PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Assessing the chronic respiratory health risk associated with inhalation exposure to powdered toner for printing in actual working conditions: A cohort study on occupationally exposed workers over 10 years
AUTHORS	Nakadate, Toshio; Yamano, Yuko; Yamauchi, Takenori; Okubo, Shigeko; Nagashima, Daichi

VERSION 1 – REVIEW

REVIEWER	Jelle Vlaanderen Utrecht University, The Netherlands
REVIEW RETURNED	22-Feb-2018

GENERAL COMMENTS	General comments: This publication presents results from a 10 year effort in collecting both exposure data and health markers, potentially a very useful resource in assessing the health effects induced by chronic exposure to powdered toner exposure. In my opinion, the current manuscript lack quite a bit of detail and I'm not convinced the chosen approaches for statistical analysis and presentation of results optimally uses the established resource. I have added general comments below and some limited specific comments on the manuscript as it currently stands. • Very little detail is provided about the exposure assessment methods that were used in this study. Please describe in more detail what methodology (device, etc.) was used to assess personal dust exposure and how a distinction was made between inhalable and respirable dust. Also describe which attempts were undertaken to assess toner particles in the collected dust samples. • Even though exposure measurements were taken, the authors did not assess the potential for exposure-response patterns. By incorporating modeled (time varying) exposure estimates for each worker in the regression analyses one would likely increase power to detect a potential association. Alternatively one could explore the existence of patterns across the different occupational categories: e.g. TPD and RCL workers among which high exposures were observed. • It is unclear to me which cut-off was used to classify continuous markers as 'abnormal. Furthermore did the authors consider conducting linear regression for these markers to assess any evidence for subclinical changes in e.g. long function, biomarkers. • In the current analytical strategy (logistic regression) the longitudinal aspect of the study is not reflected. In case within individual repeated outcome measures are available once could consider analyzing this data using a fixed-effect model or perhaps a mixed-model in which the correlation between repeated

	measurements is explicitly modeled. • I don't really see the added value of presenting the results from the univariate analysis compared to the logistic regression, corrected for (a minimal set of) confounders. • The manuscript contains a sparse number of references, which could be extended. I was surprised to see that a recent review by Pirela et al. was not included. • Even though the authors are fully transparent in listing Ricoh as the sponsor for this study, I think that this sponsorship should also be addressed under the heading of "potential conflict of interest". Specific comments: p18 – line 35; with the current presentation in Table 2, it is difficult to assess trends over time in exposure levels. Please consider including this information in a figure. Table 2: Please add the number of measurements that were taken to assess these exposure levels to the table. The way Table 3 is structured is confusing: e.g. for cough #1 and cough #2 and other categories it is not clear how they differ from each other and whether they cover different symptoms. In addition, have summary scores been suggested based on the items of the questionnaire? p23 – 6: the current argument is based on the absence of clinical effects, it might be possible that sublclinical effects will be observed in this analysis, p23 – 46: the authors suggest that pollen allergy is partly to blame for the observed findings for CRP and IgE. Was information on pollen allergy available in the cohort? Did you correct for it? p24 – starting line 20: Instead of focusing on the lack of statistical significance of the elevated Odds Ratios one could explore whether there are logical exposure-response relations (see above). Considering limited statistical power such analyses exploring consistency in observed associations might provide useful insights. p25 – starting line 6: The argument that the current study 'had sufficient sample size' based on effects observed for smoking etc. We would never expect an effect as big as the effect of smoking on health outcomes. Considering the possibility for a subtle effect, the study might very well be under-powered.

REVIEWER	Daniel Croft University of Rochester Medical Center. USA
REVIEW RETURNED	23-Feb-2018

GENERAL COMMENTS	In a concisely, well-written article, the authors detail a prospective observational cohort study of copy industry workers. One main exposure that was hypothesized to put workers at risk for chronic respiratory conditions was the toner dust exposure. This study addressed a gap in the literature due to prior studies on this subjects being retrospective cross sectional studies. Overall the study achieved its goal of following this cohort for 10 years and found an increase in respiratory symptoms including cough, the lone statistically significant result. Specific comments listed below. Major comments 1. Page 9 Line 22 Given that one of the most important components of a cohort study is the measurement of exposures and outcomes, the exposure status must be crystal clear to avoid misclassification. It is important to include more detail on the

	control population in this study. For example, were these controls working in the same building as the cases? There can be contamination of 'clean' areas with dust through the ventilation system or other anomalies present. The workers in the 'clean' area may also have to walk through the factory area. 2. It is not clear to me from reading the study whether or not any or all of the workers were using personal protective equipment like N95 masks or Respirators. It is very important to include this information in the authors' article. For example, if all the workers exposed to toner dust were wearing masks, the study may indicate that wearing masks was one reason for the lack of significant differences between exposed workers and the control population. 3. The potential healthy worker bias is a concern but correctly highlighted by the authors. Including a flowchart of inclusion and attrition would be a helpful addition for the reader to follow along the text (Page 8, 9). 4. The authors' discussion section could use improvement. The first paragraph on page 21 line 6 may be more effective if it reviewed/summarized the high level findings of the results section. Then, the comparison to others' studies can continue. In the limitations section on page 25, line 6, it becomes confusing as positive and negatives are both discussed together. Please confine the content of the limitations section to include only the limitations of the study. Minor comments 5. P12 line 3. The current approach (As recommended by the American Thoracic Society (ATS)/European Respiratory Society (ERS) to PFT interpretation dictates the use of confidence intervals rather than a standard cutoff of 70%. It would be reasonable to consider including a sensitivity analysis with this approach rather than using the 70% approach. When the authors mentioned the 'reference range' p 19 line 12, I assumed that the authors are referring to the 70% range in authors' methods. 6. Use of CXR alone is a limitation and expanding the definition of abnormal is a concern. If the authors were concerned about conditions like Hypersensitivity pneumonitis or very early interstitial lung disease, CT chest imaging would be the test of choice (though increases the risk to the subject as the authors point out). I agree avoiding the chest CT was appropriate for patient safety. 7. P13 line 33. The personal exposure monitoring was limited by an inability to estimate the fraction of dust from toner dust. To help other researchers planning a similar study, please report the type of personal exposure monitoring device used in the authors' study. 8. Page 24 Line 38. It would be worth discussing the role of the size of the toner particles from the authors' prior experience when considering the area of the respiratory tract that will be affected. For example, larger particles (PM 10) will generally affect the trachea while smaller particles (PM2.5) can travel deeper into the respiratory tract. And it would be interesting to comment on whether different work groups (i.e. TPD vs. RCL) would have exposure to different sized particles. 9. Page 15 line 16. The outcome breathlessness could be better measured with a standardized approach like the 6 minute walk test. This outcome appears to have a limitation of subjectivity. 10. I recommend highlighting the paucity of women included in the study (Table 1) to help readers understand the generalizability of the authors' results.

	11. Finding of CRP in Table 3. Discussed on page 23 Lines 21-50. It would be worth mentioning other potential causes of elevated CRP. The authors mentioned allergy, but as the following study (among others) indicates, there are multiple other causes for the reader to consider. 12. Page 25 Line 12. I would soften the statement on the 'well established health risks'. The authors' do not have causal data in this study supporting the statement on mucous hypersecretion/PFT decline due to smoking, only associations. Of note, I agree 100% that smoking can cause these findings. Landry, A., Docherty, P., Ouellette, S., & Cartier, L. J. (2017). Causes and outcomes of markedly elevated C-reactive protein levels. Canadian Family Physician, 63(6), e316–e323. 13. The authors' statistical analyses section requires improvement (page 15 Line 46). The authors' simply mention the type of test used for a type of variable in general. Please organize the section to at the very least describe what tests were done for each section of the analyses listed on Page 14-15. Overall, I applaud the authors' hard work in completing this cohort study. The limitations of the study were clearly outlined for the reader and the findings of non-statistically significant increases in respiratory symptoms within these workers is something that can expanded on in future work. If I had one overarching critique, it would be that this article lacks sufficient detail for a reader to replicate the study. By improving the detail (outlined in my comments) of this study, others will be able to more effectively build upon its findings.

REVIEWER	Veruscka Leso Department of Public Health, Section of Occupational Medicine, University of Naples Federico II, Naples, Italy.
REVIEW RETURNED	03-Mar-2018

GENERAL COMMENTS	I have carefully read the manuscript titled "Chronic respiratory health risk associated with powdered toner exposure in the longitudinal observation of occupationally exposed Japanese workers", manuscript ID bmjopen-2018-022049. I have found it well done and easy to read. Additionally, it faces the interesting topic concerning the debated adverse health effects of toner dust exposure in the long term. I can suggest the authors to consider few revisions to improve their manuscript: - Abstract: to my opinion it may be important to introduce a brief introduction to the topic that may help the reader to better contextualize the research rationale; - Introduction/discussion: it can be useful to cite and consider some additional references, e.g.: 1. Elango N(1), Kasi V, Vembhu B, Poornima JG. Chronic exposure to emissions from photocopiers in copy shops causes oxidative stress and systematic inflammation among photocopier operators in India. Environ Health. 2013 Sep 11;12(1):78. doi: 10.1186/1476-069X-12-78. 2. Kasi V(1)(2), Elango N(1)(3), Ananth S(1), Vembhu B(1), Poornima JG(1).Occupational exposure to photocopiers and their toners cause genotoxicity. Hum Exp Toxicol. 2018 Feb;37(2):205-217. doi: 10.1177/0960327117693068. 3. Yanagi N(1), Kitamura H(1), Mizuno M(1), Hata K(1), Uchiyama T(1), Kuga H(1), Matsushita T(1), Kurosaki S(1), Uehara M(1), Ogami A(1), Higashi T(1). A 4-Year Follow-up Cohort Study of the

	Respiratory Functions in Toner-handling Workers. Saf Health Work. 2014 Dec;5(4):222-6. doi: 10.1016/j.shaw.2014.07.001. - Discussion: “however, only a few epidemiological reports have studied the possible health effects of everyday office pollutants, including toner dust used in photocopiers and laser printers”, please introduce the supporting references. - Discussion: “…in what it seems to our knowledge to be the only longitudinal study reported so far ”, please check this information. - Discussion: it may be interesting if the authors could bring together their considerations concerning future research needs on the argument in a brief concluding paragraph. - Table 1 legeng. “Values are presented as the numbers…”

VERSION 1 – AUTHOR RESPONSE

RESPONSE TO REVIEWER 1

General comments
• Very little detail is provided about the exposure assessment methods that were used in this study. Please describe in more detail what methodology (device, etc.) was used to assess personal dust exposure and how a distinction was made between inhalable and respirable dust. Also describe which attempts were undertaken to assess toner particles in the collected dust samples.

Response: We have now added some sentences describing the details of exposure measurement in this study, including the names of the devices used and the method for dividing the respirable fraction from the total dust sampled. We also described how we estimated the toner particle fraction separately from the total dust sampled.

(Highlighted in page 14 lines 7-14, page 15 lines 4-10)

• Even though exposure measurements were taken, the authors did not assess the potential for exposure-response patterns. By incorporating modeled (time varying) exposure estimates for each worker in the regression analyses one would likely increase power to detect a potential association. Alternatively one could explore the existence of patterns across the different occupational categories: e.g. TPD and RCL workers among which high exposures were observed.

Response: We have now added text on our analysis of the incidence of chronic health indices by work categories in the Methods and Results sections and discussed the results with regard to differences in the exposure conditions.

(Highlighted in page 17 lines 2-4, page 21 lines 15-17, page 22 lines 8-13, page 28 lines 5-6, page 29 lines 7-12, Table3,)

• It is unclear to me which cut-off was used to classify continuous markers as ‘abnormal. Furthermore did the authors consider conducting linear regression for these markers to assess any evidence for subclinical changes in e.g. long function, biomarkers.

Response: We had already shown the cut-off values for continuous markers in the original manuscript. You can also see them in the final paragraph of the “Serum and urine biomarkers” and “Spirometry” subheadings in the Methods section.

(Highlighted in page 12 lines 11-13, page 14 lines 2-4 (not highlighted))

Regarding the analyses of continuous variables, we have now added the findings for the longitudinal decline in the pulmonary function indices as suggested. A detailed description of this analysis was added as follows:

(Highlighted in page 12 line 15 – page 13 line 1, page 22 lines 14-18, page 28 lines 7-11, Table 4 newly added)

We did not perform the same analysis on the serum and urine biomarkers, as we were not sure about the linearity of the responses of those markers against exposure to harmful substances.

• In the current analytical strategy (logistic regression) the longitudinal aspect of the study is not reflected. In case within individual repeated outcome measures are available once could consider analyzing this data using a fixed-effect model or perhaps a mixed-model in which the correlation between repeated measurements is explicitly modeled.

Response: We agree with your comment concerning lung function indices, but we are not sure that small increases or decreases within the normal range observed in biomarkers such as KL6, SPD, and OHdG were clinically or subclinically meaningful with regard to adverse health effects. We therefore conducted analyses on the lung function decline during the follow-up period. We added the results of our analyses on the longitudinal change in the pulmonary function indices as described earlier (described in the previous section).
We did not perform a mixed model analysis since we were not sure we could properly adapt the model to the data of this study in cases where the time at which the data were collected differed among subjects (e.g. one subject started the survey in 2003 and was followed annually until 2008, while another started in 2005 and was followed in 2009 and 2010 and ended in 2012).

• I don’t really see the added value of presenting the results from the univariate analysis compared to the logistic regression, corrected for (a minimal set of) confounders.

Response: While we understand the reviewer’s concern, we believe it is useful to compare the results of univariate and multivariate analyses. When both results show consistency, we can conclude that there are no major confounding factors and that the multivariate models used are appropriate. Therefore, we would like to retain this part without changes.

• The manuscript contains a sparse number of references, which could be extended. I was surprised to see that a recent review by Pirela et al. was not included.

Response: We have now added references mainly focusing on epidemiological studies. We also changed the text in the first paragraph of the Discussion section according to another reviewer’s comments.

(Highlighted in page 24 line 6 – page 25 line 13 [1st and 2nd paras in Discussion])

• Even though the authors are fully transparent in listing Ricoh as the sponsor for this study, I think that this sponsorship should also be addressed under the heading of “potential conflict of interest”.

Response: All of the authors report no personal conflicts of interest regarding this study, including no conflicts of interest with RICOH. We have now clarified this point under the "Funding" heading, clearly indicating that the study’s funder is a photocopier industry company.

(Highlighted in page 32 lines 9-10)

Specific comments
p18 – line 35; with the current presentation in Table 2, it is difficult to assess trends over time in exposure levels. Please consider including this information in a figure.
Table 2: Please add the number of measurements that were taken to assess these exposure levels to the table.

Response: As suggested, we re-constructed the tables. The first part of Table 2 concerning the average exposure levels by work categories was merged into Table 1. The latter part concerning the time trend of exposure levels is now represented in a figure (Fig. 2 in the revised manuscript). The number of measurements was indicated in table 1. The tables have now been appropriately re-numbered in the revised manuscript.

(Highlighted in table 1. Fig. 2 is newly added)

The way Table 3 is structured is confusing: e.g. for cough #1 and cough #2 and other categories it is not clear how they differ from each other and whether they cover different symptoms. In addition, have summary scores been suggested based on the items of the questionnaire?

Response: We have now added a brief explanation of the graded symptoms (cough, phlegm, wheeze, and breathlessness) in the footnote of the table (Table 2 in the revised manuscript). We also added a sentence in the “Questionnaire survey” section to indicate that a symptom was considered to be present when a subject gave an affirmative response to a question about that symptom.

(Highlighted in page 11 lines 15-16, page 42 Footnote in Table 2,)

p23 – 6: the current argument is based on the absence of clinical effects, it might be possible that sublclinical effects will be observed in this analysis,

Response: While we agree with your comment, this sentence simply describes the necessity of longitudinal observation. We have therefore slightly modified the text to clarify this point.

(Highlighted in page 25 lines 12-13)

p23 – 46: the authors suggest that pollen allergy is partly to blame for the observed findings for CRP and IgE. Was information on pollen allergy available in the cohort? Did you correct for it?

Response: We have information on nasal allergies including pollen allergy but not on pollen allergy alone. Therefore we could not conduct an analysis considering pollen allergy as a confounder. As Reviewer 3 pointed out, there are multiple factors affecting the CRP as well as the IgE levels. We have therefore added one sentence to the end of the paragraph.

(Highlighted in page 27 lines 10-12)

p24 – starting line 20: Instead of focusing on the lack of statistical significance of the elevated Odds Ratios one could explore whether there are logical exposure-response relations (see above). Considering limited statistical power such analyses exploring consistency in observed associations might provide useful insights.

Response: We agree with this comment and have already mentioned our findings regarding the pulmonary function decline in this paragraph in response to an earlier comment. Furthermore, we

have now added several new sentences to the end of the paragraph to show the importance of the consistency in the results obtained.

(Highlighted in page 28 lines 7-8, page 29 lines 3-12)

p25 – starting line 6: The argument that the current study 'had sufficient sample size' based on effects observed for smoking etc. We would never expect an effect as big as the effect of smoking on health outcomes. Considering the possibility for a subtle effect, the study might very well be under-powered.

Response: Reviewer 2 also made comments on this part, and we completely agree. We have therefore revised the text of this paragraph.

(Highlighted in page 29 lines 13-17)

RESPONSE TO REVIEWER 2

Major comments

1. Page 9 Line 22 Given that one of the most important components of a cohort study is the measurement of exposures and outcomes, the exposure status must be crystal clear to avoid misclassification. It is important to include more detail on the control population in this study. For example, were these controls working in the same building as the cases? There can be contamination of 'clean' areas with dust through the ventilation system or other anomalies present. The workers in the 'clean' area may also have to walk through the factory area.

Response: We have now added two sentences on this point to the end of the "Subjects" section.

(Highlighted in page 9 line 19 – page 10 line 2)

2. It is not clear to me from reading the study whether or not any or all of the workers were using personal protective equipment like N95 masks or Respirators. It is very important to include this information in the authors' article. For example, if all the workers exposed to toner dust were wearing masks, the study may indicate that wearing masks was one reason for the lack of significant differences between exposed workers and the control population.

Response: We have now added text describing the conditions surrounding the usage of the respiratory protection device.

(Highlighted in page: 8, lines:13-17, the end of the 1st paragraph of "Subjects")

3. The potential healthy worker bias is a concern but correctly highlighted by the authors. Including a flowchart of inclusion and attrition would be a helpful addition for the reader to follow along the text (Page 8, 9).

Response: As suggested, we have now added a flowchart as Figure 1 showing the inclusion and exclusion of subjects for the analysis.

(Highlighted in page:9 , lines:11-12, Fig. 1 on page 51)

4. The authors' discussion section could use improvement. The first paragraph on page 21 line 6 may be more effective if it reviewed/summarized the high level findings of the results section. Then, the comparison to others' studies can continue. In the limitations section on page 25, line 6, it becomes

confusing as positive and negatives are both discussed together. Please confine the content of the limitations section to include only the limitations of the study.

Response: 1st part: According to the comments from you and the other reviewers, we have now added some references and largely re-structured the first paragraph as suggested.

(Highlighted in page:24 , line:6 – page 25, line 16)

2nd part: Reviewer 1 also commented on this part, and we completely agree. We have therefore revised this paragraph.

(Highlighted in page:29 , lines:13-18)

Minor comments
5. P12 line 3. The current approach (As recommended by the American Thoracic Society (ATS)/European Respiratory Society (ERS) to PFT interpretation dictates the use of confidence intervals rather than a standard cutoff of 70%. It would be reasonable to consider including a sensitivity analysis with this approach rather than using the 70% approach. When the authors mentioned the 'reference range' p 19 line 12, I assumed that the authors are referring to the 70% range in authors' methods.

Response: As suggested, we changed the cut-off values for pulmonary function indices from fixed values (70% or 80%) to the lower limit of the confidence interval of the authorized reference equations. Those values were derived from the formula recommended by the Japan Respiratory Society (Kubota M, Kobayashi H, Quanjer PH, Omori H, Tatsumi K, Kanazawa M; Clinical Pulmonary Functions Committee of the Japanese Respiratory Society. Reference values for spirometry, including vital capacity, in Japanese adults calculated with the LMS method and compared with previous values. Respir Investig. 2014 Jul;52(4):242-50).
As a result, the individual figures for the prevalence and incidence of %FVC, %FEV1, and FEV1/FVC abnormalities have changed, although the overall tendency of the results was unchanged. We have now revised the descriptions as necessary.

(Highlighted in page:12 , lines:12-14, figures in tables 2, 3, and 5)

6. Use of CXR alone is a limitation and expanding the definition of abnormal is a concern. If the authors were concerned about conditions like Hypersensitivity pneumonitis or very early interstitial lung disease, CT chest imaging would be the test of choice (though increases the risk to the subject as the authors point out). I agree avoiding the chest CT was appropriate for patient safety.

Response: Thank you for your comment.

7. P13 line 33. The personal exposure monitoring was limited by an inability to estimate the fraction of dust from toner dust. To help other researchers planning a similar study, please report the type of personal exposure monitoring device used in the authors' study.

Response: We have now added a detailed explanation (see our response to the first comment of Reviewer 1).

(Highlighted in page:14 , lines:7-14, page:15, lines:3-10)

8. Page 24 Line 38. It would be worth discussing the role of the size of the toner particles from the authors' prior experience when considering the area of the respiratory tract that will be affected. For

example, larger particles (PM 10) will generally affect the trachea while smaller particles (PM2.5) can travel deeper into the respiratory tract. And it would be interesting to comment on whether different work groups (i.e. TPD vs. RCL) would have exposure to different sized particles.

Response: We have now added a sentence mentioning the size of the particles contained in the toner products used for photocopiers. However, the lack information on the size distribution of the toner particles workers were actually exposed to makes it difficult to discuss the relationship between the toner particle size and the results observed in this study.

(Highlighted in page:14 , lines:7-8)

9. Page 15 line 16. The outcome breathlessness could be better measured with a standardized approach like the 6 minute walk test. This outcome appears to have a limitation of subjectivity.

Response: While we agree with your comment, we were unable to perform the standardized 6-minute walk test in this study. We have made it clear that “Breathlessness” in this manuscript refers to a subjective symptom and not an objective test result.

(Highlighted in page:11 , lines:15-16)

10. I recommend highlighting the paucity of women included in the study (Table 1) to help readers understand the generalizability of the authors’ results.

Response: We have now added text on this point to the second paragraph of the Results section.

(Highlighted in page:19 , lines:14-15)

11. Finding of CRP in Table 3. Discussed on page 23 Lines 21-50. It would be worth mentioning other potential causes of elevated CRP. The authors mentioned allergy, but as the following study (among others) indicates, there are multiple other causes for the reader to consider.

Response: We have now added the reference you suggested and included more text on this point.
(Highlighted in page:27 , lines:10-12)

12. Page 25 Line 12. I would soften the statement on the ‘well established health risks’. The authors’ do not have causal data in this study supporting the statement on mucous hypersecretion/PFT decline due to smoking, only associations. Of note, I agree 100% that smoking can cause these findings.

Response: In response to your previous comment 4 (part 2), we edited the original description to a simple and brief sentence in the revised manuscript.

(Highlighted in page:29 , lines:13-18)

13. The authors’ statistical analyses section requires improvement (page 15 Line 46). The authors’ simply mention the type of test used for a type of variable in general. Please organize the section to at the very least describe what tests were done for each section of the analyses listed on Page 14-15.

Response: We have now described the statistical tests used in the cross-sectional and longitudinal analyses as suggested.

(Highlighted in page:15 , line:17 – page;16, line:2, page:17, lines: 2-6)

RESPONSE TO REVIEWER 3

- Abstract: to my opinion it may be important to introduce a brief introduction to the topic that may help the reader to better contextualize the research rationale;

Response: We have now added text on the background information and re-structured the Abstract.

(Highlighted in page:3 , lines:2-4)

- Introduction/discussion: it can be useful to cite and consider some additional references, e.g.: ….

Response: As suggested, we re-structured the Discussion section by adding the references mentioned as well as several others.

(Highlighted in page:24 , line:6 – page: 25, line: 11)

Discussion: “however, only a few epidemiological reports have studied the possible health effects of everyday office pollutants, including toner dust used in photocopiers and laser printers”, please introduce the supporting references.

Response: As stated above, we re-structured the first paragraph of the Discussion section and revised the description as suggested.

(Highlighted in page:24 , line:6 – page: 25, line: 11)

Discussion: “…in what it seems to our knowledge to be the only longitudinal study reported so far ”, please check this information.

Response: We identified more references and re-structured the first paragraph of the Discussion section as suggested.

(Highlighted in page:25 , lines:4-11)

Discussion: it may be interesting if the authors could bring together their considerations concerning future research needs on the argument in a brief concluding paragraph.

Response: As suggest, we have now added a relevant sentence to the final portion of the Conclusion section.

(Highlighted in page:31 , lines:5-8)

Table 1 legends. “Values are presented as the numbers…”

Response: We have now corrected this point in Table 1 on page 39. RESPONSE TO REVIEWER 1

General comments
• Very little detail is provided about the exposure assessment methods that were used in this study. Please describe in more detail what methodology (device, etc.) was used to assess personal dust exposure and how a distinction was made between inhalable and respirable dust. Also describe which attempts were undertaken to assess toner particles in the collected dust samples.

Response: We have now added some sentences describing the details of exposure measurement in this study, including the names of the devices used and the method for dividing the respirable fraction from the total dust sampled. We also described how we estimated the toner particle fraction separately from the total dust sampled.

(Highlighted in page 14 lines 7-14, page 15 lines 4-10)

• Even though exposure measurements were taken, the authors did not assess the potential for exposure-response patterns. By incorporating modeled (time varying) exposure estimates for each worker in the regression analyses one would likely increase power to detect a potential association. Alternatively one could explore the existence of patterns across the different occupational categories: e.g. TPD and RCL workers among which high exposures were observed.

Response: We have now added text on our analysis of the incidence of chronic health indices by work categories in the Methods and Results sections and discussed the results with regard to differences in the exposure conditions.

(Highlighted in page 17 lines 2-4, page 21 lines 15-17, page 22 lines 8-13, page 28 lines 5-6, page 29 lines 7-12, Table3,)

• It is unclear to me which cut-off was used to classify continuous markers as ‘abnormal. Furthermore did the authors consider conducting linear regression for these markers to assess any evidence for subclinical changes in e.g. long function, biomarkers.

Response: We had already shown the cut-off values for continuous markers in the original manuscript. You can also see them in the final paragraph of the “Serum and urine biomarkers” and “Spirometry” subheadings in the Methods section.

(Highlighted in page 12 lines 11-13, page 14 lines 2-4 (not highlighted))

Regarding the analyses of continuous variables, we have now added the findings for the longitudinal decline in the pulmonary function indices as suggested. A detailed description of this analysis was added as follows:

(Highlighted in page 12 line 15 – page 13 line 1, page 22 lines 14-18, page 28 lines 7-11, Table 4 newly added)

We did not perform the same analysis on the serum and urine biomarkers, as we were not sure about the linearity of the responses of those markers against exposure to harmful substances.

• In the current analytical strategy (logistic regression) the longitudinal aspect of the study is not reflected. In case within individual repeated outcome measures are available once could consider analyzing this data using a fixed-effect model or perhaps a mixed-model in which the correlation between repeated measurements is explicitly modeled.

Response: We agree with your comment concerning lung function indices, but we are not sure that small increases or decreases within the normal range observed in biomarkers such as KL6, SPD, and OHdG were clinically or subclinically meaningful with regard to adverse health effects. We therefore conducted analyses on the lung function decline during the follow-up period. We added the results of our analyses on the longitudinal change in the pulmonary function indices as described earlier (described in the previous section).

We did not perform a mixed model analysis since we were not sure we could properly adapt the model to the data of this study in cases where the time at which the data were collected differed among subjects (e.g. one subject started the survey in 2003 and was followed annually until 2008, while another started in 2005 and was followed in 2009 and 2010 and ended in 2012).

• I don't really see the added value of presenting the results from the univariate analysis compared to the logistic regression, corrected for (a minimal set of) confounders.

Response: While we understand the reviewer's concern, we believe it is useful to compare the results of univariate and multivariate analyses. When both results show consistency, we can conclude that there are no major confounding factors and that the multivariate models used are appropriate. Therefore, we would like to retain this part without changes.

• The manuscript contains a sparse number of references, which could be extended. I was surprised to see that a recent review by Pirela et al. was not included.

Response: We have now added references mainly focusing on epidemiological studies. We also changed the text in the first paragraph of the Discussion section according to another reviewer's comments.

(Highlighted in page 24 line 6 – page 25 line 13 [1st and 2nd paras in Discussion])

• Even though the authors are fully transparent in listing Ricoh as the sponsor for this study, I think that this sponsorship should also be addressed under the heading of "potential conflict of interest".

Response: All of the authors report no personal conflicts of interest regarding this study, including no conflicts of interest with RICOH. We have now clarified this point under the "Funding" heading, clearly indicating that the study's funder is a photocopier industry company.

(Highlighted in page 32 lines 9-10)

Specific comments
p18 – line 35; with the current presentation in Table 2, it is difficult to assess trends over time in exposure levels. Please consider including this information in a figure.
Table 2: Please add the number of measurements that were taken to assess these exposure levels to the table.

Response: As suggested, we re-constructed the tables. The first part of Table 2 concerning the average exposure levels by work categories was merged into Table 1. The latter part concerning the time trend of exposure levels is now represented in a figure (Fig. 2 in the revised manuscript). The number of measurements was indicated in table 1. The tables have now been appropriately re-numbered in the revised manuscript.

(Highlighted in table 1. Fig. 2 is newly added)

The way Table 3 is structured is confusing: e.g. for cough #1 and cough #2 and other categories it is not clear how they differ from each other and whether they cover different symptoms. In addition, have summary scores been suggested based on the items of the questionnaire?

Response: We have now added a brief explanation of the graded symptoms (cough, phlegm, wheeze, and breathlessness) in the footnote of the table (Table 2 in the revised manuscript). We also added a

sentence in the “Questionnaire survey” section to indicate that a symptom was considered to be present when a subject gave an affirmative response to a question about that symptom.

(Highlighted in page 11 lines 15-16, page 42 Footnote in Table 2,)

p23 – 6: the current argument is based on the absence of clinical effects, it might be possible that sublclinical effects will be observed in this analysis,

Response: While we agree with your comment, this sentence simply describes the necessity of longitudinal observation. We have therefore slightly modified the text to clarify this point.

(Highlighted in page 25 lines 12-13)

p23 – 46: the authors suggest that pollen allergy is partly to blame for the observed findings for CRP and IgE. Was information on pollen allergy available in the cohort? Did you correct for it?

Response: We have information on nasal allergies including pollen allergy but not on pollen allergy alone. Therefore we could not conduct an analysis considering pollen allergy as a confounder. As Reviewer 3 pointed out, there are multiple factors affecting the CRP as well as the IgE levels. We have therefore added one sentence to the end of the paragraph.

(Highlighted in page 27 lines 10-12)

p24 – starting line 20: Instead of focusing on the lack of statistical significance of the elevated Odds Ratios one could explore whether there are logical exposure-response relations (see above). Considering limited statistical power such analyses exploring consistency in observed associations might provide useful insights.

Response: We agree with this comment and have already mentioned our findings regarding the pulmonary function decline in this paragraph in response to an earlier comment. Furthermore, we have now added several new sentences to the end of the paragraph to show the importance of the consistency in the results obtained.

(Highlighted in page 28 lines 7-8, page 29 lines 3-12)

p25 – starting line 6: The argument that the current study ‘had sufficient sample size’ based on effects observed for smoking etc. We would never expect an effect as big as the effect of smoking on health outcomes. Considering the possibility for a subtle effect, the study might very well be under-powered.

Response: Reviewer 2 also made comments on this part, and we completely agree. We have therefore revised the text of this paragraph.

(Highlighted in page 29 lines 13-17)

RESPONSE TO REVIEWER 2

Major comments

1. Page 9 Line 22 Given that one of the most important components of a cohort study is the measurement of exposures and outcomes, the exposure status must be crystal clear to avoid misclassification. It is important to include more detail on the control population in this study. For example, were these controls working in the same building as the cases? There can be contamination

of ‘clean’ areas with dust through the ventilation system or other anomalies present. The workers in the ‘clean’ area may also have to walk through the factory area.

Response: We have now added two sentences on this point to the end of the “Subjects” section.

(Highlighted in page 9 line 19 – page 10 line 2)

2. It is not clear to me from reading the study whether or not any or all of the workers were using personal protective equipment like N95 masks or Respirators. It is very important to include this information in the authors’ article. For example, if all the workers exposed to toner dust were wearing masks, the study may indicate that wearing masks was one reason for the lack of significant differences between exposed workers and the control population.

Response: We have now added text describing the conditions surrounding the usage of the respiratory protection device.

(Highlighted in page: 8, lines:13-17, the end of the 1st paragraph of “Subjects”)

3. The potential healthy worker bias is a concern but correctly highlighted by the authors. Including a flowchart of inclusion and attrition would be a helpful addition for the reader to follow along the text (Page 8, 9).

Response: As suggested, we have now added a flowchart as Figure 1 showing the inclusion and exclusion of subjects for the analysis.

(Highlighted in page:9 , lines:11-12, Fig. 1 on page 51)

4. The authors’ discussion section could use improvement. The first paragraph on page 21 line 6 may be more effective if it reviewed/summarized the high level findings of the results section. Then, the comparison to others’ studies can continue. In the limitations section on page 25, line 6, it becomes confusing as positive and negatives are both discussed together. Please confine the content of the limitations section to include only the limitations of the study.

Response: 1st part: According to the comments from you and the other reviewers, we have now added some references and largely re-structured the first paragraph as suggested.

(Highlighted in page:24 , line:6 – page 25, line 16)

2nd part: Reviewer 1 also commented on this part, and we completely agree. We have therefore revised this paragraph.

(Highlighted in page:29 , lines:13-18)

Minor comments
5. P12 line 3. The current approach (As recommended by the American Thoracic Society (ATS)/European Respiratory Society (ERS) to PFT interpretation dictates the use of confidence intervals rather than a standard cutoff of 70%. It would be reasonable to consider including a sensitivity analysis with this approach rather than using the 70% approach. When the authors mentioned the ‘reference range’ p 19 line 12, I assumed that the authors are referring to the 70% range in authors’ methods.

Response: As suggested, we changed the cut-off values for pulmonary function indices from fixed values (70% or 80%) to the lower limit of the confidence interval of the authorized reference equations. Those values were derived from the formula recommended by the Japan Respiratory Society (Kubota M, Kobayashi H, Quanjer PH, Omori H, Tatsumi K, Kanazawa M; Clinical Pulmonary Functions Committee of the Japanese Respiratory Society. Reference values for spirometry, including vital capacity, in Japanese adults calculated with the LMS method and compared with previous values. Respir Investig. 2014 Jul;52(4):242-50).
As a result, the individual figures for the prevalence and incidence of %FVC, %FEV1, and FEV1/FVC abnormalities have changed, although the overall tendency of the results was unchanged. We have now revised the descriptions as necessary.

(Highlighted in page:12 , lines:12-14, figures in tables 2, 3, and 5)

6. Use of CXR alone is a limitation and expanding the definition of abnormal is a concern. If the authors were concerned about conditions like Hypersensitivity pneumonitis or very early interstitial lung disease, CT chest imaging would be the test of choice (though increases the risk to the subject as the authors point out). I agree avoiding the chest CT was appropriate for patient safety.

Response: Thank you for your comment.

7. P13 line 33. The personal exposure monitoring was limited by an inability to estimate the fraction of dust from toner dust. To help other researchers planning a similar study, please report the type of personal exposure monitoring device used in the authors' study.

Response: We have now added a detailed explanation (see our response to the first comment of Reviewer 1).

(Highlighted in page:14 , lines:7-14, page:15, lines:3-10)

8. Page 24 Line 38. It would be worth discussing the role of the size of the toner particles from the authors' prior experience when considering the area of the respiratory tract that will be affected. For example, larger particles (PM 10) will generally affect the trachea while smaller particles (PM2.5) can travel deeper into the respiratory tract. And it would be interesting to comment on whether different work groups (i.e. TPD vs. RCL) would have exposure to different sized particles.

Response: We have now added a sentence mentioning the size of the particles contained in the toner products used for photocopiers. However, the lack information on the size distribution of the toner particles workers were actually exposed to makes it difficult to discuss the relationship between the toner particle size and the results observed in this study.

(Highlighted in page:14 , lines:7-8)

9. Page 15 line 16. The outcome breathlessness could be better measured with a standardized approach like the 6 minute walk test. This outcome appears to have a limitation of subjectivity.

Response: While we agree with your comment, we were unable to perform the standardized 6-minute walk test in this study. We have made it clear that "Breathlessness" in this manuscript refers to a subjective symptom and not an objective test result.

(Highlighted in page:11 , lines:15-16)

10. I recommend highlighting the paucity of women included in the study (Table 1) to help readers understand the generalizability of the authors' results.

Response: We have now added text on this point to the second paragraph of the Results section.

(Highlighted in page:19 , lines:14-15)

11. Finding of CRP in Table 3. Discussed on page 23 Lines 21-50. It would be worth mentioning other potential causes of elevated CRP. The authors mentioned allergy, but as the following study (among others) indicates, there are multiple other causes for the reader to consider.

Response: We have now added the reference you suggested and included more text on this point. (Highlighted in page:27 , lines:10-12)

12. Page 25 Line 12. I would soften the statement on the 'well established health risks'. The authors' do not have causal data in this study supporting the statement on mucous hypersecretion/PFT decline due to smoking, only associations. Of note, I agree 100% that smoking can cause these findings.

Response: In response to your previous comment 4 (part 2), we edited the original description to a simple and brief sentence in the revised manuscript.

(Highlighted in page:29 , lines:13-18)

13. The authors' statistical analyses section requires improvement (page 15 Line 46). The authors' simply mention the type of test used for a type of variable in general. Please organize the section to at the very least describe what tests were done for each section of the analyses listed on Page 14-15.

Response: We have now described the statistical tests used in the cross-sectional and longitudinal analyses as suggested.

(Highlighted in page:15 , line:17 – page;16, line:2, page:17, lines: 2-6)

RESPONSE TO REVIEWER 3

- Abstract: to my opinion it may be important to introduce a brief introduction to the topic that may help the reader to better contextualize the research rationale;

Response: We have now added text on the background information and re-structured the Abstract.

(Highlighted in page:3 , lines:2-4)

- Introduction/discussion: it can be useful to cite and consider some additional references, e.g.: ….

Response: As suggested, we re-structured the Discussion section by adding the references mentioned as well as several others.

(Highlighted in page:24 , line:6 – page: 25, line: 11)

Discussion: "however, only a few epidemiological reports have studied the possible health effects of everyday office pollutants, including toner dust used in photocopiers and laser printers", please introduce the supporting references.

Response: As stated above, we re-structured the first paragraph of the Discussion section and revised the description as suggested.

(Highlighted in page:24 , line:6 – page: 25, line: 11)

Discussion: "…in what it seems to our knowledge to be the only longitudinal study reported so far ", please check this information.

Response: We identified more references and re-structured the first paragraph of the Discussion section as suggested.

(Highlighted in page:25 , lines:4-11)

Discussion: it may be interesting if the authors could bring together their considerations concerning future research needs on the argument in a brief concluding paragraph.

Response: As suggest, we have now added a relevant sentence to the final portion of the Conclusion section.

(Highlighted in page:31 , lines:5-8)

Table 1 legends. "Values are presented as the numbers…"

Response: We have now corrected this point in Table 1 on page 39.

VERSION 2 – REVIEW

REVIEWER	Jelle Vlaanderen Utrecht University
REVIEW RETURNED	09-May-2018

GENERAL COMMENTS	The authors adequately addressed the concerns raised by me and other reviewers. I have no further comments to add.

REVIEWER	Daniel Croft University of Rochester Medical Center, United States of America
REVIEW RETURNED	19-Apr-2018

GENERAL COMMENTS	In reviewing this revised version of the manuscript the authors have addressed all of my concerns and I have only two remaining minor comments. 1. The authors revised pulmonary function testing analysis in Table 4 adds depth to the article. In the discussion, the authors mention that the declines are similar among groups. However, I see the largest effect in the MTN group for both FEV1 and FVC. It would be worth highlighting that in the discussion so that future studies could potentially focus on this group's exposure or at least reinforce the need to include this MTN group in all future studies. I would even add this to the conclusion stating 'non-significant declines in lung function' as an area that deserves future study.

	2. In reference to my prior comment which was answered (comment 3) Response: As suggested, we have now added a flowchart as Figure 1 showing the inclusion and exclusion of subjects for the analysis. (Highlighted in page:9 , lines:11-12, Fig. 1 on page 51) Revision comment: This flowchart in Figure 1 addresses my comment. However it would be improved if the number of subjects lost at each step was detailed (i.e. arrows to the side showing xx number of subjects lost after each step).

VERSION 2 – AUTHOR RESPONSE

RESPONSE TO REVIEWER 2

• 1. The authors revised pulmonary function testing analysis in Table 4 adds depth to the article. In the discussion, the authors mention that the declines are similar among groups. However, I see the largest effect in the MTN group for both FEV1 and FVC. It would be worth highlighting that in the discussion so that future studies could potentially focus on this group's exposure or at least reinforce the need to include this MTN group in all future studies. I would even add this to the conclusion stating 'non-significant declines in lung function' as an area that deserves future study.

Response: We agree with the reviewer on the importance of performing an evaluation by the decline in the pulmonary function. We therefore added descriptions in two parts (in the Results and Discussion sections) in order to describe the differences observed in the pulmonary function decline among work categories and the need for future studies focusing on a specific work category, as the reviewer suggested. However, we did not make any changes to the Conclusion section in order to keep this part as concise as possible.

Revision 1

We added a sentence to show that MTN workers had a greater annual pulmonary function decline than the other work categories in the last part of the paragraph describing the results of Table 4.

(Highlighted in 2nd paragraph on page 22 – 1st paragraph on page 23 of Results section)

Revision 2

In one paragraph in the Discussion section, we described the need for a sufficient sample size and accurate exposure assessment in future studies. In accordance with the context of this paragraph, we inserted several descriptions describing the faster annual loss of pulmonary function in MTN subjects and the importance of future analyses focusing on a specific work category.

(Highlighted in 1st paragraph on page 29 of Discussion section)

• 2 In reference to my prior comment which was answered (comment 3)

Response: As suggested, we have now added a flowchart as Figure 1 showing the inclusion and exclusion of subjects for the analysis.

(Highlighted in page:9 , lines:11-12, Fig. 1 on page 51)

Revision comment: This flowchart in Figure 1 addresses my comment. However it would be improved if the number of subjects lost at each step was detailed (i.e. arrows to the side showing xx number of subjects lost after each step).

Response: In Figure 1, we added the number of subjects who satisfied the inclusion criterion at each step instead of showing the number of lost subjects. We hope this satisfies the reviewer's request.

(Fig. 1)