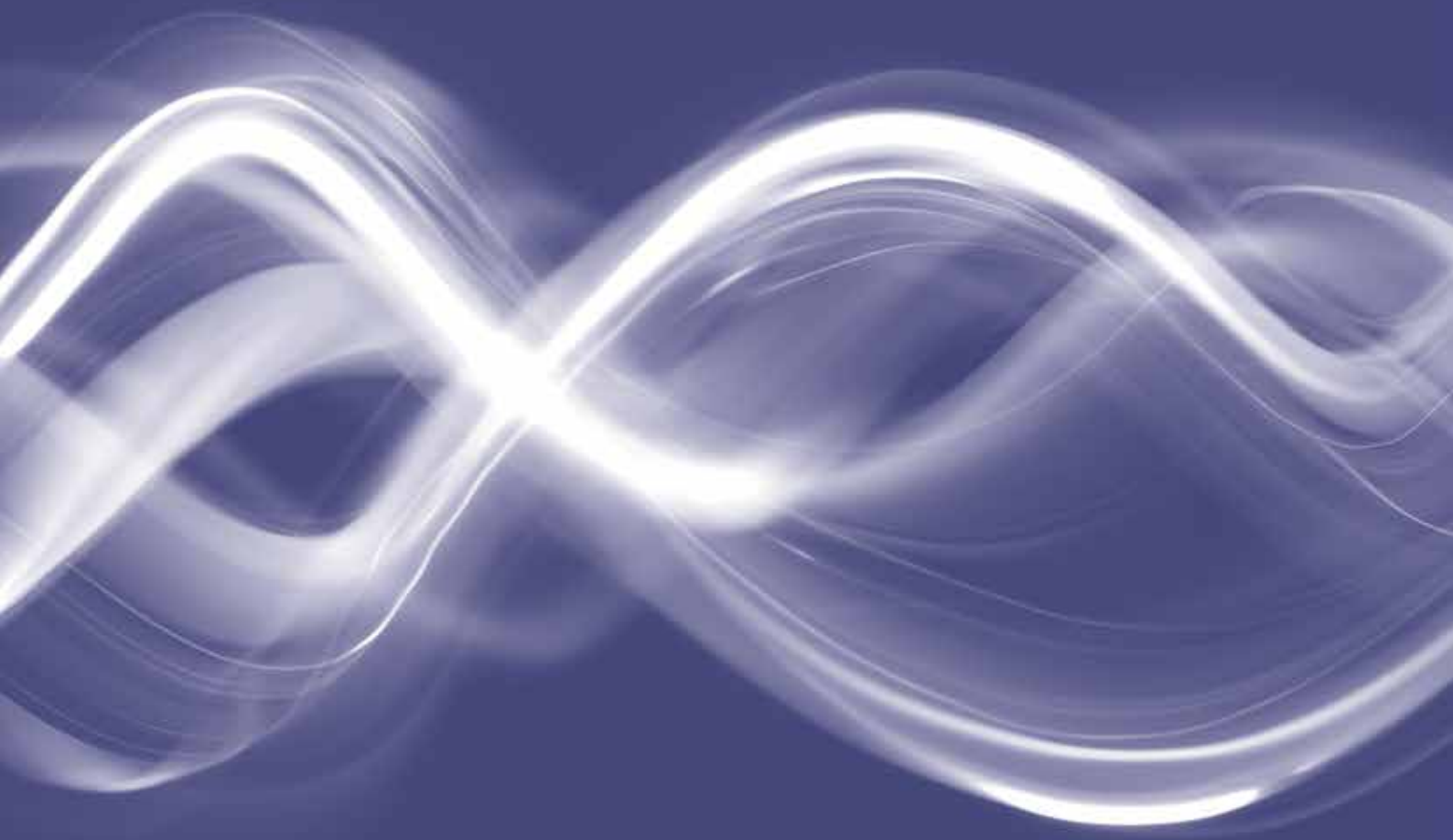
Summary of the International Agency for Research on Cancer (IARC) Monograph

Volume 102: Radiofrequency Electromagnetic Fields
Conclusions of the IARC Working Group Meeting
May 2011



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For further information about the content of this document please contact
Dr Jack Rowley
Senior Director Research & Sustainability
jrowley@gsma.com.

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Executive Summary

The International Agency for Research on Cancer (IARC) Monograph[1] (volume 102) for Radiofrequency Electromagnetic Fields (RF-EMF) was published in April 2013. It represents the views and expert opinions of an IARC Working Group (IARC WG) which met in Lyon during May 2011 to evaluate the carcinogenic hazard of RF-EMF to humans.

Although the Monograph is of significant importance to on-going debates about possible health risks, its considerable length (470 pages) has hindered proper and widespread understanding of it. This report is therefore provided by the GSMA as a short factual summary that highlights the major contents of the Monograph that would be informative to GSMA members, industry and other stakeholders. To help ensure a faithful representation of the IARC WG's views, this report draws extensively from summaries provided within the Monograph itself, with the addition of references and observations from the main text, and further précis.

The Monograph is divided into standard sections which are addressed in this report: Exposure Data; Cancer in Humans; Cancer in Experimental Animals; Other Relevant Data; Evaluation. These sections provide useful pointers on how the IARC WG made its assessments and where it sees further research would help resolve questions about RF-EMF cancer risk.

The most influential studies for the IARC WG were the INTERPHONE and Swedish (Hardell et al) epidemiological investigations on brain cancer associations with wireless phone use (mobile and cordless). Despite some misgivings on methodologies, suggestions of positive associations with glioma and acoustic neuromas in long term heavy wireless phone users led the IARC WG to conclude that there is *limited evidence* in humans for the carcinogenicity of RF-EMF. In respect of environmental exposures the IARC WG concluded that the available evidence was insufficient for any conclusion.

The IARC WG also concluded that there was *limited evidence* from experimental animal studies for the carcinogenicity of RF-EMF. The main area identified for positive effects were co-carcinogenesis studies in rodents.

The IARC WG expressed concern or interest for a number of study areas addressed in the 'Other Relevant Data' section. These included: genotoxic effects in human non-lymphocytic cells; oxidative stress in human cells; blood-brain barrier effects; and ODC activity in human and animal cells. However, it considered that the overall evidence was weak for oxidative stress in brain tissue and neural function effects arising from low level (athermal) RF-EMF exposures.

Despite acknowledging physical arguments to the contrary, the IARC WG expressed a belief that it is likely that not all mechanisms of interaction between weak RF-EMF (with the various signal modulations used in wireless communications) and biological structures have been discovered or fully characterized. It particularly made repeated reference to the possibility that reactive oxygen species might be induced by RF-EMF.

The overall assessment of the IARC WG was that RF-EMF be classified as 2B: possibly carcinogenic to humans.

It is important to place this assessment within context. Firstly, the IARC Monographs are

1. Henceforth 'the Monograph' refers to the IARC monograph on Radiofrequency Electromagnetic Fields

an exercise in evaluating cancer *hazards*, not cancer *risk*. Thus IARC evaluations assess if the agent can be carcinogenic under *any* circumstances, but not necessarily for all or even most exposure scenarios. Secondly, the IARC do not make any recommendations on regulation or legislation arising from their assessment, recognising that this is best left to individual governments or international organisations who weigh other factors such as socioeconomic considerations and national priorities. Lastly, the IARC WG 2B evaluation was not unanimous. A dissenting minority opinion found that current evidence in humans was inadequate, therefore permitting no conclusion about a causal association between RF-EMF and cancer.

TABLE OF ABBREVIATIONS

AMPS	Advanced Mobile Phone Technology, an analog mobile phone technology
CDMA	Code Division Multiple Access
D-AMPS	Digital AMPS, a 2G mobile phone technology
DNA	Deoxyribonucleic Acid, genetic material
DECT	Digital Enhanced Cordless Telecommunications, a cordless phone technology
EMF	Electro-Magnetic Field
ENU	Ethyl-nitrosourea
kHz	kilohertz, a unit of frequency equal to 1,000 Hz
GHz	gigahertz, a unit of frequency equal to 1,000,000,000 Hz
GSM	Global System for Mobile communications, a 2G mobile phone technology
IARC	International Agency for Research on Cancer
LTE	Long Term Evolution, a 4G mobile phone technology
MAPK	Mitogen-activated protein kinase
NMT	Nordic Mobile Telephony, an analog mobile phone technology
NTT	Nippon Telegraph and Telephone, an analog mobile phone technology
ODC	Ornithine decarboxylase
PDC	Personal Digital Cellular, a 2G mobile phone technology
RF	Radio-Frequency
SAR	Specific Absorption Rate, a measure of RF tissue heating in W/kg
SMR	Standardised Mortality Rate
TACS	Total Access Communications Technology, an analog mobile phone technology
WHO	World Health Organization
WiMAX	Worldwide Interoperability for Microwave Access
WG	Working Group for the IARC Monograph
WLAN	Wireless Local Area Network

Monograph Process

The IARC Monograph on RF-EMF (Vol. 102) [1] is the product of an IARC program started in 1970 to provide government authorities with expert, independent, scientific opinion on environmental carcinogenesis. The Monographs represent the *first* step in carcinogen risk assessment, which involves examination of all relevant information to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans. The Monographs provide critical reviews of data on the carcinogenicity for the agent under review, evaluates these data in terms of human risk, and indicates where additional research efforts are needed.

IARC assembles and supports a separate IARC Working Group of international experts in carcinogenesis and related fields to develop each volume of the Monographs. The IARC WG for the RF-EMF evaluation consisted of 30 members from 14 countries, assisted by two invited specialists. Participants serve in their individual capacities as scientists and not as representatives of their government or any organization with which they are affiliated. All participants were asked to disclose pertinent research, employment, and financial interests, which are listed in the Monograph.

The IARC Monograph program has been supported since 1982 by the European Commission Directorate-General for Employment, Social Affairs and Equal Opportunities, and the U.S. National Cancer Institute, National Institute of Environmental Health Sciences, and Department of Health and Human Services. However, the contents of IARC volumes are solely the responsibility of the IARC WG and do not necessarily represent the official views of the supporting organizations. Although IARC provides the Monographs to assist national and international authorities in formulating public health policies on exposure to agents, it makes no recommendations with regard to regulation or legislation. IARC recognizes that public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities which must be weighed by individual governments or other international organizations.

It should also be understood that the IARC Monographs are an exercise in evaluating cancer *hazards,* not cancer *risk*. A cancer hazard is an agent that is capable of causing cancer under *some* circumstances, while a cancer risk is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. This distinction is important, as the Monographs identify cancer hazards even when risks are very low at current exposure levels, since new uses or unforeseen exposures might engender risks that are significantly higher.

The IARC WG for a Monograph reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. Those judged inadequate or irrelevant to the evaluation may be cited but not summarized. Mechanistic and other relevant data are also reviewed, where relevant, as well as exposure data. Generally, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed. Publically available government agency reports may also be considered and, occasionally, doctoral theses. Monographs are divided into standardised sections, which have been summarized in the following parts of this report.

Each Monograph provides a classification rating for its evaluation of the potential carcinogenicity of the agent to humans: Group 1 – is carcinogenic; Group 2A – probably carcinogenic; Group 2B – possibly carcinogenic; Group 3 – not classifiable; Group 4 – probably not carcinogenic. The reasoning for the evaluation is presented and discussed, including concise statements of the principal line(s) of argument that emerged, the conclusions of the IARC WG on the strength of the evidence for each group of studies, citations to pivotal studies, and an explanation of the reasoning of the IARC WG in weighing data and making evaluations. Differences of opinion are allowed within the IARC WG, and are noted if significant.

Exposure Data

The Monograph's section on *Exposure Data* explains the physical principles and terminology relating to sources, exposures and dosimetry for human exposures to radiofrequency electromagnetic fields (RF-EMF) and is a very useful primer for any person with an interest in this area. It also identifies critical aspects of exposure for consideration in the interpretation of biological and epidemiological studies cited in the Monograph.

The frequency range of RF-EMF is defined in the Monograph as extending from 30 kHz to 300 GHz. Ambient exposure to RF induces EMF and currents inside the body, which are noted as the cause of interactions with biological processes.

The specific energy absorption rate (SAR) is recognised as the most important indicator of internal dose and is expressed in units of watts per kg (W/kg). It provides a measure of RF power absorption (and heating) and is expressed as a whole body average (WBA SAR), or as a peak spatial value (psSAR) for a point or averaged over 1 or 10 gram (g) of tissue. The pattern of induced SAR is generally highly non-uniform and variable. The Monograph does not cover microdosimetry, that is, assessment of RF-EMF at subcellular resolution.

The main factors which influence the coupling of external RF-EMF into the body are identified as: a) properties of the exposure fields, such as frequency, polarization, intensity and direction of incidence; b) anatomical features of the exposed person, including height, posture, body mass index, shape of the head and associated structures such as the pinna; and c) dielectric properties of tissues. The highest doses generally occur for near field exposures when a person is in very close proximity to an RF source.

RF-EMF from natural sources arises mostly from "black body radiation" as described by Planck's Law. Natural RF-EMF emissions have a much broader frequency spectrum than those produced by man-made sources and it is necessary to define a bandwidth of interest when making comparisons. For a bandwidth of 1 MHz, man-made fields typically appear to be orders of magnitude stronger than natural ones, whereas if the entire bandwidth of up to 300 GHz of interest to the Monograph is chosen, natural fields may appear to be stronger than man-made ones at typical environmental levels.

Mobile base stations were noted as the main source of environmental exposure, followed by TV and radio broadcasting, though relative exposure levels can change markedly from place to place. Although it is commonly perceived that RF-EMF exposures are greatest

THE MONOGRAPH IDENTIFIES FOUR GENERAL CATEGORIES OF RF SOURCES THAT HUMANS ARE EXPOSED TO:

- **Natural sources,** for example: the sun, cosmos and earth
- **Environmental sources,** for example: mobile phone base stations, radio and television broadcasting
- **Occupational sources,** for example: high-frequency dielectric and induction heaters, broadcast antennas, high-power pulsed radars, and medical applications (MRI, diathermy)
- **Personal devices,** for example: mobile phones, cordless phones, Wi-Fi, Bluetooth, and amateur radios

when close to base stations, the Monograph observes that measurement studies have shown that distance is *not* a good proxy for exposure due to the considerable variability in characteristics of the antennas, and shielding and reflection of the waves. Environmental surveys have tended to rely on spot measurements during burst activity of sources. However, the Monograph considers that average measurements over time would be better.

Occupational sources are generally the most powerful of the man-made RF sources and typically generate the highest whole body doses. Again, spot measurements have been the norm, though cumulative assessments over working time would have been the Monograph's preferred option. However, it is recognised that this is not straightforward due to the many different types of RF sources that are usually present in a workplace.

The Monograph devotes a large part of the Exposure Data section to personal devices, particularly mobile and DECT cordless phones. This is for two reasons. Firstly, these devices generate relatively high RF-EMF doses in the brain and are used widely by the general public. At peak levels, these brain exposures are many orders of magnitude higher than those induced from environmental sources, such as base stations, though still within international safety limits. Secondly, the most robust and statistically powerful epidemiological studies on RF cancer associations have focussed on brain cancer incidence in mobile and cordless phone users.

While the number of mobile-phone subscriptions has been increasing rapidly around the world, changes in mobile systems technology have led to a trend of progressively lower SAR levels induced in the head from the phones during normal use. Mobile phones for the early analogue systems (AMPS, TACS, NTT, NMT) had the highest peak radiated powers (~600 mW), and the larger size of the handsets and antennas led to a wider, though more diffuse pattern of RF energy absorption in the head. Other factors which affect SAR distribution in the head include the phone's position relative to the head, the anatomy of the head, and how the hand holds the phone. The use of handsfree kits substantially reduces exposure. Analog mobile systems were progressively replaced by second generation (2G) digital networks (GSM, PDC, PCS, D-AMPS, CDMA) from the early 1990s to around 2000 and have lower peak radiated power (250 mW). They also feature power control and discontinuous transmission capabilities which can substantially reduce the phone's radiated power during normal use, depending on the quality of phone's radio link with the base station and the proportion of the user's talk time respectively. Most 2G systems employed a time division multiple access (TDMA) scheme which causes pulsed RF transmissions from the phone.

The third generation of mobile phones (3G), with comprehensive data services, became available in the early 2000s. These phones use spread spectrum code division multiple access (CDMA) technology and have highly efficient power control schemes. Relative to peak power levels, this reduces SAR in the brain by almost two orders of magnitude for average use, compared with a lesser 50 per cent average reduction for 2G GSM phones. The newer fourth generation (4G) devices (LTE, WiMax) likewise emit considerably lower average radiated power during normal use.

Cordless phones were considered in the Monograph as another important source of RF exposure to the head. Like the 2G GSM phones, the widely used digital DECT system emits pulsed RF transmissions, though at a lower average peak power (10 mW). Peak SAR levels in the brain from the use of DECT phones are around 5x lower than those measured for mobile phones. However for exposures during normal use, average brain SAR levels for DECT (and WLAN) cordless phones are higher than for CDMA, 3G and 4G mobile phones but less than 2G GSM phones.

When not in use during standby mode, the cordless phone base station continually emits 100 beacon pulses per second at a duty factor of 0.8 per cent, which can produce RF exposures in the home similar to levels received from mobile base stations.

Measures of mobile and cordless phone use for epidemiological studies have mostly relied on self-reporting. However, the Monograph notes that recent validation studies among adults and children have demonstrated that there can be considerable random and systematic errors in the reported number of calls, the duration of calls, and the side of head where the phone is held during use. This is particularly problematic for epidemiological studies of cancer in humans, where information is collected on phone use many years in the past.

The Monograph reviews various proposed mechanisms for inducing RF bioeffects and recognizes tissue heating as the most firmly established. It considers that temperature changes approaching 1°C are likely to affect several biological processes, and that temperature-sensitive molecular and physiological effects might occur with temperature rises of ≤ 0.1 °C. It notes numerous reports of specific biological effects from modulated RF-EMF, and considers that mechanistic studies will be needed to determine how effects that are reproducible might be occurring, for example: via the induction of reactive oxygen species, induction of ferromagnetic resonance, demodulation of pulsed RF signals, or alteration of ligand binding to hydrophobic sites in receptor proteins. Although the Monograph acknowledges arguments that RF-EMF cannot induce physiological effects at exposure intensities that do not cause an increase in tissue temperature, it nonetheless takes the view that it is likely that not all mechanisms of interaction between weak RF-EMF (with the various signal modulations used in wireless communications) and biological structures have been discovered or fully characterized.

The section concludes with reference to international RF safety guidelines from the ICNIRP and IEEE, noting that these are designed to provide protection against tissue heating and electrostimulation effects.

Cancer in Humans

This section of the Monograph reviewed epidemiological evidence for occupational and general public exposure to RF-EMF for a diverse range of study designs and RF sources. The IARC WG was selective in which studies were reviewed. It included studies that assessed RF-EMF exposures for RF sources or job titles that were specifically linked to RF exposure, but excluded those that used job titles only for classification, or source surrogates only, without specifically addressing RF-EMF exposure.

The main findings for studies are summarized in Tables but do not uniformly capture the results for all exposure metrics or all subgroups given in the original publications. Comments are provided on those findings with greatest relevance to the evaluation, for example: risk in the overall exposed group, patterns of increase in risk with increasing exposure, and changes in risk with duration of exposure or latency.

The study populations included people exposed in occupational settings, people exposed through sources in the general environment, for example, transmitter towers, and people exposed through use of wireless (mobile and cordless) telephones. It was considered that the most robust evidence was for mobile phones, the most extensively investigated exposure source.

Studies were reviewed with consideration to the possibility that observed associations reflect chance, bias, or confounding, rather than an underlying causal effect. It was observed that mobile phone cancer studies presented complex methodological challenges in the conduct of the research and in the analysis and interpretation of the findings.

Personal use of wireless telephones

(a) Glioma

Time-trend studies: The IARC WG reviewed several ecological studies of time trends in a wide range of countries comparing mobile phone use to brain cancer rates (including glioma) in the general population. Dramatic increases in mobile phone use were reported in all countries over relatively short periods within 1985 to the early 2000s, but were not matched by increases in brain tumour rates. Since most studies reviewed by the IARC WG examined time trends only before the early 2000s, long latency effects could not be excluded. However, the data was considered to argue against a promptly acting and powerful carcinogenic effect of mobile-phone use.

Danish cohort study: This was a large cohort study [2] [3] within the entire population of Denmark and included mobile-phone subscribers with a median of eight years of subscription. The study showed no excess risk of glioma, based on 257 exposed cases. The study was considered useful by the IARC WG, but limited by considerable misclassification in exposure assessment due to its reliance on subscription to a mobile-phone provider as a surrogate for mobile-phone use.

Early case–control studies: The IARC WG reviewed several case–control studies that were conducted during the early period of rising mobile phone use. Three of these studies used self-reported histories of mobile-phone use [4] [5] [6], while a Finnish study [7] made a link to mobile phone subscription records. The IARC WG considered that effect estimates from these studies were generally too imprecise to make them informative.

The INTERPHONE study: This was one of two studies to which the IARC WG attached high importance. It was a multicentre case–control study, comprising the largest investigation of mobile-phone use and brain tumours, including component studies of glioma, acoustic neuroma, and meningioma. The IARC WG primarily considered the pooled analyses published in 2010 [8] and 2011 [9], rather than the findings as reported by centre investigators or groups of investigators.

The pooled analysis of the INTERPHONE study on the risk of glioma in relation to use of mobile phones included 2,708 cases of glioma and 2,972 controls. Participation rates were 64 per cent among cases of glioma and 53 per cent among controls, with a wide variation in control participation rates among centres. For regular users, an overall reduced odds ratio (OR) was seen for glioma (OR, 0.81; 95 per cent confidence interval [CI], 0.70–0.94). This was also observed in most study centres. Odds ratios of below unity were also found for all categories of time since start of use and of cumulative number of calls. The reason for these low odds ratios has not been established but were considered to probably reflect selection bias, at least in part.

In terms of cumulative call time, all odds ratios were uniformly below unity for all deciles of exposure except for the highest decile (≥ 1,640 hours of cumulative call time). For this exposure group, the odds ratio for glioma was 1.40 (95 per cent CI, 1.03–1.89). Some other analyses of the same data also pointed to a possible association of mobile-phone use with risk of glioma, including the findings related to location of tumour (a higher odds ratio for tumours in the temporal lobe) and laterality of mobile-phone use (an apparently higher odds ratio in those who used a mobile phone on the same side of the head as the tumour).

In an attempt to remove the distortions that might have been generated by differential non-participation, an analysis was conducted with the lowest exposure decile as the reference; this showed a high odds ratio in the highest exposure decile. Recent reports presented findings based on methodological enhancements that derived dose indicators based on models applied to magnetic resonance imaging or computed tomography scans of the cases; these analyses in subsets of the INTERPHONE studies provide additional insights into the patterns of risk of glioma associated with mobile-phone use.
The IARC WG recognized several strengths of the INTERPHONE study, including its large sample size, the common core protocol, rapid case ascertainment, comprehensive data collection, and in-depth data analyses that included a wide variety of sensitivity and validation studies. However, the rather low participation rates may well have led to complicated and important patterns of selection bias.

In summary, the IARC WG found that the INTERPHONE study indicated no increased risk of glioma associated with having ever been a regular user of mobile phones. However, there were indications of an increased risk of glioma at the highest levels of cumulative call time, for ipsilateral exposures, and for tumours in the temporal lobe, but chance or bias may explain this increased risk.

Swedish Research Group (Hardell et al): These were the other studies which the IARC WG considered as having higher importance. In 2011, the Swedish investigators reported the findings of a pooled analysis of associations of mobile-phone and cordless-phone use and risk of glioma [10] for cases ascertained from 1997 through 2003 in two waves. Both cases and controls were selected by use of population registries. A sequential approach by self-administered questionnaire and interview was used to collect information on the exposures and covariates of interest, including the use of mobile and cordless phones.

The analysis included 1,148 cases with a diagnosis of glioma, and 2,438 controls. When mobile phone users were compared with

people who reported no use of mobile or cordless phones, or exposure > 1 year before the reference date, an increased odds ratio was estimated (OR, 1.3; 95 per cent CI, 1.1–1.6). The odds ratios increased progressively with increasing time since first mobile phone use, and with increasing cumulative call time for the ordered categories of exposure duration (1–1000, 1001–2000, and > 2000 hours) as follows: 1.2 (95 per cent CI, 0.98–1.4), 1.5 (95 per cent CI, 1.1–2.1), and 2.5 (95 per cent CI, 1.8–3.5), respectively. Ipsilateral (same side) use of the mobile phone was associated with higher risk. Further, there were similar findings in relation to the use of cordless phones.

The IARC WG noted several strengths of the study. It was the only study to assess exposure to cordless phones. By using registries for case ascertainment and population-based controls, and by achieving high response rates, the investigators minimized the potential for selection bias. However, the possibility of information bias cannot be excluded, and specific validation studies were not carried out in this population.

Comparison of the findings of INTERPHONE and the Swedish studies: The IARC WG compared the methods and findings of the two studies, drawing on comparisons made by the Swedish investigators published in 2008 and 2010. The data were collected in overlapping calendar periods (1997–2003 for Hardell et al., with separate analyses available for 2000–2003, and 2000–2004 for INTERPHONE) and had some shared design features, for example, collection of exposure information via a comprehensive set of questions.

The studies differ in their general design, a single population- based study in the case of Hardell et al. and a multicentre study based in case ascertainment through hospitals, although with backup case ascertainment through cancer registries and other sources. The INTERPHONE study was considered to be probably more affected by selection bias due to differential participation between cases and controls, while the findings of both studies are subject to information bias, probably comparable in directionality. The generally null findings in the two large case–control studies for meningioma speak against information bias providing a full explanation for the associations reported for glioma.

Overall: The IARC WG reviewed all the available evidence with regard to the use of wireless phones, including both mobile and cordless phones, and the risk of glioma. Time trends were considered, as were several early case–control studies and one cohort study. The evidence from these studies was considered less informative than the results of the INTERPHONE study and the Swedish case–control study. While both of these are susceptible to bias, the IARC WG concluded that these findings could not be dismissed as reflecting bias alone, and that a causal interpretation was possible.

(b) Acoustic neuroma

The IARC WG considered several early case–control studies and one cohort study from Denmark [11] which found no association. The major sources of evidence for acoustic neuroma were essentially the same as for glioma, as was the general pattern of findings, though the case numbers were substantially smaller. The Swedish study [12] provided positive results with estimates quite similar to those observed for glioma. The pattern of findings from the INTERPHONE study [9] also paralleled that for glioma, with a decreased risk overall and an indication of a possibly increased risk in the stratum with the longest cumulative call time. A case–case study in Japan published in 2011 [13] also found some evidence of an increased risk of acoustic neuroma associated with ipsilateral mobile-phone use.

In considering the evidence on acoustic neuroma, the IARC WG considered the same methodological concerns as for glioma, but concluded that bias was not sufficient to explain the positive findings, particularly those of the study from Sweden.

(c) Meningioma

For meningioma, the IARC WG found that the same two studies [9], [12] mentioned above for acoustic neuroma provided the key evidence. Overall, in each, the findings generally indicated no increase in risk.

(d) Leukaemia/lymphoma

The IARC WG reviewed results of four studies of mobile-phone use and leukaemia, including two cohort and two case–control studies. Two population-based case–control studies addressed lymphoma. The IARC WG found the evidence to be insufficient to reach a conclusion as to the potential association of mobile-phone use and either leukaemia or lymphoma.

(e) Other malignancies

The IARC WG found that evidence to date does not point to a causal association of mobile-phone use with the various additional malignancies addressed, including ocular or cutaneous melanoma, cancer of the testis, cancer of the breast, or tumours of the parotid gland. With the exception of cancer of the breast, all these malignancies had been investigated explicitly in one or more case–control studies. No increased risk was observed for the above-mentioned sites in the 2006 report of the cohort study of Danish mobile-phone subscribers [3].

Occupational exposure

(a) Tumours of the brain

While the association of RF-EMF exposure with cancer of the brain has been examined in a substantial number of studies, exposure misclassification and insufficient attention to possible confounding limit the interpretation of the findings. Thus, the IARC WG determined that there is no clear indication of an association of occupational exposure to RF-EMF with risk of cancer of the brain.

(b) Leukaemia/lymphoma

Seven cohort studies and one cross-sectional analysis examined the relationship between occupational exposure to RF-EMF and risk of lymphoma and leukaemia. Most studies were based on small numbers of cases and limited exposure assessments. Increased standardized mortality ratios (SMRs) were seen for lymphomas and some leukaemias in a study of radio amateurs in the USA [14], but there was no association with an exposure-level surrogate (licence class). A substantially increased risk was also seen among Belgian military personnel who had worked with moveable radar, based on 11 cases, but exposure to RF-EMF was not characterized individually and may have been confounded by ionizing radiation [15]. In addition, follow-up of the cohort was problematic.

The largest and most informative study was that of male United States navy veterans of the Korean War [16]. Increased relative risks for leukaemia (in particular, acute myeloid and acute non-lymphocytic leukaemia) were seen among subjects with the highest compared with the lowest exposure. The highest odds ratio was seen among technicians in aviation electronics, judged by the authors to be those with highest potential exposure. There was, however, no adjustment for potential confounders.

In summary, the IARC WG found that while there were weak suggestions of a possible increase in risk of leukaemia or lymphoma associated with occupational exposure to RF-EMF, the limited exposure assessment and possible confounding make these results difficult to interpret.

(c) Other malignancies

Studies of occupational groups with potential exposure to RF-EMF have addressed several additional types of malignancy including uveal melanoma, and

cancers of the testis, breast, lung, and skin. The IARC WG noted that these studies had methodological limitations and the results were inconsistent.

Environmental exposure

(a) Cancer of the brain

Ecological studies and case–control studies have been carried out to investigate potential associations of brain cancer with RF-EMF exposures from fixed transmitters. The IARC WG found that because these studies are generally limited by reliance on measures of geographical proximity to the antennas as an exposure surrogate, substantial exposure misclassification is unavoidable. Taken together, the ecological studies did not suggest to the IARC WG a positive association between RF exposures from fixed transmission sources and cancer of the brain.

There have been five case–control studies of environmental exposure to RF-EMF and risk of cancer of brain. Cohort studies have not been reported. In all of the case–control studies, exposure estimation was based on residential proximity to RF-transmitter antennas. Two of these studies used estimates of exposure based on recorded locations of subjects' residences relative to recorded locations of AM radio-transmitters [17] [18] or mobile-phone base-station antennas [19]. Neither found convincing indications of an increase in risk of brain cancer with increasing estimated exposure to RF-EMF.

A hospital-based study from France [20] depended on subjects' recall of the proximity of their residence to a mobile phone base station and found no evidence of an increased risk with closer proximity. However, the hospital-based controls may not represent exposure in the general population. The fourth study assessed proximity of subjects' beds to base stations of DECT cordless phones in the home. It found a weak and imprecise increase in risk of brain cancer associated with sleeping near a base station. Another study found high risks for brain, breast and other cancers associated with the place of residence where the highest power density from a nearby base-station antenna was measured, but the results were imprecise and based on only a few cases. Together, these studies provide no indication to the IARC WG that environmental exposure to RF-EMF increases the risk of brain tumours.

(b) Leukaemia/lymphoma

Ecological studies in which distance was taken as a proxy for exposure consistently showed a pattern of increased risk of adult and childhood leukaemia with closer proximity to the exposure source [21], while studies that used analytical designs and better exposure assessments showed no increased risk [23] [22]. In adults, the evidence of an association indicating increased risk was weak at most, and effect estimates were generally imprecise. There was no evidence of an increased risk of childhood leukaemia. Consequently, from the limited data available the IARC WG could draw no conclusions on the risk of leukaemia or lymphoma from environmental exposure to RF-EMF.

(c) Other malignancies

The IARC WG dismissed several small ecological studies on the correlation between all cancers and distance from mobile base stations [24] [25] [26] [27] as uninformative due to their low quality. The IARC WG's interpretation of five additional ecological studies regarding exposures from radio and TV broadcast towers [17] [18] [22] [23] and mobile phone relay stations [19] was limited by their small sample numbers and crude exposure classification. Overall, they found the evidence from these studies as uninformative.

Cancer in Experimental Animals

In this section of the Monograph, four classes of cancer bioassays in animals were reviewed and assessed by the IARC WG. These studies involved a variety of animal models, exposure metrics and durations of exposure.

Two year cancer bioassays

Seven two-year cancer bioassays of RF-EMF were reported, two in mice [28] and five in rats [29] [30] [31] [32] [33]. Six studies were performed to examine the effects of exposure to various mobile-phone RF signals, and one study involved exposure to pulsed RF-EMF. When compared with sham controls, no statistically significant increases in the incidence of benign or malignant neoplasms at any organ site were identified in animals exposed to mobile-phone RF-EMF in any study.

In the study with exposure to pulsed RF-EMF [29], an increased incidence of total malignant tumours (all sites combined) was observed in rats. However, the IARC WG considered this finding to be of limited biological significance since it resulted from pooling of non-significant changes in tumour incidence at several sites. Exposure to RF-EMF did not increase total tumour incidence in any of the other six studies that were evaluated.

The IARC WG concluded that the results of the two year cancer bioassays provided no evidence that long-term exposure to RF-EMF increases the incidence of any benign or malignant neoplasm in standard-bred mice or rats.

Transgenic and tumour prone animals

The IARC WG evaluated twelve studies that used four different tumour-prone animal models. Two of these studies demonstrated an increased incidence of tumours in animals exposed to RF-EMF.

The first study [34] with positive results demonstrated an increased incidence of lymphoma in *Eμ-Pim1*-transgenic mice exposed to GSM mobile-phone RF-EMF at 900 MHz. However, the IARC WG considered the complete lack of pathology data to be a major limitation in the design of this study, and two subsequent studies by other investigators [35] [36] using the same model system failed to confirm its finding.

In the second study with positive results [37], an increased incidence of tumours of the mammary gland was observed in C3H/HeA mice exposed to RF-EMF at 2450 MHz. This study also lacked histopathology and two later follow on studies [38] [39] did not confirm its finding, though were performed at lower levels of exposure.

The IARC WG concluded that studies in three tumour-prone animal models (the *Eμ-Pim1* mouse model of lymphoma, the AKR mouse model of lymphoma, and the *Patched1*$^{+/-}$ mouse model of brain cancer) do not support the hypothesis that the incidence of tumours in the brain or lymphoid tissue would increase as a result of exposure to RF-EMF.

Initiation-promotion studies in animal tissue models of tumorigenesis

The IARC WG evaluated 16 studies of initiation and promotion that were performed with animal models of tumorigenesis (cancer formation) in skin, mammary gland, brain, and lymphoid tissue.

None of the five studies in models of skin cancer and none of the six studies in models of brain cancer showed an association with exposure to RF-EMF. One of four studies with the model of mammary-gland tumour in Sprague-Dawley rats gave positive results [40]. The other three studies [41] [42] [43] – one with a nearly identical protocol [43] – did not show an association, although they used the same experimental model and the same conditions of exposure to RF-EMF. Likewise, the study with the model of lymphoma was negative.

The IARC WG concluded that the evidence from these studies of initiation and promotion failed to demonstrate a consistent pattern of enhancement of carcinogenesis by exposure to RF-EMF in any of the tissues studied.

Co-carcinogenesis studies

The IARC WG evaluated six co-carcinogenesis studies involving five different animal models. Four positive responses were reported. Two studies giving positive results, one in Wistar rats [44] continuously exposed to drinking-water containing MX – a by-product of water disinfection – and another study in pregnant B6C3F1 mice [45] given a single dose of ethyl-nitrosourea (ENU), involved exposures to mobile-phone RF-EMF at 900 and 1966 MHz, respectively. The IARC WG noted that the experimental models used in these studies had not been used previously in other hazard-identification studies and its relevance to human carcinogenic response is unknown.

The other two studies with positive results involved co-exposure of BALB/c mice to RF-EMF at 2450 MHz and benzo[a]pyrene [46] [47]. The IARC WG noted that the design and experimental data of these studies were poorly presented and difficult to interpret.

Despite the misgivings noted above, the IARC WG concluded that these studies did provide some additional evidence supporting the carcinogenicity of RF-EMF in experimental animals.

Other Relevant Data

This section of the Monograph reviewed data on mechanisms by which RF-EMF may cause or enhance carcinogenesis and was drawn from extensive and diverse data from human, animal, and in vitro studies. The IARC WG noted that many studies were confounded by significant increases in the temperature of the cells, leading to thermal effects that could not be dissociated from purported non-thermal RF-induced changes, and hence did not figure in the IARC WG's conclusions.

Genetic and related effects

Human: Most of the reviewed studies were of occupational exposure and the others evaluated mobile-phone users. The IARC WG noted substantial methodological flaws across this group of studies, such as: a) lack of consideration of potential confounders, for example tobacco, age, other occupational exposures; b) small subject numbers and sampling problems; c) failure to measure RF-EMF exposures; d) the use of small numbers of cells for evaluating genetic damage; e) failure to use proper controls while culturing cells; f) incomplete reporting and improper interpretation of results. Virtually all the large studies did not show an association with exposure to RF-EMF for any type of genetic damage.

Drosophila: A few studies in Drosophila (fruit flies) that addressed mutagenicity after exposure to RF-EMF gave negative results.

Mammalian: The IARC WG considered that approximately half of these studies, generally in rats and mice, had limitations related to exposure assessment, small sample sizes and exposures that either induced thermal effects or were so low as to be no challenge to the animals. The remaining satisfactory studies showed contradictory results.

Human lymphocyte in vitro: These comprised roughly half of the human in vitro studies. The IARC WG found that short-term, high-intensity exposures to RF-EMF resulted in consistently positive results for DNA damage, but felt that thermal effects were the likely cause. A large number of studies on DNA strand breaks and the studies on sister chromatid exchange generally gave negative results, as well as exposures to RF-EMF in the non-thermal range.

Human other in vitro: The IARC WG considered that positive results for other human non-lymphocyte cell types exposed to short-term, high-intensity exposures were likely due to thermal effects. There were acceptable reports showing both positive and negative results in the remaining studies with exposures in the non-thermal range. In addition, studies showing chromosomal abnormalities (aneuploidy and spindle disturbances) in human hamster hybrid AL cells [48] [49] [50] [51], and studies at low exposures showing DNA single-strand breaks [52] were of concern. The IARC WG felt that oxidative stress and production of reactive oxygen species induced by RF-EMF may explain these results.

Non-human in vitro: The remaining few studies that gave positive results for genetic damage at lower doses could not be replicated after multiple attempts in different laboratories, raising serious questions for the IARC WG regarding the original findings. A single study showing altered microtubule structures at low exposures [53] [54] was a concern for the IARC WG.

Overall: The IARC WG concluded that there was weak evidence that RF-EMF is genotoxic (alters DNA), but no evidence for its mutagenicity (increase in the frequency of mutations).

Reaction of the immune system

Human: The IARC WG reviewed several studies which assessed the effects of exposure to RF-EMF on indicators of immune function in humans. While some positive results were reported the IARC WG noted variability in the data and that many of these studies used small numbers of subjects and generally did not control for possible confounders.

Animal: The IARC WG found that numerous experimental studies in vivo clearly indicated that short-term and prolonged low level exposure to RF-EMF can shift the number and/or activity of immunocompetent[2] cells, though the direction of change was inconsistent between and within studies, and also appeared to change depending on duration of exposure. Thus, the relevance of these observations in relation to carcinogenicity was considered unclear.

In vitro: The effects of RF-EMF on various types of human lymphocytes in vitro were found to be variable and dependent on the mitotic state[3] of the cells and modulation of the exposure (pulsed or continuous wave). The IARC WG noted that weaknesses in the description of experimental procedures and dosimetry in many of the studies.

Overall: The IARC WG concluded that there was insufficient evidence to determine that alterations in immune function induced by exposure to RF-EMF affects carcinogenesis in humans.

Effects on genes, proteins and signalling pathways

Animal: The IARC WG reviewed nearly 30 studies investigating gene/protein changes in rodents exposed to RF-EMF. Many were found to be unreliable due to deficiencies in the exposure system or methodological shortcomings. The data from the remaining studies were limited and presented mixed results with no consistent pattern of response.

Human in vitro gene/protein expression/ activity: The majority of studies assessing effects of RF-EMF on expression and activity of heat-shock proteins reported no effect. Three studies found changes in mitogen-activated protein kinase (MAPK) signalling [55] [56] [57], while another did not [58]. No clear dose/ response trend was evident to the IARC WG.

Human in vitro genomics/proteomics: The IARC WG reviewed 16 studies using high-throughput genomics/proteomics. Many had serious methodological shortcomings related to poor exposure conditions, inadequate statistical analysis, and lack of validation of alternative approaches. The remaining data were limited with no consistent pattern of response, but some studies demonstrated changes in both gene and protein expression, for some proteins in some cell lines.

Overall: On the basis of the above considerations, the IARC WG concluded that data from studies of genes, proteins and changes in cellular signalling show weak evidence of effects from RF-EMF, but did not provide mechanistic information relevant to carcinogenesis in humans.

Other mechanistic end-points

With the exception of changes in cerebral blood flow, many of the mechanistic studies reviewed by the IARC WG provided conflicting, negative or very limited information, which made it difficult to draw conclusions, especially in relation to carcinogenesis.

Oxidative stress: The IARC WG reviewed animal studies which sought changes in biochemical markers for the production of reactive oxygen species[4] in multiple organs during in vivo exposure to RF-EMF. They found many of these

2. Capable of responding to external agent such as infection

studies were weakened by methodological shortcomings in design, such as absence of sham-exposed or cage-control groups, use of mobile phones as the exposure source, and lack of dosimetry.

With regard to in vitro studies on human cells, the IARC WG found one study showed a marginal effect, while other studies demonstrated an increase in activity with increasing exposures [59] [60] [61], though there were not enough studies to make a reasonable assessment of the consistency of these findings. Most in vitro studies on non-human cells did not find changes, though one study evaluated the formation of DNA adducts from reactive oxygen species and was able to demonstrate reversal of this effect by melatonin [62]. While the overall evidence was inconclusive, the IARC WG considered that results from in-vitro studies with animal models raise some concern.

Overall, the IARC WG concluded that there was weak evidence that exposure to RF-EMF affects oxidative stress and alters the levels of reactive oxygen species. The IARC WG also noted Adair's biophysics analysis [63] which concluded that any RF effect on free radical concentrations would likely be limited to about 10 MHz or less.

Blood-brain barrier: The IARC WG identified numerous studies assessing the function of the blood–brain barrier in rodents exposed to RF-EMF. Consistent results from one laboratory [64] [65] [66] suggested an increase in the permeability of the blood–brain barrier, but the majority of the studies, many of them attempted replications, failed to observe this effect for either continuous or pulsed RF-EMF. The evidence that exposure to RF-EMF alters the blood–brain barrier was considered weak but nonetheless important even though it cannot be directly related to carcinogenesis.

Apoptosis: A number of studies dealt with alterations induced by RF-EMF in cell differentiation or induction of apoptosis[5] in the brain or other organs. While most showed an association, the IARC WG was not convinced that they were of sufficient scientific rigour to assess apoptotic effects in these organs. An additional 14 studies focused on apoptosis in cultured human cells. Only two demonstrated an increase in apoptosis: one compared the results observed in treated cells with controls that were not subject to the same conditions as the exposed cells [67], while thermal effects may have had an impact in the other [68]. Finally, other in-vitro studies with non-human cells gave essentially negative results, with the exception of one study that demonstrated mixed results [69] [70]. The evidence that exposure to RF-EMF alters apoptosis was considered weak by the IARC WG.

Cellular replication: The IARC WG reviewed multiple in vitro studies testing proliferation of primary cells or established cell lines after exposure to various intensities and durations of RF-EMF. Many used small sample sizes and description of experimental details was lacking in several cases. Studies with positive results showed increases and decreases in cellular replication, and no consistent pattern could be discerned. The IARC WG concluded that evidence that RF-EMF alters cellular replication was weak.

Ornithine decarboxylase (ODC): ODC is an enzyme involved in the metabolism of polyamines, which are critical components of cellular replication and differentiation processes. The IARC WG noted that some in vitro studies of human and animal cells exposed to GSM900 and GSM1800 signals showed significantly increased ODC activity [71] [72] [73] [74], while one suggested it may be reduced [75]. They concluded there was moderate evidence that exposure to RF-EMF alters ODC activity, though it was unclear how these changes in activity relate to human cancer.

Overall: The evidence that exposure to RF-EMF at intensities below the level of thermal effects may produce oxidative stress in brain tissue and may affect neural functions was considered weak.

3. Stage in cycle of cell reproduction
4. High levels of reactive oxygen species may cause cell damage
5. The process of programmed cell death

Evaluation

The IARC WG summarized its evaluation of the carcinogenicity of RF-EMF as follows. The italicised text within the [ ] brackets are direct quotations from the Preamble to the IARC Monograph explaining the evaluation rationale.

Cancer in Humans

There is limited evidence in humans for the carcinogenicity of RF-EMF. Positive associations have been observed between exposure to RF-EMF from wireless phones and glioma, and acoustic neuroma. [*A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the IARC WG to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence*].

Cancer in Experimental Animals

There is *limited evidence* in experimental animals for the carcinogenicity of RF-EMF. [*The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs*].

Overall Evaluation

RF-EMF is possibly carcinogenic to humans (Group 2B).

Rationale of the evaluation of the epidemiological evidence

The human epidemiological evidence was mixed. Several small early case–control studies were considered to be largely uninformative. A large Danish cohort study showed no increase in risk of relevant tumours, but it lacked information on level of mobile-phone use and there were several potential sources of misclassification of exposure. The bulk of evidence came from reports of the INTERPHONE study, a very large international, multicentre case–control study and a separate large case–control study from Sweden (Hardell et al).

While affected by selection bias and information bias to varying degrees, these studies showed an association between glioma and acoustic neuroma and mobile-phone use; specifically in people with highest cumulative use of mobile phones, in people who had used mobile phones on the same side of the head as that on which their tumour developed, and in people whose tumour was in the temporal lobe of the brain (the area of the brain that is most exposed to RF radiation when a wireless phone is used at the ear). The Swedish study found similar results for cordless phones.

The comparative weakness of the associations in the INTERPHONE study and inconsistencies between its results and those of the Swedish study led to the evaluation of *limited evidence* for *glioma* and *acoustic neuroma,* as decided by the majority of the members of the Working Group. A small, recently published Japanese case–control study, which also observed an association of acoustic neuroma with mobile phone use, contributed to the evaluation of limited evidence for acoustic neuroma.

There was, however, a minority opinion that current evidence in humans was inadequate, therefore permitting no conclusion about a causal association. This minority saw inconsistency between the two case–control studies and a lack of exposure–response relationship in the INTERPHONE study. The minority also pointed to the fact that no increase in rates of glioma or acoustic neuroma was seen in a nationwide Danish cohort study, and that up to now, reported time trends in incidence rates of glioma have not shown a trend parallel to time trends in mobile-phone use.

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For further information please contact
health@gsma.com

GSMA Head Office
Level 7, 5 New Street Square, New Fetter Lane
London, EC4A 3BF, United Kingdom
Tel: +44 (0)207 356 0600

www.gsma.com/health