Authors' response to the Comments from S.M.J. Mortazavi regarding: "Occupational exposure to high-frequency electromagnetic fields and brain tumor risk in the INTEROCC study: An individualized assessment approach"

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We reviewed the comments on our publication sent by S.M.J. Mortazavi and would like to clarify some of the concerns from this reader, especially those due to misunderstanding of our study methods.

The first concern raised by Dr. Mortazavi is that he states that "*the confounding factors were limited to only age, sex, region and country and major confounding factors such as socioeconomic status or education of the participants which play a crucial role in each individuals' life style and diet are ignored.*"

This is not the case since, as explained in the paper (Section 2.4. Statistical analysis; p. 355) in INTEROCC, as well as in INTERPHONE, matching factors (age group, sex, country and region) were used to stratify the subjects, while the subjects' education level was used to adjust logistic regression models created to estimate the odds ratios for glioma and meningioma. As in most epidemiological studies outside of the US, collection of information on income is not possible and hence we could not control for it. However, education was used as a proxy for socioeconomic status (SES) or social class. Although it is possible that some residual confounding may still be present due to the use of education as surrogate for SES, it is unlikely that this may have strongly affected our results (Kaufman et al., 1997; Rothman et al., 1998).

Dr. Mortazavi continues asking whether "*… a selection bias has possibly affected the findings? It is also likely that "healthy worker effect" is involved in forming those less than 1 ORs.*"

We discuss in our paper selection bias as one of the study's possible limitations (Section 4. Discussion; p. 362). Selection bias was studied in INTERPHONE (the parent study of INTEROCC) using non-response questionnaire's data on mobile phones, the main exposure source of exposure of interest in the study (Vrijheid et al., 2009, 2006). Like in previous studies, the authors found that refusal to participate was related to less prevalent use of mobile phones. A downward bias of around 10% in odds ratios for regular mobile phone use was estimated (Vrijheid et al., 2009). While a selection bias is possible in relation to occupational exposure, this was not included specifically in the presentation of the study to potential participants. Moreover, the impact of selection bias, if any, is likely to be smaller than that for mobile phones.

In relation to the comment on a potential "healthy worker effect", it is well established that using the general population as a reference for studies of occupational exposures may lead to underestimation of risk incidence, especially for cancers of the head in men (Kirkeleit et al., 2013). However, when we analyzed exposed subjects only (i.e. which includes workers only), by using the lowest exposed group as reference instead of non-exposed subjects (which includes both workers and general population), most ORs obtained (in Supplementary material) were above 1.0, although results were inconsistent, and no clear exposure-response associations were identified.

According to the reader, "*Another major problem comes from the criteria used for considering exposures as occupational. If we ask anyone who works in a factory, office, school, shop, etc. whether he/she works with or nearby antennas, his/her answer should be positive because there are many antennas near any work place.*"

The questions included in the INTEROCC questionnaire were designed to identify subjects who may have been exposed to high levels of EMF during their working lives (Vila et al., 2016). For this purpose, screening questions were asked to identify subjects who worked with/nearby RF and/or IF EMF sources. Those who answered affirmatively, were then asked a series of more specific questions regarding the type of equipment used, the purpose and process (e.g. material being heated), and the frequency and duration of use, as well as other information depending on the occupational sector (e.g. for industrial heating we asked whether the process was automated or done manually, for radars we asked whether the subject operated or maintained the radar(s) reported and the distance to the radar(s), etc.). Therefore, since all this detailed information was needed to assess the subjects' exposure, it is unlikely that subjects who were identified as exposed did not actually work with the sources reported. Furthermore, this study focused on exposure to occupational sources of RF and/or IF EMF while potential environmental sources, which yield ubiquitous but usually low background levels (Gajsek et al., 2013), particularly at the time relevant for this study (Tell and Mantiply, 1982), were not considered.

Although as stated in the conclusions, we did not find a clear association between cumulative occupational exposure to RF or IF EMF and risk of glioma or meningioma, the results for recent exposure to RF magnetic fields show indication of a potential increased risk in this exposure time window, which could be related to a possible role of RF exposure in brain tumor promotion/progression. Moreover, in our analyses using the continuous exposure data, although the linear models obtained the best fit results (i.e. lowest AIC and BIC), overall the models giving a J-shaped exposure-response curve obtained only slightly higher fit results showing that it is possible that this type of curve may explain this relationship better than the linear model. We, therefore, expect that the new study by Mortazavi et al. (in press),

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showing a nonlinear J-shaped dose–response relationship for carcinogenesis and exposure to RF-EMF, may provide more evidence on this issue.

References

Gajsek, P., Ravazzani, P., Wiart, J., Grellier, J., Samaras, T., Thuróczy, G., 2013. Electromagnetic field (EMF) exposure assessment in Europe - radio frequency fields (10 MHz–6 GHz). J. Expo. Sci. Environ. Epidemiol. 25, 37–44. https://doi.org/10.1038/jes.2013.40.

Kaufman, J.S., Cooper, R.S., McGee, D.L., 1997. Socioeconomic status and health in blacks and whites: the problem of residual confounding and the resiliency of race. Epidemiology 8, 621–628.

Kirkeleit, J., Riise, T., Bjorge, T., Christiani, D.C., 2013. The healthy worker effect in cancer incidence studies. Am. J. Epidemiol. 177, 1218–1224. https://doi.org/10.1093/aje/kws373.

Mortazavi, S.M.J.; Mortazavi, S.A.R.; Haghani, M. Evaluation of the Validity of a Nonlinear J-Shaped Dose-Response Relationship in Cancers Induced by Exposure to Radiofrequency Electromagnetic Fields. J. Biomedical Phys. Eng. (in press).

Rothman, K.J., Greenland, S., Buehler, J.W., Cahill, J., Haloran, M.E., Hartge, P., Hertz-Picciotto, I., Khoury, M.J., Lee, J.A.H., Moolgavkar, S.H., Morgenstern, H., Morrison, A.S., Stevens, R.G., Weinberg, C.R., Weiss, N.S., Wilcox, A.J., Willett, W.C., 1998. Modern Epidemiology. Lippincott-Raven, Philadelphia.

Tell, R.A., Mantiply, E.D., 1982. Population exposure to VHF and UHF broadcast radiation in the United States. Radio Sci. 17, 39S–47S. https://doi.org/10.1029/RS017i05Sp0039S.

Vila, J., Bowman, J.D., Richardson, L., Kincl, L., Conover, D.L., McLean, D., Mann, S., Vecchia, P., van Tongeren, M., Cardis, E., INTEROCC Study Group, 2016. A source-based measurement database for occupational exposure assessment of electromagnetic fields in the INTEROCC study: a literature review approach. Ann. Occup. Hyg. 60, 184–204. https://doi.org/10.1093/annhyg/mev076.

Vrijheid, M., Deltour, I., Krewski, D., Sanchez, M., Cardis, E., 2006. The effects of recall errors and of selection bias in epidemiologic studies of mobile phone use and cancer risk. J. Expo. Sci. Environ. Epidemiol. 16, 371–384. https://doi.org/10.1038/sj.jes.7500509.

Vrijheid, M., Richardson, L., Armstrong, B.K., Auvinen, A., Berg, G., Carroll, M., Chetrit, A., Deltour, I., Feychting, M., Giles, G.g., Hours, M., Iavarone, I., Lagorio, S., Lönn, S., Mcbride, M., Parent, M.E., Sadetzki, S., Salminen, T., Sanchez, M., Schlehofer, B., Schüz, J., Siemiatycki, J., Tynes, T., Woodward, A., Yamaguchi, N., Cardis, E., 2009. Quantifying the impact of selection bias caused by nonparticipation in a case-control study of mobile phone use. Ann. Epidemiol. 19, 33–41. https://doi.org/10.1016/j.annepidem.2008.10.006.

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