Author's response to reviews

Title: Cardiovascular mortality and exposure to extremely low frequency magnetic fields: a cohort study of Swiss railway workers

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Author's response to reviews: see over

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To the *Environmental Health*
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Submission of the revised manuscript: 'Cardiovascular mortality in a cohort of Swiss railway workers exposed to extremely low frequency magnetic fields.'
Röösli M, Egger M, Pfluger D, Minder C.

Dear Madam, dear Sir

Thank you very much for your interest in the above mentioned manuscript. We enclose a revised version of the manuscript, which takes into account the valuable comments and suggestions provided by reviewers.
A point by point discussion of the changes made follows:

Reviewer 1

Major compulsory revisions:
1. The reader will be helped by reversing the order of the four columns in Tables 3 and 4, so that the order (left to right) is now in order of increasing exposure (station master, train attendant, shunting yard engineer, train driver). This will place the lowest exposure category, the refernce category, as the first category.
Authors' response: We have changed the order of the four columns in all tables as suggested.

2. The data analysis section (page 6) needs to differentiate between the approach used for the tabulated results and those only used for ancillary analyses not referred to in the tables. This could be done by describing the "main analyses", and then referring to "additional" analyses. For example, the reader is told that age at entry was introduced as a "linear, quadratic and cubic" term. But is this relevant to what the reader is shown in the tables? I would also encourage the authors not to introduce complications that they make no real use of.
Authors' response: Because we dealt with a dynamic cohort, we were concerned that age at entry might be a confounder in our analysis. Thus, we tested whether the age when entering in the cohort is a confounder or whether it improves the model fits. The exposure-response association did not change markedly when considering age at entry. Thus, age at entry is not a confounder. However, the goodness of the fit increased and the standard errors of the model coefficients decreased when age at entry was considered as a linear, quadratic and cubic term.
As suggested, we differentiate now between the main analysis using two different exposure metrics (job category, cumulative lifetime exposure) and the sensitivity analysis with censored datasets. We believe it is important to test the consistency of the results with different analyses

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approaches. This is particular the case because there is no established biological mechanism that would inform about the relevant exposure metric.

3. It may help the reader to be given the formula for the models used to generate Tables 3 and 4. Are five year calendar periods being included in the model, with a further stratification for pre- and post-1996 periods? If so, I would question whether the latter is necessary as the change from ICD-8 to ICD-10 did not include important changes for the diseases under investigation.

Authors' response: We used 5 year calendar periods in the model (described in the chapter "data analysis"). We agree that the incidence of the investigated diseases has not abruptly changed in 1995. However, we found indications that the coding praxis has changed in 1995 when the ICD-10 codes were introduced. A change in coding praxis would result in an apparent change of the baseline hazard function. This was considered with the stratification: equal coefficients across strata but with baseline hazard unique to each stratum.

4. Tables 3 and 4 need footnotes making clear all the details about the applied models and censoring.

Authors' response: We agree and made the following footnotes in both tables:

adjusted for age and 5 year calendar periods as well as stratified for the period before and after 1995, when coding changed from ICD-8 to ICD-10.

The caption of Table 4 was changed as following:

Table 4: Hazard ratios (HR) based on a dataset where all observations were censored at age 65 (age of retirement).

5. Some comment on the findings for all causes mortality in shunting yard engineers and train attendants needs to be made. One imagines that socio-economic status might offer an obvious explanation. Do these job categories attract lower salaries from less well-qualified applicants?

Authors' response: We have revised this point in the discussion and made it more explicit (p. 11):

We controlled for potential confounding from age and time trends but we had no data about individual cardiovascular risk factors which may have acted as confounders in these analyses, for example smoking and levels of physical activity. A survey of 378 railway employees carried out in 1994 found that station masters and train drivers were less likely to smoke (8% and 12%, respectively) than shunting yard engineers and train attendants (38% and 29%, respectively) [12]. Socio-economic status showed a corresponding pattern: the salary is similar for train drivers and station masters but somewhat lower for shunting yard engineers and train attendants. In our view, lifestyle factors are probably responsible for the generally increased cardiovascular mortality of shunting yard engineers and train attendants compared to station masters and train drivers. However, the similar socio-economic status of train drivers and station masters and the mortality patterns observed make it unlikely that confounding factors have masked an association between cardiovascular diseases and ELF-MF.

Reviewer 2

Major comment

This study is a report from a nationwide cohort of workers employed at the Swiss railway system. The cohort covers a long time span and seems to include all relevant persons employed at the Swiss railways. The exposure assessment is based on measurements conducted with almost a ten year time span and the assignment of the actual exposure is based on these measurements and a number of historical information about engines, railway organization and job duties. The outcome is defined as a number of cardiovascular diseases on the death certificate. The study do not include information on well defined risk factors for these diseases such as smoking, physical activity, diet, weight (BMI) or other lifestyle variables. The study follows a straightforward cohort analysis plan. However, I do not see that this study contribute that much to the evidence concerning the supposed association. As mentioned in the reference no 7, there is a need for more sophisticated studies in order to shed more light on the hypothesis. One may say that the conclusion in reference no 7 'buries' the idea that exposure to EMF in any way would be associated with the occurrence of

cardiovascular diseases.

Authors' response: We are convinced that this study has some unique features that are worth to be published. Firstly, it is the first study that investigated long term exposure to intermittent 16.7 Hz ELF-MF. Previous studies focused on 50 and 60 Hz. Secondly, exposure levels in our study were considerably higher than in previous occupational studies. This allows more general conclusions about this topic. We made these points more explicit in the conclusions (p. 12):

> *Our data provide evidence against an association between long-term exposure to 16.7 Hz magnetic fields and cardiovascular mortality, including arrhythmia related deaths or deaths from acute myocardial infarction. These results are in line with most epidemiological studies on exposure to power frequency magnetic fields although we investigated another frequency of the magnetic field spectrum and dealt with higher exposure levels than previous studies. The results from our study suggest that previous negative findings can be generalized to higher exposure levels and to a wider frequency range of the extremely low frequency spectrum including 16.7 Hz.*

Therefore the lack of confounder information in the present study becomes a problem. One may suggest that the authors by revisiting the death certificates would be able to come up with some more causes of death in order to validate the cause of death which they include as their measure of the outcome. The immediate cause of death in combination with a contributing and/or underlying cause of death indicating a lifestyle, which characterizes a person at high risk for cardiovascular disease would indirectly validate the immediate cause of death. These two other causes of death indicates the degree to which a given person may be expected to have lived a life which we would characterise as a 'risk life' with regard to the risk for cardiovascular disease. I am only emphasizing this opportunity because the current data, in my opinion, would benefit of a more aggressive and ambitious approach.

Authors' response: Inspired by these suggestions, we have performed additional analyses. For all diagnostic groups we distinguished between initial diagnoses on the one hand and consecutive or concomitant diagnoses on the other hand. The results were similar, and we did not find any indication for an exposure response association in these analyses. We included a table with these results as supplementary material for editorial inspection (file "Extra table separate analysis.doc"). However, we feel that it is not worth to be published as reviewer 1 encouraged us "not to introduce complications that they make no real use of."
However, if reviewer 2 has a specific hypothesis in his mind about combination of cause of deaths that should be tested in our data, we are happy to do that.

In addition it is often used in cohort studies of an occupational exposure to interview fellow workers and/or spouses or family members. This would also be possible in a sample of the cohort in order to obtain more information on the lifestyle of cohort members. Once more, the approach is too conservative especially in the light of the conclusions of reference no 7.

Authors' response: Certainly, this would be great. However, in this cohort with >20,000 workers and a follow-up period that started in 1972, this would need an enormous effort. This is not possible to do.

Minor

The probabilistic method by which death certificates and actual persons in the cohort become linked is somehow mysterious in the current explanation. I am not sure that I really understand the exact procedure. Would it be possible to enlarge this section in order to be able to understand the discussion of this procedure with regard to bias (?)

Authors' response: We give now more information about the linkage methods and the result of the linkage.
Method section (p. 4):

> *We used a probabilistic record linkage method to match employee records with the anonymous death certificates. Records were linked using the software LinkPro 3.0 by an investigator blinded to occupation and*

exposure status. Linkage variables were date of birth, date of death, place of residence at time of death, occupation, marital status, and duration of marriage, if married. In a first linkage cycle only records with a date of death were considered for the lining. Death certificates were accepted if there was complete agreement on date of birth and death and probabilistic weight calculated from the other linkage variables was positive. In a second cycle records without a date of death were considered and links with death certificates were accepted if the dates of birth matched and the probabilistic weight was at least 40 percent of the maximum weight.

Result section (p. 7):

Personnel and pension records contained files for 3406 men with an exact date or year of death. Among these, 76 men (2.2 percent) could not be linked to a death certificate. Most were probably foreigners who returned to their country of origin. These deaths were considered as deaths with unknown cause. A total of 1968 additional deaths were identified among the remaining 16,735 men. None of these matched more than one death certificate. Data from the 39 men found to be older than 100 years at study end (December 31, 2002) were censored at the age of 100 years.

The reference number 12 on second line from the bottom on page 10 lacks brackets

Authors' response: This was corrected.

The first two lines of the Acknowledgement is redundant of the following two lines
One may consider too leave out the figure, which does not provide the reader with any special information but seems to be included just to show that actual measures exist.

Authors' response: The acknowledgement was revised. We believe that Figure 1 is important because it shows the high temporal variability of the ELF-MF exposure in our study. This should be demonstrated because in experimental research reduced heart rate variability was found for intermittent exposure but not for continuous exposure.

I confirm that the manuscript corresponds to the journal style. Reference list is based on EndNote.

Sincerely,

Martin Röösli, PhD