Health Effects

Studies on Tumor Incidence in Mice Exposed to GSM Cell-Phone Radiation

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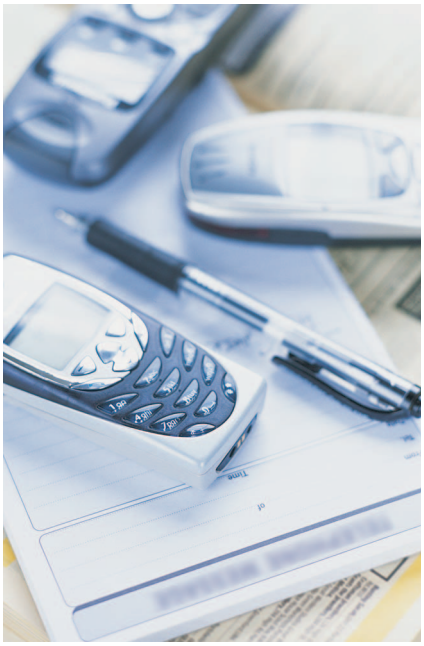
The first study of lymphomas in female Eμ_Pim1 transgenic mice using frequencies and modulations specific to cellular mobile phones was conducted in Australia in which the incidence was shown to be significantly higher (odds ratio, OR = 2.4) in the exposed mice (43%) than in the sham controls (22%) [8] following 18 months of two 30-min periods per day exposure to 900-MHz plane-wave radiation repeated at 217 Hz [signals that mimic global system for mobile communication (GSM) digital mobile phones].

Lymphomas are a type of cancer that affect the lymphatic system, which is part of the body's immune system. Specifically, the lymphatic system is the body's blood-filtering tissue that helps fight infection and disease (see [6] for more discussions on lymphomas). Follicular lymphomas were the major contributor to the increased tumor incidence. At the end of the entire experiment, 53% of the exposed mice had lymphomas, compared to 22% of the unexposed controls. The exposed transgenic mice also recorded a faster onset of lymphomas. In this study, 100 mice were sham-exposed and 101 were exposed for up to 18 months. The pulse width was 0.6 ms. The average incident power density and SAR were 2.6 to 13 W/m^2 and 0.13 to 1.4 W/kg, respectively. It should be noted that the Eμ-Pim1 transgenic mice were genetically engineered for a predisposition to lymphoma. Thus, the extrapolation of results found in a very sensitive animal model to possible carcinogenesis in humans is not well established.



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Moreover, this study suffered from two general types of identifiable deficiencies. One type was dosimetric in nature. Specifically, the plane-wave-equivalent exposure system used in this study allowed mice to roam and huddle freely during exposure to incident power densities of 2.6 to 13 W/m^2. Consequently, there was a wide variation of SARs (0.008 to 4.2 W/kg, averaging 0.13 to 1.4 W/kg). Only an average response could be inferred from an average SAR, not an individual SAR. Moreover, it is conceivable that the higher incidence of lymphomas was associated with the higher SAR instead of the reported average SAR. Further, mice selected for necropsy during the experiment were not replaced with either other mice or tissue-equivalent phantoms, thus altering dosimetry in the remaining animals. There are also some critical shortcomings concerning the biological assay, methods, and procedures. The study lacked any standardized assessment criteria for deciding which mice would be selected for necropsy, and surviving mice were disposed of without performing necropsy to ascertain whether there were infections and/or other relevant diseases, such as kidney failure, in those animals.

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Digital Object Identifier 10.1109/MMM.2008.919958

Apparently, cage control animals were not included as part of the experiment.

Subsequently, another study [9] was set up to test the same central hypothesis as that of the earlier study [8] but with refinements to overcome some of the perceived shortcomings. For example, the variation in SAR was reduced by restraining the mice and by using tissue-equivalent phantoms to replace autopsied mice. The new exposure system, supplied by Motorola, consisted of 15 lossy, radial, parallel-plate electromagnetic cavities (the Ferris wheel), configured for far-field operation. Each cavity had 40 mice restrained individually in clear Perplex tubes, cylindrically arranged around a dipole antenna. To facilitate SAR determination, the tubes were constructed to prevent each mouse from changing its orientation relative to the field. The exposed groups were divided into four SAR levels: 0.25, 1.0, 2.0, and 4.0 W/kg. A standardized set of criteria (10% reduction in body mass over a week) was used for selecting mice for necropsy, and all surviving animals were necropsied. A total of 120 lymphoma-prone, Eμ-Pim1 mice and 120 wild-type mice were exposed for 1 h/day, five days/week, at each of the four SAR levels, for up to 24 months. In addition, 120 Eμ-Pim1 and 120 wild-type mice were sham-exposed; there was also an unrestrained negative control group.

This paper concluded that the results of the double-blind study did not show an increase in lymphomas, following a two-year exposure to GSM cell-phone radiation [9]. Furthermore, there was no significant difference in the incidence of lymphomas between exposed and sham-exposed groups at any of the exposure levels (with one exception). A dose-response effect was not detected. The findings showed that long-term exposures of lymphoma-prone mice to 898.4 MHz (referred to as 900 MHz) GSM RF radiation at SARs of 0.25, 1.0, 2.0, and 4.0 W/kg had no significant effects when compared to sham-irradiated animals. This was in contrast to the previous study, which reported that long-term (18 months) exposure of lymphoma-prone mice significantly increased the incidence of nonlymphoblastic lymphomas when compared to sham-irradiated animals.

Because this study was designed to test the same central hypothesis as that of the earlier study [8] but with refinements to overcome some of the perceived shortcomings, the study deserves close examination.

To be sure, the latter was not a replication of the earlier study. A replication, as a standard practice of the scientific approach, requires that the same methods and materials are followed as in the earlier study. Given that there are major differences in materials and methods (beyond refinements), the design of the latter is more appropriately characterized as an attempt to confirm or refute, rather than replicate. More significantly, close examination of the source of mice, exposure regime, animal restraint, and the omission of data from analysis in the later study could lead to a different conclusion than that stated in the publication. It was stated in the paper that the mice were supplied from the same source used in the earlier study, and listed Taconic Farms, New York, as the source. However, mice for the earlier study came from GenPharm International of Mountainview, California. Thus, the Eμ-Pim1 mice appear not to be the same after all. Even the same strain of mice, from different suppliers, may have different characteristics and may respond differently, which is a factor to be considered further.

Mice in the later study were exposed to daily 1-h sessions, while those in the earlier study were exposed for two 30-min periods per day. The biological effect of fragmenting exposure duration is not well known. However, diurnal variations and the temporal dependence of physiologic, cellular, and molecular processes are well established. The use of free-roaming versus restrained animals by themselves is not a problem so long as the effects on these mice are characterized, with appropriate cage controls. Unfortunately, data for the cage-control mice were missing from the publication [9]. Restraining the animal in a tight tube during the exposure session constitutes a continuing stress to the animal, which may lead to significant stress responses that potentially could obscure any effect from the exposure to cell-phone radiation.

There are also some rather glaring inconsistencies in the published data. For example, some or all of the mice were dead after 18 or 20 months but had weight gains up to 26 months [9]. The study design included equal numbers of freely moving mice for negative controls (cage controls). However, data for the cage-control group were not given in the paper and appear to have been excluded from the statistical analyses. By not having the free-moving mice form a part of the statistical-analysis group, the report was deprived of the pathophysiology of cage-control mice for comparison. The cage controls can and should serve as valuable background materials, which potentially might be masked by stress response induced by the restraining tube used for sham control. It is noteworthy that the number of lymphomas among the sham controls (mice are restrained but not exposed) was abnormally high in this study. Specifically, among the transgenic mice, the incidence of lymphomas was 75% for the sham-control group (89 out of 120 mice developed lymphomas: 15 with lymphoblastic lymphomas, 74 with nonlymphoblastic lymphomas). In contrast, the incidence of lymphomas in the earlier study [8] was 22% for the sham-control mice (22 out of 100 mice developed the disease: three with lymphoblastic lymphomas, 19 with nonlymphoblastic lymphomas). The high degree of incidence in the sham controls (75% versus 22%) makes the experimental protocol impractical. It could have masked an effect from cell phones, or any other agent for that matter. It is unfeasible to come to any firm conclusions about lymphomas in transgenic mice exposed to cell-phone radiation. These flaws—possibly in the sourcing or handling of mice, the statistical analysis of the data, or in the fundamental design of the experiment—limit the conclusions that can be drawn for the outcome of the Utteridge et al. study [9], despite the paper's claim.

Utteridge et al. have published a response to several comments [2], [3], [5] on their original article [9]. Unfortunately, acceptability of results of the Utteridge et al. study has not been

enhanced and clear, unambiguous data and information remain elusive for an unequivocal interpretation of the Utteridge et al. study [4]. The need for other investigators to replicate or confirm these two studies [8], [9] and to help appraise the acceptability and reliability of the reported results persisted.

Later, a dosimetric evaluation of the Ferris-wheel exposure system used by Utteridge et al. [9] for exposure of the Eμ-Pim1 transgenic mice to RF energy at 898.4 MHz was reported by Faraone et al. [1]. Twin-well calorimetry was used to measure the whole-body SAR of exposed mice. One major conclusion was that since the average lifetime weight was slightly higher than originally projected (30 g), the lifetime exposure received by the mice was somewhat less than anticipated. In particular, the mean lifetime exposure levels were lower by about 18% than the original targets for the wild-type mice and about 10% for the transgenic mice. Specifically, the lifetime average whole-body SARs were 0.21, 0.86, 1.7, and 3.4 W/kg for the four exposure groups. Infrared thermography showed SAR peaks in the abdomen, neck, and head in thermograms taken over the sagittal plane of mouse cadavers. The peak local SAR (1 g) at these locations, determined by thermometric measurements, showed peak-to-average SAR ratios with typical values around 3:1, but some are close to 6:1. Thus, the average SARs were slightly lower than originally reported in [9].

The effect of chronic exposure to GSM-modulated 900-MHz fields and tumor development in mouse strains genetically predisposed to lymphoma development was the subject of a more recent publication [7]. This, too, was intended as a follow-up to the study by Repacholi et al. [8] with improvements in dosimetry and methodology. The exposure system consisted of four "Ferris wheels," and each wheel was composed of two parallel, circular, stainless-steel metal plates with a conical antenna in its center. Dosimetry was improved by restraining the mice in plastic tubes to obtain more uniform exposure. The incident field was adjusted as a function of body mass to obtain an age-independent exposure dose. Tissue-equivalent phantoms were used to replace necropsied mice to maintain a more consistent and symmetrical absorption profile. The study used identical RF signals as the previous study; i.e., animals were exposed to 217-Hz pulsed 900-MHz fields, but at average whole-body SARs of 0.5, 1.4, or 4.0 W/kg. In addition to whole-body, dosimetric information about organ and spatial-average-peak SARs as well as their life-time variations were reported. It is interesting to note that ratio of organ or tissue average SAR to the whole-body average SAR varied between 0.18 and 1.90. Moreover, the spatial peak SAR relative to the whole-body average SAR was as high as 62 and 85 for tissue mass of 5 mg and 0.5 mg, respectively.

At variance with Repacholi et al. [8] and Utteridge et al. [9], who used only female Eμ-Pim1 transgenic mice in their studies, this blinded study presented data on 500 female and male Eμ-Pim1 mice (250 females and 250 males purchased from Taconic Farms, New York). The mice were trained to the exposure system before exposure started. Fifty female and 50 male mice were randomly selected for exposure at each SAR level (0.5, 1.4 or 4.0 W/kg), for sham exposure, or as cage controls. The exposure was performed 1 h/day, seven days/week for 18 consecutive months. Necropsy was performed on-site both for animals that died and for those that survived up to termination of the study.

The results of this study showed a large gender difference in the overall incidence of lymphomas in these Eμ-Pim1 transgenic mice. The incidence in females is two to three times higher than in males. However, to compare results with the other two experiments, we will restrict our discussion to female mice. In females, incidence was 52% in cage controls, 44% in sham-exposed controls, 36% at 0.5 W/kg, 60% at 1.4 W/kg, and 40% at 4.0 W/kg. The results for malignant lymphoma (lymphoblastic and nonlymphoblastic) did not show any relationship to GSM-900 exposure. In females, the combined incidence of malignant lymphoma was 46.4% (116/250). Nonlymphoblastic lymphoma (mainly pleomorphic and follicular) was the prevailing type of lymphoma, similar to that of the Repacholi et al. [8] and Utteridge et al. [9] studies.

It was reported that for all tumors, there was no significant difference in the number of animals with tumors (incidence of tumors), regardless of malignancy. However, the number of mice with tumors was about 20% higher in the cage controls than in the sham or any of the exposed groups. The incidence of benign tumors in females did not show any significant differences among the various groups. However, the incidence was reduced by 34% at 4.0 W/kg for females.

At the end of the experiment, the incidence of lymphomas in decedents was 42% (cage controls), 41% (sham controls), 16.6% (0.5 W/kg), 37.5% (1.4 W/kg), and 37.5% (4.0 W/kg) in females. Thus, the data did not show any increase in lymphomas in the exposed animals. In females, the only significant finding on survival was a reduction in time to death at 0.5 W/kg ($P < 0.05$).

Oberto et al. [7] indicated that their study did not confirm the finding of a 2.0–2.4-fold increase in lymphomas by Repacholi et al. Indeed, they consider the finding by Repacholi et al. as incidental. Oberto et al. claimed that the culprit was the low tumor rates of the female Eμ-Pim1 transgenic mice used for sham controls. In the study by Repacholi et al., only 22% of the sham-control mice had lymphomas, whereas 44% of the sham-control female mice in their 18-month study had lymphomas.

Conclusions

While all three studies used Eμ_Pim1 transgenic female mice and GSM-900 RF fields, they may be characterized at best as attempts to confirm or refute, rather than replicate, the earlier study. First, the exposure systems and protocols were different. Mice were free roaming, not restrained, in a plane-wave exposure field for the initial study, but the Utteridge et al. and Oberto et al. studies used restrained animals in plastic tubes placed in radial waveguides for exposure. The tumor incidence varied among all three studies. Cage-control data are available only from the Oberto et al. study, which exhibited a tumor incidence of 52%. The reported incidences of lymphomas in the sham controls are 22%, 74%, and 44% for the Repacholi et al., Utteridge et al., and Oberto et al. studies, respectively. (Since sham-control mice in Repacholi et al. were free roaming, not restrained, it might be reasonably compared to the 52% in cage controls of Oberto et al.) Clearly, the incidence of lymphomas among the sham controls varied widely. Moreover, the restraining and sham exposure of mice are supposedly the same for the Utteridge et al. and Oberto et al. studies, but they presented totally different rates of tumor incidence, thus rendering a realistic comparison between and among these studies difficult, if not impossible. These flaws—possibly in the sourcing or handling of mice or in the fundamental design of the experiments—limit the conclusions that can be drawn.

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