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5. SUMMARY OF DATA REPORTED

5.1 Exposure data

This Monograph is concerned with non-ionizing radiation in the radiofrequency (RF) range of the electromagnetic spectrum, i.e. between 30 kHz and 300 GHz. The corresponding wavelengths – the distance between successive peaks of the RF waves – range from 10 km to 1 mm, respectively. Human exposure to RF radiation can occur from many different sources and under a wide variety of circumstances, including the use of personal devices (mobile phones, cordless phones, Wi-Fi, Bluetooth, amateur radios, etc.), occupational sources (high-frequency dielectric and induction heaters, broadcast antennas, high-power pulsed radars, and medical applications), and environmental sources (mobile-phone base stations, broadcast antennae). These multiple sources contribute to an individual's total exposure, with contributions varying by different characteristics, e.g. place of residence. The dominant sources of human exposure to RF radiation are near-field sources for workers, and transmitters operating on or in close vicinity to the body, such as hand-held devices, for the general population.

Electromagnetic fields generated by RF sources couple with the human body, which results in induced electric and magnetic fields and associated currents inside body tissues. The most important factor that determines exposure is the distance of the transmitter from the human body, within the main radiation beam. In a first approximation, the induced field strength is proportional to the time-averaged radiated power and inversely proportional to the distance from the source. In addition to distance, the efficiency of coupling and the resulting field distribution inside the body strongly depend on properties of the fields, such as frequency, polarization, distance from the antenna and direction of incidence, and on anatomical features of the exposed person, including height, posture, body mass index, shape of the head and associated structures such as the pinna (the outer ear), and dielectric properties of tissues. Induced fields within the body are highly non-uniform, with local hotspots and variations of several orders of magnitude. An important theme in studies on RF dosimetry is the focus on demonstrating compliance with exposure limits defined in terms of the localized and whole-body specific absorption rate (SAR) of energy. In recent years, measurement and simulation tools have been refined to allow exposure estimates in specific tissues or organs to be made for particular exposure scenarios, including those involving devices such as mobile phones.

While the number of mobile-phone subscriptions has been increasing rapidly around the world (4.6 billion subscribers in 2009), changes in mobile-phone technology have led to lower time-averaged RF power emitted from mobile phones used at present than those of previous generations. Of major interest to this *Monograph* is the exposure scenario in which mobile phones are held against the ear during a voice call. The

magnitude and spatial distribution of the ensuing SAR inside the brain depend on the design of a phone and its antenna, its position relative to the head, the anatomy of the head, how the hand holds the phone, as well as on the quality of the connection between the base station and the phone. GSM900/1800/PCS phones (Global System for Mobile communications/Personal Communications Service, operating at 900 or 1800 MHz) held next to the ear induce high spatial-averaged SAR values in the brain. This is because adaptive power control on average only reduces the output power to about 50% of its maximum during calls, but this would vary depending on the network software. The use of discontinuous transmission during voice calls would give a further 30% reduction in power. Analogue phones, which ceased to be used around the year 2000, produced still higher absorption of energy in the brain for two reasons: the handsets had higher output powers than modern phones, and the larger size of the handsets and antennae led to a more diffuse pattern of energy absorption in the head. Adaptive power control is much more effective with third-generation (3G) phone technologies, and this has led to a reduction of SAR in the brain by almost two orders of magnitude compared with that from GSM phones. The DECT (Digital Enhanced Cordless Telecommunications) phone is another widely used device that is held against the ear to make and receive voice calls. The average SAR in the brain from use of DECT phones is around five times lower than that measured for GSM phones.

The maximum spatial peak exposure to RF fields from mobile phones is very similar between different technologies. However, it may vary by up to a factor of 10 dependent on specific phone design. The spatial maximum exposure from cordless DECT phones is an order of a magnitude lower than that from mobile phones. Modulation and access schemes have also evolved to give a complicated output-power variation with time, while analogue technologies had a more constant pattern of output power.

Mobile-phone use is widespread in industrialized countries and rapidly growing elsewhere. Certain phone functions, such as text messaging, which involves considerably less exposure than voice calls, have become very popular among teenagers. Due to the closer proximity of the phone to the brain of children compared with adults, the average exposure from use of the same mobile phone is higher by a factor of 2 in a child's brain and higher by a factor of 10 in the bone marrow of the skull. In addition, dielectric properties of certain tissues, notably the bone marrow, change with age. The marrow progressively incorporates more fat, and the bone itself increases in thickness, hardens, and loses water over time. Both these tissues, therefore, have a higher conductivity in children than in adults and they receive a higher energy deposition from RF sources.

The use of hands-free kits lowers exposures from mobile phones to less than 10% of the value resulting from use at the ear, but it may increase exposure to other parts of the body. The rise in temperature inside the brain from use of a typical 3G mobile phone is small, approximately 0.1 °C or less.

Measures of mobile-phone use for epidemiological studies have historically relied on self-reporting, but 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 needed on phone use many years in the past.

Assessments of household exposures to RF radiation often rely on spot measurements with a focus on burst activity, rather than on average values over time, which are better measures of RF exposure. Environmental sources are dominated

by possible RF exposures from being in close proximity to mobile-phone base stations, but actual measurements have shown that distance to a base station is not a good proxy for exposure, due to the considerable variability in characteristics of the antennae, and shielding and reflection of the waves. Typical exposures from rooftop- or tower-mounted mobile-phone base stations are lower by more than five orders of magnitude than those from GSM handsets. Exposures to the brain from television and radio stations are typically lower than those from base stations. Epidemiological studies of environmental RF sources need to include rigorous assessments of exposures to RF radiation, documented by direct measurements or through validated models.

Many occupations involve the use of sources of RF radiation at much higher power levels than those from mobile phones. For people exposed to high-power RF sources at work, cumulative energy deposition in the whole body may be much greater than from mobile-phone use, but the spatial peak SAR in the head will be less.

Tissue heating is the most firmly established mechanism for effects of RF radiation in biological systems. Although it has been argued that RF radiation cannot induce physiological effects at exposure intensities that do not cause a detectable increase in tissue temperature, except for reactions mediated by free radical pairs, it is likely that not all mechanisms of interaction between weak RF fields, with the various signal modulations used in wireless communications, and biological structures have yet been discovered or fully characterized.

The International Commission on Non-Ionizing Radiation Protection (ICNIRP) and the Institute of Electrical and Electronics Engineers (IEEE) have developed guidelines for maximum human exposures to RF fields. These guidelines are designed to protect against adverse effects due to whole-body or partial body heating as a result of energy absorption above 100 kHz, and against nervous system effects at frequencies up to 10 MHz.

5.2 Human carcinogenicity data

The epidemiological evidence on possible associations of exposure to RF radiation with cancer comes from studies of diverse design that have assessed a range of sources of exposure: the populations included people exposed in occupational settings, people exposed through sources in the general environment, e.g. transmission towers, and people exposed through use of wireless (mobile and cordless) telephones. The most robust evidence is for mobile phones, the most extensively investigated exposure source. The general methodological concerns related to this evidence are covered in the introduction to Section 2 and are not reviewed again here.

As for any compilation of findings of epidemiological studies, interpretation of this evidence needs to give consideration to the possibility that observed associations reflect chance, bias, or confounding, rather than an underlying causal effect. The investigation of risk of cancer of the brain associated with mobile-phone use poses complex methodological challenges in the conduct of the research and in the analysis and interpretation of the findings.

5.2.1 Personal use of wireless telephones

(a) Tumours of the central nervous system: gliomas of the brain

One cohort study from Denmark and five case–control studies (from the USA, Finland, Greece, Sweden, and a multicentre international study) were judged by the Working Group to offer useful epidemiological information regarding associations between use of wireless phones and glioma. There are also several studies of time trends in occurrence of cancer of the brain in relation to the great temporal increase in mobile-phone use.

(i) Time-trend studies

It has been suggested that time trends in the incidence of cancer might reflect the impact of increasing use of mobile phones on cancer risk. In that regard, there have been some reports from various countries describing rates of brain cancer over time. In general, there has not been a documented and stable increase in rates since the advent of the mobile-phone era. However, the general absence of any documented increase in rates of tumours of the brain must be interpreted in light of the fact that most time trends were examined only before the early 2000s. However, any large risk associated with relatively recent exposure should have been detected in the studies conducted to date. Time trends in cancer of the brain have not shown evidence of a trend that would indicate a promptly acting and powerful carcinogenic effect of mobile-phone use.

(ii) Cohort study and early case–control studies

A large cohort study in the entire population of Denmark included mobile-phone subscribers with a median of 8 years of subscription. The study showed no excess risk of glioma, based on 257 exposed cases. Because of the reliance on subscription to a mobile-phone provider as a surrogate for mobile-phone use, this study involved considerable misclassification in exposure assessment.

Several case–control studies were carried out in a time window that was relatively early in the period of rising use. Three of these studies used self-reported histories of mobile-phone use, while a Finnish study made a link to mobile-phone subscription records. Effect estimates from these studies were generally too imprecise to make them informative.

(iii) The INTERPHONE study

The INTERPHONE study, a multicentre case–control study, comprised the largest investigation so far of mobile-phone use and brain tumours, including component studies of glioma, acoustic neuroma, and meningioma. The Working Group primarily considered the pooled analyses published in 2010 and 2011, rather than the findings as reported by site 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 2708 cases of glioma and 2972 controls. Participation rates were 64% among cases of glioma and 53% 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% 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 they 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 (≥ 1640 hours of cumulative call time). For this exposure group, the odds ratio for glioma was 1.40 (95% 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 obviate 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 Working Group 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, in the INTERPHONE study there was 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.

(iv) Studies from Sweden

In 2011, Swedish investigators reported the findings of a pooled analysis of associations of mobile-phone and cordless-phone use and risk of glioma. Cases were ascertained from 1997 through 2003 in two waves. The Working Group considered the latest combined analysis of the study data. 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 1148 cases with a diagnosis of glioma, and 2438 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% 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% CI, 0.98–1.4), 1.5 (95% CI, 1.1–2.1), and 2.5 (95% CI, 1.8–3.5), respectively. Ipsilateral use of the mobile phone was associated with higher risk. Further, there were similar findings in relation to the use of cordless phones.

The Working Group 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.

(v) Comparison of the findings of INTERPHONE and the Swedish studies

Because these two studies represent the most robust evidence on risk of tumours of the brain associated with wireless-phone use, the Working Group compared the methods and findings of the two studies, drawing on comparisons made by the Swedish investigators – Hardell and colleagues – 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, e.g. 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 is 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 Working Group 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 Working Group concluded that these findings could not be dismissed as reflecting bias alone, and that a causal interpretation was possible.

(b) Other tumours of the central nervous system: acoustic neuroma

Several early case–control studies and one cohort study from Denmark 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. The case numbers, however, were substantially smaller than for glioma. The study from Sweden provided positive results with estimates quite similar to those observed for glioma. The pattern of findings from the INTERPHONE study 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 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 Working Group 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 same two studies mentioned above provided the key evidence. Overall, in each, the findings generally indicated no increase in risk.

(d) Leukaemia/lymphoma

The Working Group 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 Working Group 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

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 have 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.

5.2.2 Occupational exposure

(a) Tumours of the brain

Four independent case–control studies investigated the association of occupational exposure to RF radiation with risk of brain tumours through specific assessment of individual RF exposure. One study was based on death certificates, the others were population-based studies. Two nested case–control studies (one from the USA and another from Canada and France) also investigated this association. For

the category of highest exposure in each study – determined with the best exposure measure reported, i.e. some form of expert assessment of work history in each case – the odds ratios were above unity, but with wide confidence intervals, thus suggesting that occupational exposure to RF radiation might increase the risk of tumours of the brain. Only two studies (a nested case–control analysis from the USA and a case–control study from Australia) provided dose–response assessments, and neither of these showed more than moderate evidence of a dose–response relationship. In addition, only two studies examined the possibility of confounding by other occupational exposures. A study from Germany adjusted the odds ratios for exposure to ionizing radiation and a study from the USA, based on death certificates, evaluated the sensitivity of the observed positive association of exposure to RF radiation with cancer of the brain with respect to confounding with known coexposures: solder fumes, lead and organic solvents. The observed odds ratio of 1.7 (95% CI, 1.1–2.7) for classification of RF exposure based on expert assessment decreased to 1.4 (95% CI, 0.7–3.1) when men exposed to solder fumes and lead were excluded from the exposed group, and dropped further to 0.4 when those exposed to organic solvents were also removed (although only two exposed cases and five exposed controls were left in the analysis). Chance and/or confounding cannot be ruled out as likely explanations for the observed association between occupational exposure to RF radiation and cancer of the brain.

Eight cohort studies (including the two nested case–control studies mentioned above) and a Polish cross-sectional study examined the relationship between occupational exposure to RF radiation and risk of tumours of the brain. Relative risks for the categories of highest exposure in all but three of the studies were close to or below unity. Among the three exceptions, one study from Italy was based on only one death from cancer of the brain; the cross-sectional study from Poland showed a relative risk of 1.91 (95% CI, 1.08–3.47) but had methodological limitations that could explain the apparent increase in risk; and an American study had only a weakly increased relative risk (OR, 1.39; 95% CI, 0.93–2.00). On balance, therefore, the cohort studies did not suggest a positive association between exposure to RF radiation and cancer of the brain. Their exposure measures, however, were generally of less quality than those in the case–control studies.

While the association of exposure to RF radiation 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, there is no clear indication of an association of occupational exposure to RF radiation 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 radiation 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, 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 radiation was not characterized individually and may have been confounded by ionizing radiation. 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. 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, while there were weak suggestions of a possible increase in risk of leukaemia or lymphoma associated with occupational exposure to RF radiation, 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 radiation have addressed several additional types of malignancy including uveal melanoma, and cancers of the testis, breast, lung, and skin. The Working Group noted that these studies had methodological limitations and the results were inconsistent.

5.2.3 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 emissions from transmission antennae. These studies are generally limited by reliance on measures of geographical proximity to the antennae as an exposure surrogate. Substantial exposure misclassification is unavoidable.

Taken together, the ecological studies do not suggest a positive association between RF emissions from fixed transmission sources and cancer of the brain.

There have been five case–control studies of environmental exposure to RF radiation 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 antennae. Two of these studies used estimates of exposure based on recorded locations of subjects' residences relative to recorded locations of AM radio-transmitters or mobile-phone base-station antennae. Neither found convincing indications of an increase in risk of brain cancer with increasing estimated exposure to RF radiation. A hospital-based study from France 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 that environmental exposure to RF radiation 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, while studies that used analytical designs and better exposure assessments (e.g. measured and modelled) showed no increased risk. 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 no conclusions could be drawn on the risk of leukaemia or lymphoma from environmental exposure to RF radiation.

(c) Other malignancies

The Working Group identified five studies that addressed other malignancies and environmental exposure to RF radiation, and found the available evidence uninformative.

5.3 Animal carcinogenicity data

Four classes of cancer bioassays in animals were reviewed and assessed by the Working Group. These studies involved a variety of animal models, exposure metrics, durations of exposure, and other criteria on which the evaluation of carcinogenicity was based.

Seven two-year cancer bioassays of RF radiation were reported, two in mice and five in rats; six studies were performed to examine the effects of exposure to mobile-phone RF metrics, and one study involved exposure to pulsed RF radiation. 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 radiation in any study. In the study with exposure to pulsed RF radiation, an increased incidence of total malignant tumours (all sites combined) was observed in rats; however, the Working Group 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 radiation did not increase total tumour incidence in any of the other six studies that were evaluated. The Working Group concluded that the results of the 2-year cancer bioassays provided no evidence that long-term exposure to RF radiation increases the incidence of any benign or malignant neoplasm in standard-bred mice or rats.

The Working Group 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 radiation. The first study with positive results demonstrated an increased incidence of lymphoma in *Eμ-Pim1*-transgenic mice exposed to GSM mobile-phone RF radiation at 900 MHz; however, two subsequent studies by other investigators using the same model system failed to confirm this finding. In the second study with positive results, an increased incidence of tumours of the mammary gland was observed in C3H/HeA mice exposed to RF radiation at 2450 MHz; although two later studies using the same exposure metric did not confirm this finding, these follow-on studies were performed at lower levels of exposure. The Working Group concluded that the results of 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 radiation.

The Working Group evaluated 16 studies of initiation and promotion that were performed with animal models of tumorigenesis 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 radiation. One of four studies with the model of mammary-gland tumour in Sprague-Dawley rats gave positive results; the other three studies – one with a nearly identical protocol – did not show an association, although they used the same experimental model and the same conditions of exposure to RF radiation. Likewise, the study with the model of lymphoma was negative. The Working Group 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 radiation in any of the tissues studied.

The Working Group evaluated six co-carcinogenesis studies involving five different animal models. Four positive responses were reported.

Two studies giving positive results, one in Wistar rats continuously exposed to drinking-water containing MX – a by-product of water disinfection – and another study in pregnant B6C3F$_1$ mice given a single dose of ethyl-nitrosourea, involved exposures to mobile-phone RF radiation at 900 and 1966 MHz, respectively. The other two studies with positive results involved coexposure of BALB/c mice to RF radiation at 2450 MHz and benzo[*a*]pyrene. Although the value of two of these studies was weakened by their unknown relevance to cancer in humans, the Working Group concluded that they did provide some additional evidence supporting the carcinogenicity of RF radiation in experimental animals.

5.4 Other relevant data

The data to evaluate the mechanisms by which RF radiation may cause or enhance carcinogenesis are extensive and diverse. Studies in humans from occupational cohorts, mobile-phone users and controlled exposures in experimental settings provide information on effects in various tissues, including blood and brain. Studies in animals have been focused on a variety of organs and tissues. Assays *in vitro* in human cells, other mammalian cells, and cells from other organisms provide the largest set of data from which to evaluate mechanisms. Many studies were confounded by significant increases in the temperature of the cells, leading to thermal effects that could not be dissociated from non-thermal RF-induced changes. The conclusions presented in this section for results *in vivo* and *in vitro* pertain only to those studies for which the Working Group concluded that thermal confounding did not occur.

5.4.1 Genetic and related effects of exposure

Multiple studies in humans were conducted on the possible genetic damage associated with exposure to RF radiation. Most of these studies were of occupational exposure and the others evaluated mobile-phone users. Several common exposures to the general population that are likely to be confounders were generally not considered, including tobacco use and age. In addition, other occupational exposures that might have contributed to the findings were rarely discussed. Most of the occupational studies that suggested a positive association of the effect with exposure to RF radiation involved workers from the same facility, included small numbers of subjects, and provided no indication of the extent to which the same individuals were sampled in multiple studies. Virtually all the large studies did not show an association with exposure to RF radiation, for any type of genetic damage. Finally, there were methodological flaws and weaknesses in reporting in many studies, including the failure to actually measure exposure to RF radiation, the use of small numbers of cells for evaluating genetic damage, the failure to use proper controls while culturing cells, incomplete reporting, and improper interpretation of results.

A few studies in *Drosophila* that addressed mutagenicity after exposure to RF radiation gave negative results.

Approximately half of the laboratory studies of genetic damage in mammalian systems, generally rats and mice, had limitations related to reporting on the exposure system, small sample sizes and exposures that induced thermal effects, or that were so low as to be no challenge to the animals. Of the remaining studies, many were satisfactory and of comparable quality, but showed contradictory results. Some were attempts to repeat original laboratory findings. Also these studies provided mixed and sometimes contradictory results. Some of the discrepancies could be due to differences in species or

exposure conditions, but others were in direct contrast.

Roughly half of the studies of human cells *in vitro* were done in lymphocytes cultured from the blood of donors. Short-term, high-intensity exposures to RF radiation resulted in consistently positive results for DNA damage, but the Working Group felt that thermal effects were the likely cause of these effects. A large number of studies on DNA strand breaks and the studies on sister chromatid exchange generally gave negative results. Exposures to RF radiation in the non-thermal range also generally gave negative results.

The remaining in-vitro studies with human cells and the in-vitro studies with non-human cells also involved short-term, high-intensity exposures that consistently gave positive results for DNA damage. The Working Group considered that these results 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 aneuploidy and spindle disturbances in human-hamster hybrid A_L cells, and studies at low exposures showing DNA single-strand breaks were of concern. While RF radiation has insufficient energy to produce these types of direct genetic damage, other changes such as oxidative stress and production of reactive oxygen species may explain these results.

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 regarding the original findings. A single study showing altered microtubule structures at low exposures remains a concern.

Overall, the Working Group concluded that there was weak evidence that RF radiation is genotoxic, and no evidence for the mutagenicity of RF radiation.

5.4.2 Reaction of the immune system after exposure

Several studies assessed the effects of exposure to RF radiation on indicators of immune function in humans. In two studies, increased concentrations of some immunoglobulins (Ig) and changes in numbers of lymphocytes (T8, natural killer [NK] cells) were observed in blood samples from radar operators and workers at television-transmission stations, but the results were variable and the alterations seemed to be within the normal variation. Two studies among workers exposed to very high frequency RF radiation showed a significant increase in IgG and IgM, and a higher number of NK cells, respectively. Patients with atopic eczema dermatitis showed an increase in allergen-provoked production of IgE when they had been exposed to RF radiation from a mobile phone. Many of these studies used small numbers of subjects and generally did not control for possible confounders.

The available evidence from numerous experimental studies *in vivo* that aimed to assess effects of short-term and prolonged low-level exposure to RF radiation on function and status of the immune system, clearly indicates that various shifts in number and/or activity of immunocompetent cells are possible. However, in some cases the same lymphocyte functions are reported to be weakened or enhanced in different single experiments, despite exposures to RF radiation at similar intensities and under similar exposure conditions. Short-term exposure to weak RF fields may temporarily stimulate certain humoral or cellular immune functions, while prolonged irradiation inhibits the same functions. Thus, even though there are indications that changes are occurring, the relevance of these observations in relation to carcinogenicity is unclear.

The effects of RF radiation on various types of human lymphocytes *in vitro* are variable and depend on the mitotic state of the cells during

exposure. A difference was reported between the effects of exposure to continuous-wave and pulsed-wave RF radiation, the latter preferentially stimulating the immunogenic and pro-inflammatory activity of monocytes. Many of these studies had weaknesses in the description of experimental procedures and from lack of detail on dosimetry.

Overall, the Working Group concluded that there was insufficient evidence to determine that alterations in immune function induced by exposure to RF radiation affect carcinogenesis in humans.

5.4.3 Effects on genes, proteins and signalling pathways

No studies assessing gene expression in humans exposed to RF radiation were identified, and only one pilot study assessed protein changes in exposed human subjects.

Nearly 30 studies investigated gene/protein changes in rodents exposed to RF radiation. Many of these studies were unreliable due to deficiencies in the exposure system or methodological shortcomings. The data from the remaining studies are limited and present mixed results with no consistent pattern of response.

A large number of studies have assessed the ability of RF radiation to affect gene/protein expression and protein activation in human-derived cell lines *in vitro*. The majority of studies assessing effects of RF radiation on expression and activity of heat-shock proteins reported no effect. A limited number of studies assessed the ability of RF radiation to influence the activity of signal-transduction pathways in human cells *in vitro*. Three studies found changes in MAPK signalling, while another did not. The role of reactive oxygen species in mediating these responses is unclear.

A total of 16 studies used high-throughput genomics/proteomics approaches to evaluate the effect of exposure to RF radiation on human cell lines *in vitro*. Many of these studies 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.

On the basis of the above considerations, the Working Group concluded that data from studies of genes, proteins and changes in cellular signalling show weak evidence of effects from RF radiation, but did not provide mechanistic information relevant to carcinogenesis in humans.

5.4.4 Other mechanistic end-points

Several potential changes resulting from exposure to RF radiation are summarized here. With the exception of changes in cerebral blood flow, many of the other studies reviewed by the Working Group provided conflicting, negative or very limited information, which made it difficult to draw conclusions, especially in relation to carcinogenesis. These studies focused on electrical activity in the brain, cognitive function, general sensitivity to RF radiation and alterations in brain biochemistry. Even though the relationship between alterations in cerebral blood flow during exposure to RF radiation cannot be directly related to carcinogenesis, the Working Group concluded that the available data were sufficiently consistent to identify them as important findings.

Some studies were conducted in experimental animals to explore the possibility that exposure to RF radiation *in vivo* may induce the production of reactive oxygen species in multiple organs, most frequently brain, but also kidney, liver and eye. Markers of oxidative stress included increases in the concentration of malondialdehyde (related to lipid peroxidation) and nitric oxide, enhanced activities of antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase) and pro-oxidant enzymes, and reductions in

glutathione. Many of these studies are 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.

A few studies in human cells *in vitro* evaluated the possible role of exposure to RF radiation in altering levels of intracellular oxidants or activities of antioxidant enzymes. One study showed a marginal effect, while other studies demonstrated an increase in activity with increasing exposures. There were not enough studies to make a reasonable assessment of the consistency of these findings. Additional studies addressed this issue in in-vitro systems with non-human cells. While most of these did not find changes, one study evaluated the formation of DNA adducts from reactive oxygen species (8-hydroxy-deoxyguanosine) and was able to demonstrate reversal of this effect by melatonin. While the overall evidence was inconclusive, the results from in-vitro studies with animal models raise some concern.

Overall, the Working Group concluded that there was weak evidence that exposure to RF radiation affects oxidative stress and alters the levels of reactive oxygen species.

Numerous studies have assessed the function of the blood–brain barrier in rodents exposed to RF radiation at various intensities. Consistent results from one laboratory suggest an increase in the permeability of the blood–brain barrier, but the majority of the studies, many of which aimed at replicating published results, failed to observe any effect on this point from exposure to either continuous or pulsed RF radiation. The evidence that exposure to RF radiation alters the blood–brain barrier was considered weak.

A few studies dealt with alterations induced by RF radiation in cell differentiation or induction of apoptosis in the brain or other organs. While most of the studies showed an association, the Working Group was not convinced that these data 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 studies 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, while thermal effects may have had an impact in the other study. Finally, other in-vitro studies with non-human cells gave essentially negative results, with the exception of one study that demonstrated mixed results. The evidence that exposure to RF radiation alters apoptosis was considered weak.

Multiple assays *in vitro* were conducted to test proliferation of primary cells or established cell lines by analysis of cell-cycle progression and thymidine uptake, after exposure to various intensities of RF radiation at various time intervals. Many of these studies 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 evidence that RF radiation alters cellular replication was considered weak.

Ornithine decarboxylase is an enzyme involved in the metabolism of polyamines, which are critical components of cellular replication and differentiation processes. The activity of this enzyme was the object of several studies *in vitro* in human and animal cells exposed to GSM900 and GSM1800 signals. Some of these studies showed significantly increased ornithine decarboxylase activity. The result of one study suggested that ornithine decarboxylase activities may be reduced. It was unclear how these changes in activity relate to human cancer. There was weak evidence from in-vitro studies that exposure to RF radiation alters ornithine decarboxylase activity.

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

6. EVALUATION

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of radiofrequency radiation. Positive associations have been observed between exposure to radiofrequency radiation from wireless phones and glioma, and acoustic neuroma.

6.2 Cancer in experimental animals

There is *limited evidence* in experimental animals for the carcinogenicity of radiofrequency radiation.

6.3 Overall evaluation

Radiofrequency electromagnetic fields are *possibly carcinogenic to humans (Group 2B).*

6.4 Rationale for 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 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 on gliomas and meningiomas of the brain and acoustic neuromas. 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.