115 anesthetists by use of x-ray fluorescence spectrometry. Bromide levels peaked at $184 \pm 21 \mu\text{M}$ in anesthetists regularly exposed to halothane ($n = 20$), at $58 \pm 4 \mu\text{M}$ in anesthetists sporadically exposed to halothane ($n = 71$), and at $46 \pm 3 \mu\text{M}$ in nonexposed anesthetists ($n = 24$). Kinetic studies were carried out in five other anesthetists after ten days of exposure to halothane. Average daily halothane concentration was $19.2 \pm 3.2 \text{ ppm}$; duration of exposure was $3.8 \pm 0.2 \text{ hours/day}$. Mean serum bromide level increased from $40 \pm 4 \mu\text{M}$ before exposure to $220 \pm 36 \mu\text{M}$ on the last day of exposure. Serum bromide half-life was $14 \pm 1.7 \text{ days}$. The study demonstrates that anesthetists debrominate halothane in a dose-related fashion. Serum bromide levels achieved, however, were far below those reported to result in clinical bromism. (Key words: Anesthetics, volatile: halothane, trace concentrations. Biotransformation. Ions: bromide. Operating rooms: contamination. Toxicity: metabolites, trace concentrations.)

INORGANIC BROMIDE is one of the major metabolites of halothane biotransformation.^{1,2} In several recent studies, serum bromide levels of 500–4,500 μM were measured in surgical patients, with the highest values observed in those having the greatest exposures to halothane.^{3–5} There has been no systematic study of serum bromide levels in anesthetists, although Johnstone *et al.*⁶ concluded that bromide levels were not increased in anesthetists working in unscavenged operating rooms. In the present study, serum and urinary bromide levels in anesthetists were measured by use of a highly sensitive method of analysis, x-ray fluorescence spectrometry.⁷

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Methods

The study was performed in two parts. First, a single serum bromide level was measured in anesthetists working in several hospitals in Paris, France. A survey of 115 anesthetists (80 physicians and 35 nurses) was made. The group included 39 men and 76 women. Their mean age was 32 years. Each anesthetist's exposure to halothane during the preceding two months was estimated from responses to a questionnaire designed to elicit the daily number of hours spent in the operating room and the frequency of halothane use. The respondents were questioned about use of waste gas scavenging devices and exposure to drugs or chemicals containing bromide. From the replies to the questionnaire, three groups evolved: a group not exposed to halothane during the preceding two months ($n = 24$); a group regularly administering halothane to at least 50 per cent of anesthetized patients and spending at least 20 hours/week in the operating room ($n = 20$); and a group who used halothane only sporadically, usually less than five hours each week ($n = 71$). Data from the one anesthetist who was exposed to a bromide-containing substance and from two anesthetists who employed scavenging devices, both of whom regularly employed halothane in their practices, were excluded from the study.

A 15-ml sample of blood was drawn from each subject in the morning before the subject entered the operating room. Samples were coded by number, then centrifuged and the sera frozen at -20 C until subsequent analysis. Samples were analyzed for bromide concentrations and subjects were assigned to exposure groups without prior knowledge of the other variable. Bromide concentrations in serum were determined by x-ray fluorescence spectrometry with a CGR** alpha 10 spectrometer.⁷ Analysis and detection of the $K\alpha_{1,2}$ bromide band ($\lambda = 1.041 \text{ \AA}$) was accomplished with a lithium fluoride crystal and a scintillation computer. Three measurements, each lasting 30 sec, were made: one at the peak, one offset at an angle of $+0.5$ degree to the peak and one at an angle of -0.5 degree to the peak (fig. 1). The latter two measurements were used to estimate the baseline of the $K\alpha_{1,2}$ bromide

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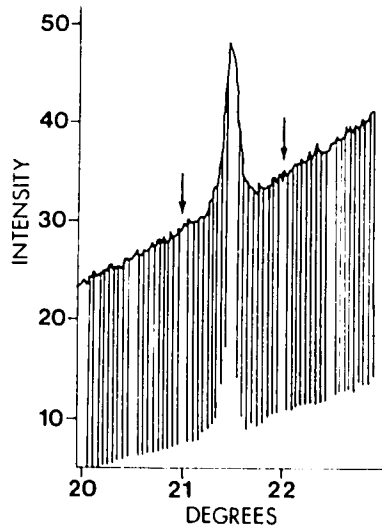


FIG. 1. Tracing of bromide measurement. One measurement is made at the peak of the $K\alpha_{1,2}$ bromine band, one offset at an angle of $+0.5$ degree (arrow) and one offset at an angle of -0.5 degree (arrow). Bromide concentration of the sample was $150 \mu\text{M}$.

band. This method measures total bromine rather than bromide ion. However, in preliminary experiments in which bromine was first trapped in, then eluted from, ion-exchange resins,⁸ we determined that more than 95 per cent of the bromine in serum obtained 12–24 hours after the last exposure to halothane was in the form of bromide ion. X-ray fluorescence spectrometry is a highly sensitive method of analysis. At low concentrations it can distinguish $10\text{-}\mu\text{M}$ differences in serum bromide concentrations, and it is accurate to ± 5 per cent. The standard calibration curve was linear over a range of 0–10 mM.

In the second part of the study, the kinetics of halothane biotransformation to bromide ion were studied in five anesthetists who had not been exposed to halothane for the preceding two months (table 1). Halothane exposures occurred in a pediatric hospital during two five-day periods, at which times the

anesthetists administered halothane–oxygen anesthesia for ear, nose and throat procedures. One additional subject had part of his exposure in the research laboratory during a holiday period, when the operating room was not in use; his data are not included in the group means. Gas flow employed by all subjects was 4–8 l/min; a nonbreathing system without waste-gas scavenging was used. In order to quantitate exposure to halothane, time-weighted average air samples were obtained from the anesthetist's breathing zone with a portable sampling pump†† and collection bag. Halothane concentrations in the samples were measured with a Varian 1440 gas chromatograph equipped with a flame-ionization detector. Exposure to halothane was expressed as ppm \times hours. After the two five-day periods of halothane administration there was no further exposure to this anesthetic for the remaining two weeks of the study.

Serum samples were obtained before exposure to halothane, at 48-hour intervals during exposure, and several times during the 14 days after exposure. Daily 24-hour urine collections were obtained from three subjects, beginning the day before exposure and continuing for 19, 21 and 23 days, respectively. Serum and urinary bromide levels were measured and the number of moles of biotransformed halothane was estimated by calculating the moles of bromide in the bromide space (approximately 25 per cent of body weight^{9,10}) prior to exposure to halothane and on the last day of the experiment. To the difference between these two values was added the total amount of bromide excreted in the urine in excess of baseline excretion during the experiment. These measurements permitted estimation of the amount of biotransformed halothane, since urinary excretion accounts for more than 95 per cent of total bromide excretion¹¹ and the stoichiometry of bromide ion evolution from halo-

†† Spectrex Corporation, Redwood City, California.

TABLE 1. Data for Individual Anesthetists

	Age (Years), Sex	Average Daily Halothane Exposure			Serum Br ⁻ , μM			U ₂₄ Br ⁻ Days	Total Urinary Br ⁻ Excretion (μmol)
		ppm	Hours	ppm \times Hours	Pre-exposure	Day 5	Day 12		
Anesthetist 1	25, M	29.7	3.6	106	50	120	140	19	1,660
Anesthetist 2	34, M	20.7	3.9	79	40	150	210	17	3,060
Anesthetist 3*	43, M	78.5	3.3	258	50	250	610	13	10,970
Anesthetist 4	30, M	12.1	3.4	44	50	100	270	11	—
Anesthetist 5	26, F	13.6	4.4	62	30	50	150	10	—
Anesthetist 6	31, M	19.7	3.8	71	30	250	330	13	—
MEAN	32	19.2	3.8	72.4	40.0	134	220	14.0	—
\pm SE*	± 3	± 3.2	± 0.2	± 10.2	± 4.4	± 33.3	± 36.1	± 1.7	—

* Anesthetist 3 excluded from calculation of group means.

thane is 1:1. Finally, the half-life of bromide in serum was determined.

Data are presented as means \pm SE. T tests of the mean were used for statistical comparisons, and $P < 0.05$ was considered significant.

Results

The survey indicated that serum bromide concentrations were significantly higher in anesthetists regularly exposed to halothane than in sporadically exposed or non-exposed cohorts (table 2). Bromide levels among sporadically exposed anesthetists were significantly higher than those among the non-exposed group. There was no difference within each group between physicians and nurses or between male and female anesthetists. The highest bromide concentration, 500 μM , occurred in a female physician regularly exposed to halothane. This anesthetist practiced pediatric anesthesia and had used 4–8 l/min gas flows with halothane, without scavenging devices, for more than five years. The two anesthetists who regularly employed halothane and scavenging devices had bromide levels of 51 and 58 μM , respectively. These were the lowest values observed among halothane users.

For the five anesthetists for whom kinetic studies were done, mean daily inspired concentration was 19.2 ± 3.2 ppm (fig. 2). The mean daily duration of exposure was 3.8 ± 0.2 hours. This corresponded to a mean daily inhaled dose of halothane of 72.4 ± 10.2 ppm \times hrs for each of the ten days of exposure. Serum bromide levels before halothane exposure averaged 40 ± 4 μM (fig. 3). There was a progressive increase in serum bromide during halothane administration, with mean values of 134 ± 33 μM at the end of the first week and 220 ± 36 μM at the end of the second week; peak concentrations ranged from 150 to 330 μM . The serum bromide half-life measured at the end of the experiment was 14.0 ± 1.7 days. This value is higher than the half-life of 9.3 ± 1.2 days in healthy

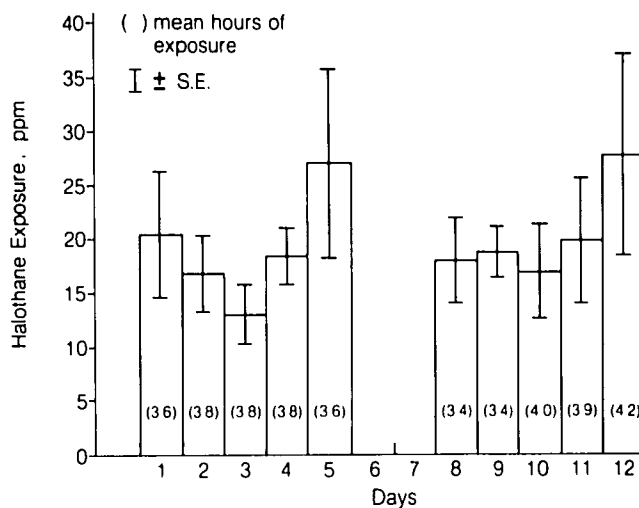


FIG. 2. Mean daily halothane exposures for five anesthetists in the kinetic study. Daily halothane concentrations ranged from 13 to 28 ppm, with a mean for the ten-day period of 19.2 ± 3.2 ppm. The daily durations of exposure ranged from 3.4 to 4.2 hours, with a mean of 3.8 ± 0.2 hours/day.

volunteers receiving infusions of sodium bromide in our laboratory.##

Complete collections of urine were obtained from two of the five subjects and from the individual exposed in both the laboratory and the operating room. Urinary bromide excretion for these three anesthetists averaged 50 $\mu\text{mol/day}$ before halothane exposure, increasing progressively during exposure (fig. 4). Bromide excretion was still markedly increased ten days after the last anesthetic exposure. The amounts of halothane these three anesthetists metabolized during the experiment were 2.6, 4.6 and 17.3 mmol, the latter value obtained from the individual exposed in both the operating room and the laboratory. The highest individual bromide level, 610 μM , occurred in this individual (fig. 5), who also had the greatest total halothane exposure, 258 ppm \times hours/day. There were large fluctuations in urinary bromide excretion among subjects, which may have been related to dietary chloride intake, a variable not controlled in this study.¹²

Discussion

This study clearly indicates that anesthetists debrominate halothane when exposed to trace concentrations found in unscavenged operating rooms. The results differ from those of Johnstone *et al.*,⁶ who found that serum bromide concentrations in anesthetists exposed to halothane were the same as those

TABLE 2. Serum Bromide in Anesthetists (Mean \pm SE)

Group	n	Sex	Age (Years)	Serum Br ⁻ (μM)
Non-exposed	24	F = 14 M = 10	31 ± 2	46 ± 3
Sporadically exposed	71	F = 49 M = 22	32 ± 1	$58 \pm 4^*$
Regularly exposed	20	F = 13 M = 7	33 ± 2	$184 \pm 21^*$
	115	F = 76 M = 39	32 ± 1	

* $P < 0.05$ vs. non-exposed.

Duvaldestin P: Unpublished data.

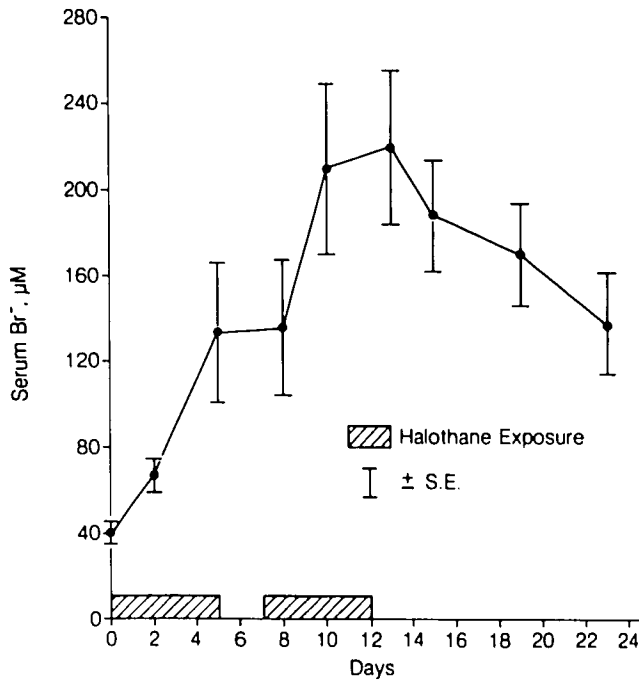


Fig. 3. Serum bromide levels before and after exposure to halothane. There was a progressive increase in serum bromide levels from the preanesthetic mean of $40 \pm 4 \mu\text{M}$ to $134 \pm 33 \mu\text{M}$ at the end of the first week and $220 \pm 36 \mu\text{M}$ at the end of the second week. Values gradually declined thereafter. The half-life of bromide measured at the end of the experiment was 14.0 ± 1.7 days.

measured in unexposed laboratory workers. They reported that ambient halothane concentrations at the anesthetists' heads ranged from 30 to 104 ppm and that serum bromide concentrations ranged from 240 to $970 \mu\text{M}$ (mean $430 \mu\text{M}$). However, Johnstone *et al.*⁶ employed an insensitive colorimetric method of bromide determination. The method is inaccurate at bromide concentrations of less than $300\text{--}500 \mu\text{M}$ and, at higher concentrations, cannot resolve differences of less than $100\text{--}300 \mu\text{M}$.^{13,14} It is not surprising, then, that they saw no difference between their groups, since unexposed anesthetists in the present study generally had bromide levels in the $40\text{--}50\text{-}\mu\text{M}$ range and those who regularly administered halothane averaged 184 and $220 \mu\text{M}$, with only occasional values of more than $250 \mu\text{M}$. The low bromide levels we report for unexposed anesthetists are similar to the control levels found in patients by Atallah and Geddes.¹⁵ The latter employed a highly sensitive method of bromide measurement, neutron activation, in their study.

The amount of halothane metabolized by anesthetists can be approximated from the kinetic data. One mole of nonvolatile bromine evolves from each mole of biotransformed halothane, whether oxidative or reductive pathways are involved.¹⁶ Also, the bromide space is relatively constant and corresponds to the extracellular fluid volume.^{9,10} Anesthetists not exposed to halothane for the preceding two months

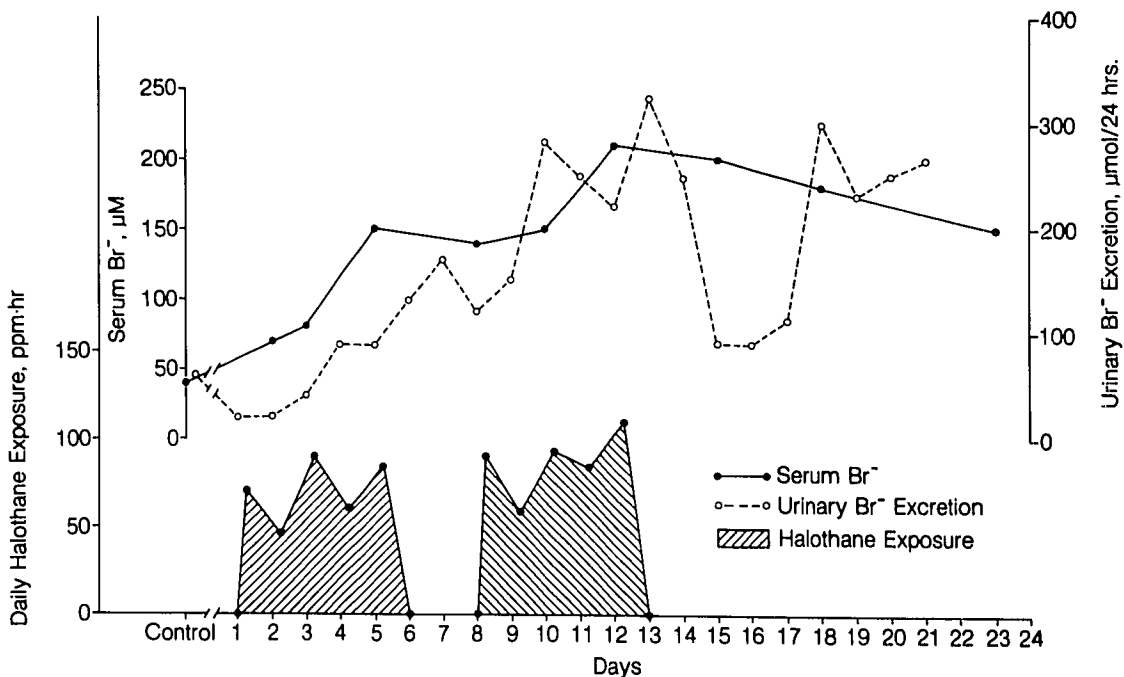


Fig. 4. Serum bromide, urinary bromide excretion and halothane exposure of Anesthetist 2. Daily exposures to halothane ranged from 50 to 100 ppm-hr . Serum bromide levels increased from $40 \mu\text{M}$ prior to exposure to $150 \mu\text{M}$ at the end of the first week and $210 \mu\text{M}$ at the end of the second week. Serum bromide levels decreased gradually thereafter, with a half life of 17 days. Volumes of urinary bromide excretion ranged from 20 to $320 \mu\text{mol}$ per day.

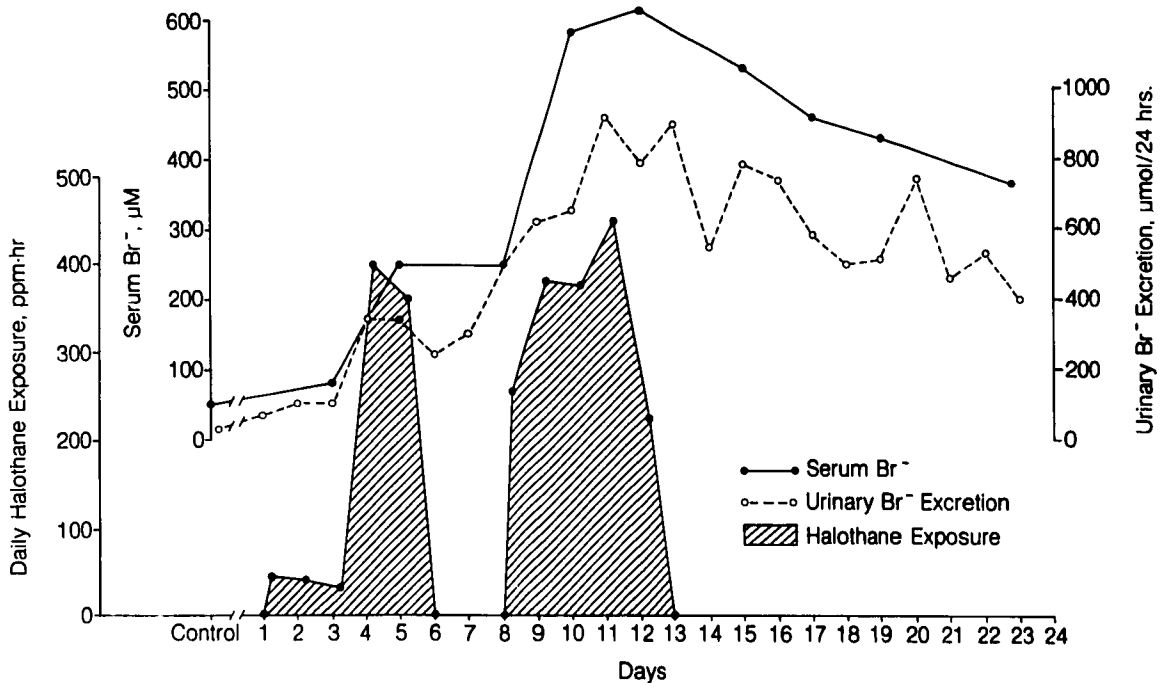


FIG. 5. Serum bromide, urinary bromide excretion, and exposure to halothane of the anesthetist exposed both in the operating room and in the laboratory. Halothane exposures ranged from 45 to 420 ppm hr. There was a marked increase in serum bromide levels, which peaked at 610 μM on the last day of exposure. Serum bromide half-life in this individual was 13 days. Urinary bromide excretion reached a peak of 920 $\mu\text{mol}/24$ hours in this anesthetist.

metabolized 2.6, 4.6 and 17.3 mmol of halothane after a ten-day period of exposure or 260, 460 and 1,730 $\mu\text{M}/\text{day}$ of exposure, respectively. The tendency towards a longer bromide half-life in anesthetists, 14.0 ± 1.7 days, compared with 9.3 ± 1.2 days, the bromide half-life in our laboratory after sodium bromide infusion,^{§§} suggests that these values may be somewhat underestimated. The longer bromide half-life may be explained by the assumption that bromide-containing metabolites which are formed and may be found in the liver are only slowly released after anesthesia has ended. Another possibility is that halothane metabolism continues many days after exposure has terminated, resulting in persistently increased serum bromide levels. Halothane is highly fat-soluble (oil/gas $\lambda = 230$), so it is probable the latter sequence of events does occur. Prolonged postanesthetic metabolism of methoxyflurane (oil/gas $\lambda = 930$) and enflurane (oil/gas $\lambda = 98$) in surgical patients already has been established.^{17,18}

The results of the present study also suggest that anesthetists who administer halothane do not metabolize it more rapidly than anesthetists who are not exposed to the drug. In a study in which ¹⁴C-halothane was administered to five anesthetists and four pharmacists, Cascorbi *et al.*¹⁹ found a tendency towards

increased urinary excretion of radiolabeled products by the anesthetists. He suggested that this might be the result of enzyme induction in anesthetists due to chronic exposure to trace levels of halothane. In a subsequent report in which additional subjects were added to the small groups previously studied, Cascorbi could find no relationship between occupation and excretion of ¹⁴C-halothane urinary products.²⁰ In the kinetic portion of our study, the mean peak serum bromide level among anesthetists not exposed to halothane for at least two months, then exposed for ten days was $220 \pm 36 \mu\text{M}$. This value was not different from the mean peak bromide level, $184 \pm 21 \mu\text{M}$, measured among anesthetists comprising the members of the survey. Members of the survey group had been regularly exposed to halothane during the preceding two months, and in some instances had been exposed to halothane for as long as 15 years. If induction of halothane biotransformation were to have taken place, it probably would have occurred in these anesthetists. Thus, our study is in agreement with the later report²⁰ by Cascorbi. However, it should be acknowledged that all of the anesthetists who comprised the kinetic study had been exposed to halothane earlier in their lives. Although there are no known mechanisms describing enhanced metabolism under these circumstances, the kinetic-study group is not a truly naive control population.

§§ Duvaldestin P: Unpublished data.

Finally, the results of the present study suggest that anesthetists are not likely to suffer bromism as a consequence of their occupation. The syndrome of chronic bromide intoxication includes headache, lethargy, dizziness, tremor, ataxia, mental confusion, hallucinations, dermatitis, slurred speech, ptosis and constipation.²¹ Early signs are said to occur at serum bromide levels of 5–10 mM, with more advanced signs occurring when levels reach 20 mM or more.^{22,23} In the present study, bromide levels of only two anesthetists peaked at values as high as 500–600 μM with mean peak values of 184 and 220 μM in the two parts of the study. Thus, there is a 10–25-fold margin of safety for anesthetists working in unscavenged operating rooms. The risk of developing bromism appears to be virtually nil for those anesthetists employing effective scavenging devices.

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