Subject: MS:9774838421190541 – Upload of revised text

Dear Dr. Makri,

We greatly appreciate your interest in our paper. We found most of the reviewers’ comments interesting and well-addressed. Please find enclosed in detail our replies and a point-by-point description of the changes made to the original manuscript. As requested, the manuscript has been copyedited by a native English-speaking colleague. We hope that its contents are now clearer and that our work is now acceptable for publication in your Journal.

We were somewhat disappointed with the comment by the first reviewer, Dr. Giuseppe Mastrangelo, as our data are not in disagreement with what he has pointed out. On the contrary, we think his studies lend even more strength to our results. In his first remark, Dr. Mastrangelo cited one of his and his co-workers’ papers on the same cohort covered by our study, saying that we failed to evidence a significant increase of lung cancer. We feel this criticism is unkind (at the least), since his was a case-control study addressing a specific pathology, while ours was a cohort investigation aiming to describe the possible pattern of pathologies experienced by all the workers employed in that plant. Case-control studies have, by definition, a greater power to detect a risk with respect to cohort studies. That is the main reason why the suggestive increase of lung cancer (RR=3.13) among PVC baggers was of borderline significance at p<0.05 (anyway, p was <0.1).

A similar distinction should be made about the second comment, since the study by Mastrangelo was again a case-control study with a specific aim and a surplus of information with respect to a cohort study based on more readily available data. We were aware about the misclassification of both exposure and disease, but our study sought to demonstrate that it was possible to evince some risk with the same data used by other cohort studies simply by applying the correct study design. We feel we achieved this goal, as our results are not in contradiction with the findings cited by Mastrangelo, which were obtained by way of a more powerful kind of study. We added the reference to this second study by Mastrangelo et al., since it was fully pertinent to our paper. For both of the above mentioned points we tried to more clearly describe in the text Mastrangelo’s papers and
their relation to ours. Regarding the third point, since the description of statistical methods was perhaps not clear enough, we improved it in order to avoid any possible misunderstanding. As for the fourth point, we merely applied a standard procedure in regression analysis of occupational data. Admittedly, while we could have presented a table with a description of length of exposure by job category, this would have implied adding a 5x3 table with a large sparseness of data (i.e., cells with no or very few cases). Finally, we thought that a list of possible toxic agents, even if not quantifiable, was relevant to the knowledge of any possible exposure risk experienced by this group of workers.

In response to the comments by dr. Kenneth A. Mundt, first of all we consider technicians and clerks as the best reference group for the following reasons:

1) they were workers, as workers were the subject under study. This means that they passed a selection in order to be hired and this selection entailed a physical examination. Using the general population would have meant comparing healthy workers with a blend of healthy and unhealthy people.

2) Their mean socio-economical status presumably did not differ compared to that of blue collar workers, and the same likely held true regarding smoking habits. This means that the job category “technicians and clerks” was the best available reference group of workers, because it was based on the same hiring procedures applied in the same plant. In any case, we can assume the application of less severe hiring criteria, given the expected minor exposure level of this group of workers. Finally, this could imply that, even after an internal comparison, the risks detected among exposed workers could result somewhat underestimated.

Cardiovascular disease mortality can be considered an indicator of occupational exposure, since it has been demonstrated that exposure to air pollution leads to an increase of cardiovascular disease risk (WHO). Limitations of our studies were outlined in the text, and we have tried to make them even clearer in the revised text. Since this was a retrospective cohort study, no individual exposure data was available, nor it was recoverable at present. Ecologic level-assessment of exposure is the most commonly available exposure assessment in cohort studies and is normally accepted for such kinds of studies. We did not apply a re-definition of standard errors: main results are reported as significant when 95% CI were above unity. At any rate, we noticed some intriguing results of borderline significance, and attempted to give these findings a statistical confirmation in order to quantify the amount of the excess instead of labelling them with a generic “of borderline significance”. We tried to clarify our reasoning on this point in the revised text. Finally, attributable deaths have been estimated after the assessment of confounding and the adjustment for any possible interaction.

We thank dr. Avima Ruder for the linguistic revision, which was very useful for us. We confirm nearly all corrections, as it is outlined below in the point-by-point list of corrections. Our replies to Ruder’s comments included in the pdf file of the manuscript follow.

As reported, there was no death from hemolymphopoietic system tumors in the reference group, thus preventing us from estimating any RR and, therefore, any significance (pag. 2, abstract). SMR have been reported merely to provide information on the possible risks with respect to the general population, bearing in mind that the risk versus the internal reference group could have been even higher. Follow-up of the cohort was updated with respect to a previous study of ours (updated to 1995), not with respect to Pirastu et al’s paper. We tried to make this clear. The follow-up by Pirastu et al. covered the period January 1972-July 1999 while ours covered the period January 1972-December 1999 (as corrected in the paper). This led to a limited difference in the amount of person-years (page 4, Subjects and Methods). PVC compound workers were exposed to a mixture of
toxic agents, according to the specific final PVC-based product, but it was not possible to know which product was produced at a particular time (page 10, Discussion). Regarding attributable number of deaths, we interpreted the consistency of the results as proof of the reliability of our findings. The formula is mentioned in the Methods section and the attributable number of deaths calculated after the 1995 update are reported in reference 25 [or 23 in the numbering of the revised version, i.e., Gennaro V. The power of numbers. Epidemiol Prev 2005, 29:133-134] (page 11, Discussion). As suggested, CAS number have been added to chemicals listed in tab. 1.

In response to Dr. Freedom Nkhululeko N Gumede's correctly addressed remarks, we calculated the statistical power of the study and clarified the point about credibility intervals.

Point-by-point description of the changes

General points:
The consistency of italicizing job categories has been checked and corrected. Autoclave workers, PVC baggers, PVC compound workers, other blue collar workers and technicians and clerks are now consistently italicized.
References have been revised and corrected as suggested. This implied a complete re-numbering. Some of the papers in Italian are cited in English when their original title and abstract were available both in English on Pubmed (and in the journal itself). We believe these references are more readily available. On the contrary, we provide titles in both languages when the paper/book was published in Italian only.

Page and line numbers of the corrections refer to the revised text.

Page 2, line 3: “some known to be” instead of “some of these known to be”
Page 2, line 7: “of unexposed workers” inserted after “reference group”
Page 2, line 11: “groups” inserted after “internal reference”
Page 2, line 13-14: “total blue collar workforce” instead of “all blue collar workers”
Page 2, line 16: deleted “, including angiosarcoma,”
Page 2, line 18-21: “Hemolymphopoietic system tumors were found only among exposed workers, with 4, 4 and 6 deaths observed among PVC baggers, PVC compound and other blue collar workers, respectively. An excess of lung cancer was found among PVC baggers.” instead of “Hemolymphopoietic system tumors were found among PVC baggers, compound and other blue collar workers (4, 4 and 6 deaths, respectively).”
Page 2, line 23-25: “liver tumors (including angiosarcoma) and liver cirrhosis among autoclave workers and for lung cancer among PVC baggers, and revealed PVC compound workers as a possible new at risk group for liver and lung tumors” instead of “cancer other than liver angiosarcoma and identified PVC compound workers as a further at risk group”
Page 3, line 2: “entails” instead of “involves”
Page 3, line 3: “, some of which” instead of “. Some of these”
Page 3, line 4: “. Indeed, a number of these compounds have been” instead of “and were”
Page 3, line 5: “in” instead of “to”
Page 3, line 5: “prevalently” moved before “hepatic”
Page 3, line 5: “the” inserted before “hemolymphopoietic”
Page 3, line 7: “groups of” inserted after “different”
Numerous investigators have analyzed a cohort of Italian VC-PVC workers, who had been the subject of a large class-action lawsuit \([1]\)` instead of “In Italy a cohort of Italian VC_PVC workers was analyzed by different groups of researchers, as it was object of a legal action \([1]\)”.  

“One study on this cohort, updated in 1995,” \textit{instead of “Our previous studies on this cohort”} 

Page 3, line 9: “exposed (i.e., blue collar) workers” \textit{instead of “exposed workers (i.e., blue collar workers)”} 

Page 3, line 9: \textit{deleted “of death”} 

Page 3, line 11: “liver cancer and liver cirrhosis” \textit{instead of “hepatic angiosarcoma”} 

Page 3, line 13: “statistically” \textit{added after “a not”} 

Page 3, line 14: “Since” \textit{instead of “As”} 

Page 3, line 14: “entire” \textit{instead of “whole”} 

Page 3, line 16-17: “used the general population of the Region where the plant is located (Veneto) as a reference, related analyses may well have hidden” \textit{instead of “the Veneto Region general population was used as a reference, related analyses could have let to hide”} 

Page 3, line 17: “the updated mortality of” \textit{instead of “the follow-up was updated and the mortality experienced by “} 

Page 3, line 18: “of” \textit{instead of “including”} 

Page 3, line 18: “in order” \textit{added after “workers”} 

Page 3, line 19: “exposed” \textit{added after “subgroup of”} 

Page 3, line 19-20: \textit{deleted “using a more appropriate comparison group for the truly exposed workers. Results of this reanalysis are reported here”} 

Page 4, line 3: “included” \textit{instead of “refers to”} 

Page 4, line 4: “located” \textit{instead of “sited”} 

Page 4, line 5-6: “The follow-up period extended from January 1972 to December 1999;” \textit{instead of “Follow-up period was between December 1972 to July 1999 and”} 

Page 4, line 7: “were maintained” \textit{instead of “have been maintained”} 

Page 4, line 7: “categories” \textit{instead of “category”} 

Page 4, Line 10: \textit{deleted “According to the job category,”} 

Page 4, line 10: “were classified” \textit{instead of “have been classified”} 

Page 4, Line 10: “According to their job categories” \textit{inserted after “classified”} 

Page 4, Line 14: \textit{deleted “sum of”} 

Page 4, line 14: “comprised” \textit{instead of “amounts to”} 

Page 4, line 15: “An additional” \textit{instead of “A further”} 

Page 4, line 15: “categorized as” \textit{instead of “named”} 

Page 4, line 16: “included” \textit{instead of “was obtained by summing”} 

Page 4, line 16: “plant employees” \textit{instead of “workers employed”} 

Page 4, line 18-19: “in previous studies” \textit{moved after “they were found”} 

Page 4, line 19: “less” \textit{instead of “minor”} 

Page 4, line 21: “previously reported” \textit{moved after “considered all”} 

Page 4, line 21: \textit{deleted “the”} 

Page 4, line 21: “being” \textit{inserted before “associated”} 

Page 4, line 21: “changes in job category” \textit{instead of “job category changes”} 

Page 4, line 23: “transferred” \textit{instead of “passed”} 

Page 4, line 24: “an exposed to an unexposed category, and that only nine moved from an unexposed to an exposed category” \textit{instead of “a job category classified as “exposed” to an unexposed one and 9 subject followed the opposite path”} 

Page 5, line 1: “Totally” \textit{instead of “Overall”} 

Page 5, line 1: \textit{deleted “have”}
"occupation" instead of "job category"

"hiring" instead of "hire"

"into" instead of "in"

"Considering overall mortality among all exposed subjects (i.e., the total blue collar workforce), the study had an estimated power of 0.80 to detect a univariate relative risk (RR) of 1.50 as significantly increased at a 0.05 level (two-sided)" inserted at the beginning of the paragraph "Statistical analysis"

"calendar period of follow-up (1972-1974, 1975-1999 by five-year periods)" instead of "calendar period (five-year periods, 1955-1995)"

"hiring" instead of "hire" (twice)

"before age 25" instead of "0-24"

"duration" instead of "length"

"hiring" instead of "employment"

"over- or underdispersion" instead of "overdispersion and underdispersion"

"a" inserted after "model with"

"Due to the low number of cases of liver and brain tumors and for liver cirrhosis, Bayesian estimates of the mean of the posterior distribution of RR (RRₚₚₘ) for these diseases were obtained by means of the Monte Carlo - Markov Chain method [13]" instead of "When the number of observed deaths from a specific cause was under 10, bayesian estimate of RR was obtained by way of Monte Carlo - Markov Chain method [15]"

"Confidence intervals at the arbitrary levels of both 95% (95% CI) and 90% (90% CI) and 95% Bayesian credibility interval (95% BCI) between the 2.5th and 97.5th percentile of the posterior distribution of RR, as well as 90% BCI, were estimated as appropriate" instead of "Confidence intervals at the arbitrary level of 95% (95% CI) were estimated. In addition, when 95% significance was borderline, 90% (90% CI) were also estimated to verify the actual size of the risk"

"only" moved after "two deaths"

"decreasing" instead of "RR"
Page 8, line 11: “two deaths, occurring among PVC compound workers only, “instead of “only two deaths occurred among compound workers”
Page 8, line 14: “,” “instead of “,” after “workers”
Page 8, line 16: “,” “inserted after “bagger”
Page 8, line 17: “excesses (not statistically significant) were observed …” instead of “a not statistically significant excess …, was observed”.
Page 8, line 19: “hemolymphopoietic system tumors” instead of “malignant neoplasms of the lymphoid and hematopoietic tissue”
Page 8, line 20: “were seen” inserted after “none”
Page 8, line 20: “or” instead of “as such as”
Page 8, line 20: “thereby” inserted before “preventing”
Page 8 line 21: “As an indicative risk for these tumors, univariate SMRs compared to the Italian population were estimated. A significantly increased SMR was observed among PVC baggers (SMR=3.77; 95% CI: 1.03-9.66) and among the total blue collar workforce (SMR=2.27; 95% CI: 1.24-2.81), while PVC compound workers and other blue collar workers showed SMRs equal to 2.26 and 2.29, respectively (not statistically significant).” inserted after “related RRs.”
Page 9, line 3: “The estimation of 90% CIs yielded an enhanced insight into the importance of some increases of borderline significance at 95% observed in some job categories. In particular, most worthy of attention were the increases found for” instead of “As described above, given the limited statistical power of this cohort, 90% CIs have also been estimated, allowing us to prove as significant some further increases, such as”
Page 9, line 6: “for” inserted after “autoclave workers,”
Page 9, line 7: “for” inserted after “bagger,”
Page 9, line 8: “PVC;” “inserted after “among”
Page 9, line 8: “for” “inserted after “workers, and”
Page 9, line 8: “deaths” deleted after “observed”
Page 9, line 10: “As a final point” instead of “Finally”
Page 9, line 10: “deaths” inserted after “34.9”
Page 9, line 11: “weren’t” inserted of “have been”
Page 9, line 11: “attributable to blue collar workers’ activity” inserted of “attributable to working as a blue collar worker”
Page 10, line 2: “Following an extensive review and evaluation of previous studies, the IARC, first in 1979 and then in 1987 [3,4], provided sound evidence” instead of “While IARC in 1979 and 1987 [4,5], evaluating preceding studies, has provided evidence”
Page 10, line 4: “cancer” “inserted of “tumor”
Page 10, line 4: “the” “inserted after “tumors of”
Page 10, line 4: “system” “inserted of “tumors”
Page 10, line 5: “Despite such an authoritative stance on the issue, a good share of” inserted of “a large part of the”
Page 10, line 6: “as” inserted after “angiosarcoma”
Page 10, line 7: “mainly because” inserted of “as”
Page 10, line 7: “proven” inserted after “only”
Page 10, line 8: “to be stastically” inserted after “found”
Page 10, line 10: “considered as misclassifications” inserted of “reported as a misclassification”
Page 10, line 10-11: “have been often excluded, with the exception of some findings for brain” “inserted of “are normally denied, except for some evidence about brain cancer”
Page 10, line 12: “hemolymphopoietic” inserted of “haemolymphopoietic”
Page 10, line 12: “Nevertheless,” inserted before “Excesses”
Page 10, line 13: “recently” moved before “been”
Page 10, line 13-16: “exposed to PVC dust employed in the same Italian plant [8,19] and our previous studies [6] found excesses of liver tumors and liver cirrhosis among autoclave workers and lung cancer among PVC baggers” instead of “employed in an Italian plant [11,21] and our previous studies on the same cohort disclosed many old and new health risks”

Page 10, line 17: “In an” instead of “In the”

Page 10, line 17: deleted “to try”

Page 10, line 17: “in which” instead of “where”

Page 10, line 18: “likely” instead of “could have”

Page 10, line 18: “the same” instead of “a large Italian”

Page 10, line 19: “composed of” instead of “constituted by”

Page 10, line 20: “population” instead of “one”

Page 10, line 20: “general” moved before “regional”

Page 10, line 20: “figures” instead of “population”

Page 10, line 20: deleted “The”

Page 10, line 21: “evaluation of” instead of “comparison between”

Page 10, line 21: “very” instead of “much too”

Page 10, line 21-22: deleted “under the initial health condition point of view”

Page 10, line 22: “the mix of healthy and” instead of “normal”

Page 10, line 23: “people in the” inserted after “unhealthy”

Page 10, line 23: deleted “As known”

Page 10, line 23: “lead to a relative” instead of “generate a relevant”

Page 10, line 25-26: “among exposed blue collar workers compared to unexposed technicians and clerks” instead of “in the overall group of exposed workers (blue collar workers) with respect to the unexposed one (technicians and clerks)”

Page 11, line 2-3: “A case-control study nested in the same cohort, by holding the confounding factors constant in a logistic regression analysis, found that each extra increase of 1,000 ppm x years of VC cumulative exposure increased the risk of hepatocellular carcinoma by 71% (OR = 1.71; 95% CI, 1.28-2.44) and the risk of liver cirrhosis by 37% (OR = 1.37; 95% CI, 1.13-1.69) [20].” inserted after “documented [10].”

Page 11, line 8-9: “An increased mortality from all causes (p<0.05) and lung cancer (p<0.10) was clearly observable in PVC baggers.” instead of “PVC baggers showed an increased mortality for all causes (statistically significant, ss), all cancers (ss), and lung cancer (borderline significance), as it was revealed by previous studies on the same cohort.”

Page 11, line 14: “employment” instead of “work”

Page 11, line 14: “in” instead of “of the”

Page 11, line 15: “working” instead of “work”

Page 11, line 16: deleted “the”

Page 11, line 16: “reflected what was” instead of “was similar to that”
Page 11, line 18: “and also by Mastrangelo et al. who reported that “In our [PVC] baggers, recent rather than distant exposure to PVC dust had the most profound effects on lung cancer risk” [19].” added after “smoking cessation [21]”

Page 11, line 19: “Furthermore, a recent case-control study nested on the same cohort found, after adjustment for age and smoking habits, a 20% increase of death risk from lung cancer for each extra year of work [21].” moved (and then modified) at page 11, line 9-12.

Page 11, line 20-26: “The main task of PVC compound workers was to mix granular PVC with many other likely toxic and carcinogenic chemical agents (Tab. 1), whose characteristics differed according to the final PVC-based product [22]. Workers performing this task should be considered as a new at risk group, since they showed a statistically significant increased risk of death from all causes (p<0.05) and from liver cancer (p<0.10), and RRs for all tumors combined and lung cancer were increased too, even though increase was not statistically significant.” instead of “PVC compound workers’ main task was to mix granular PVC with many other chemical agents likely to be toxic and carcinogenic (Tab. 1), whose characteristics were different according to the specific final PVC-based product [22]. PVC compound workers should be considered as a newly detected group-at-risk because they showed statistically significant increases of death risk from all causes (p<0.05) and from liver cancer (p<0.10); mortality from all tumors combined, lung cancer, brain cancer and from cardiovascular diseases showed non statistically significant increases.”

Page 12, line 1: “showed excess (not statistically significant) risks of death” instead of “Other blue collar workers showed not statistically significant excesses of death risk”

Page 12, line 2: “all causes considered. This result suggests” instead of “all considered causes, suggesting”

Page 12, line 3: deleted “blue collar”

Page 12, line 3: “in this category” inserted after “workers”

Page 12, line 4: “i.e., autoclave workers” inserted after “autoclave”

Page 12, line 5-12: “Deaths from hemolymphopoietic system tumors (14 cases) occurred only among exposed workers (PVC baggers, PVC compound workers, other blue collar workers), preventing any estimate of RR. For this reason, SMRs were calculated and revealed significantly increased values among the total blue collar workforce and specifically among PVC baggers, while PVC compound workers and other blue collar workers showed more than two-fold increased SMRs (not statistically significant). These findings support the causal association already reported in the scientific literature between occupational exposure and hemolymphopoietic system tumors [3,4].” added at the end of the paragraph (before “Attributable number of cases”).

Page 12, line 14: “Attributable numbers of deaths” instead of “Attributable number of cases”

Page 12, line 15: “employment” instead of “working”

Page 12, line 15: “worker” inserted after “blue collar”

Page 12, line 16: “160” instead of “170”

Page 12, line 18: “evidence” instead of “a proof”

Page 12, line 19: “longer” instead of “increase of the length of”

Page 12, line 20: “the” inserted after “while”

Page 12, line 20: “the” inserted after “after”

Page 12, line 21: “for the most” instead of “in the most”

Page 12, line 22: “the effect of the exposure” instead of “exposure”

Page 12, line 22: “— or exposure itself —” inserted after “substances”

Page 12, line 22: “may” instead of “could”
Page 12, line 23: “lower in” instead of “its effect could have faded away in the”
Page 12, line 24: “a long latency, attributable deaths” instead of “long latency time, AD”
Page 12, line 25: “duration” instead of “lenght”
Page 13, line 2: “The” inserted before “present”
Page 13, line 2: “like” instead of “as”
Page 13, line 3: “lacked” instead of “was short of”
Page 13, line 3: “over time” moved after “occupational exposures”
Page 13, line 4: “surrogate indicators of exposure type and cumulative exposure” instead of “surrogated indicators of quality and length of cumulative exposure”
Page 13, line 6-9: “Two studies on the same cohort already cited [19,20] revealed a drawback in the cohort database stemming from a misclassification of both exposure and disease (information bias). In any case, such a misclassification could have led to an underestimation of the risk among exposed workers.” inserted after “respectively”
Page 13, line 10-11: “Despite these limitations, this analysis was, in our opinion, grounded on a fairer approach” instead of “Despite this limitation, in our opinion, this study was based on some crucial points of strength”
Page 13, line 11: “the present reanalysis sough to reduce the comparison bias by” instead of “as previously pointed out, present reanalysis was aimed to reduce the comparison bias , by”
Page 13, line 14-15: “hiring criteria and duration of employment similar to those of the exposed” instead of “a selection at hiring and a permanence at work similar to the”
Page 13, line 15-17: “In addition, we tried to avoid another possible source of underestimation of the true risk, i.e. the inclusion of unexposed (or less exposed) workers in the exposed group (misclassification of exposure).” inserted after “under study. “
Page 13, line 18: “eliminated or at least controlled” instead of “restricted”
Page 13, line 19-21: “The comparison with technicians and clerks seems appropriate, and the socio-economic status of the exposed and unexposed workers should be fairly comparable. For this reason, this group of workers appears as the best available comparison group” inserted after “controlled.”
Page 13, line 22: “separating blue collar workers into” instead of “splitting blue collar workers in”
Page 13, line 23: “These two procedures revealed the pattern of diseases” instead of “and permitted to reveal the pattern of pathologies typical of each subgroup of workers”
Page 13, line 24: “exposures” instead of “the exposure”
Page 13, line 24:”, typical of each subgroup of workers.” inserted after “specific occupational risk factors [24]”
Page 13, line 25 – Page 14, line 5: “The present study confirmed the elevated risks for specific tumors, namely liver, hemolymphopoietic system and lung cancers, previously observed by the scientific community (above all, the IARC). In particular, two job categories, autoclave workers and PVC baggers, were confirmed to be at risk for liver diseases and lung cancer, respectively, and another job category, PVC compound workers, was found to be likely at risk for liver and lung tumors. Moreover, mortality risk from neoplastic and non-neoplastic diseases was shown to be high among all blue collar workers” instead of “Present study confirmed site specific tumors, such as liver tumors, hemolymphopoietic tumors, lung and brain tumors previously observed by scientific community (IARC, above all). In particular, two job categories (i.e., autoclave workers and PVC baggers) have been confirmed to be at risk and two further job categories (i.e., compound and other workers) have been found to be at risk. Anyway, mortality risk from neoplastic and non-neoplastic diseases was detected to be high among all blue collar workers”.
Page 14, line 5: deleted “our assumption”
Page 14 line 6: “become ill from” instead of “get sick for a”
Page 14 line 7: deleted “In fact, in this study specific groups of workers showed different patterns of diseases: neoplastic and non-neoplastic liver diseases among autoclave workers, lung cancer among PVC baggers and PVC compound workers, and hemolymphopoietic tumors (14 deaths) among three exposed groups of workers (none among unexposed ones).”
Page 14 line 7: “As recently reported, some occupational health studies are regretfully beset by” instead of “As it was recently recalled”
Page 14 line 8-9: “cover-up bias, often owing to the strong business interests pervading the chemical industry [25-29].” instead of “cover-up bias exist in occupational health studies, given the strong business interests that are usually present in the chemical industry. Biases of this kind lead to a negation, to a delayed acknowledgment and/or to an underestimation of the actual health risk in workplaces.[27-31]”
Page 14 line 9: deleted “and repeatable.”
Page 14 line 10: deleted “was”
Page 14 line 10: “offset” instead of “compensate”
Page 14 line 10-12: “new evidence emerging from this reanalysis confirms the already documented health risks. We believe that this methodology could be used for the analysis of several other cohort studies” instead of “new arising evidence confirmed the health risks already documented”

We hope everything is clear enough. Do not hesitate to ask for any further information.
As a final point, no approval of an ethics committee was needed as the study was a mortality retrospective one and analysed data have been object of a specific class-action lawsuit now concluded.

Yours sincerely,

Dr. Fabio Montanaro
(on the behalf of all coauthors)