DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
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May 19, 1999

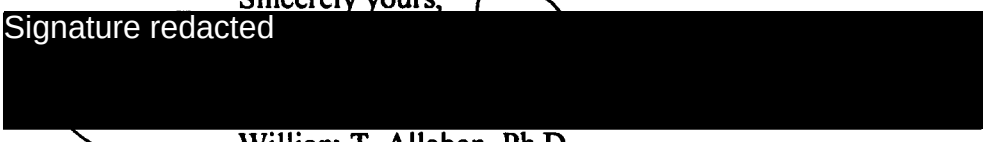
Dr. Errol Zeiger, Coordinator
Chemical Nomination and Selection
National Toxicology Program
National Institute for Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, NC 27709

Dear Dr. Zeiger:

On behalf of the Food and Drug Administration (FDA), I am nominating the following chemicals/agents to the National Toxicological Program: 1) *Center for Device and Radiological Health (CDRH)* – Radio Frequency Radiation Emissions of Wireless Communication Devices – with a high priority; 2) *Center for Biologics Evaluation and Research (CBER)* – DNA-based product safety assessment on select vaccines and/or therapeutic products – with a high priority; 3) *Center for Drug Evaluation and Research (CDER)* – a) genotoxicity and carcinogenicity testing of Cefuroxime, an oral cephalosporin antibiotic that has not been tested for carcinogenicity – with a high priority (also supported by Center for Veterinary Medicine (CVM); b) genotoxicity and carcinogenicity testing of Clarithromycin, a widely used macrolide antibiotic with no carcinogenicity study data – with a high priority; c) a study on chloral hydrate, an important hypnotic used in pediatric medicine, using the p53 hemizygous mouse model – with moderate priority; d) a p53 hemizygous Mouse Model study with Senna, and e) *Office of Orphan Product Development* – Alternative p53 and TG.AC cancer studies with the drug Pilocarpine.

Attached to this letter are brief overview documents for each chemical or agent.

Sincerely yours,



William T. Allaben, Ph.D.
FDA Liaison to the NTP

Attachments

cc: FDA Chemical Selection and Review Committee
Director, NCTR

Nominations from FDA's Center from Device and Radiological Health

Radio Frequency Radiation Emissions of Wireless Communication Devices (CDRH)

Executive Summary

Over 80 million Americans currently use wireless communications devices (e.g., cellular phones) with about 25 thousand new users daily. This translates into a potentially significant public health problem should the use of these devices even slightly increase the risk of adverse health effects. Currently cellular phones and other wireless communication devices are required to meet the radio frequency radiation (RFR) exposure guidelines of the Federal Communications Commission (FCC), which were most recently revised in August 1996. The existing exposure guidelines are based on protection from acute injury from thermal effects of RFR exposure, and may not be protective against any non-thermal effects of chronic exposures. Animal exposure research reported in the literature suggests that low level exposures may increase the risk of cancer by mechanisms yet to be elucidated, but the data is conflicting and most of this research was not conducted with actual cellular phone radiation. In one study transgenic mice exposed to a digital phone signal developed more than twice as many non-lymphoblastic lymphomas as the unexposed control group, a statistically significant increase. These results suggest a potential carcinogenic effect from the digital phone signal using this animal model. There is wide agreement within the international scientific community regarding the types of research needed to assess whether RFR from wireless communications poses a health risk to users. Research needs have been articulated by a number of groups, including the European Commission and the World Health Organization International EMF Project. Animal experiments are crucial because meaningful data will not be available from epidemiological studies for many years due to the long latency period between exposure to a carcinogen and the diagnosis of a tumor. Studies must also be performed in animals that are genetically predisposed to cancer and endpoints other than cancer, such as ocular damage and neurological effects, must also be examined. High priority must be given to replication of prior studies that indicate adverse effects, such as the transgenic mice model mentioned above. There is currently insufficient scientific basis for concluding either that wireless communication technologies are safe or that they pose a risk to millions of users. A significant research effort, involving large well-planned animal experiments is needed to provide the basis to assess the risk to human health of wireless communications devices.

A. Summary of Biological Effects - Wireless Telephone Radiation

As noted above, the use of wireless communications devices (e.g., cellular phones) is increasing rapidly. FDA concluded over five years ago that little was known about the possible health effects of repeated or long-term exposure to low levels of RFR of the types emitted by such devices. However, some scientific articles suggest a potential cancer risk may exist. While some other studies did not find evidence of carcinogenicity for RFR, data from long-term animal studies with a multi-dose exposure paradigm are unavailable. Properly conducted scientific research is needed to address these issues and

fill in the gaps in our understanding of the biological effects of exposure to RFR.

B. Physical Properties of Wireless Telephone Radiation

Personal (cellular) telecommunications is a rapidly evolving technology that uses microwave radiation to communicate between a fixed base station and a mobile user. Presently, most systems employ analog technology, where the low frequency speech signals are directly modulated on to a high frequency carrier in a manner similar to a frequency-modulated (FM) radio. The power level is effectively constant during the modulation, although some power control may occur. However, the recently introduced second-generation systems in Europe, USA and Japan employ digital technology, where the low frequency speech is digitally coded prior to modulation. There is a strong trend towards hand-held cellular telephones, which means that the radiating antenna is close to the head of the user. In the relatively near future the use of digital systems will predominate.

The electric and magnetic fields surrounding a cellular telephone handset near a person's head are complicated functions of the design and operating characteristics of the handset and its antenna and the electric and magnetic fields vary considerably from point to point.

Microwave radiation absorption occurs at the molecular, cellular, tissue and whole-body levels. The dominant factor for net energy absorption by an entire organism is related to the dielectric properties of bulk water, which ultimately causes transduction of electromagnetic energy into heat. For laboratory experiments, exposure conditions can be classified as thermal or non-thermal. There are no strict boundaries for these different exposure regimens because a number of factors may influence the characteristics of exposure. Thermal effects are well established and form the biological basis for restricting exposure to RF fields. In contrast, non-thermal effects are not well established and, currently, do not form a scientifically acceptable basis for restricting human exposure to microwave radiation at those frequencies used by hand-held cellular telephones. A large number of biological effects have been reported in cell cultures and in animals, often in response to exposure to relatively low-level fields, which are not well established but which may have health implications and are, hence, the subject of on-going research. It is not scientifically possible to guarantee those non-thermal levels of microwave radiation, which do not cause deleterious effects for relatively short exposures, will not cause long-term adverse health effects.

C. Human Exposure

For the purpose of radiation protection, dosimetric quantities are needed to estimate the absorbed energy and its distribution inside the body. A dosimetric quantity that is widely adopted for microwaves is the Specific Absorption Rate (SAR). SAR is defined as the time derivative of the incremental energy, absorbed by or dissipated in an incremental mass contained in a volume element of a given density. SAR is expressed in the unit watt per kilogram ($W\ kg^{-1}$). Numerical calculations, based upon coupling from handsets to an anatomically realistic numerical phantom of the head have been performed. Such

calculations have shown that, during normal operation, a radiated power of 1 W gives rise to a maximum SAR of 2.1 W kg^{-1} at 900 MHz and 3.0 W kg^{-1} at 1.8 GHz averaged over any 10 g of tissue. Typical handset powers are 0.6 W. To enable communication with locations not easily reachable with land networks, satellite communication systems have been recently designed and implemented. New systems will involve small portable units and hand-held sets similar to current cellular telephones. In these special cases, higher power classes can be envisioned.

Digital cellular telephones transmit information in bursts of power. The power is turned on and off, and the equipment transmits for a fraction of the time only and then is silent for the remaining part of the burst period. The basic repetition frequency is 217 Hz for GSM and DCS 1800 systems and 100 Hz for DECT; however, the spectrum also contains a number of higher harmonics due to the narrow pulse, so there are also frequencies in the kilohertz region. Owing to the complexity of these communications systems, there are also 2 and 8 Hz components in the signal, apart from multiples of 100 and 217 Hz.

D. Regulatory Status

As described previously, when tissues are exposed to microwave fields strong enough to raise the temperature, the resulting biological effects are said to be thermal. There is currently a general consensus in the scientific and standards community that the most significant parameter, in terms of biologically relevant effects of human exposure to RF electromagnetic fields, is the SAR in tissue. SAR values are of key importance when validating possible health hazards and in setting standards.

Possible thermal effects in the eye are also important. The latter is regarded as potentially sensitive to heating because of the limited cooling ability of the lens caused by the lack of a blood supply and the tendency to accumulate damage and cellular debris. Effects of electromagnetic radiation on the three major eye components essential for vision, the cornea, lens and retina, have been investigated, the largest number of studies being concerned with cataracts. It has been established that lens opacities can form after exposure to microwave radiation above 800 MHz; however, below about 10 GHz cataract induction requires long exposures at an incident power density exceeding 10^3 Wm^{-2}. SARs in the lens large enough to produce temperatures in the lens greater than 41 ^{o} C are required. Effects on the retina have been associated with levels of microwave radiation above 500 Wm^{-2}. All these data suggest that thermal effects will probably only occur in people subjected to whole body or localized heating sufficient to increase tissue temperatures by more than 1 ^{o}C. These various effects are well-established and form the biological basis for restricting exposure to RF fields. In contrast, non-thermal effects are not well-established and, currently, do not form a scientifically acceptable basis for restricting human exposure to microwave radiation at those frequencies used by handheld cellular telephones and base stations.

The setting of safety limits for human exposure to RF electromagnetic fields is currently performed in two steps. First, basic limits (or restrictions) for SARs inside the body are specified from biological considerations in terms of whole-body SAR and SAR averaged

over a small mass of tissue. Then relationships between SAR values and unperturbed field strengths are used to set derived limits (or reference or investigation levels) for field strengths and power density to be used in assessing compliance with the adopted standard. Studies to relate core temperature rise with whole-body averaged SARs (Elder and Cahill, 1984) suggested that the 1-4 W Kg^{-1} range is the threshold at which significant core temperature rise occurs. Another approach to identify thresholds of whole body thermal effects is based on the change in animal behavior exposed to RF fields. A review of animal data indicates a threshold for behavioral responses in the same 1-4 W kg^{-1} range. Another review of animal data also concluded that the threshold of RF exposure in terms of the whole body SAR is 4 W kg^{-1} (IEEE, 1991). Based on the estimated threshold and a safety factor of 10, the whole body averaged SAR of 0.4 W kg^{-1} has been widely accepted as the basic restriction for occupational exposures under controlled environmental conditions (IEEE, 1991). For the general public under uncontrolled environmental conditions, a five times smaller value of 0.08 W kg^{-1} has often been adopted as the basic restriction. In order to avoid excessive local exposures, maximum local SARs are limited as one of the basic restrictions in safety guidelines.

Basic restrictions for partial body exposure are given in terms of maximum local SARS. Local SAR values change spatially within the body depending on the depth of penetration, shape of the body part, and tissue homogeneity. It is therefore important to define the mass of tissue taken to evaluate average local body SARS. The limit values of local SARs have not been unified between various standards or guidelines. However, a local SAR limit of 8 W kg^{-1} averaged over a mass of 1g has also been adopted (IEEE, 1991).

Currently cellular phones and other wireless communication devices are required to meet the RFR exposure guidelines of the Federal Communications Commission (FCC), which were most recently revised in August 1996. Since the FCC is not a health agency, it sought and received guidance from the federal health agencies including the Environmental Protection Agency, the National Institute of Occupational Health and Safety, the Occupational Safety and Health Administration, and the FDA. These exposure guidelines incorporated the most recent exposure standards of the National Commission for Radiation Protection and the American National Standards Institute, and are subject to continuing review and revision as new scientific information which could define a better basis for such exposure guidelines becomes available. As noted above, the existing exposure guidelines are based entirely on protection from acute injury from thermal effects of RF exposure, and may not be protective against any non-thermal effects of chronic exposures.

E. Toxicological Data

The evidence for a clastogenic (chromosome breaking) or genetic effect of microwave radiation exposure is contradictory and, overall, it may be concluded that RF/microwave radiation is not genotoxic. Therefore, it may also be concluded that RF/microwave radiation is not a tumor initiator and that, if it is somehow related to carcinogenicity, this has to be by some other mechanism (e.g., by influencing tumor promotion). Tumor

promotion may be influenced by increases in cell proliferation rate via effects mediated through changes in proliferative signaling pathways, leading to enhanced transcription and DNA synthesis.

According to a series of papers, low level, low frequency, amplitude-modulated microwave radiation may affect intracellular activities of enzymes involved in neoplastic promotion without measurable influence on overall DNA synthesis. For example, a number of investigations showed some evidence of an effect on intracellular levels of ornithine decarboxylase (ODC) an enzyme implicated in tumor promotion. Tumor promoters increase ODC synthesis. Where such effects have been observed with microwave exposure, they have been much weaker and have occurred only for certain modulations of the carrier wave.

Assays of cell transformation were performed in order to detect changes consistent with carcinogenesis. For example, Balcer-Kubiczek and Harrison (1991) exposed cells to 120 Hz modulated microwave radiation followed by treatment with a phorbol ester tumor promoter. Cell transformation was induced in a dose-dependent way (increase with increasing SAR value). Overall, these results are in agreement with those from earlier studies, although there are also some inconsistencies. To date, the significance of these results is not clear in terms of *in vivo* carcinogenesis.

Along with investigations carried out *in vitro,* a number of *in vivo* investigations have also been performed. Of particular interest is, for example, the study conducted by Szmigielski et al (1983), who observed faster development of benzo(a)pyrene-induced skin tumors in mice that were exposed for some months to sub-thermal 2450 MHz microwave radiation.

Also of interest is a study where 100 rats were exposed from 2 to 27 months of age to pulsed microwave radiation (0.4 W kg^{-1}) (Guy et al, 1985). The exposed group had a significant increase in primary malignant lesions compared with the control group when lesions were pooled regardless of their location in the body, but no single type of malignant tumor was enhanced. Overall the incidence of primary malignancies was similar to that reported elsewhere in rats of this type. If the incidence of primary malignant lesions was pooled without regard to site or cause of death, however, the exposed group had a significantly higher incidence compared with the control group. Also, primary malignancies occurred early in the exposed group compared with the sham exposed group. While interesting, these data do not provide clear evidence of an increase in tumor incidence as result of microwave exposure. The incidence of benign tumors did not appear enhanced in the exposed group compared with the controls, nor was any particular type of neoplasm in the exposed group significantly elevated compared with the values reported in stock rats of this strain. Yet, overall, there was no clear evidence of an increase in tumor incidence as a result of exposure to microwave radiation.

In another study, the effects of exposure to electromagnetic fields were investigated in a rat brain glioma model. The exposure consisted of 915 MHz microwave radiation, both as continuous wave and ELF-modulated radiation (Salford, *et al*, 1993). The extensive

daily exposure did not cause tumor promotion. However, the experimental model has sometimes been questioned as the experimental animals had a high rate of spontaneous tumors. In another investigation in which cancer cells (B 16 melanoma) were injected into animals, a lack of effect of exposure to continuous wave and pulsed RFR on tumor progression was observed (Santini et al, 1988). Overall, evidence for a co-carcinogenic effect of microwave radiation on tumor progression is not substantiated. The few positive results which do exist are, however, sufficiently indicative to merit further investigation.

Repacholi et al (Repacholi, et al 1997) using Pim-l transgenic mice that are moderately predisposed to develop lymphoma spontaneously, conducted a more recent study of the co-carcinogenic potential of RFR. One hundred mice were exposed for two thirty-minute periods per day for up to 18 months to 900 MHz RFR with modulation characteristics and SAR similar to those of some wireless telephones. The mice exposed to RFR developed over twice as many lymphomas as the sham-exposed group of mice. A study of 50 Hz magnetic fields in these same transgenic mice conducted by the same investigators (Repacholi et al, 1998) did not result in greater numbers of lymphomas in the exposed mice, suggesting that the earlier positive result in RFR exposed mice is unlikely to be artifactual.

There is wide agreement within the international scientific community regarding the types of research needed to assess whether RFR from wireless communications poses a health risk to users. Research needs have been articulated by a number of groups, including the European Commission and the World Health Organization International EMF Project. Animal experiments are crucial because meaningful data will not be available from epidemiological studies for many years due to the long latency period between exposure to a carcinogen and the diagnosis of a tumor. Studies must also be performed in animals that are genetically predisposed to cancer and endpoints other than cancer, such as ocular damage and neurological effects, must also be examined. High priority must be given to replication of prior studies that indicate adverse effects, such as the transgenic mice model mentioned above. These research needs are similar to those identified by the *VVEO* EMF Project.

There is currently insufficient scientific basis for concluding either that wireless communication technologies are safe or that they pose a risk to millions of users. A significant research effort, including well-planned animal experiments, is needed to provide the basis to assess the risk to human health of wireless communications devices.

F. References

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