PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Non-interventional study evaluating exposure to inhaled, low-dose methoxyflurane experienced by hospital emergency department personnel in France
AUTHORS	Frangos, John; Belbachir, Anissa; Dautheville, Sandrine; Jung, Christiane; Herklotz, Key; Amon, Freya; Dickerson, Sara; Chomier, Berangere

VERSION 1 – REVIEW

REVIEWER	Owen Williams Defence Medical Services, UK
REVIEW RETURNED	20-Nov-2019

GENERAL COMMENTS	Overall, this is a useful addition to the literature, providing clearly presented results on a topic where there is currently a research gap. Occupational exposure to methoxyflurane is a legitimate concern and to date, no research has bene conducted to assess the real-world exposure of healthcare professionals in the Emergency Department. The maximum exposure limit of 15ppm over an eight hour period is the only current data of safe limits, so is a sensible upper limit to compare actual exposure to. The results correlate to previous studies investigating occupational exposure to methoxyflurane in a different setting. In terms of the methods, more information needs to be provided about why the study was conducted for two weeks at one site and three weeks at the other. Although there was no patient involvement, there was involvement of healthcare professionals who presumably consented to participation in the study. Information is required about this consent process, as well as their knowledge of the study process. It is unclear how they did not introduce bias to this study, or how this risk was minimised. Did each nurse package their own badge sampler or was this done by an independent researcher? Were they given instructions about how to use the badge sampler? Did anyone ensure they were using the badge samplers correctly? Were any steps taken to stop/reduce interference with the badge samplers? Further information is required on why a badge sampler was chosen to measure occupational exposure- is this validated, is this the best method of analysing exposure, and is the badge sampler used the best available, how quickly does the sampler need to be transported to the laboratory for testing before results are inaccurate, why was it wrapped in aluminium foil? Use of a control sampler was a good addition. More information needs to be supplied about why samples with concentrations below the lower limit of quantification were assigned a value of 0.7ug per sample.

	From the results, it is unclear where numbers of staff badges analysed has come from. In the methods, it was planned for 28 staff badges + 1 ambient air monitor badge to be collected each week. This would be 58 badges for Tenon and 87 badges for Cochin. There is no mention of why these numbers were not achieved. The medical methoxyflurane concentrations are reported as 0.02ppm (Cochin) and 0.01ppm (Tenon)- this is not a ten fold increase as reported. Is this difference statistically or clinically significant (I suspect not given the wide range of values)? The difference in concentrations found may also be a result of the size of the rooms used given Tenon is roughly twice the size of Cochin, with half the methoxyflurane concentration found on the samplers. This is a useful, pragmatic study assessing the occupational exposure of healthcare providers to methoxyflurane from the use of Penthrox inhalers. There are obvious drawbacks to any observational study which the authors may not have been able to control. However, more information is required about how the risks of bias were reduced, which is one of the main limitations of the study.

REVIEWER	Dr Stuart Hartshorn Birmingham Children's Hospital
REVIEW RETURNED	22-Nov-2019

GENERAL COMMENTS	Dear authors Thank you for opportunity to review your interesting and important article on the potential exposure of hospital ED personnel to inhaled, low-dose methoxyflurane. This is an important topic for a drug that is relatively new to most European institutions. The methodology and statistical analysis all appear sound, and the overall quality of the manuscript write-up is excellent. My only recommendation is the need for some additional information to help readers to judge the relevance of these results to their own practice: 1) You have provided the volume of the triage rooms at each of the two sites. Are you able to comment about how representative these are compared to the "average" sized triage room? 2) For EDs who are currently using Penthrox, do you have any data on the range of number of daily administrations? This will allow readers to judge how the amount of Penthrox administered during the study compares with that in standard clinical practice.

VERSION 1 – AUTHOR RESPONSE

	Reviewer comments	**Response**
	Reviewer 1	

1	Overall, this is a useful addition to the literature, providing clearly presented results on a topic where there is currently a research gap. Occupational exposure to methoxyflurane is a legitimate concern and to date, no research has bene conducted to assess the real-world exposure of healthcare professionals in the Emergency Department. The maximum exposure limit of 15ppm over an eight hour period is the only current data of safe limits, so is a sensible upper limit to compare actual exposure to. The results correlate to previous studies investigating occupational exposure to methoxyflurane in a different setting.	No response required
2	In terms of the methods, more information needs to be provided about why the study was conducted for two weeks at one site and three weeks at the other.	The shorter study duration at Tenon Hospital (2 weeks) compared with Cochin Hospital (3 weeks) reflects the 1-week feasibility study which was performed at Tenon Hospital. This was performed prior to initiating the main study at the request of Agence Générale des Equipements et Produits de Santé (AGEPS), a group representing hospitals in Paris, in order to assess the feasibility of the proposed use, storage and analysis of the badge samplers. This information had been added to the first paragraph of the methods.
3	Although there was no patient involvement, there was involvement of healthcare professionals who presumably consented to participation in the study. Information is required about this consent process, as well as their knowledge of the study process.	Please refer to responses to Editorial request point 5 and Reviewer 1 request point 4 (below)
4	It is unclear how they did not introduce bias to this study, or how this risk was minimised. Did each nurse package their own badge sampler or was this done by an independent researcher? Were they given instructions about how to use the badge sampler? Did anyone ensure they were using the badge samplers correctly? Were any steps taken to stop/reduce interference with the badge samplers?	The third paragraph of the Methods (page 7) has been amended to state that selection of the nurses who wore the badges was based on hospital rotas (no other selection criteria were applied); badge samplers were stored in a locked cupboard before use; at the end of their shift each nurse packaged their own badge sampler for storage in designated box; and prior to study start the nurses underwent training on the use, package and storage of the badge samplers and were provided with a protocol. Nurse coordinates also oversaw correct usage of the badges. As captured in the first paragraph on page 8, a 'trip blank' sampler (unopened and unworn badge sampler, repackaged for transportation to the laboratory) was also included to assess potential cross contamination during storage /transport. Also, as the personal badge

		sampler used for ambient air monitoring was suspended from the ceiling of each room in the vicinity of the patient treatment area while not impeding clinical procedures or being easily reached by hand (described in the last paragraph on page 7) While the last paragraph of the discussion referred to potential bias arising from the study design, the text has been amended to make this more explicit: *"While this study aimed to reflect real-world exposure to low-dose methoxyflurane experienced by nurses in hospital emergency departments, as with all observational studies it was associated with structural limitations and potential biases. For example, assessments in this study were limited to a small number of individuals working in just two emergency treatment rooms who were supervising ≤5 applications of Penthrox® inhalers per shift. Consequently, these data may not reflect methoxyflurane exposure for emergency care staff elsewhere…"*
5	Further information is required on why a badge sampler was chosen to measure occupational exposure- is this validated, is this the best method of analysing exposure, and is the badge sampler used the best available, how quickly does the sampler need to be transported to the laboratory for testing before results are inaccurate, why was it wrapped in aluminium foil? Use of a control sampler was a good addition.	Further details of the badge sampler have been incorporated into the second paragraph of the Methods: *'3M Organic Vapor Monitor 3500 badge samplers are specifically designed to monitor personal and area exposure to a wide range of organic vapours. They were selected for this study based on ease of use, as well as being small and lightweight, thereby minimizing interference with nursing activities. These badge samplers have been validated across a range of settings and can be stored at room temperature or refrigerated for ≤21 days prior to analysis* The badges were wrapped in aluminum foil for additional protection during transportation to the laboratory, as a precaution against accidental damage to the boxes in which badges were stored.
6	More information needs to be supplied about why samples with concentrations below the lower limit of quantification were assigned a value of 0.7ug per sample.	While treatment of censored data varies between regulatory agencies and scientific disciplines, 0.5 µg/sample is often assumed of the limit of reporting and censored data are at this limit. The use of 0.7 µg/sample was based on guidance from the analytical laboratory and CDM Smith (responsible for data acquisition and data analysis), as a conservative approach.

7	From the results, it is unclear where numbers of staff badges analysed has come from. In the methods, it was planned for 28 staff badges + 1 ambient air monitor badge to be collected each week. This would be 58 badges for Tenon and 87 badges for Cochin. There is no mention of why these numbers were not achieved.	Text has been added to the third paragraph of the methods to clarify that badges worn during a total of 140 8-hour shifts were planned. At Tenon Hospital 55 of 56 planned badges were obtained (plus 2 ambient air monitors and 2 trip blanks). At Cochin Hospital 83 of 84 planned badges were obtained (plus 3 ambient air monitors and 3 trip blanks). The first paragraph of the results now specifies that one planned sample badge was not obtained from each study site.
8	The medical methoxyflurane concentrations are reported as 0.02ppm (Cochin) and 0.01ppm (Tenon)- this is not a ten-fold increase as reported. Is this difference statistically or clinically significant (I suspect not given the wide range of values)? The difference in concentrations found may also be a result of the size of the rooms used given Tenon is roughly twice the size of Cochin, with half the methoxyflurane concentration found on the samplers.	The corresponding sentence in the second paragraph of the results 'Approximately 10-fold' has been replaced with '…2-fold. As is captured in the penultimate paragraph of the methods, methoxyflurane concentrations are described using summary statistics only. For clarity, text has been added stating that statistical testing was not performed. In line with the reviewer's feedback, text has also been added to the second paragraph of discussion: *'The reason for lower median (range) methoxyflurane concentrations detected in the badge samplers from Tenon hospital (0.011 [0.008, 0.079] ppm) compared with Cochin Hospital (0.020 [0.009, 0.736] ppm) is unclear, and may in part reflect the smaller treatment room dimensions of the latter (102 m^3versus 43m^3).'*
9	This is a useful, pragmatic study assessing the occupational exposure of healthcare providers to methoxyflurane from the use of Penthrox inhalers. There are obvious drawbacks to any observational study which the authors may not have been able to control. However, more information is required about how the risks of bias were reduced, which is one of the main limitations of the study.	Please see Reviewer 1 request point 4
	Reviewer 2	
10	The methodology and statistical analysis all appear sound, and the overall quality of the manuscript write-up is excellent.	No response required
11	My only recommendation is the need for some additional information to help readers to judge the relevance of these results to their own practice: 1) You have provided the volume of the triage rooms at each of the two sites. Are you able to comment about how representative these are compared to the "average" sized triage room?	Text has been added to the last paragraph of the discussion to specify that, based on the authors' experience, the size of the ED triage rooms included in this study is representative of those commonly found across France

12	2) For EDs who are currently using Penthrox, do you have any data on the range of number of daily administrations? This will allow readers to judge how the amount of Penthrox administered during the study compares with that in standard clinical practice.	The last paragraph of the discussion now captures the following information: '*While, based on the authors' experience, the size of the ED triage rooms included in this study (43 and 102m^3) and the frequency of Penthrox® inhaler administrations supervised by the triage nurses (0–5 vials per shift) are representative of hospital EDs in France, it is conceivable that methoxyflurane exposure levels may be greater for individuals working in smaller emergency rooms, enclosed rooms without ventilation systems and when overseeing greater utilization of Penthrox® inhalers.* *Of note, exposure modelling based on a treatment room smaller than included in the present study (32.4 m^3) and 6 air changes per hour (in line with Australian guidelines) alongside a substantially higher usage rate of Penthrox® inhalers (2 vials every hour) indicated an 8 h TWA exposure of 1.48 ppm, which is substantially lower than the previously calculated safety threshold of 15 ppm. (Frangos J Regul Toxicol Pharmacol 2016;80:210)'*