World Health Organization **15 December, 2014**
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Comments on the WHO draft: Radio Frequency fields: Environmental Health Criteria Monograph

The following comments relate to section 12.1 Cancer Epidemiology. Due to the short time for submission of comments it is not possible to make a full review. That would require an in-depth review checking the original publications in detail.

Unfortunately the WHO draft does not state the names of the authors and any conflicts of interest. However, it must be clear that if any current or previous member of ICNIRP is part of this draft it would be a serious conflict of interest. ICNIRP has produced guidelines for radiofrequency electromagnetic (RF-EMF) exposure and accepts only thermal effects. Thus the large bulk of evidence on non-thermal effects is ignored, see the update of ICNIRP guidelines:

ICNIRP statement on the "Guidelines for limiting exposure to time-varying electric, magnetic and electromagnetic fields (up to 300 GHz)". Health Physics. 2009; 97:257-8.

"*However, it is the opinion of ICNIRP that the scientific literature published since the 1998 guidelines has provided no evidence of any adverse effects below the basic restrictions and does not necessitate an immediate revision of its guidance on limiting exposure to high frequency electromagnetic fields…..With regard to non-thermal interactions, it is in principle impossible to disprove their possible existence but the plausibility of the various non-thermal mechanisms that have been proposed is very low. In addition, the recent in vitro and animal genotoxicity and carcinogenicity studies are rather consistent overall and indicate that such effects are unlikely at low levels of exposure. Therefore, ICNIRP reconfirms the 1998 basic restrictions in the frequency range 100 kHz–300 GHz until further notice."*

ICNIRP has not published any later statement. Thus, ICNIRP has not changed their guidelines in spite of increasing evidence of adverse health effects from RF-EMF exposure. Being a present or a former member of ICNIRP creates intellectual bias, not the least to adopt their evaluation in any further review outside ICNIRP. In fact, it would be remarkable if an ICNIRP member comes to a conclusion other than the ICNIRP paradigm of "no health effects."

Another remarkable drawback of the draft is that the following important chapters are missing: *Chapter 1: Summary and recommendations for further study. Chapter 13: Health risk assessment, Chapter 14: Protective measures.*

It is unclear why these chapters are excluded. Is it so that WHO aims to produce their conclusions without comments from the international scientific community?

Certain comments on cancer epidemiology in the WHO draft:

Cohort studies

The Danish cohort study

The draft lacks a critical approach to the Danish cohort study. The many weaknesses are not explored, for example by IARC in the May 2011 evaluation of RF-EMF and human cancer risk:

"In this study, reliance on subscription to a mobile phone provider, as a surrogate for mobile phone use, could have resulted in considerable misclassification in exposure assessment."

Baan R, Grosse Y, Lauby-Secretan B, et al. Carcinogenicity of radiofrequency electromagnetic fields. Lancet Oncology. 2011; 12: 624-626.

We made a review of the Danish cohort study and noted:

"Although at least non-response and recall bias can be excluded, the study has serious limitations related to exposure assessment. In fact, these limitations cloud the findings of the four reports to such an extent that render them uninformative at best. At worst, they may be used in a seemingly solid argument against an increased risk – as reassuring results from a large nationwide cohort study, which rules out not only non-response and recall bias but also an increased risk as indicated by tight confidence intervals."

Söderqvist F, Carlberg M, Hardell L. Review of four publications on the Danish cohort study on mobile phone subscribers and risk of brain tumors. Reviews on Environmental Health. 2012; 27: 51-58.

In summary the Danish cohort study is uninformative regarding brain tumour risk (and other malignancies) due to its serious limitations in assessment of exposure both in the cohort and the Danish population used for comparison.

Some of the many shortcomings of the Danish cohort study include:
1) Corporate subscribers of mobile phones (200,507 people), which are likely to have been heavy users, were classified as 'unexposed'.
2) Mobile phone subscription holders not using the phone were classified as 'exposed'.
3) Users of cordless phones not using a mobile phone were classified as 'unexposed'.
4) Non-subscribers using the mobile phone were classified as 'unexposed'
5) Persons with a mobile phone subscription later than 1995 were classified as 'unexposed'
6) No individual exposure data (e.g. on cumulative exposure or side of head mostly used).
7) No operator-verified data on years of subscription assessed.

These limitations are likely to have led to an underestimate of any risk in this study. One would expect considerable misclassification of mobile phone use both among subscribers and the reference population since no new subscribers were included in the exposed cohort after 1995.

UK Million Women Study, Benson et al 2013:

Benson et al published in 2013 a study on UK mobile phone users. Use of mobile phones was assessed in about 65 % of a cohort of women established for other purpose during 1996-2001. Only baseline data collected at one time between 1999-2005 were used with the questions:

"About how often do you use a mobile phone?" (never, less than once a day, every day); and *"For how long have you used one?"* (total years of use).

In 2009, the participants were asked how much they did talk on a mobile phone and how many years they had used the phone. However, these later data were not used in the analysis. Of those reporting no use of a mobile phone at baseline, 49 % reported such use in 2009. The incidence of brain tumours was assessed in 2005 and the average follow-up was only 7 years. No increased incidence of glioma was found (n=571 cases). For acoustic neuroma (n=96 cases), there was an increase in risk with long term use versus never use (10+ years: RR = 2.46, 95% CI = 1.07–5.64, p = 0.03), the risk increasing with duration of use (trend among users, p = 0.03), although later commented in a letter.

The WHO draft notes at page 5 that:

"[The strength of this large cohort study is the prospective design with individual information on amount of mobile phone use, which prevents the major sources of bias identified in the case-control studies, i.e. recall bias and selection bias, and reduces non-differential exposure misclassification, identified as a limitation in the Danish cohort study. ……]"

It is unclear why recall bias would be excluded in the self-reported use of mobile phones in this study. Furthermore, in contrast to the case-control studies with assessment of use during the whole life, use of mobile phones was only assessed at baseline in the Benson et al study. Only about 65 % of the cohort participated so selection bias cannot be ruled out.

No data were available on handedness for mobile phone use or tumour localisation in the brain. Use of cordless phones was ignored. This study has poorly assessed exposure and has the same shortcomings as the Danish cohort study. These shortcomings make this study uninformative as to tumour risk associated with use of wireless phones (mobile phones and cordless phones).

Hardell studies

This part of the WHO draft represents a biased evaluation towards the null hypothesis. The authors seem to be less informed in medical science, not the least in oncology. Some studies are excluded, others are misinterpreted. It would take considerable time to review this part in detail so in the following some details are given.

Line 306:

"[Despite apparently high participation rates, only about one third of the total number of brain tumour cases appears to have been included in the study (Ahlbom & Feychting, 1999)….]"

Comment: A letter to the Editor is cited. This seems to be somewhat unusual in the draft and is in contrast to other comments and overviews on this whole topic that are not included

in the draft. The authors have avoided to include our response to the false statements made in that letter:

Hardell L, Näsman Å, Påhlson A, Hallquist A, Hansson Mild K. Reply to: Use of cellular phones and the risk of brain tumours: A case-control study. Int J Oncol 1999;15:1045-1047.

Thus, for clarity our response should have been included which is usual in the scientific debate. This represents a less valid and biased scientific approach among the draft authors.

Lines 331-333:

"The authors report a higher response rate, but unconventionally exclude from the denominator cases who were too ill, deceased, whose physician did not allow contact, or had no known address."

Comment: Similar statements are made in other parts of the draft. However, the authors have not grasped the definition of the case series in our studies. These have clearly been stated in the publications, for example at page 631 in:

Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of two case-control studies on use of cellular and cordless telephones and the risk for malignant brain tumours diagnosed in 1997-2003. International Archives of Occupational Environmental Health. 2006; 79: 630-639.

"Both men and women aged 20–80 years at the time of diagnosis, as defined according to the date of the histopathology report, were included. Cases were reported in a consecutive way from the regional cancer registries, in total 3,729 patients. Subjects that did not meet the study prerequisites were excluded, i.e., brain metastases or wrong reporting to the registry (n=288), wrong year for diagnosis (n=73), missing histopathology (n=5), not resident in study area (n=14), deceased (n=745), physician refusal (n=81), not capable to participate (n=84) and unknown address (n=2), in total 1,292 cases."

Thus, controls were drawn from the Population Register to these finally included cases. The response rate should be similarly calculated for the finally included cases and controls. The *ad hoc* method used by the draft authors creates unbalanced numbers for cases and controls and do not represent sound epidemiology.

Lines 333-342:

"Overall, the proportion of mobile phone users in the second study seems to be unexpectedly low. It is noteworthy that the reported prevalence of mobile phone use had not increased much between the first and second Swedish study; the increase in the proportion of users among controls is at the most 6%. According to the Swedish Post and Telecom Agency, the number of mobile phone subscriptions divided by the total Swedish population size (including also age groups with no mobile phone use) increased from 28% to 71% between 1996 and 2000 (PTS, 2011). Although some persons may have had multiple subscriptions, these cannot explain the entire difference in the increase in proportion of users. In addition, the second study had no requirement on amount of use to be defined as a mobile phone user which the

first study had, reflected by the higher median hours of use in the first study compared to the second. Therefore, an even higher increase in the proportion of mobile phone users would have been expected."

Comment: The 2nd study included cases diagnosed during 1997 – June 30, 2000. Those exposed ≤ 1 year were considered to be unexposed (minimum latency period). Furthermore, they were aged 20-80 years. If we apply no latency period the following mobile phone use was reported in our study:

1997: 37 %
1998: 47 %
1999: 46 %
2000: 56 %

According to the Swedish PTS (2013) the frequency of subscription in the whole Swedish population was:

1997: 36 %
1998: 46 %
1999: 58 %
2000: 72 %

However, these numbers are not quite compatible. PTS calculates numbers in the whole population regardless of age, some persons may have several subscriptions, and company subscriptions are included. Note also that our study period ended June 30, 2000 whereas PTS includes the whole 2000. In summary these numbers are quite similar in contrast to what the WHO draft claims.

Lines 342-346:

A self-administered paper questionnaire has the disadvantage that it immediately reveals all questions to the participant, and with no clear definition of mobile phone use in terms of amount required, participants with small amounts of phone use may be more inclined to answer "no" when they see the complicated follow-up questions that need to be filled out after a "yes" answer."

Comment: This is a speculation without any scientific evidence and no reference is given.

Lines 362-364:

"[As results of matched analyses with the new exposure definition were not presented or discussed, there is no possibility to assess the impact on the results from resolving the matching.]"

Comment: In later studies we have shown results for both matched and unmatched analyses with similar results, see e.g. page 1843 in:

Hardell L, Carlberg M, Söderqvist F, Hansson Mild K. Case-control study of the association between malignant brain tumours diagnosed between 2007 and 2009 and mobile and cordless phone use. Int J Oncol. 2013;43:1833-1845.

"*In the unconditional logistic regression analysis, all controls, both to cases with malignant and benign brain tumours, were used so as to maximise the statistical power. Analysis using conditional logistic regression yielded overall for wireless phones OR=2.1, 95% CI=1.1-3.7 versus OR=1.7, 95% CI=1.04-2.8 using unconditional logistic regression, see Table III. Using unconditional logistic regression only with controls matched to the malignant cases yielded overall for wireless phones OR=2.0, 95% CI=1.1-3.5. Similar differences were seen for the different phone types i.e. slightly higher risk estimates using conditional logistic regression or unconditional logistic regression with matched controls, although with wider confidence intervals. The latter was due to the fact that only controls matched to malignant cases could be included and also because only discordant matched pairs are considered in a conditional logistic regression analysis. The considerably smaller material would limit the possibility of performing several of the subgroup analyses in this article using this method. Using unconditional logistic regression analysis was possible since adjustment was made for the matching variables of age, gender and year of diagnosis. In addition, adjustment was made for socio-economic index since an association between white-collar work and brain tumours has been reported."*

It should be noted that this issue was discussed among the experts in epidemiology at the IARC evaluation on RF-EMF exposure and human cancer risk in May 2011. It was concluded that as long as the matching variables were adjusted for it was scientific OK to use unconditional logistic regression analysis (L Hardell present). In summary the critique in the WHO draft is not valid.

Lines 447-451:

"The low prevalence of mobile phone use in the third study is surprising, especially when considering that no minimum amount of use was required; only 51% of the controls were mobile phone users (56% of cases). The Swedish Post and Telecom Agency (PTS) reported that 87% of a random sample of the Swedish population in the age range 16–75 years were mobile phone users in 2002, and 90% in 2003 (PTS, 2003)."

Comment: See above regarding PTS data. Furthermore, note the different age groups, 16-75 years in PTS survey and 20-80 years in our study. Few subjects aged 75-80 years use a mobile phone, see Table 10 in:

Hardell L, Carlberg M, Hansson-Mild K. Use of mobile phones and cordless phones is associated with increased risk for glioma and acoustic neuroma. Pathophysiology 2013;20:85-110.

The authors do not note that all use in 2003 was disregarded in our study (minimum latency period 1 year) and thus the frequency of mobile use in 2003 should not be discussed. The PTS survey had a low response rate, 60 %, and the distribution of the included ages is not presented. Table 10 in our study cited above gives an indication of the different use according to age group. In summary the comments in the WHO draft are speculative and not based on science.

Lines 523-524:

"The first handheld mobile phones were available on the market in Sweden from 1987"

Lines 534-535:

"[this category does not include any use of handheld phones]."

Line 565:

"[only bag phones and car phones],"

Lines 570-571 (etc):

"The highest ORs were observed for time periods when handheld mobile phones were not yet available on the market"

Comment: As clearly stated in the articles NMT was introduced in Sweden in 1981. Use of a mobile phone in a car with external antenna was disregarded as exposure as well as use of a hands free device. The first handheld mobile phone was demonstrated by Motorola in 1973. It was available for use in early 1980's.

Lines 577-581:

"In previous studies, the unexposed group was defined as "no wireless phone use", while the fourth study also included persons with in total ≤39 h of wireless phone use into the unexposed group (3rd percentile). The reason for choosing this particular cutpoint is unclear, as it does not correspond to a workweek in Sweden (which the authors claim), the legal working time in Sweden is 40 h/week, and it still leaves a very small unexposed group.

Comment: The authors of the draft have not grasped this. If $\leq$ 39 hours is unexposed then $\geq$ 40 hours is considered to be exposed. A working time in Sweden is 40 h/week as the authors state. So what is the problem?

Lines 581-582:

"Furthermore, results for the temporal lobe are not reported separately, only together with overlapping lobes, which is not how analyses have been performed in any previous study."

Comment: The importance of that comment in the draft is questionable. According to Table VIII in the cited article (Hardell et al 2013) most cases were located in the temporal lobe but we included also those cases extended to nearby lobes as clearly stated:

"Odds ratio (OR) and 95% confidence interval (CI) for malignant brain tumours located in temporal (n=161) and overlapping lobes [temporofrontal (n=31), temporoparietal (n=22), temporooccipital (n=13)]; in total n=227."

This seems to be a nonsense comment in the draft merely confusing the reader.

Lines 627-629:

"Adding users of cordless phones to the unexposed category lowered the risk estimates only marginally. Risk estimates for tumours in the temporal lobe were not higher than in other, less exposed areas of the brain."

Comment: All risk estimates were biased versus null with cordless phone use in the 'unexposed' group, see Tables 1 and 2 in the cited article. No separate analyses were performed for tumour locations other than the temporal lobe.

See:

Hardell L, Carlberg M, Hansson Mild K: Re-analysis of risk for glioma in relation to mobile telephone use: comparison with the results of the Interphone international case-control study. Int J Epidemiol 2011;40(4):1126-1128.

"We examined the results if we considered use of cordless phone as involving no exposure to microwaves, which yielded lower ORs indicating that excluding such use, as in Interphone, would also bias the risk towards unity.
Table 2 gives the results for glioma in the temporal lobe. Similarly, as for overall findings, risk estimates were lower in our studies when we restricted the age group to 30–59 years and considered use of cordless phone as no exposure."

Table, page 26:

"Participation rate among malignant brain tumour cases 45%, benign 81%, controls 85%."

Comment: The participation rate among the cases with malignant brain tumour was 87 %.

Different results according to type of malignancy/tumour in the Hardell group studies

Our group has performed case-control studies on several types of cancer and tumours using the same epidemiological methods. Interestingly the results differ for brain tumours, salivary gland tumours, malignant lymphoma, testicular cancer and melanoma in the head and neck region. It must be stressed that a systematic bias in the studies leading to spurious results would have been equal in the different studies performed during a similar time period.

Regarding brain tumours, including acoustic neuroma, a consistent result with increased risk was found for glioma and acoustic neuroma in contrast to meningioma. This finding is also in agreement with other studies. Interestingly these different tumour types were studied in the same case-control studies, but analysed separately. In fact meningioma cases were used as the reference group to both malignant brain tumours and acoustic neuroma yielding similar results as when using population based controls.

See page 1836 in:

Hardell L, Carlberg M, Söderqvist F, Hansson Mild K. Case-control study of the association between malignant brain tumours diagnosed between 2007 and 2009 and mobile and cordless phone use. Int J Oncol. 2013;43:1833-1845.

"In Table IV results are displayed when patients with meningioma in the same study are used as controls. The results were similar as in Table III using the population based controls. Most ORs were somewhat higher using meningioma cases as controls."

See page 1042 in:

Hardell L, Carlberg M, Söderqvist F, Hansson Mild K. Pooled analysis of case-control studies on acoustic neuroma diagnosed 1997-2003 and 2007-2009 and use of mobile and cordless phones. Int J Oncol. 2013;;43(4):1036-1044.

"To further validate exposure in the present study we used meningioma cases (n=1,624) as the referents to the acoustic neuroma cases (n=315). Similar results were found. Thus, wireless phone use gave in total (>1 year latency) OR = 1.4, 95% CI = 1.005-1.9, and in the latency group >20 years OR = 3.2, 95% CI = 1.5-6.8 with meningioma cases as referents. The corresponding results with population based controls were OR = 1.5, 95% CI = 1.1-2.0 and OR = 4.4, 95% CI = 2.2-9.0, respectively (Table I). These results clearly show that the results in this study can not be explained by recall or observational bias."

See page 7 in:

Hardell L, Carlberg M. Mobile phone and cordless phone use and the risk for glioma – Analysis of pooled case-control studies in Sweden, 1997–2003 and 2007–2009. Pathophysiology. 2014. doi: 0.1016/j.pathophys.2014.10.001.

"3.9. Using meningioma cases as referents

These case-control studies included all types of brain tumours reported to the Swedish cancer register, the majority of benign brain tumours being meningioma. In one analysis, meningioma cases (n = 1624) were used as the reference entity to glioma cases (n = 1379). Table 9 shows a statistically significant increased risk for glioma associated with ipsilateral use of all phone types. Ipsilateral mobile phone use gave OR = 1.4, 95% CI = 1.1–1.8, and ipsilateral cordless phone OR = 1.4, 95% CI = 1.1–1.9."

In summary these results using meningioma cases as the comparison group clearly indicate that the increased risk for glioma and acoustic neuroma cannot be caused by recall or observational bias. On the contrary these results strengthen a causal association between use of mobile and cordless phones and glioma and acoustic neuroma.

Survival of patients with glioma

Our study published in 2013 on survival of patients after glioma diagnosis in relation to use of wireless phones was excluded from the WHO draft for unclear reasons. That publication gives further biological relevance to the epidemiological findings of increased risk, see page 107 in:

Hardell L, Carlberg M. Use of mobile and cordless phones and survival of patients with glioma. Neuroepidemiology. 2013;40:101-108.

"Conclusion

This study showed elevated HR, indicating decreased survival of glioma cases with long-term and high cumulative use of wireless phones. The results differed according to WHO grade of astrocytoma: with an increased HR for astrocytoma WHO grade IV, a survival disadvantage. However, a decreased HR was found for astrocytoma WHO grade I-II, indicating a survival benefit in that group of cases. This could be caused by RF-EMF exposure leading to tumour promotion and earlier detection and surgery with better prognosis in that patient group. Further studies are needed to confirm these findings and to investigate cellular genetic profile alterations from RFEMF exposure."

See also conclusions pages 10803-10801 in:

Carlberg M, Hardell L. Decreased Survival of Glioma Patients with Astrocytoma Grade IV (Glioblastoma Multiforme) Associated with Long-Term Use of Mobile and Cordless Phones. Int. J. Environ. Res. Public Health 2014, 11, 10790-10805; oi:10.3390/ijerph111010790

"5. Conclusions

The study strengthens the proposed causal association between use of mobile and cordless phones and glioma [21]. Elevated HR (decreased survival) for the most malignant glioma type, astrocytoma grade IV, was found for long-term use of mobile and cordless phones. HR increased slightly for increasing cumulative use. Highest HR was found for cases with first use before the age of 20 years. These results indicate a survival disadvantage for use of wireless phones in that patient group. In contrast decreased HR (improved survival) was found for low-grade astrocytoma indicating survival benefit from wireless phone used. This may be explained by the fact that tumour volume was larger in exposed than in unexposed cases which would cause earlier detection and surgery. Surgery is a determinant for prognosis in this patient group. However, it should be noted that we have reported increased risk for both low-grade (grade I–II) and high-grade astrocytoma (grade III–IV) associated with use of mobile and cordless phones [22]."

To conclude these studies show an impact on survival of glioma cases related to exposure to RF-EMF emissions from mobile and cordless phones and must be included in the WHO report. These findings are certainly of biological relevance as to glioma risk.

Pooled results

Clearly the draft must include the results from our pooled publications on brain tumours. They should be properly discussed in the text and included in the Table. To exclude these important findings has no scientific justification but represents bad epidemiological practise. These studies are listed in the following:

Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of two case-control studies on use of cellular and cordless telephones and the risk for malignant brain tumours diagnosed in 1997-2003. International Archives of Occupational Environmental Health. 2006; 79: 630-639.

"Abstract Objectives: To study the use of cellular and cordless telephones and the risk for malignant brain tumours. Methods: Two case–control studies on malignant brain tumours diagnosed during 1997–2003 included answers from 905 (90%) cases and 2,162 (89%)

controls aged 20–80 years. We present pooled analysis of the results in the two studies. Results: Cumulative lifetime use for >2,000 h yielded for analogue cellular phones odds ratio (OR)=5.9, 95% confidence interval (CI)=2.5–14, digital cellular phones OR=3.7, 95% CI=1.7–7.7, and for cordless phones OR=2.3, 95% CI=1.5–3.6. Ipsilateral exposure increased the risk for malignant brain tumours; analogue OR=2.1, 95% CI=1.5–2.9, digital OR=1.8, 95% CI=1.4–2.4, and cordless OR=1.7, 95% CI=1.3–2.2. For high-grade astrocytoma using >10 year latency period analogue phones yielded OR=2.7, 95% CI=1.8–4.2, digital phones OR=3.8, 95% CI=1.8–8.1, and cordless phones OR=2.2, 95% CI=1.3–3.9. In the multivariate analysis all phone types increased the risk. Regarding digital phones OR=3.7, 95% CI=1.5–9.1 and cordless phones OR=2.1, 95% CI=0.97–4.6 were calculated for malignant brain tumours for subjects with first use <20 years of age, higher than in older persons. Conclusion: Increased risk was obtained for both cellular and cordless phones, highest in the group with >10 years latency period."

Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of two case-control studies on the use of cellular and cordless telephones and the risk for benign brain tumours diagnosed during 1997-2003. Int J Oncol 2006; 509-518.

"Abstract. *The use of cellular and cordless telephones and the risk of brain tumours is of concern since the brain is a high exposure area. We present the results of a pooled analysis of two case-control studies on benign brain tumours diagnosed during 1997-2003 including answers from 1,254 (88%) cases and 2,162 (89%) controls aged 20-80 years. For acoustic neuroma, the use of analogue cellular phones gave an odds ratio (OR) of 2.9 and a 95% confidence interval (CI) of 2.0-4.3; for digital cellular phones, OR=1.5; 95% CI=1.1-2.1; and for cordless telephones, OR=1.5, 95% CI=1.04-2.0. The highest OR was found for analogue phones with a latency period of >15 years; OR=3.8, 95% CI=1.4-10. Regarding meningioma, the results were as follows: for analogue phones, OR=1.3, 95% CI=0.99-1.7; for digital phones, OR=1.1, 95% CI=0.9-1.3; and for cordless phones, OR=1.1, 95% CI=0.9-1.4. In the multivariate analysis, a significantly increased risk of acoustic neuroma was found with the use of analogue phones."*

Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of case-control studies on malignant brain tumours and the use of mobile and cordless phones including living and deceased subjects. Int J Oncol 2011;38(5):1465-1474.

*"**Abstract.*** *We studied the association between use of mobile and cordless phones and malignant brain tumours. Pooled analysis was performed of two case-control studies on patients with malignant brain tumours diagnosed during 1997-2003 and matched controls alive at the time of study inclusion and one case-control study on deceased patients and controls diagnosed during the same time period. Cases and controls or relatives to deceased subjects were interviewed using a structured questionnaire. Replies were obtained for 1,251 (85%) cases and 2,438 (84%) controls. The risk increased with latency period and cumulative use in hours for both mobile and cordless phones. Highest risk was found for the most common type of glioma, astrocytoma, yielding in the >10 year latency group for mobile phone use odds ratio (OR) = 2.7, 95% confidence interval (CI) = 1.9-3.7 and cordless phone use OR = 1.8, 95% CI = 1.2-2.9. In a separate analysis, these phone types were independent risk factors for glioma. The risk for astrocytoma was highest in the group with first use of a wireless phone before the age of 20; mobile phone use OR = 4.9, 95% CI = 2.2-11, cordless phone use OR = 3.9, 95% CI = 1.7-8.7. In conclusion, an increased risk was found for glioma and use of mobile*

or cordless phone. The risk increased with latency time and cumulative use in hours and was highest in subjects with first use before the age of 20."

Hardell L, Carlberg M, Söderqvist F, Hansson Mild K. Pooled analysis of case-control studies on acoustic neuroma diagnosed 1997-2003 and 2007-2009 and use of mobile and cordless phones. Int J Oncol. 2013;;43(4):1036-1044.

*"**Abstract.** We previously conducted a case-control study of acoustic neuroma. Subjects of both genders aged 20-80 years, diagnosed during 1997-2003 in parts of Sweden, were included, and the results were published. We have since made a further study for the time period 2007-2009 including both men and women aged 18-75 years selected from throughout the country. These new results for acoustic neuroma have not been published to date. Similar methods were used for both study periods. In each, one population-based control, matched on gender and age (within five years), was identified from the Swedish Population Registry. Exposures were assessed by a self-administered questionnaire supplemented by a phone interview. Since the number of acoustic neuroma cases in the new study was low we now present pooled results from both study periods based on 316 participating cases and 3,530 controls. Unconditional logistic regression analysis was performed, adjusting for age, gender, year of diagnosis and socio-economic index (SEI). Use of mobile phones of the analogue type gave odds ratio (OR) = 2.9, 95% confidence interval (CI) = 2.0-4.3, increasing with >20 years latency (time since first exposure) to OR = 7.7, 95% CI = 2.8-21. Digital 2G mobile phone use gave OR = 1.5, 95% CI = 1.1-2.1, increasing with latency >15 years to an OR = 1.8, 95% CI = 0.8-4.2. The results for cordless phone use were OR = 1.5, 95% CI = 1.1-2.1, and, for latency of >20 years, OR = 6.5, 95% CI = 1.7-26. Digital type wireless phones (2G and 3G mobile phones and cordless phones) gave OR = 1.5, 95% CI = 1.1-2.0 increasing to OR = 8.1, 95% CI = 2.0-32 with latency >20 years. For total wireless phone use, the highest risk was calculated for the longest latency time >20 years: OR = 4.4, 95% CI = 2.2-9.0. Several of the calculations in the long latency category were based on low numbers of exposed cases. Ipsilateral use resulted in a higher risk than contralateral for both mobile and cordless phones. OR increased per 100 h cumulative use and per year of latency for mobile phones and cordless phones, though the increase was not statistically significant for cordless phones. The percentage tumour volume increased per year of latency and per 100 h of cumulative use, statistically significant for analogue phones. This study confirmed previous results demonstrating an association between mobile and cordless phone use and acoustic neuroma."*

Hardell L, Carlberg M. Mobile phone and cordless phone use and the risk for glioma – Analysis of pooled case-control studies in Sweden, 1997–2003 and 2007–2009. Pathophysiology. 2014. doi: 0.1016/j.pathophys.2014.10.001.

***"Abstract** We made a pooled analysis of two case-control studies on malignant brain tumours with patients diagnosed during 1997–2003 and2007–2009. They were aged 20–80 years and 18–75 years, respectively, at the time of diagnosis. Only cases with histopathological verification of the tumour were included. Population-based controls, matched on age and gender, were used. Exposures were assessed by questionnaire. The whole reference group was used in the unconditional regression analysis adjusted for gender, age, year of diagnosis, and socio-economic index. In total, 1498 (89%) cases and 3530 (87%) controls participated. Mobile phone use increased the risk of glioma, OR = 1.3, 95%CI = 1.1–1.6 overall, increasing to OR = 3.0, 95% CI = 1.7–5.2 in the >25 year latency group. Use of cordless phones increased the risk to OR = 1.4, 95% CI = 1.1–1.7, with highest risk in*

the >15–20 years latency group yielding OR = 1.7, 95% CI = 1.1–2.5. The OR increased statistically significant both per 100 h of cumulative use, and per year of latency for mobile and cordless phone use. Highest ORs overall were found for ipsilateral mobile or cordless phone use, OR = 1.8, 95% CI = 1.4–2.2 and OR = 1.7, 95% CI = 1.3–2.1, respectively. The highest risk was found for glioma in the temporal lobe. First use of mobile or cordless phone before the age of 20 gave higher OR for glioma than in later age groups."

Other publications to be included

Since this review process is on-going also recent important studies must be included as listed below:

Coureau G, Bouvier G, Lebailly P, et al. Mobile phone use and brain tumours in the CERENAT case-control study. Occup Environ Med. 2014;71(7):514-522.

"ABSTRACT
The carcinogenic effect of radiofrequency electromagnetic fields in humans remains controversial. However, it has been suggested that they could be involved in the aetiology of some types of brain tumours.
Objectives The objective was to analyse the association between mobile phone exposure and primary central nervous system tumours (gliomas and meningiomas) in adults.
Methods CERENAT is a multicenter case-control study carried out in four areas in France in 2004–2006. Data about mobile phone use were collected through a detailed questionnaire delivered in a face-to-face manner. Conditional logistic regression for matched sets was used to estimate adjusted ORs and 95% CIs.
Results A total of 253 gliomas, 194 meningiomas and 892 matched controls selected from the local electoral rolls were analysed. No association with brain tumours was observed when comparing regular mobile phone users with non-users (OR=1.24; 95% CI 0.86 to 1.77 for gliomas, OR=0.90; 95% CI 0.61 to 1.34 for meningiomas). However, the positive association was statistically significant in the heaviest users when considering life-long cumulative duration (≥896 h, OR=2.89; 95% CI 1.41 to 5.93 for gliomas; OR=2.57; 95% CI 1.02 to 6.44 for meningiomas) and number of calls for gliomas (≥18 360 calls, OR=2.10, 95% CI 1.03 to 4.31). Risks were higher for gliomas, temporal tumours, occupational and urban mobile phone use.
Conclusions These additional data support previous findings concerning a possible association between heavy mobile phone use and brain tumours."

Akhavan-Sigari R, Baf MMF, Ariabod V, Rohde V, Rahighi S. Connection between Cell Phone use, p53 Gene Expression in Different Zones of Glioblastoma Multiforme and Survival Prognoses. Rare Tumors 2014;6(3):5350. doi:10.4081/rt.2014.5350.

Abstract: *The aim of this paper is to investigate p53 gene expression in the central and peripheral zones of glioblastoma multiforme using a real-time reverse transcription polymerase chain reaction (RT-PCR) technique in patients who use cell phones ≥3 hours a day and determine its relationship to clinicopathological findings and overall survival. Sixty-three patients (38 males and 25 females), diagnosed with glioblastoma multiforme (GBM), underwent tumor resection between 2008 and 2011. Patient ages ranged from 25 to 88 years, with a mean age of 55. The levels of expression of p53 in the central and peripheral zone of the GBM were quantified by RT-PCR. Data on p53 gene expression from the central and*

peripheral zone, the related malignancy and the clinicopatholagical findings (age, gender, tumor location and size), as well as overall survival, were analyzed. Forty-one out of 63 patients (65%) with the highest level of cell phone use (≥3 hours/day) had higher mutant type p53 expression in the peripheral zone of the glioblastoma; the difference was statistically significant (P=0.034). Results from the present study on the use of mobile phones for ≥3 hours a day show a consistent pattern of increased risk for the mutant type of p53 gene expression in the peripheral zone of the glioblastoma, and that this increase was significantly correlated with shorter overall survival time. The risk was not higher for ipsilateral exposure. We found that the mutant type of p53 gene expression in the peripheral zone of the glioblastoma was increased in 65% of patients using cell phones ≥3 hours a day.

Hardell L, Carlberg M. Mobile phone and cordless phone use and the risk for glioma – Analysis of pooled case-control studies in Sweden, 1997–2003 and 2007–2009. Pathophysiology. 2014. doi: 0.1016/j.pathophys.2014.10.001.

Abstract: See above

Carlberg M, Hardell L. Decreased Survival of Glioma Patients with Astrocytoma Grade IV (Glioblastoma Multiforme) Associated with Long-Term Use of Mobile and Cordless Phones. Int. J. Environ. Res. Public Health 2014, 11, 10790-10805; oi:10.3390/ijerph111010790

Abstract: *On 31 May 2011 the WHO International Agency for Research on Cancer (IARC) categorised radiofrequency electromagnetic fields (RF-EMFs) from mobile phones, and from other devices that emit similar non-ionising electromagnetic fields, as a Group 2B, i.e., a "possible", human carcinogen. A causal association would be strengthened if it could be shown that the use of wireless phones has an impact on the survival of glioma patients. We analysed survival of 1678 glioma patients in our 1997–2003 and 2007–2009 case-control studies. Use of wireless phones in the >20 years latency group (time since first use) yielded an increased hazard ratio (HR) = 1.7, 95% confidence interval (CI) = 1.2–2.3 for glioma. For astrocytoma grade IV (glioblastoma multiforme; n = 926) mobile phone use yielded HR = 2.0, 95% CI = 1.4–2.9 and cordless phone use HR = 3.4, 95% CI = 1.04–11 in the same latency category. The hazard ratio for astrocytoma grade IV increased statistically significant per year of latency for wireless phones, HR = 1.020, 95% CI = 1.007–1.033, but not per 100 h cumulative use, HR = 1.002, 95% CI = 0.999–1.005. HR was not statistically significant increased for other types of glioma. Due to the relationship with survival the classification of IARC is strengthened and RF-EMF should be regarded as a human carcinogen requiring urgent revision of current exposure guidelines."*

Other studies to be considered in the draft

Myung SK, Ju W, McDonnell DD, et al. **Mobile phone use and risk of tumors: a meta-analysis. J Clin Oncol 2009;27(33):5565-5572.**

"Abstract

PURPOSE:

Case-control studies have reported inconsistent findings regarding the association between mobile phone use and tumor risk. We investigated these associations using a meta-analysis.

METHODS:

We searched MEDLINE (PubMed), EMBASE, and the Cochrane Library in August 2008. Two evaluators independently reviewed and selected articles based on predetermined selection criteria.

RESULTS:

Of 465 articles meeting our initial criteria, 23 case-control studies, which involved 37,916 participants (12,344 patient cases and 25,572 controls), were included in the final analyses. Compared with never or rarely having used a mobile phone, the odds ratio for overall use was 0.98 for malignant and benign tumors (95% CI, 0.89 to 1.07) in a random-effects meta-analysis of all 23 studies. However, a significant positive association (harmful effect) was observed in a random-effects meta-analysis of eight studies using blinding, whereas a significant negative association (protective effect) was observed in a fixed-effects meta-analysis of 15 studies not using blinding. Mobile phone use of 10 years or longer was associated with a risk of tumors in 13 studies reporting this association (odds ratio = 1.18; 95% CI, 1.04 to 1.34). Further, these findings were also observed in the subgroup analyses by methodologic quality of study. Blinding and methodologic quality of study were strongly associated with the research group.

CONCLUSION:

The current study found that there is possible evidence linking mobile phone use to an increased risk of tumors from a meta-analysis of low-biased case-control studies. Prospective cohort studies providing a higher level of evidence are needed."

Comment: Our investigations were considered to be low-biased case-control studies by this study group with no stated conflicts of interest. It should be noted that in contrast to the other discussed studies we assessed also use of cordless phones, a fact that was not considered in more detail in this study but is an important source of exposure to RF-EMF.

Aydin D, Feychting M, Schüz J, et al. Impact of random and systematic recall errors and selection bias in case--control studies on mobile phone use and brain tumors in adolescents (CEFALO study). Bioelectromagnetics 2011;32(5):396-407

"Abstract

Whether the use of mobile phones is a risk factor for brain tumors in adolescents is currently being studied. Case--control studies investigating this possible relationship are prone to recall error and selection bias. We assessed the potential impact of random and systematic recall error and selection bias on odds ratios (ORs) by performing simulations based on real data from an ongoing case--control study of mobile phones and brain tumor risk in children and adolescents (CEFALO study). Simulations were conducted for two mobile phone exposure categories: regular and heavy use. Our choice of levels of recall error was guided by a validation study that compared objective network operator data with the self-reported

amount of mobile phone use in CEFALO. In our validation study, cases overestimated their number of calls by 9% on average and controls by 34%. Cases also overestimated their duration of calls by 52% on average and controls by 163%. The participation rates in CEFALO were 83% for cases and 71% for controls. In a variety of scenarios, the combined impact of recall error and selection bias on the estimated ORs was complex. These simulations are useful for the interpretation of previous case-control studies on brain tumor and mobile phone use in adults as well as for the interpretation of future studies on adolescents."

Comment: It is remarkable that this study is omitted in the draft WHO although three references by Vrijhed et al on recall bias and selection bias regarding the Interphone study are included.

Aydin et al report that:

"*In our validation study, cases overestimated their number of calls by 9% on average and controls by 34%. Cases also overestimated their duration of calls by 52% on average and controls by 163%."*

Thus these results indicate that the increased risks in the so called CEFALO study (Aydin et al 2011) are valid.

Aydin D, Feychting M, Schüz J, et al. Predictors and overestimation of recalled mobile phone use among children and adolescents. Prog Biophys Mol Biol. 2011;107(3):356-361.

"Abstract

A growing body of literature addresses possible health effects of mobile phone use in children and adolescents by relying on the study participants' retrospective reconstruction of mobile phone use. In this study, we used data from the international case-control study CEFALO to compare self-reported with objectively operator-recorded mobile phone use. The aim of the study was to assess predictors of level of mobile phone use as well as factors that are associated with overestimating own mobile phone use. For cumulative number and duration of calls as well as for time since first subscription we calculated the ratio of self-reported to operator-recorded mobile phone use. We used multiple linear regression models to assess possible predictors of the average number and duration of calls per day and logistic regression models to assess possible predictors of overestimation. The cumulative number and duration of calls as well as the time since first subscription of mobile phones were overestimated on average by the study participants. Likelihood to overestimate number and duration of calls was not significantly different for controls compared to cases (OR=1.1, 95%-CI: 0.5 to 2.5 and OR=1.9, 95%-CI: 0.85 to 4.3, respectively). However, likelihood to overestimate was associated with other health related factors such as age and sex. As a consequence, such factors act as confounders in studies relying solely on self-reported mobile phone use and have to be considered in the analysis."

Comment: Also this study is not included in the WHO draft. Especially it should be noted that

"Likelihood to overestimate number and duration of calls was not significantly different for controls compared to cases (OR=1.1, 95%-CI: 0.5 to 2.5 and OR=1.9, 95%-CI: 0.85 to 4.3, respectively). However, likelihood to overestimate was associated with other health related factors such as age and sex. As a consequence, such factors act as confounders in studies relying solely on self-reported mobile phone use and have to be considered in the analysis."

It should be noted that we have adjusted for age and sex in all of our studies in addition to year of diagnosis (corresponding year for the matched control) and socioeconomic index. Furthermore all cases and controls were living in the same geographical area (same source population) making adjustment for geographical area not necessary.

Hardell L, Carlberg M. Using the Hill viewpoints from 1965 for evaluating strengths of evidence of the risk for brain tumors associated with use of mobile and cordless phones. Rev Environ Health 2013;28(2-3):97-106.

"Abstract
Background: *Wireless phones, i.e., mobile phones and cordless phones, emit radiofrequency electromagnetic fields (RF-EMF) when used. An increased risk of brain tumors is a major concern. The International Agency for Research on Cancer (IARC) at the World Health Organization (WHO) evaluated the carcinogenic effect to humans from RF-EMF in May 2011. It was concluded that RF-EMF is a group 2B, i.e., a "possible", human carcinogen. Bradford Hill gave a presidential address at the British Royal Society of Medicine in 1965 on the association or causation that provides a helpful framework for evaluation of the brain tumor risk from RF-EMF.*
Methods: *All nine issues on causation according to Hill were evaluated. Regarding wireless phones, only studies with long-term use were included. In addition, laboratory studies and data on the incidence of brain tumors were considered.*
Results: *The criteria on strength, consistency, specificity, temporality, and biologic gradient for evidence of increased risk for glioma and acoustic neuroma were fulfilled. Additional evidence came from plausibility and analogy based on laboratory studies. Regarding coherence, several studies show increasing incidence of brain tumors, especially in the most exposed area. Support for the experiment came from antioxidants that can alleviate the generation of reactive oxygen species involved in biologic effects, although a direct mechanism for brain tumor carcinogenesis has not been shown. In addition, the finding of no increased risk for brain tumors in subjects using the mobile phone only in a car with an external antenna is supportive evidence. Hill did not consider all the needed nine viewpoints to be essential requirements.*
Conclusion: *Based on the Hill criteria, glioma and acoustic neuroma should be considered to be caused by RF-EMF emissions from wireless phones and regarded as carcinogenic to humans, classifying it as group 1 according to the IARC classification. Current guidelines for exposure need to be urgently revised."*

Comment: To further evaluate strengths of evidence, Bradford Hill gave a presidential address at the British Royal Society of Medicine in 1965 that appeared afterward as an article in the Proceedings of the Royal Society of Medicine at the height of the tobacco and lung cancer controversy. That article on causation provides a helpful framework for assessing the brain tumour risk from wireless phones and offers some very insightful comments that are useful in this context. Based on Hill's viewpoints and his discussion on how these issues should be used, the conclusion of this review is that glioma and acoustic neuroma are caused by RF-EMF emissions from wireless phones. According to the IARC Preamble, the

classification should be group 1, i.e., “the agent is carcinogenic to humans”, and urgent revision of current guidelines for exposure is needed.

Söderqvist F, Carlberg M, Hansson Mild K, Hardell L. Childhood brain tumour risk and its association with wireless phones: a commentary. Environ Health. 2011;10(1):106.

Carlberg M, Hardell L. On the association between glioma, wireless phones, heredity and ionising radiation. Pathophysiology 2012; 19:243-252

Hardell L, Carlberg M, Hansson-Mild K. Use of mobile phones and cordless phones is associated with increased risk for glioma and acoustic neuroma. Pathophysiology 2013;20:85-110.

Comment: These studies should also be considered in the WHO draft.

Concluding remarks:

In conclusion the WHO draft is biased towards the null results. Findings on an association between use of wireless phones (mobile phones and cordless phones) and increased risk for brain tumours are misinterpreted, selectively reported and/or omitted in total. The draft cannot be used as science-based evaluation of increased risk. It needs to be re-written in a balanced way by scientists trained in epidemiology and oncology, not the least in medicine, and without conflicts of interest.

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