SERUM FLUORIDE LEVELS IN AMBULANCE STAFF AFTER COMMENCEMENT OF METHOXYFLURANE ADMINISTRATION COMPARED TO META-ANALYSIS RESULTS FOR THE GENERAL PUBLIC

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Abstract

Objectives: Ambulance officers administering methoxyflurane as an inhalational analgesic may be exposed to trace vapor. Fluoride is a methoxyflurane metabolite, and has been associated with acute renal failure in anesthesia patients and skeletal fluorosis with chronic elevated serum levels from other sources. However, there has been no direct measurement of serum fluoride in occupationally exposed ambulance officers. Thus, this study directly measures serum fluoride over a prolonged period in order to determine renal toxic and skeletal fluorosis risk to ambulance officers who are administering methoxyflurane. **Material and Methods:** Serum inorganic fluoride concentrations were measured in a prospective observational study of 12 emergency medical technicians (EMTs). The study took 7 serum fluoride measurements over 24 months. A meta-analysis of healthy adult serum fluoride ranges was also conducted. **Results:** The typical healthy adult serum fluoride range was determined to be 0.21–2.11 µmol/l (p < 0.001). The EMTs' baseline median (IQR) serum fluoride concentrations were 0.4 µmol/l (0.2; 1.0) with maximum 1.6 µmol/l. The EMTs' overall median serum fluoride was 0.4 µmol/l [0.2; 1.3] with maximum 4.0 µmol/l, usually within healthy reference ranges. All results were ≤10% of the suggested single-dose renal toxic threshold. One result was above a threshold for skeletal fluorosis. The highest measured serum fluoride was 24% of the lowest level associated with radiologic evidence of fluorosis. There was no evidence overall of increasing serum fluoride levels. **Conclusions:** There was no evidence that EMTs' exposure to methoxyflurane resulted in sustained increased serum fluoride. These results imply EMTs' occupational safety from acute renal toxicity when activated carbon filtration is used on patient exhalation. However, 1 serum fluoride result above a skeletal fluorosis threshold suggests that the risk of mild skeletal fluorosis cannot be excluded. Int J Occup Med Environ Health. 2021;34(6):767–77

Key words:
meta-analysis, prospective studies, fluorides, ambulances, fluoride poisoning, methoxyflurane

INTRODUCTION

Methoxyflurane is a volatile halogenated ether [1] recommended for use as an inhaled analgesic for pre-hospital and other pain relief [2,3]. Methoxyflurane undergoes hepatic metabolism [1], producing fluoride and other products. Approximately two-thirds of these products are excreted in urine over subsequent days [4]. An association exists between increased fluoride metabolite concentration in blood and increased nephrotoxicity [5–8]. A high-dose anesthetic use of methoxyflurane has thus been associated with renal failure [9,10].

In contrast, low-dose analgesia administered to patients and the environmental concentrations to which healthcare staff are exposed are believed to be well below a level that might cause renal toxicity [6]. Calculations of risk have relied on extrapolation over several orders of magnitude and, therefore, require verification [7,11]. International limit values (ILVs) have been set at 2 ppm for 8-hour exposure [12]. In a clinical setting with modern use, cohort mean 8-hour exposure to methoxyflurane was below the ILVs. However, the highest 8-hour exposure in that setting was 2.88 ppm, which exceeds those limits [13]. Direct measurement of fluoride levels in workers consistently exposed to methoxyflurane has not been undertaken and is, therefore, needed to confirm renal safety.

Another reason for direct measurement is to ascertain temporal effects such as fluoride accumulation due to repeated exposure. Approximately one-third of absorbed methoxyflurane and metabolites remain in the body 9 days following exposure [4]. Rodent skeletal fluoride content was found to increase following methoxyflurane exposure [14,15], suggesting that compartmental storage and saturation might result in a delayed increase in serum fluoride. This outcome suggests, for frequently exposed individuals, the possibility of serum fluoride reaching renal toxic levels with some delay. Therefore, direct measurement of serum fluoride over a prolonged period is required to confirm an absence of compartment saturation with delayed serum fluoride increase.

A further health concern, i.e., skeletal fluorosis, is caused by the accumulation of fluoride in bones over a prolonged period leading to stiffness, pain, connective tissue calcification, osteosclerosis, bone deformities, and increased fracture risk [16,17]. Skeletal fluorosis might be a potential long-term occupational hazard due to fluoride metabolite deposition from methoxyflurane [14,18]. Therefore, direct serum fluoride measurement is also important to investigate skeletal fluorosis risk. A threshold for serum fluoride levels associated with the onset of skeletal fluorosis is not immediately apparent in the literature [19–22]. Therefore, meta-analysis of the serum fluoride of the general public is also required to identify a healthy serum fluoride range not associated with skeletal fluorosis, against which individuals exposed to methoxyflurane might be compared.

This research hypothesized that emergency medical technicians (EMTs) would exhibit increasing serum fluoride concentrations after introduction of methoxyflurane. The absence of reported adverse effects due to occupational exposure was noted [23]. However, the accumulation of fluoride following repeated occupational exposure to methoxyflurane vapor has not been previously studied, and identifying whether such accumulation occurs is a necessary first step to quantifying risk and optimizing safety. Thus, this study directly measured serum fluoride over a prolonged period in order to determine renal toxic and skeletal fluorosis risk to ambulance officers who are administering methoxyflurane.

MATERIAL AND METHODS

The study was approved by the University of Canterbury Human Ethics Committee with ref. No. HEC 2017/23/LR, and by the ambulance service Research Committee. The study was registered with the Australian New Zealand Clinical Trials Registry with ID No. ACTRN12617001334392.

Written informed consent was obtained from all participants prior to any blood measurement.

Meta-analysis of published serum fluoride levels associated with healthy individuals was performed by the following process. First, the healthy reference range for serum fluoride was determined by searching PubMed for literature reporting serum fluoride in healthy adults. The inclusion criteria were as follows: any study reporting serum fluoride levels for a group consisting of healthy persons with an absence of reported skeletal fluorosis or altered renal function, regardless of their occupational or environmental exposure to fluoride or any substance believed to alter fluoride levels. Only English language studies were considered. The analysis was performed using R 3.6.1. Subsequently, the meta-analysis of search results was conducted by the generic inverse variance method with a random-effects model [24].

A New Zealand metropolitan ambulance service introduced methoxyflurane, administered via the Penthrox® inhaler with an activated carbon filter (Medical Developments International, Australia), as an analgesic option on June 1, 2017. Ambulance officers administered 3 or 6 ml to patients, as needed for analgesia [25]. The Penthrox® inhaler contains a carbon filter which adsorbs vapor exhaled by the patient, limiting vapor from entering the workspace of the ambulance officer. However, uncertain patient compliance with exhaling through the filter implied that staff would be exposed to some methoxyflurane vapor during administration [6].

A prospective observational cohort study was undertaken. At first, EMTs were recruited by general requests for participation sent via the ambulance service's internal e-mail system, and respondents were provided further information and gave their written consent for participation, until the goal of 12 participants was achieved. This sample size was selected to provide 95% power to detect a 1 μmol/l difference between test results with p < 0.01, allowing for 30% attrition [26]. Consent was only given

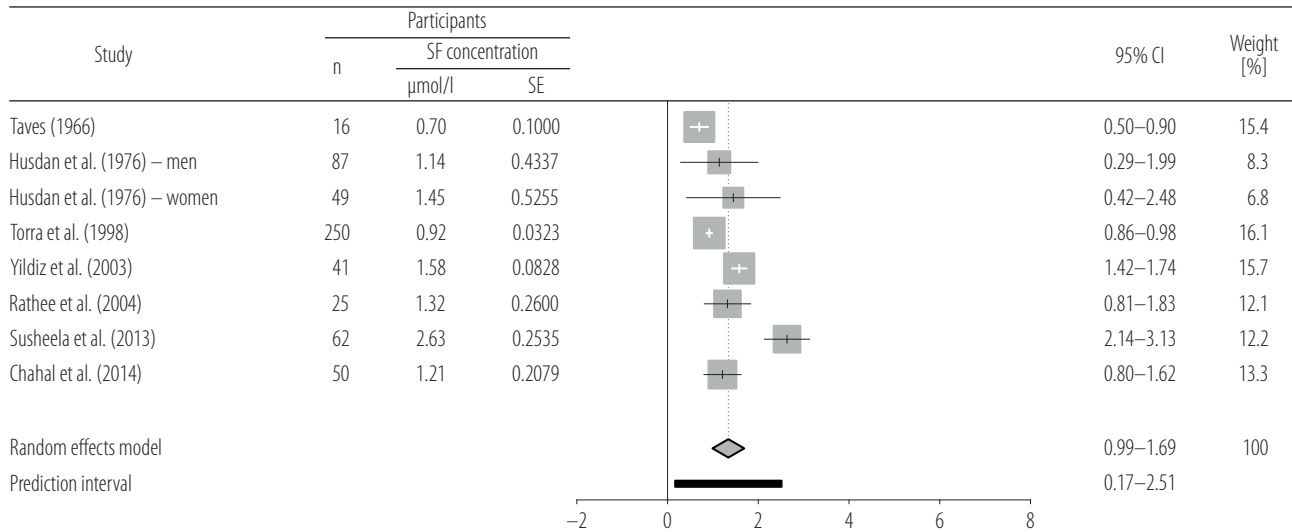for the collection, analysis, and publication of serum fluoride results.

The inclusion criteria were as follows:
– EMTs' practice level;
– employment in full-time patient contact duties by the ambulance service;
– age ≥18 years.

The reason why EMTs were recruited was that they can administer oral or inhaled analgesia agents, including methoxyflurane, but not intravenous agents [25]. Hence, it was assumed that EMTs would be more likely than other qualified staff to utilize methoxyflurane, and thus to be most exposed to methoxyflurane vapor. There were no exclusion criteria. The authors did not seek or obtain ethical approval to collect data on the participants' characteristics such as age, weight, or sex.

Blood serum measurements were taken in months 0, 1, 4, 8, 12, 18, and 24 following the introduction of methoxyflurane. The participants were e-mailed reminders at the start and mid-point of each of the 7 study months to provide a blood sample at a day and time convenient to them. Blood sampling was performed by a trained phlebotomist at a clinic convenient to each participant. Samples were separated locally and serum was sent to Canterbury Health Laboratories, Christchurch, New Zealand for analysis. Serum fluoride concentration was measured by a Thermo Scientific™ Orion Star™ A214 pH/ISE Benchtop Meter with a Thermo Scientific™ fluoride ion specific electrode. Equipment was calibrated by the laboratory using suitable sodium fluoride standards in accordance with the manufacturer's instructions. Uncertainty of measurement was ±0.48 μmol/l at 1 μmol/l, and ±2.11 μmol/l at 27 μmol/l. The lower limit of quantification was 0.2 μmol/l. Canterbury Health Laboratories is an entity accredited by International Accreditation New Zealand (IANZ) in all disciplines and for all medical testing procedures it performs, and is ISO 15189 accredited.

Exposure frequency data were not recorded due to an inability to directly observe the cohort, concern about

Study	Participants				95% CI	Weight [%]
	n	SF concentration				
		µmol/l	SE			
Taves (1966)	16	0.70	0.1000		0.50–0.90	15.4
Husdan et al. (1976) – men	87	1.14	0.4337		0.29–1.99	8.3
Husdan et al. (1976) – women	49	1.45	0.5255		0.42–2.48	6.8
Torra et al. (1998)	250	0.92	0.0323		0.86–0.98	16.1
Yildiz et al. (2003)	41	1.58	0.0828		1.42–1.74	15.7
Rathee et al. (2004)	25	1.32	0.2600		0.81–1.83	12.1
Susheela et al. (2013)	62	2.63	0.2535		2.14–3.13	12.2
Chahal et al. (2014)	50	1.21	0.2079		0.80–1.62	13.3
Random effects model					0.99–1.69	100
Prediction interval					0.17–2.51	

Heterogeneity: $I^2 = 94\%$, $\tau^2 = 0.1975$, $p < 0.001$.
The 95% CI was determined by the generic inverse variance method with a random-effects model, and is shown as the "prediction interval" ($p < 0.001$).

Figure 1. Forest plot of serum fluoride (SF) ranges of healthy individuals

the reliability of the participants' self-reporting, and ethical and time constraints in setting up the study.

Two-sample, 2-sided Wilcoxon signed-rank tests were performed, comparing the serum fluoride results from each study month against the results from month 0, removing from each test any participants who had not provided a blood sample in both the specific month and month 0 to ensure pairing. Two-sample 2-sided Kolmogorov-Smirnov tests were performed, comparing all serum fluoride results for each participant with a constant serum fluoride value equal to that participant's first test result. Statistical significance for all tests was defined as $p < 0.05$. The Kolmogorov-Smirnov test was selected after all serum fluoride test results had been received. Thus, results of that analysis should be regarded as hypothesis-generating.

The serum fluoride levels associated with skeletal fluorosis were determined by searching PubMed for literature reporting this association. Engauge v. 10.10 software was used to determine the value of serum fluoride and bone mineral density data points in figures.

RESULTS

Identification of a healthy serum fluoride range

Overall, 8 studies reporting serum fluoride ranges in healthy adults were identified [19–21,27–31]. Insufficient statistical measures were provided in 1 study, preventing its inclusion in the meta-analysis [21]. One other study reported ranges for men and women separately [28]. Therefore, these ranges were input as separate samples for meta-analysis. None of the studies included New Zealand subjects. Meta-analysis, as shown in Figure 1, determined mean (95% CI) serum fluoride in healthy individuals to be 1.16 µmol/l (0.21–2.11) with $p < 0.001$, indicating statistically significant homogeneity supporting this determination of a normal range.

Participants' serum fluoride results

The target of recruiting 12 EMTs was achieved by June 15, 2017. One participant withdrew late during the study and ethical constraints prohibit presentation or discussion of that person's data. Some participants failed to undertake ≥1 tests.

Table 1. Blood test dates and serum fluoride (SF) results for the participants (N = 11) following the introduction of methoxyflurane into clinical practice, June 2017–June 2019, New Zealand

Participant	2017						2018						2019	
	June (month 0)		July (month 1)		October (month 4)		February (month 8)		June (month 12)		December (month 18)		June (month 24)	
	test date	SF concentration [μmol/l]	test date	SF concentration [μmol/l]	test date	SF concentration [μmol/l]	test date	SF concentration [μmol/l]	test date	SF concentration [μmol/l]	test date	SF concentration [μmol/l]	test date	SF concentration [μmol/l]
1	–	–	31 Jul	<0.2	2 Nov*	<0.2	2 Mar*	<0.2	3 Jul*	1.3	24 Dec	0.9	24 Jul*	1.3
2	20 Jun	1	25 Jul	<0.2	30 Oct	0.4	20 Feb	<0.2	29 Jun	1	13 Dec	0.4	26 Jun	0.6
3	30 Jun	<0.2	31 Jul	<0.2	31 Oct	0.4	14 Feb	<0.2	8 Jun	<0.2	–	–	3 Jul*	0.3
4	4 Jul*	<0.2	20 Jul	<0.2	30 Oct	0.4	28 Feb	<0.2	29 Jun	<0.2	20 Dec	0.8	29 Jun	0.4
5	19 Jun	0.4	20 Jul	<0.2	27 Oct	1	28 Feb	<0.2	20 Jun	1.5	22 Dec	1.1	21 Jun	0.4
6	3 Jul*	1.3	–	–	11 Oct	4	28 Feb	1.4	8 Jun	<0.2	–	–	–	–
7	15 Jun	1.6	27 Jul	1.8	5 Oct	2.2	23 Feb	1.2	7 Jun	1.9	7 Dec	1.4	17 Jun	2
8	16 Jun	0.8	31 Jul	<0.2	30 Oct	0.8	27 Feb	<0.2	2 Jul*	<0.2	28 Dec	<0.2	3 Jul*	0.3
9	22 Jun	<0.2	24 Jul	<0.2	13 Oct	2.2	7 Feb	1	7 Jun	1	5 Dec	1.5	19 Jun	0.6
10	–	–	28 Jul	1.3	31 Oct	0.6	12 Mar*	1.2	–	–	28 Dec	2.2	–	–
11	24 Jun	<0.2	–	–	–	–	–	–	–	–	–	–	–	–
First quartile		0.2		0.2		0.4		0.2		0.2		0.7		0.4
Me		0.4		0.2		0.7		0.2		1.0		1.0		0.5
Third quartile		1.0		0.2		1.9		1.2		1.3		1.4		0.8
Wilcoxon p		–		0.201		0.090		0.462		0.892		0.462		1.000

* Occasionally, the participants took the test slightly after the end of the intended month, and this is reported with the date the test was taken.
Median and quartiles are calculated based on the assumption that the results reported by the laboratory as "<0.2 μmol/l" have the value of 0.2 μmol/l.
Wilcoxon signed-rank tests compared each month with month 0.

Table 2. Results of Kolmogorov-Smirnov tests for each participant's serum fluoride results against a constant serum fluoride value equal to that participant's initial test result, following the introduction of methoxyflurane into clinical practice, June 2017–June 2019, New Zealand

Participant	Kolmogorov-Smirnov p
1	0.395
2	0.056
3	0.865
4	0.541
5	0.541
6	0.548
7	0.203
8	0.056
9	0.056
10	0.548

One participant undertook only the initial blood test but did not withdraw formally from the study, and 6 participants provided blood samples for every requested study month.
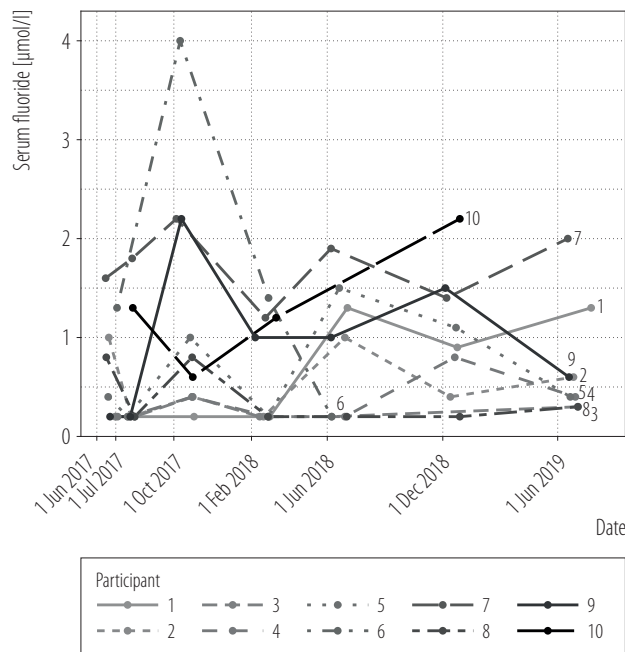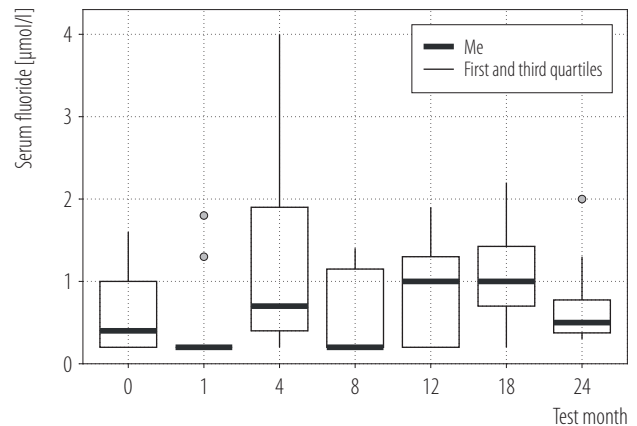

Figure 2. Serum fluoride results for participants 1–10, June 2017–June 2019, New Zealand

Vertical lines extend from the smallest observation greater than or equal to the first quartile minus 1.5 times the interquartile range, to the largest observation less than or equal to the third quartile plus 1.5 times the interquartile range; dots indicate outlier serum fluoride results not included within the vertical line range.

Figure 3. Box plots for serum fluoride in each test month, June 2017–June 2019, New Zealand

The resulting data set includes initial (baseline) values for 9 participants and longitudinal results for 10 participants, as shown in Table 1. Some results were below the lower limit of quantification. The analysis (Tables 1 and 2, Figures 2 and 3) and discussion of the results assume those results to be equal to the lower limit of quantification: 0.2 μmol/l. To determine whether this assumption introduced error, an analysis was also performed with these values equal to 0.0, which did not elicit any new statistical significance in any results.

Longitudinal results for the participants are displayed in Figure 2, and summary statistics for each month are shown in Table 1 and Figure 3. The overall median (first quartile, third quartile) of serum fluoride was 0.4 μmol/l (first and third quartiles: 0.2, 1.3) with max 4.0 μmol/l. The p-values determined by Wilcoxon signed-rank tests for the difference between month 0 and each subsequent month are shown in Table 1, and support a conclusion that there is no statistically significant change in serum fluoride over time. The results of Kolmogorov-Smirnov tests for 10 partici-pants are shown in Table 2. This compares each partici-

pant's serum fluoride results against a constant serum fluoride value equal to that participant's initial test result, to identify whether a statistically significant change occurred. No results met the criteria for statistical significance, though several were close.

Identification of skeletal fluorosis thresholds

Overall, 6 studies reporting serum fluoride levels associated with skeletal fluorosis were identified [21,22,29,30,32,33]. The lowest reported serum fluoride level for a person with some evidence of skeletal fluorosis was 3.42 µmol/l [29]. However, the lowest serum fluoride level for a person satisfying skeletal fluorosis criteria with spinal bone mineral density measured by dual-energy X-ray absorptiometry greater than 2 standard deviations above the control mean was 3.65 µmol/l [29]. This latter value was selected as the lowest observed adverse effect level (LOAEL). The lowest serum fluoride at which standard radiologic features of skeletal fluorosis were evident was 16.63 µmol/l [21].

DISCUSSION

This study observed a small statistically insignificant increase in serum fluoride in EMTs after methoxyflurane had been introduced into clinical practice (Tables 1 and 2, Figures 2 and 3). A power analysis was conducted to identify the appropriate sample size to detect large differences (1 µmol/l) in serum fluoride, accounting for attrition. The study recruited the number of participants identified by that power analysis, implying that the study was appropriately powered to test a hypothesis of large increases in serum fluoride concentrations after introduction of methoxyflurane. However, the large number of missing test results limits the determination of statistical significance.

Comparison with a healthy serum fluoride range

The meta-analysis determined a 95% CI for healthy serum fluoride to be 0.21–2.11 µmol/l (Figure 1). This meta-analysis is important as it provides a comparison and evaluation of the study of serum fluoride in ambulance staff exposed to a substance known to alter serum fluoride.

Serum fluoride concentration in month 0 established a participant's baseline serum fluoride of 0.2–1.6 µmol/l (Table 1). Participants 1 and 10 did not provide their blood sample in month 0, but their serum fluoride values in month 1 were <0.2 and 1.3 µmol/l, respectively. This outcome suggests that all participants were within the identified healthy range when methoxyflurane was introduced into clinical practice.

The results in Table 1 show a mild variation of serum fluoride for the participants over the 24-month study period. One test result exceeded the 95% CI for healthy serum fluoride (participant 6 in month 4, S_f = 4.0 µmol/l), while 3 other test results were at the upper limit of the 95% CI (participants 7 and 9 in month 4; and participant 10 in month 18, S_f = 2.2 µmol/l on each occasion). This set of higher results suggests the possibility of an effect from occupational exposure to methoxyflurane, and the possibility of methoxyflurane inconsistently causing an elevation of serum fluoride above a normal healthy adult range.

Comparison with the renal toxic threshold

Serum fluoride remained well below the previously suggested single-dose renal toxic threshold of 40 µmol/l [5,6]. The peak serum fluoride value determined by this research (Table 1) is only 10% of that threshold. There is no data available of whether this toxic threshold would change with frequent exposure and chronic serum fluoride elevation. However, this difference and the results presented imply safety from renal toxicity for these ambulance officers occupationally exposed to methoxyflurane.

Skeletal fluorosis risk

Skeletal fluorosis is associated with a wide range of serum fluoride levels [21,22,29,30,32,33], from 45 patients
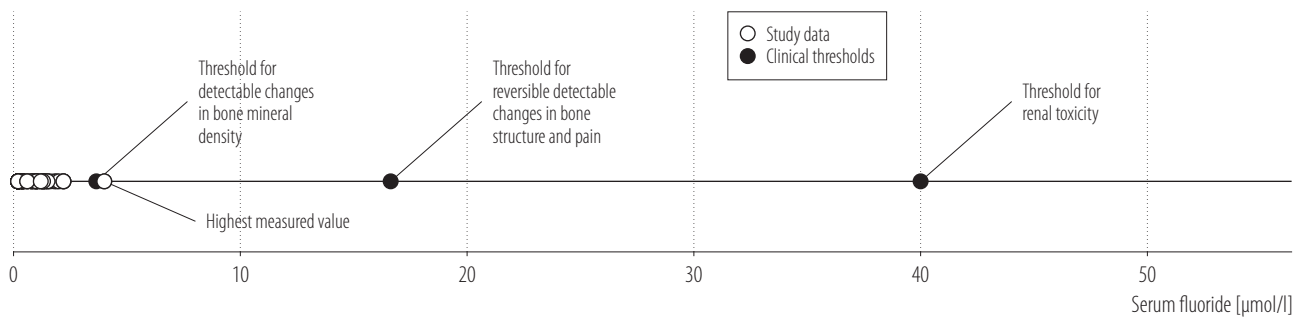
Figure 4. Summary of all participants' serum fluoride results compared with clinical thresholds, June 2017–June 2019, New Zealand

with mean serum fluoride of 5.79 µmol/l associated with a measurable change in bone mineral density [29] to a case report with serum fluoride of 205.28 µmol/l associated with pronounced painful skeletal changes [22]. This very wide range of serum fluoride values, with the highest value identified in this study corresponding to approx. 2–69% of those mean values, coupled with an absence of case studies of skeletal fluorosis in ambulance officers at other sites administering methoxyflurane repeatedly, implies a reasonable but unsatisfying degree of safety.

The LOAEL for skeletal fluorosis is 3.65 µmol/l of serum fluoride, likely due to long-term ingestion of contaminated ground water [29]. One result exceeded this LOAEL (participant 6 in month 4, S_f = 4.0 µmol/l), suggesting a possibility of skeletal fluorosis effects for some ambulance officers (1 in 10 EMTs in this case). This subject was informed by the study author of that result compared with the identified thresholds, and encouraged to contact a general practitioner. That participant's serum fluoride level did not remain above the LOAEL in subsequent tests, and the period of elevated serum fluoride required for the adverse effect to occur is unknown. Notably, the highest serum fluoride result was 24% of the lowest level known to be associated with radiologic evidence of fluorosis [21]. Figure 4 illustrates serum fluoride results for all participants compared with identified clinical thresholds for skeletal fluorosis and renal toxicity.

Serum fluoride accumulation
The Wilcoxon signed-rank test evaluates a hypothesis of similarity between repeated groups of measurements of the same subjects. These tests did not identify any statistically significant differences in blood test results compared with results from month 0. The Kolmogorov-Smirnov test evaluated a hypothesis of similarity for each participant's test results over the study period from their baseline. These tests also did not identify statistically significant changes in serum fluoride for any participant (Tables 1 and 2). Therefore, this study provided no statistically significant evidence that occupational exposure to methoxyflurane led to increasing serum fluoride. More frequent serum fluoride sampling may have improved the likelihood of achieving statistical significance.

Limitations
This research has a number of limitations. To protect participants' anonymity, ethical approval was not sought for the collection of demographic data such as participants' age, sex, or fluoride intake from fluoridated water or other sources, as the group of ambulance officers being approached is relatively small and such information would potentially identify them to the study authors. Therefore, the effect of these variables cannot be determined. Methoxyflurane was introduced into practice on the June 1, 2017. Due to ethical and organizational constraints, month 0 blood tests were taken on June 15–July 4, 2017.

Therefore, the participants may have been exposed to methoxyflurane prior to the baseline blood test, and that result might not represent a non-exposed value, thus limiting the potential to detect any increase from a non-exposed baseline. This study, nonetheless, determined that the levels of serum fluoride in a cohort of EMTs were generally within normal limits.

Furthermore, the study was not blinded and the participants were able to opt-in to receiving each test result. Therefore, the participants may have adjusted their methoxyflurane administration behavior in response to their test results. This potential self-regulation of administration amongst the participants may have led to lower than representative rates of administration and, thus, exposure. However, any change in behavior cannot be confirmed within the constraints of the ethical approval obtained, and this study makes no attempt to correlate frequency or duration of exposure of individual participants with serum fluoride results.

Clinical implications

Previous studies have attempted to determine occupational risk by extrapolation from limited patient anesthesia data [6,7,11]. This research is the first report of serum fluoride associated with occupational exposure in the modern setting using the Penthrox® inhaler. Direct measurements of serum fluoride provide a much greater certainty than extrapolation over several orders of magnitude. While extrapolation did not identify values approaching a single-dose renal toxic threshold, or within a skeletal fluorosis range, the direct measurement undertaken in this research provides more convincing evidence of safety. Additionally, this study provides evidence of renal safety and evidence suggesting that fluoride accumulation does not occur in EMTs with repeated methoxyflurane exposures, which extrapolation from single high-dose data cannot provide. Furthermore, skeletal fluorosis is identified as a risk associated with EMTs' occupational exposure to methoxyflu-

rane. Further quantification of skeletal fluorosis risk may be a valuable subject for future research.

The present study involved the presence of an activated carbon filter on the patient's exhalation. Filtration is a potentially important factor that should be considered in the interpretation and design of studies. Given other evidence for risks associated with occupational exposure to methoxyflurane, it is suggested that conservative clinical practice would be to use activated carbon filters until such time as the effect of filtration can be better understood.

Investigation of the degree of occupational exposure experienced under various conditions would assist in the determination of risks faced by ambulance officers and healthcare workers in other settings. Serum fluoride measurement with greater fidelity (more frequently than approximately every 1–6 months as was the case in this study), and/or a larger number of subjects than included in this study, might improve the degree of certainty of the risk posed by occupational methoxyflurane exposure. Determination of serum fluoride from methoxyflurane exposure in environments other than ambulance care, such as in a hospital or clinical setting, would be of value to the wider healthcare community.

Until the degree of the risk posed by methoxyflurane is further clarified, it may be beneficial for ambulance officers and other healthcare staff to maximize environmental ventilation in order to minimize their occupational exposure and consequent skeletal fluorosis risk.

CONCLUSIONS

There was no statistically significant change in the serum fluoride results across the combined data set. Thus, there was no evidence of EMTs' exposure to methoxyflurane resulting in sustained increased serum fluoride levels. There was no evidence to support the hypothesis that increasing serum fluoride occurs over a prolonged (up to 2-year) period. One serum fluoride result exceeded, and some serum fluoride results reached, the upper limit of the expected reference range. The maximum serum fluoride level was only 10% of the pro-

posed acute renal toxic threshold, suggesting ambulance officer safety from acute renal toxicity within the administration parameters of the study subjects. The margin for safety from skeletal fluorosis effects is less clear, and the study could not exclude the possibility of some risk of mild skeletal fluorosis in the form of increased bone mineral density.

ACKNOWLEDGMENTS

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