A Bootstrap Approach for Predicting Methoxyflurane Occupational Exposure in Paramedicine

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Abstract: Background - Methoxyflurane was used as an anaesthetic agent from 1958 until it was withdrawn around 1974 after dose-related patient nephrotoxicity was identified. It is now available only for administration via the Medical Developments International Penthrox Inhaler device for analgesia. When administering methoxyflurane, ambulance officers will be exposed to some methoxyflurane vapour. A previous study has extrapolated data from anaesthetized patients to suggest that such occupational exposure is within safe limits. There is a need to explore the robustness of these thresholds. **Approach –** A model is created to investigate the range of possible regression lines from repeated bootstrap samples of the same patient data, and to describe the probability distribution of those regression lines. **Findings –** The model shows a wide range of possible extrapolations due to the limited patient data set and the extrapolation being conducted over 2 - 5 orders of magnitude of exposure. With the range of ambulance officer exposures reported elsewhere, 95.7% of these regressions fall within an identified safe limit, suggesting that one-off exposures of this nature are safe. This model does not account for repeated exposures over days or weeks as would be seen in occupational settings. **Originality –** Bootstrapping methods are applied to test the statistical robustness of extrapolation. Results indicate that ambulance crews could be safe if exposed between the limits currently in place.

Keywords: Identification and validation; Clinical validation; Healthcare management; Physiological models; Physiology; Parameter identification; Health and safety.

1. INTRODUCTION

Methoxyflurane is a fluorinated hydrocarbon that was used as an anaesthetic agent from 1958, and was once considered suitable for "any patient and any operation" (Van Poznak, 1972). Early adopters of methoxyflurane noted cardiac stability, stable sedation and unconsciousness, low irritability, and a gradual return to consciousness. A noted issue was the slow induction of anaesthesia (Thomason, Light & Holaday, 1962). By 1968 methoxyflurane made up 10% of annual purchases of inhaled anaesthetics in the USA (Van Poznak, 1972). In later years, however, methoxyflurane was noted to cause post anaesthetic high output renal failure which was sometimes transient but occasionally remained for 12 months or more (Crandell, Pappas & Macdonald, 1966). The cause of patient nephrotoxicity was identified as being primarily due to fluoride ions, a metabolite of methoxyflurane (Cousins & Mazze, 1972).

At around the same time, Corbett and Ball (1971) also identified exposure to methoxyflurane vapour as a possible occupational hazard. Operating room vapour inhaled by the anaesthetist ranged from 1.3ppm to 9.8ppm, and resulted in methoxyflurane being detectable on the anaesthetist's breath for 12 to 30 hours depending also on the duration of surgery attended. Additionally, there was an up to fivefold increase in fluoride ions in the anaesthetist's urine following exposure.

This appears to be the sole study of biological markers following occupational exposure.

Methoxyflurane was also used in lower doses as an analgesic agent. From 1968, Abbott Laboratories (Chicago, IL, USA) manufactured the Penthrane Analgizer® for managing the pain of labour and short medical procedures (Coffey *et al.*, 2014). Abbott Laboratories later refined the device as the Penhalor®, and Cyprane Ltd. (Keighley, UK) manufactured the Cardiff Penthrane Inhaler® for the same purpose. Two studies utilising these devices failed to find indications of nephrotoxicity in patients when methoxyflurane was used in analgesic doses (Artusio *et al.*, 1971; Rosen, Latto & Asscher, 1972).

From 1958 to 1974, a total of ~100 cases of postoperative nephrotoxicity due to anaesthetic administration of methoxyflurane were reported, with approximately ~20 attributable patient deaths (Mazze, 2006). Methoxyflurane use for both anaesthesia and analgesia was discontinued in the USA in 1974 (Dayan, 2015) and in the UK at a similar time (Fletcher, 2015). As a result of methoxyflurane falling out of favour, there is a significant paucity of safety research since the 1970s until fairly recently.

In contrast, Medical Developments International, then Medical Developments Australia (Scoresby, Victoria,

Australia) has been manufacturing an analgesic methoxyflurane device called Penthrox® from 1978 through to present day (Dayan, 2015). The Penthrox inhaler is similar in appearance to the Analgizer, and is a simple device shaped like a whistle (Dayan, 2016). This device features a 'dilution hole' which allows the patient to control the concentration of methoxyflurane delivered to them: 0.2% to 0.4% with the dilution hole open, and 0.5% to 0.7% with the hole closed (Medsafe, 2013). The manufacturer reports that Penthrox has been used by about 2.5 to 3 million patients in Australia and New Zealand (Dayan, 2015). Two recent studies have failed to find signs of nephrotoxicity in patients administered Penthrox (Jacobs, 2010; Coffey *et al.*, 2014). However both studies received funding from the manufacturer, raising the possibility of bias.

At the present time Penthrox is widely used by ambulance services across Australia, and is the typical analgesic agent for use by less qualified staff (ACT Ambulance Service, 2012; Ambulance Victoria, 2015; Ambulance Service NSW, 2011; Queensland Ambulance Service, 2016; St. John NT, 2013). This widespread and on-going use of methoxyflurane with no reported adverse events implies occupational safety (Therapeutic Goods Administration, 2014). Most Australian ambulance services implement a strategy to reduce occupational exposure, such as limiting the number of doses that can be given in an ambulance (Ambulance Service NSW, 2011), or encouraging use of adequate ventilation and the use of a proprietary charcoal filter attached to the device (St. John NT, 2013). It is possible that these mitigating measures are responsible for a lack of adverse occupational events. However, the contribution of these measures to reductions in methoxyflurane exposure has not been reported and remains ambiguous.

Methoxyflurane is currently utilised in the New Zealand ambulance setting (St. John NZ, 2013). Given a recent Cochrane review's finding that flurane derivatives such as methoxyflurane are suitable analgesics (Klomp *et al.*, 2012), wider uptake of methoxyflurane is possible and re-evaluation

of occupational safety is warranted.

Frangos *et al.* (2016) was sponsored by the Penthrox manufacturer to develop a computational model of methoxyflurane vapour exposure in an ambulance, and compared this model to an extrapolation of data from anaesthetised patients to confirm occupational safety. They concluded the degree ambulance crews were exposed to methoxyflurane was safe. However, the findings were dependent on the extrapolation of limited data. Those authors applied a high degree of extrapolation using simple linear assumptions. It is worth re-evaluating the validity of the findings by applying alternative extrapolation methods.

This paper re-evaluates the findings of Frangos *et al.* (2016) using a bootstrapping method with alternative extrapolation functions to yield a more statistically defensible risk assessment.

2. METHODS

2.1 Data

Data from 18 male patients that underwent methoxyflurane anaesthesia for surgery were used in this study (Cousins and Mazze, 1973), and are re-evaluated here. In the original study the anaesthesia was performed at Veterans Administration Hospital (Palo Alto, CA, USA). The patients were randomized to receive either 0.5, 1.0 or 1.5 MAC of methoxyflurane, and total anaesthetic dose for each patient was reported as a concentration-duration composite: MAC hours. Post-operative serum fluoride levels were monitored and peak values reported. Table 1 and Figure 1 (left) show the measured values for each patient. Methoxyflurane exposure is converted to the concentration-duration composite with units of thousands of parts-per-million (ppm) minutes, using MAC = 0.16% (Cousins and Mazze, 1973). Patient toxicity identification (as 'none', 'subclinical', 'mild', or 'toxic') is reproduced from the original study.
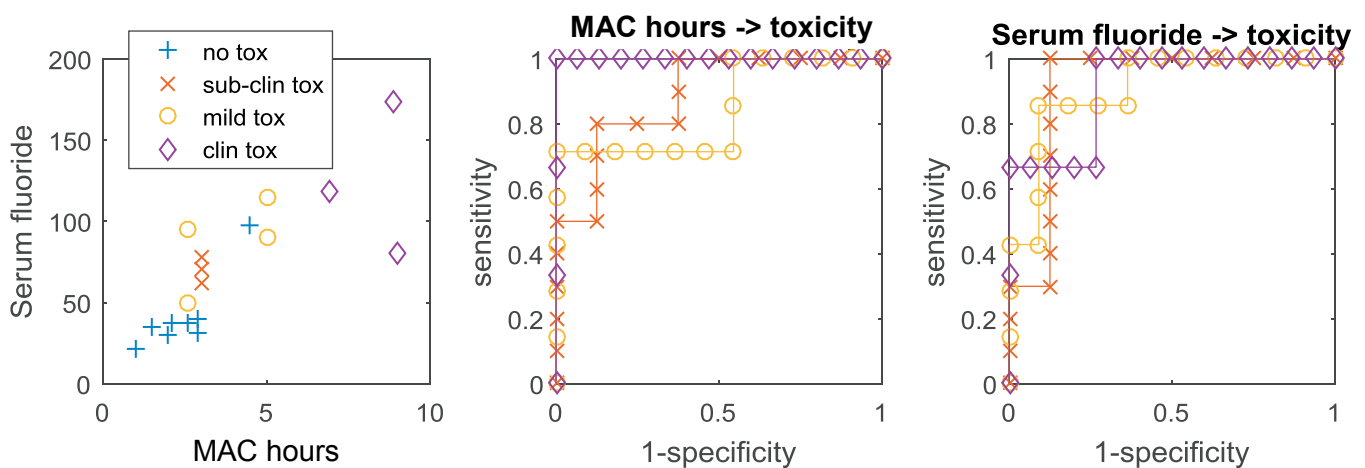

Figure 1: Distribution of serum fluoride vs exposure in MAC hours (left), ROC curves for toxicity as a function of exposure in MAC hours (centre), or serum fluoride (right)

Table 1: Dose-peak response data from Cousins and Mazze (1973), extracted from graphical presentation using the technique described in Frangos *et al.* (2016).

Patient	MAC hours	Thousand ppm min	Serum F⁻ μmol/L	Toxicity
1	1	96.0	21	None
2	1.5	144.0	35	None
3	2	192.0	30	None
4	2.1	201.6	38	None
5	2.6	249.6	37	None
6	2.6	249.6	50	Mild
7	2.6	249.6	95	Mild
8	2.9	278.4	31	None
9	2.9	248.4	40	None
10	3	288.0	62	Subclinical
11	3	288.0	70	Subclinical
12	3	288.0	78	Subclinical
13	4.5	432.0	98	None
14	5	480.0	90	Mild
15	5	480.0	115	Mild
16	6.9	662.4	119	Toxic
17	8.9	854.4	174	Toxic
18	9	864.0	80	Toxic

2.2 Model

In the present analysis, two models were used to link exposure: 1000 ppm-mins (TPM) and serum fluoride (SF) data. We used a simple linear regression and a power law relationship, see Eq.1 and Eq.2 respectively.

$$SF = x_1 TPM + x_2 \qquad (1)$$

$$SF = x_3 TPM^{x_4} \qquad (2)$$

Least-squares linear regression was used to determine x_1 and x_2 and least-squares linear regression of log(SF) and log(TPM) data was used to determine x_3 and x_4.

A bootstrapping analysis was undertaken to determine the range of possible regression lines that could reasonably be expected by the models. Specifically 18 (TPM, SF) data pairs were randomly selected with replacement from Table 1. Linear regression was undertaken for both models to yield lines of best fit through the re-sampled data. This process was repeated 10,000 times yielding 10,000 parameter sets for each model. The cumulative probability of any such regression line occurring for a given level of methoxyflurane exposure was calculated. All analysis was undertaken on an Ubuntu 16.04 framework with GNU Octave 4.0.2 on an Intel Core 2 Duo 64-bit laptop with 4GB RAM. Results are shown in Figure 2.

In plotting results, the green vertical lines illustrate the lowest ambulance crew exposure and the 'worst case' ambulance exposure modelled by Frangos *et al.* (2016). The horizontal dashed magenta line illustrates serum fluoride of 40μmol/L. Peak serum fluoride data from Cousins and Mazze (1973) showed no patient suffered renal toxicity below 40μmol/L, suggesting this level may be non-toxic in the setting of methoxyflurane exposure.

2.3 Estimated safety and exposure levels

Figure 1 centre and right show that toxicity is sensitive to exposure and serum fluoride. Ranksum values were p=0.005, 0.019 and 0.002 for the TPM score with respect to sub-clinical, mild and clinical toxicity, respectively. Serum fluoride exhibited similar distinction across toxicity groups (0.002, 0.003, and 0.027, for sub-clinical, mild and clinical toxicity, respectively). Hence, both serum fluoride and exposure were indicators of toxicity risk.

Paramedic methoxyflurane exposure has not been quantified in the workplace. Frangos *et al.* (2016) provided mean attendant exposure from 134 paramedics (0.11 thousand ppm minutes) but did not explicitly provide peak exposure levels – which is critical to occupational health. However, minimum and peak levels could be determined via the models provided by Frangos *et al.*, with a range of 0.005 to 0.3 thousand ppm minutes implied. No corresponding fluoride levels were reported.

Desmond (1974) observed 11 patients following anaesthesia with methoxyflurane doses ranging from 1.3 to 4.0 MAC hours, noting high-volume renal failure in the majority of patients. That author recommended an upper limit of methoxyflurane exposure of 2.5 MAC hours (240 TPM), although no statistical analysis was given to provide insight into how the figure was arrived at.

3. RESULTS

Bootstrapping analysis on regression models provides the level of certainty of extrapolation from the existing post-anaesthesia patient dataset to paramedic exposure (Figure 2). The upper 95th percentile regression line for the linear model (Figure 2 upper) closely followed the 40μmol/L serum fluoride level identified as an upper limit for safe exposure. The cumulative probability of serum fluoride curves for the reported minimum and maximum paramedic exposure were virtually indistinguishable for the linear model (Figure 3 upper). This consistency in serum fluoride probability distribution occurred despite nearly 2 orders of magnitude across exposure levels. In contrast, the extrapolated power-law model implied certain occupational safety in the extrapolated region (Figure 3 lower).

The cumulative probability curve in the linear model for the 2.5 MAC hours exposure limit suggested by Desmond (1974) fell almost entirely beyond the 40μmol/L safe fluoride limit (Figure 4). This finding implies that an exposure threshold 2.5 MAC affords inadequate safety.
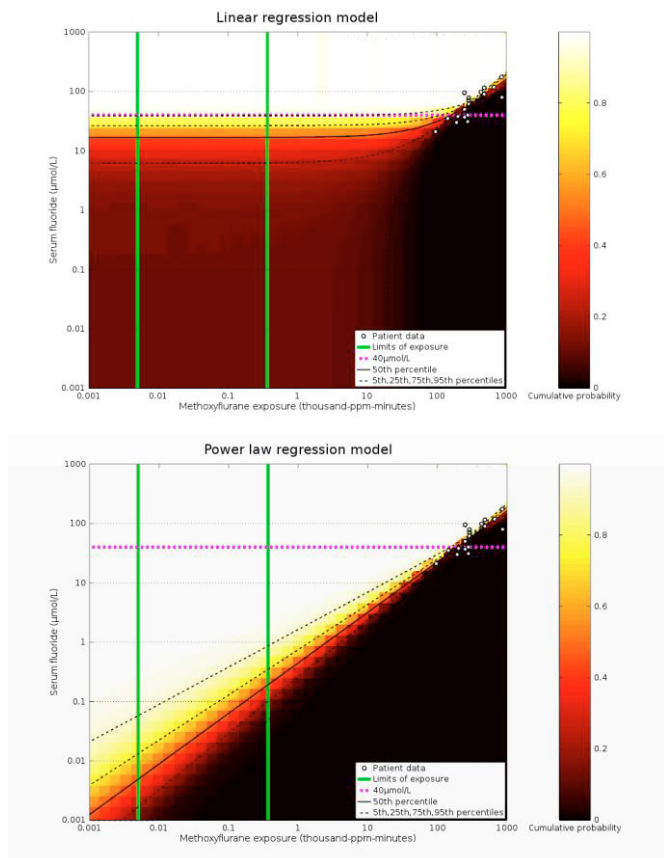
Figure 2: Regression of bootstrap samples from the linear and power law models of serum fluoride vs. methoxyflurane exposure data.

4. DISCUSSION

The bootstrap analysis of the linear model implied a wide range of possible serum fluoride levels in the occupational exposure region, compared with the single extrapolation proposed by Frangos *et al.* (2016). Note that the upper 5% likelihood threshold aligned with the clinically derived threshold for elevated risk for nephrotoxicity. In contrast, the power-law model implied much lower levels of serum fluoride due to occupational exposure. The cumulative probability curves for reported minimum and modelled maximum exposure show that 95.7% of linear regression lines from the data are below the 40µmol/L serum fluoride threshold. This result is reassuring, and mitigates some of the concern due to the range of possible regression lines. This finding suggests that ambulance crews will be safe if exposed between the limits described.

The small cluster of data reduces the certainty of extrapolation beyond the range of the data cluster, hence the wide probability distribution for the linear model. The power law model retained a relatively consistent distribution compared to the linear model due to the constraint that it must pass through (0,0). This constraint on the power law means that the serum level due to exposure must always track to a low value at low exposure levels, even if clearance of fluoride is non-linear.
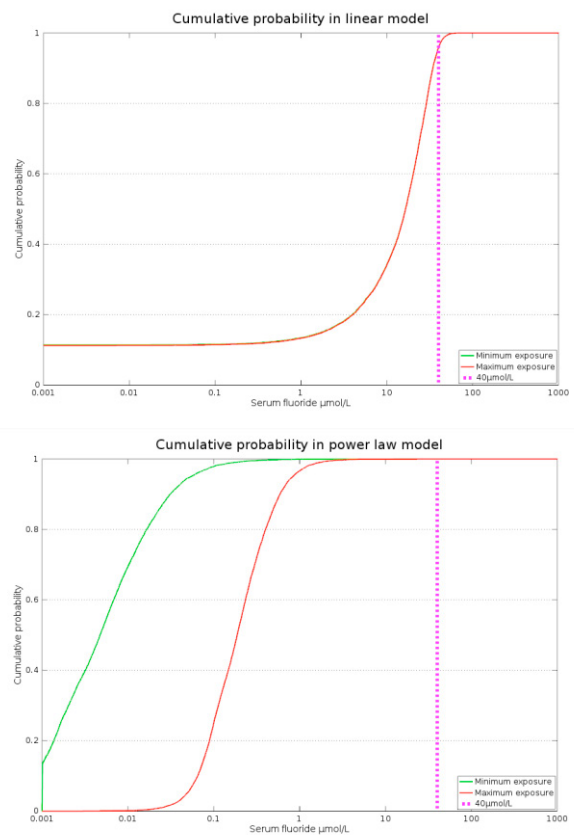

Figure 3: Cumulative probability curves for the purported minimum and maximum limits of exposure for linear (top) and power law (bottom) models. In the linear model the curves are so similar as to be indistinguishable.
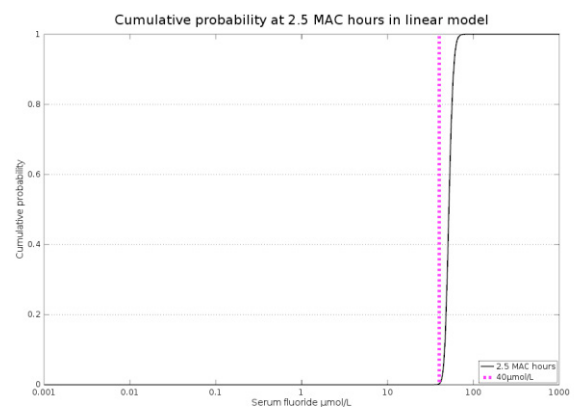

Figure 4: Cumulative probability curve for 2.5 MAC hours exposure in the linear model.

The exposure for anaesthetised patients (Cousins and Mazze, 1973) is 2 - 5 orders of magnitude greater than the proposed exposure of ambulance officers (Frangos *et al.*, 2016). In the absence of low-exposure data, there is no reason to believe that either a linear or a power law model is more representative of the serum fluoride levels caused by exposure to methoxyflurane. In particular, a linear model could be possible even when the serum intercept is below zero. In such cases, the low dose may not be absorbed by the

lung and there would be no peak serum fluoride at all. In contrast, a positive serum fluoride level intercept may occur due to environmental fluoride intake (i.e. fluoridated water, some foods). In contrast, the power-law model may be appropriate when methoxyflurane or fluoride excretion curves are considered (Corbett and Ball, 1971).

A number of significant questions remain unaddressed. The data used to identify the 'minimum paramedic exposure' was from a secondary source, and its accuracy has not been confirmed. Ambulance officer qualification could affect methoxyflurane exposure, as higher-qualified officers have a wider range of analgesia options (Ambulance Victoria, 2015; St. John NT). The 'maximum paramedic exposure' modelling in Frangos *et al.* (2016) assumes that the ambulance is mobile and that air conditioning systems are activated, which is not truly a worst case scenario.

Accumulation could occur in occupational use where the ambulance officer is exposed on subsequent days or weeks. There is potential for greater and greater accumulation of methoxyflurane in tissue and for subsequent increased fluoride levels with re-exposure, and this needs to be further investigated. Hence, it is possible that this analysis yields risk prediction that is relevant only to single dose scenarios, and fluoride ion accumulation may significantly increase the occupational risk.

Some medications alter the risk profile of methoxyflurane. Churchill (1976) describes a patient whose serum fluoride was significantly higher than expected after 90 minutes' exposure to 0.16% methoxyflurane (114µmol/L after 144 TPM). This was identified as likely due to the patient having previously ingested a drug (secobarbital) which increased methoxyflurane metabolism. Additionally, nephrotoxicity appears to be altered in exposed persons simultaneously taking nephrotoxic medications such as tetracycline (Proctor, 1971; Cousins and Mazze, 1972).

Ambulance officers are at risk of interactions between occupationally absorbed methoxyflurane and personal concomitant use either of medications that increase methoxyflurane metabolism or of other nephrotoxic medications, although the effect of these interactions with occupationally exposed levels is unknown.

This model has demonstrated the high degree of uncertainty with regards to serum fluoride and therefore of nephrotoxic risk to those occupationally exposed to methoxyflurane. There is a need to obtain further data in order to more accurately assess that risk. As anaesthetic toxicity has been demonstrated, the anaesthetic data set will never be expanded to improve extrapolation. Therefore further research is needed which directly measures the serum fluoride of those who are exposed in specific occupational environments.

5. CONCLUSIONS

The occupational risk of methoxyflurane remains ambiguous despite its sustained use in analgesia. This research has shown that previous attempts to verify the occupational safety of attendant ambulance officers have been incomplete and did not conclusively determine the risk. In order to fully appraise the occupational risk of methoxyflurane, low dose vs. serum fluoride data must be taken and the characteristics of fluoride accumulation in ambulance staff must be assessed.

CONFLICTS OF INTEREST

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