Japan EMF Information Center
Rapid Response Group

Professor Michael H. Repacholi *

Technical review March 2015

Paper: Tumor promotion by exposure to radiofrequency electromagnetic fields below exposure limits for humans. Alexander Lerchl, Melanie Klose, Karen Grote, Adalbert FX Wilhelm , Oliver Spathmann, Thomas Fiedler, Joachim Streckert, Volkert Hansen, Markus Clemens. Biochem Biophys Res Commun. Dx.doi.org/10.1016/j.bbrc.2015.02.151.

Introduction

Many animal studies have investigated the effects of long-term exposure to radiofrequency (RF) fields on the promotion of nervous system tumours and tumours in other systems, initiated by prenatal administration of the chemical carcinogen, ethylnitrosourea (ENU). The majority of these studies have reported negative results (AGNIR, 2012). Most studies were conducted to determine whether exposure to RF signals from mobile phones and bases stations could initiate or promote cancer, especially in the brain where most of the RF energy is absorbed when using a mobile phone. In contrast, a pilot study published by Tillmann et al. (2010) reported that long-term, daily exposure of mice to 1966 MHz UMTS RF signals at 5 W/kg (peak) following maternal injection with ENU was associated with an increased incidence of lung and liver tumours. However, there were suggestions that an infection in the mice during RF exposure could have influenced the final results. Given the potential importance of the Tillmann results, a replication of this study was recommended (e.g. SCENIHR, 2015).

Lerchl and colleagues recently published a replication of the Tillmann study, closely following their procedures, but using larger numbers of animals and two additional RF exposure levels. While these authors generally confirmed the Tillmann results, a dose-response was absent. The authors suggest that their finding may help to understand the reported increased incidence of brain tumours in heavy mobile phone users.

Methods

Pregnant mice were injected intraperitoneally with ENU at 40 mg/kg on day 14 of gestation and were continuously exposed to an RF field for 24 h/day from day 6 of gestation for 73 weeks, except for 30 min each night (presumably to shut down exposure system to facilitate cage cleaning and to allow recording of animals' body weights). Mice were exposed in 4 groups, each containing 96 animals, in cages of 3 mice each, using 8 radial waveguides to produce RF exposures at nominal whole-body specific energy absorption rates (SARs) of 0 (sham) 0.04, 0.4 or 2 W/kg. Another group of mice acted as cage controls. The effects of the RF field alone on mice were not investigated.

The frequency and other characteristics of the applied field were not explicitly stated although it can be assumed that the RF field characteristics were the same as in the Tillmann study (UMTS, 1966 MHz). When animals showed signs of disease or suffered a sudden drop in weight, the animals were removed from the experiment and examined for the number, size and morphology of any tumours in different tissues.

The study design is a major improvement over that used by Tillmann in that the Lerchl study used mice of both sexes, enough animals in each group to provide statistically significant results, mice

were tested for Helicobacter, and histopathological examinations were conducted on all key tissue samples.

Results

The results of tumour incidence are summarized as follows:

Lung tumours: Compared to mice given ENU and sham exposure, the incidence of benign bronchiolo-alveolar adenoma was significantly increased (2 fold) in all exposure groups. There was no evidence of a dose response. The incidence of malignant bronchiolo-alveolar carcinomas was significantly increased only in the animals exposed at 0.4 W/kg.

Liver tumours: The incidence of malignant hepatocellular carcinoma was significantly increased (2 fold) in all exposure groups. There was no evidence of a dose response.

Lymphoma: The incidence of lymphomas was significantly increased (2.5 fold) only in the group exposed at 0.4 W/kg: in other exposed groups, the increase was smaller and non-significant

Other tumours: Exposure had no significant effect on tumours in the brain, kidney or spleen.

Survival rate and body weight: Treatment with ENU reduced mouse survival rates, but survival was not affected by RF exposure. The body weights from exposed or sham exposed animals were only slightly different from the cage controls

Discussion

This study comes from a well-respected and very experienced team of scientists in Germany. The study was well designed and performed. The exposure system was well characterized but its main limitation is the poor uniformity of exposure; highly variable SARs occurred within each group of mice. While the authors attempted to reduce this variability by rotating cages, local SARs were calculated to be up to 3 to 5 times higher than the nominal SAR due to unavoidable variations in animal size and their movement in the cages resulting in a continuously changing orientation to the exposing RF field. Modern reverberation chambers provide much greater uniformity of RF exposures.

Generally, the Lerchl study results are consistent with those of the pilot study of Tillmann et al (2010): the incidences of both benign and malignant lung tumours in the Lerchl study following exposure was approximately half those reported by Tillmann; the incidence of malignant lung tumours was around 20 % higher and the incidence of benign lung tumours was about 20% lower. Tillmann also did not report any effect on malignant lymphoma in exposed mice, and differences of plus or minus 20-30% are also apparent in tumour incidence rates between the ENU-treated sham exposed groups in each study. This indicates the inherent variability in tumour incidence within the groups. A possible explanation for this is the high dose of ENU injected into the pregnant mice (40 mg/kg) where Adey et al 1999, Shirai et al 2005, Zook and Simmens 2006, used significantly smaller doses (usually 4 mg/kg) in larger rodents (rats). Injection of a 40 mg/kg ENU dose in smaller rodents could lead to ENU-induced tumour saturation that might mask effects on tumour incidence, as suggested by the higher tumour incidence in some RF-exposed groups regardless of the SAR.

Prenatal ENU transplacental treatment has been considered an ideal experimental model for the mutagenicity of brain tissue in transgenic mice (Slikker et al, 2004) and was used in previous studies investigating potential promoting effects of RF fields in rats (for example, Adey et al 1999, Shirai et al 2005, 2007; Zook and Simmens 2006). The absence of any increase in brain tumours in either the Tillmann or Lerchl study seems intriguing, but could be due to strain specificity, dosage

of ENU used or the time at which ENU was injected. However, this is an untested model for evaluating brain tumour incidence in mice since the IARC Working Group noted that this experimental model had not been used previously in other studies for hazard identification, and its concordance with the human carcinogenic response is unknown (IARC, 2013). Although very low incidences of brain tumours have been reported by Vesselinovitch et al (1977) using B6C3F1 mice, these came from a different genetic background to those used by Tillmann or Lerchl.

The lack of any apparent dose-response relationship is a concern for our understanding of the results. In this study the SAR of 0.4 W/kg generally increased the incidence of lung and liver tumours whereas the highest SAR never caused the greatest incidence in any tumour. Lerchl and colleagues suggested that heating produced by the RF exposure may have caused local thermal effects resulting in metabolic or blood flow changes in the mother and/or foetus that in turn produced changes in the biokinetics of the ENU. This seems unlikely since injected ENU has been reported to be cleared from the body of rodents in minutes (Dora Il'yasova et al. 2009). Further, if this thermal explanation were correct, it would suggest that the greatest effects should have been obtained using the highest SAR, and this was not seen. At present, no mechanistic explanation can be offered for these results.

Lerchl and colleagues suggest a connection between their results and the epidemiological studies reporting increased incidences of brain tumours in heavy users of mobile phones. Given that they did not find any increased brain tumour incidence in their study, support for their suggestion that "Our findings may help to understand the repeatedly reported increased incidences of brain tumours in heavy users of mobile phones" is weak and without any evidence from their own study. Further, the authors start their discussion with a sentence: "promoting effects at levels below the accepted exposure limits for humans is worrying". This is also without a scientific basis.

Conclusions

Lerchl et al (2015) have conducted a solid experimental study but with their only aim being to replicate the pilot study of Tillmann et al (2010). The Lerchl study both confirms and extends the results of the pilot study, which found that lifelong exposure to 1966 MHz UMTS signals had a tumour-promoting effect in the lungs and livers of mice following *in utero* treatment with ENU. However, the lack of a dose-response relationship is of concern, with no good explanation offered as to why whole-body exposure at 0.4 W/kg should have the most consistent effect on tumour promotion. Nonetheless, the study raises questions that could lead to a better understanding the carcinogenic potential of RF fields, and indicates a likely fruitful direction for future research in this area.

Overall, the most that one can take from the Lerchl study is that their results suggest the need for more focussed follow-up studies to clarify the scientific issues they raise.

References

AGNIR (2012). Doc HPA, RCE-20, Chilton, UK

Dora Il'yasova et al. (2009) J Toxicol Environ Health B Crit Rev. 2009 March ; 12(3): 175–187. doi:10.1080/10937400902894152.

IARC (2013) International Agency for Research on Cancer. Monograph 102. Radiofrequency Electromagnetic Fields. IARC, Lyon, France

SCENIHR (2015). http://ec.europa.eu/health/scientific_committees/index_en.htm

Slikker et al (2004). Toxicol Sci, 81, 112-120

Shirai et al (2005). Bioelectromagnetics, 26, 59-68.

Shirai et al (2007). Bioelectromagnetics, 28, 562-72.

Tillmann et al (2010). Int J Radiat Biol, 80, 529-541

Vesselinovitch et al (1977). Cancer Res. 37, 1822-1828

Zook and Simmens (2006). Radiat Res, 165, 608-15.

* Professor Michael H. Repacholi

- Department of Information Engineering, Electronics and Telecommunications, "La Sapienza" University of Rome, Italy.
- Former coordinator of the Radiation and Environmental Health Unit, World Health Organization (WHO) .