Health risks related to polyurethan foam degradation in CPAP devices used for sleep apnoea treatment

Andreas Palm, Ludger Grote, Magnus Ekström, Mirjam Ljunggren


This manuscript has recently been accepted for publication in the European Respiratory Journal. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Copyright ©The authors 2022. For reproduction rights and permissions contact permissions@ersnet.org
Health risks related to polyurethan foam degradation in CPAP devices used for sleep apnoea treatment

Andreas Palm, MD, PhD¹,², Ludger Grote, MD, PhD³,⁴, Magnus Ekström, MD, PhD⁵, Mirjam Ljunggren, MD, PhD ¹

¹ Department of Medical Sciences, Respiratory, Allergy and Sleep Research, Uppsala University, 751 85 Uppsala, Sweden
² Centre for Research and Development, Region of Gävleborg / Uppsala University, Gävle Hospital, 801 87 Gävle, Sweden
³ Sleep Disorders Centre, Pulmonary Department, Sahlgrenska University Hospital, 413 90 Gothenburg, Sweden
⁴ Centre for Sleep and Wake Disorders, Sahlgrenska Academy, Gothenburg University, 413 90 Gothenburg, Sweden
⁵ Lund University, Faculty of Medicine, Department of Clinical Sciences Lund, Respiratory Medicine and Allergology, 221 84 Lund, Sweden.

Corresponding author:
Andreas Palm, Centre for Research and Development, Region of Gävleborg / Uppsala University, Gävle Hospital, 801 87 Gävle, Sweden, E-Mail: andreas.palm@medsci.uu.se, Tel: +46 70 357 3595
Keywords: Obstructive sleep apnoea, CPAP, polyurethane foam, airway obstruction, hospitalizations, cancer, mortality

Word count for body of text: 1,168
To the editor:

A recent medical device recall notification reported on risk for degradation of polyurethane foam (PUF) in continuous positive airway pressure (CPAP) devices used for obstructive sleep apnoea (OSA) treatment [1]. The degraded foam particles may cause airway irritation, and the volatile gas products (diethylene glycol, toluene di-isocyanate isomers, toluene diamine isomers) released during the degradation process may also have cyto- and genotoxic effects [1]. Kendzerska et al. reported no increase in cancer incidence in 1,220 patients using PUF devices over a mean observation time of 7.5 years.[2] However, studies assessing airway symptoms and other health outcomes than cancer are lacking. Airway irritation from degraded foam particles may be particularly harmful for patients with pre-existing obstructive lung disease (OLD). This study aimed to evaluate the association between PUF-CPAP use and adverse health outcomes in OSA patients with/without comorbid OLD.

This was a longitudinal analysis of the national, population-based DISCOVERY cohort of OSA patients aged ≥ 16 years starting CPAP treatment from July 2010 to March 2018 in Sweden [3]. Counties prescribing PUF-CPAP (≥80% PUF-CPAP prescribed) and non-PUF-CPAP (<10% PUF-CPAP) could be identified. Remaining counties (10-<80% PUF-CPAP) were excluded from subsequent analyses. Data were crosslinked with mandatory governmental registries: a) Swedish Prescribed Drug Registry using Anatomical Therapeutic Chemical (ATC) codes)[4]. Comorbid OLD was defined as at least two collections of anti-obstructive medication ([ATC code] R03) during the 12 months before baseline; deteriorated airway obstruction was defined as collection of ≥ 3 short acting beta-agonists (SABA, R03AC02) or oral corticosteroids (OCS, H02AB) during first year or during any 1-year timespan of the study. Incident OLD after starting CPAP was defined as collection of two or more anti-obstructive medications within a window of consecutive 365 days after starting
PAP in patients without OLD at baseline; b) the National Patient Register for hospitalizations using ICD-10 codes [5] for defining comorbid heart failure (ICD-10 codes I11, I42 and I50) and ischemic heart disease (I20-25) five years before PAP-start and for identifying hospitalisation due to OLD during follow-up (primary diagnosis J44-46); c) the National Cancer Registry [6] and d) the Cause of Death Registry [7]. Patients with PUF-CPAP versus non-PUF-CPAP were compared using propensity score matching, accounting for age, sex, body mass index (BMI), apnea-hypopnea index (AHI), heart failure, ischemic heart disease, and study observation time. Sensitivity analyses were performed: a) excluding the county of Skåne, a county known for a slightly high smoking rate [8]; b) clustering the regression models by county, and c) adjusted for anthropometric data and comorbidities instead of propensity score matching using multivariable logistic and Cox regression models. Analyses were conducted using Stata version 16.0 (StataCorp LP; College Station, TX 77845 USA). The study was approved by the Ethics Committee at Medical Faculty, Lund University, Log Nos. 2018/51, (amendments 2020-02721, 2021-04984).

We included 18,561 individuals in four PUF-CPAP dominated counties (27.2% females, age 57.8±12.4 years, BMI 31 (IQR 28-35) kg/m², OLD at baseline 13.4%, nocturnal CPAP use 6.0±1.6 hours, observation time 2.6 (IQR 1.1-4.7) years), and 29,830 individuals from ten non-PUF-CPAP counties (30.2% females, age 56.9±12.6 years, BMI 31 (IQR 28-36) kg/m², OLD at baseline 12.2%, nocturnal CPAP use 5.6±2.0 hours, observation time 2.3 (IQR 0.9-4.6). The cohort was followed for a total 139,056 person-years. Deteriorated airway obstruction first year after CPAP-initiation was more frequent in the PUF-CPAP group (Table 1). Deteriorated airway obstruction anytime during follow-up was also more frequent in the PUF-CPAP group (SABA use 9.4% versus 8.8% p=0.047, and OCS use 19.7% versus 17.3%, p<0.001) in matched groups (Table 1).
In patients with OLD at baseline, use of PUF-CPAP devices was associated with increased SABA use (22.4% versus 18.2%, p<0.001) and OCS use (26.0% versus 23.2% p=0.027) during the first year after CPAP initiation. For the entire observation period, a total of 2,797 OLD patients (38.5%) collected OCS, and PUF-CPAP was associated with an increased risk of OCS collection, (41.7% versus 36.8% p<0.001). SABA use for the entire observation period was comparable in PUF-CPAP (47.0%) and non-PUF-CPAP (44.6%).

All-cause cancer and lung cancer incidence was higher in the PUF-CPAP group (4.5% versus 4.1%, p=0.045 and 0.3% versus 0.1%, p=<0.001, respectively). However, in the sensitivity analysis excluding the county Skåne with known higher smoking rates [8], the associations between PUF-CPAP exposure and incident cancer disappeared (cancer: 3.6% in PUF-CPAP versus 4.0% in non-PUF-CPAP, p=0.29, lung cancer: 0.21% in PUF-CPAP versus 0.15% in non-PUF-CPAP, p=0.491). Hospitalization due to OLD and mortality did not differ between groups (Table 1). The results from the adjusted logistic and Cox regression models did not differ significantly from the propensity score matched analyses (data not shown).

In this nationwide study of patients with OSA, PUF-CPAP use was associated with mild deterioration of OLD control during a median follow-up of 2.4 years. However, severe OLD exacerbations requiring hospitalization or increased OLD incidence were not observed. Further, we identified signals of increased lung cancer incidence in the PUF-CPAP group, but this finding needs further confirmation in other studies as it was not robust in sensitivity analyses and may be related to regional differences in lung cancer risk factors.

Hazardous effects of PUF-CPAP devices have only recently been reported [1]. Experimental data simulating the 6-8 hours daily PUF-CPAP user pattern of OSA patients do not exist yet. The lack of a firm association between use of PUF-CPAP devices and overall cancer incidence is consistent with a recent report.[2] Strengths of the present study include the
unselected national cohort of OSA patients, which increases precision, validity and
generalizability of results and permits identification of rare outcomes [9]. No patients are lost
to follow-up due to cross-linkage with mandatory national registries. A key advantage of the
design is that the choice of CPAP device (and hence PUF-CPAP exposure) was made
centrally on the sleep unit level and was not based on individual patient characteristics or
preferences. This could be considered to approach an ‘instrumental variable’ or ‘quasi-
randomized’ design, as suggested by the fact that characteristics were similar between the
treatment groups. Several limitations need to be acknowledged. PUF-CPAF use was
categorized retrospectively by the responsible staff for each sleep unit. To limit
misclassification, only counties with very high (≥80%) or very low (<10%) PUF-CPAF
prescription were compared. This design still enabled us to include most CPAP patients in
Sweden in the analyses (74.4% of Swedevox patients). It cannot be excluded that some
individuals changed the device category during follow-up. However, this misclassification
would align the treatment groups and, if anything, underestimate any influence of PUF-CPAP
on patient outcomes. Data were lacking on smoking, but this is unlikely to bias the findings as
PUF-CPAP use was decided on county level independent of smoking status. Finally, mean
exposure time of PUF-CPAP was rather short to evaluate any risk estimate on cancer
incidence.

In conclusion, PUF-CPAP associates with increased use of anti-obstructive medication after
CPAP initiation, particularly in people with underlying OLD. PUF in CPAP may contribute to
increased airway symptoms and OLD exacerbations. For lung cancer incidence the results
were less conclusive and further studies are urgently needed.
**Data availability statement**

The steering committee of the Swedevox quality registry will consider reasonable requests for the sharing of deidentified patient level data. Requests should be made to the corresponding author.

**Acknowledgements**

The authors gratefully acknowledge Krister Ågren, MSc, Gävle university for statistical support. The authors would also like to acknowledge all centres in Sweden reporting data to the Swedevox registry and all patients letting themselves be reported. We would also like to thank the Swedish Heart and Lung Association for the commitment in the Swedevox registry’s steering committee.

**Support statement**

AP was supported by the Swedish Society for Sleep Research and Sleep Medicine, Uppsala-Örebro Regional Research Council (Log Nos RFR-931234), Centre for Research and Development, Uppsala University/Region Gävleborg (Log Nos CFUG-925881), Bror Hjerpstedt’s Foundation, Uppsala County Association against Heart and Lung Diseases, and the Fagerström foundation. LG was supported by the Swedish Heart and Lung Foundation (No 20210529) and the agreement concerning research and education of doctors (ALFGBG-966283). ME was supported by unrestricted grants from the Swedish Society for Medical Research and the Swedish Research Council (Log No. 2019-02081).

The sponsors had no role in study design, data collection, data analysis, data interpretation, or writing of the report.
Competing interests

No conflicts of interest exist for the authors regarding the submitted manuscript. Outside the submitted work LG reports non-financial research support from Itamar Medical, Resmed, research grant and clinical trial support from Desitin, speaker bureau activities for Itamar Medical, Resmed, Philips, Astra Zeneca, and Breas. In addition, LG reports ownership in a patent on sleep apnoea therapy licensed. All remaining authors did not report any conflicts of interest.

Patient and public involvement

Neither patients nor public were involved in the design, conduct, or reporting of the research.

Author contributions

AP, LG, ME and ML contributed to the conception and design of the study. AP performed statistical analyses and all authors verified the underlying data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors participated in data interpretation, drafting of the manuscript, and final approval for submission.
### Table 1. Outcomes in all patients and in patients with obstructive lung disease.

<table>
<thead>
<tr>
<th></th>
<th>Unmatched analysis</th>
<th></th>
<th>P-value</th>
<th>Matched analysis</th>
<th></th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non PUF-CPAP</td>
<td>PUF-CPAP</td>
<td></td>
<td>Non PUF-CPAP</td>
<td>PUF-CPAP</td>
<td></td>
</tr>
<tr>
<td>A) Outcomes in all patients.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collection of SABA ≥ 3 times first year</td>
<td>785 (2.6%)</td>
<td>616 (3.3%)</td>
<td>&lt;0.001</td>
<td>470 (2.7%)</td>
<td>573 (3.3%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Collection of SABA ≥ 3 times any year</td>
<td>2,591 (8.7%)</td>
<td>1,765 (9.5%)</td>
<td>0.002</td>
<td>1,516 (8.8%)</td>
<td>1,622 (9.4%)</td>
<td>0.047</td>
</tr>
<tr>
<td>Prescription of OCS first year</td>
<td>2,697 (9.0%)</td>
<td>1,923 (10.4%)</td>
<td>&lt;0.001</td>
<td>1,579 (9.1%)</td>
<td>1,775 (10.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prescription of OCS during follow-up</td>
<td>4,957 (16.6%)</td>
<td>3,651 (19.7%)</td>
<td>&lt;0.001</td>
<td>2,990 (17.3%)</td>
<td>3,405 (19.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization due to OLD</td>
<td>153 (0.5%)</td>
<td>114 (0.6%)</td>
<td>0.14</td>
<td>102 (0.6%)</td>
<td>100 (0.6%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Incident OLD</td>
<td>2,025 (6.8%)</td>
<td>1,296 (7.0%)</td>
<td>0.41</td>
<td>1,184 (6.8%)</td>
<td>1,197 (6.9%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Incident cancer (except skin cancer)</td>
<td>1,183 (4.0%)</td>
<td>838 (4.5%)</td>
<td>0.003</td>
<td>711 (4.1%)</td>
<td>787 (4.5%)</td>
<td>0.045</td>
</tr>
<tr>
<td>Incident lung cancer</td>
<td>47 (0.16%)</td>
<td>58 (0.31%)</td>
<td>&lt;0.001</td>
<td>24 (0.14%)</td>
<td>56 (0.32%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality during follow-up</td>
<td>712 (2.4%)</td>
<td>490 (2.6%)</td>
<td>0.082</td>
<td>406 (2.3%)</td>
<td>441 (2.5%)</td>
<td>0.22</td>
</tr>
<tr>
<td>B) Outcomes in patients with obstructive lung disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collection of SABA ≥ 3 times 1st year</td>
<td>668 (18.4%)</td>
<td>552 (22.2%)</td>
<td>&lt;0.001</td>
<td>403 (18.2%)</td>
<td>514 (22.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Collection of SABA ≥ 3 times in a 1-year timespan</td>
<td>1,632 (44.4%)</td>
<td>1,165 (46.7%)</td>
<td>0.14</td>
<td>988 (44.6%)</td>
<td>1,079 (47.0%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Prescription of OCS first year</td>
<td>858 (23.6%)</td>
<td>654 (26.2%)</td>
<td>0.017</td>
<td>513 (23.2%)</td>
<td>597 (26.0%)</td>
<td>0.027</td>
</tr>
<tr>
<td>Prescription of OCS</td>
<td>1,325 (36.4%)</td>
<td>1,037 (41.6%)</td>
<td>&lt;0.001</td>
<td>815 (36.8%)</td>
<td>957 (41.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization due to OLD</td>
<td>122 (3.4%)</td>
<td>93 (3.7%)</td>
<td>0.43</td>
<td>79 (3.6%)</td>
<td>80 (3.5%)</td>
<td>0.88</td>
</tr>
<tr>
<td>Incident cancer (except skin cancer)</td>
<td>174 (4.8%)</td>
<td>120 (4.8%)</td>
<td>0.95</td>
<td>108 (4.9%)</td>
<td>107 (4.7%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Incident lung cancer</td>
<td>13 (0.36%)</td>
<td>13 (0.52%)</td>
<td>0.33</td>
<td>9 (0.41%)</td>
<td>13 (0.57%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Mortality during follow-up</td>
<td>159 (4.4%)</td>
<td>115 (4.6%)</td>
<td>0.65</td>
<td>101 (4.6%)</td>
<td>99 (4.3%)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Data are presented as n (%) for categorical measures. Outcomes were compared between groups unmatched (crude) and after propensity score matching, accounting for sex, age, BMI, AHI, presence of obstructive lung disease at baseline, ischemic heart disease, heart failure and observation time.

AHI: Apnea-hypopnea index; BMI: Body mass index; CPAP: continuous positive airway pressure; OCS: oral corticosteroids; PUF: polyurethane foam; SABA: short acting beta-agonist
REFERENCES

8. Tobacco consumption by region, sex and year. [cited 14 Dec 2021]; Available from: http://fohmsapp.folkhalsomyndigheten.se/Folkhalsodata/pxweb/sv/B_HLV/B_HLV__aLevvanor__aagLevvanortobak/hlv1tobxreg.px/table/view/layout1/?rxid=19215807-23cd-44cf-8f63-b1ed980d297