21 Mobile phone use and brain tumour risk: early warnings, early actions?

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In 2011 the World Health Organization's International Agency for Research on Cancer (IARC) categorised the radiation fields from mobile phones and other devices that emit similar non-ionizing electromagnetic fields (EMFs), as a Group 2B i.e. 'possible' human carcinogen. Nine years earlier IARC gave the same classification to the magnetic fields from overhead electric power lines.

The IARC decision on mobile phones was principally based on two sets of case-control human studies of possible links between mobile phone use and brain tumours: the IARC Interphone study and the Hardell group studies from Sweden. Both provided complementary and generally mutually supportive results. This chapter gives an account of the studies by these two groups — and others coming to different conclusions — as well as reviews and discussions leading up to the IARC decision in 2011. The chapter also describes how different groups have interpreted the authoritative IARC evaluation very differently.

There are by now several meta-analyses and reviews on mobile phones and brain tumours, which describe the challenges of doing epidemiology on this issue, the methodological limitations of the major studies published so far and the difficulties of interpreting their results.

It has been suggested that national incidence data on brain tumours could be used to qualify or disqualify the association between mobile phones and brain tumours observed in the case-control studies. However, in addition to methodological shortcomings, there might be other factors that influence the overall incidence rate such as changes in exposure to other risk factors for brain tumours that are unknown in descriptive studies. Cancer incidence depends on initiation, promotion and progression of the disease. As the mechanism for radiofrequency electromagnetic fields carcinogenesis is unclear, it supports the view that descriptive data on brain tumour incidence is of limited value.

The chapter points to mobile phone industry inertia in considering the various studies and taking the IARC carcinogenic classification into account and a failings from the media in providing the public with robust and consistent information on potential health risks. The IARC carcinogenic classification also appears not to have had any significant impact on governments' perceptions of their responsibilities to protect public health from this widespread source of radiation.

The benefits of mobile telecommunications are many but such benefits need to be accompanied by consideration of the possibility of widespread harms. Precautionary actions now to reduce head exposures would limit the size and seriousness of any brain tumour risk that may exist. Reducing exposures may also help to reduce the other possible harms that are not considered in this case study.

Evidence is increasing that workers with heavy long-term use of wireless phones who develop glioma or acoustic neuroma should be compensated. The first case in the world was established on 12 October 2012. The Italian Supreme Court affirmed a previous ruling that the Insurance Body for Work (INAIL) must grant worker's compensation to a businessman who had used wireless phones for 12 years and developed a neuroma in the brain.

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21.1 Introduction

On May 31, 2011 the WHO International Agency for Research on Cancer (IARC) categorised the radiation fields from mobile phones, and from other devices that emit similar non-ionizing electromagnetic fields (EMFs), as a Group 2B i.e. a 'possible' human carcinogen. Nine years earlier IARC had also classified the magnetic fields from overhead electric power lines as a Group 2B carcinogen.

The IARC decision on mobile phones was principally based on two sets of case-control human studies: the IARC Interphone study and the Hardell group studies from Sweden. Both provided complementary but generally mutually supportive results.

But why were these case-control studies into possible brain tumours from mobile phones initiated?

21.2 The Hardell group studies — 1999–2011

Sweden, along with Israel, was one of the first countries in the world to widely adopt wireless telecommunications technology. Analogue phones (NMT; Nordic Mobile Telephone System) were introduced in the early 1980's using both 450 and 900 Megahertz (MHz) fields. NMT 450 was used in Sweden since 1981 but closed down in 31 December, 2007, whereas NMT 900 operated during 1986–2000.

The digital system (GSM; Global System for Mobile Communication) using dual band, 900 and 1 800 MHz, started to operate in 1991 and now dominates the market. The third generation of mobile phones, 3G or UMTS (Universal Mobile Telecommunication System), using 1900/2100 MHz RF fields has been introduced worldwide since a few years, in Sweden in 2003. Currently the fourth generation, 4G, operating at 800/2 600 MHz, and Trunked Radio Communication (TETRA, 380–400 MHz) are being established in Sweden and elsewhere in Europe.

Desktop cordless phones (e.g. Digital Enhanced Cordless Telecommunications; DECT) have been used in Sweden since 1988, first using analogue 800–900 MHz RF fields, but since early 1990's the digital 1900 MHz system has been used.

Nowadays mobile phones are used more than landline phones in Sweden. (http://www.pts.se/upload/Rapporter/Tele/2011/sv-telemarknad-halvar-2011-pts-er-2011-21.pdf).

The real increase in use and exposures to their radiation fields has been since the end of the 1990's. Wireless phones emit radiofrequency (RF) EMFs and the brain is the main target organ during use of the handheld phone (Cardis et al., 2008).

One of the author's (LH) interest in this research area was initiated by his involvement in a Swedish committee that evaluated cancer risks from exposure to extremely low frequency (ELF) EMFs from power lines. The conclusion was that there was an increased risk for childhood leukemia based on distance to power lines (Hardell et al., 1995). In 2002 IARC concluded that ELF electric and magnetic fields from power lines etc. is a human Group 2B carcinogen (IARC, 2002).

From a review of the literature there seemed to be an increased risk for brain tumours in the electronics industry (Hardell et al., 1995). It was decided to study it further in a case-control study. However, at that time there was also some media attention to a US lawsuit against cell phone industry companies.

It was alleged that repeated use of mobile phone had caused a fatal brain tumour in a woman. The head line in Los Angeles Times was *'Suit Over Cellular Radiation Raises Hazard Questions'* (Carlo and Schram, 2001). It was therefore decided to add questions on mobile phone use in the first of 4 linked case-control studies that are briefly described below.

This is followed by the results of the other major publications with some data on long-term use, the Interphone study, and the IARC evaluation of the RF and cancer evidence, and related responses and discussions.

The aim is not to give a thorough review of this research area, nor to deal with possible other effects of RF exposures which can be found in other publications including meta-analyses of the risk of brain tumours related to use of wireless phones (Hardell et al., 2006d; 2009; Myung et al., 2009; Kundi, 2009; Cardis and Sadetzki, 2011; Levis et al., 2011; IARC Monograph, in press).

21.3 First Hardell group study on mobile phone use and brain tumours — 1999

In 1999 the Hardell group in Sweden published results from their first case-control study on brain tumours and use of mobile phones (Hardell et al.,

1999a). In total 209 (90 %) of the cases and 425 (91 %) of the controls that fullfilled the inclusion criteria answered the mailed questionnaire. Overall no association between use of mobile phones and brain tumours was found.

A slightly increased (but not statistically significant) risk was found for analogue phone (NMT) use and for a *latency* period greater than 10 years, Odds Ratio (OR) = 1.20 (95 % Confidence Interval; CI = 0.56–2.59). For tumours located in the temporal ([2]), occipital or temporoparietal lobe areas of the brain an increased risk was found for ipsilateral ([3]) exposure, OR = 2.42 (95 % CI = 0.97–6.05) (Hardell et al., 1999a, 2001). However, all results were based on low numbers of exposed subjects and different histopathological types of brain tumours so no firm conclusions could be drawn. Furthermore, in this first study use of cordless phones was not included.

Authors of an Editorial in 2001, in commenting on a 'negative' US study (Inskip et al., 2001) that was published after the first Hardell et al. (1999a) study, stated that *…the use of cellular telephones does not detectably increase the risk of brain tumors'* and that *'This study allays fears raised by alarmist reports that the use of cellular telephones causes brain tumors* (Trichopoulos and Adami, 2001). This statement goes far beyond what was scientifically defensible. For example, among the 782 patients with brain tumours only 22 had 5 years or more of mobile phone use and no data with longer latencies were presented. The Editorial illustrates a common misconception which is that a 'non–positive' study is often assumed to be a 'negative' study when in fact the data do not support this assumption.

21.4 Second and third Hardell group studies — 2002–2006

This initial study by the Hardell group gave some support for an association between use of mobile phones and brain tumours. However, the results were based on low numbers especially regarding tumour type and long-term use. The first study was thus followed by two larger studies with cases diagnosed during the time period 1997–2003. The second study encompassed cases diagnosed during 1 January 1997 to 30 June 2000 and the third study 1 July 2000 to 31 December 2003. The methods were the same including an identical questionnaire in both studies. Results for these two study periods were published separately (Hardell et al., 2002, 2005, 2006a), but here pooled results for the whole study period 1997–2003 are presented (Hardell et al., 2006b, 2006c; Hardell and Carlberg 2009). More details can be found in the different publications.

In short, all cases were reported to a cancer registry and had histopathological verfication of tumour diagnosis. Both men and women aged 20–80 years at the time of diagnosis were included. Matched controls were identified from the Swedish Population Registry. The study included use of both mobile and cordless (DECT) phones (wireless phones), the latter an exposure which most other studies ignore ([4]). Also questions e.g. about occupational exposures were asked. Use of wireless phones was assessed by a self-administered questionnaire. The information was supplemented over the phone, if necessary.

The ear that had mostly been used during calls with mobile phone and/or cordless phone was assessed by separate questions; more than 50 % of the time for one side, or equally both sides. This information was checked during the supplementary phone call. Moreover every person that had used a wireless phone received after that a letter asking them again to specify the ear that had been used during phone calls and to what extent that side of the head was mostly used. There was a very good agreement for the result using these three methods to assess these data.

Separately, tumour localisation was defined by using medical records, such as computer tomography (CT) and/or magnetic resonance imaging (MRI). Use of mobile and cordless phones was defined as ipsilateral (more than 50 % of the time), equally ipsi/contralateral or contralateral (less than 50 %) in relation to tumour side. Calculation of cumulative hours of use over the years was based on information on first and last year of use (time period) and average number of minutes per day during that period. Use in a car with external antenna was disregarded as well as use of a handsfree device. A minimum latency period of one year was adopted. Hence, latency period and cumulative use for the different phone types could be defined.

([2]) A review of 110 phone models showed that exposure to radiations is generally higher in the temporal lobe, which is a part of the brain that is near to the ear, (Cardis et al., 2008).
([3]) i.e. the tumour appears on the side of head at which the phone is normally used.
([4]) The Interphone study (see Section 20.9) had some questions on cordless phone use at least in some countries but that information has never been properly analysed or published.

Box 21.1 Some concepts and tools for identifying cancer risks in human studies

OR: Odds ratio. The odds ratio is an estimate of the relative risk, showing how much more likely it is that someone who is exposed to a factor (e.g. cell phones) will develop an outcome (e.g. brain tumour) compared to someone who is not exposed. An OR of 1 indicates no risk, OR < 1 decreased risk and OR > 1 increased risk. For example, an OR of 1.5 indicates that those who are exposed have a 1.5 times higher risk of developing a disease compared to those who are not exposed.

SIR: Standardized incidence ratio. The SIR compares the observed number of cases in a specific population (e.g. cell phone subscribers) to the number of cases expected would the same rates apply as observed in a reference population (e.g. general population). A SIR of 1 indicates no risk, SIR < 1 decreased risk and SIR > 1 increased risk.

CI: Confidence interval. A confidence interval shows the uncertainty of the statistical estimate. In the case of OR and SIR, if the corresponding CI range does not cover 1.0, the result is considered **statistically significant**. Usually 95 % confidence intervals are reported indicating the range of the true OR/SIR with 95 % statistical confidence. The absence of 'statistical significance' can often be a weak guide to the strength of evidence for a risk compared to the power of a study to detect a risk ([5]).

Latency period. Time between first exposure and identification of the disease. For cancer, particularly the solid tumours like brain cancers in contrast to cancers of the blood, such as leukemia, the latency period can be from 15–45 years on average, depending on age at exposure, type and intensity of exposure ([6]) etc. This means that any study of cancer has to be at least as long as the average latent period for the tumour being studied before there will be any clear evidence of a cancer risk.

21.5 Fourth Hardell group study — 2010

In a review commissioned by the former Swedish Radiation Protection Agency (now called the Swedish Radiation Safety Authority) it was suggested that the exclusion of deceased cases was a source of bias in the Hardell group studies (Boice and McLaughlin, 2002). The scientific reason for this suggestion was not given.

As a response to that critique a fourth study was performed. This included the cases with a malignant brain tumour who had died before inclusion in the case-control studies 1997–2003. These cases represented patients with a poor prognosis, mostly with a astrocytoma grade IV tumour. Controls were selected from the Death Registry in Sweden.

Two groups of controls were included, one group consisted of controls that had died from other types of malignant diseases than brain tumour and one group of controls that had died from other diseases than cancer. Relatives to both cases and controls were identified through the Swedish Population Registry at the Swedish Tax Agency. The study encompassed 464 cases and 464 controls that had died from a malignant disease and 463 controls with other causes of death. A similar questionnaire as in previous studies was used and exposure was assessed by a questionnaire sent to the next of kin to each deceased case and control.

Replies were obtained for 346 (75 %) cases, 343 (74 %) cancer controls and 276 (60 %) controls with other diseases. Use of mobile phones gave an increased risk, highest in the >10 years latency group yielding an OR of 2.4 (95 % CI = 1.4–4.1). The risk increased with cumulative number of life-time hours of use, being highest in the more than 2000 hours group who had an OR of 3.4 (95 % CI = 1.6–7.1).

([5]) See Sir Bradford Hill's classic epidemiology paper, 'The Environment and Disease: Association or Causation?' (Proceedings of the Royal Society of Medicine, 1965) where he warned not to overrate the value of statistical significance since it often led people to 'grasp the shadow and loose the substance' of what was in the data. See Chapter 26 on science for precautionary decision-making.

([6]) Stein, Y., Levy-Nativ, O., Richter, E.D., 'A sentinel case series of cancer patients with occupational exposures to electromagnetic non-ionising radiation and other agents', *Eur. J. Oncol.*, 2011, (16/1) 21–54. It has taken almost 50 years to be sure that the atomic bomb dropped on Japan in 1945 also caused brain cancers: the data before then were not clear or robust enough. (Shibata, Y. et al., 'Intercranial meningiomas among Nagasaki atomic bomb survivors', *Lancet*, 1994, (344) 1 770).

No clear association was found for use of cordless phones, although an OR of 1.7 (95 % CI = 0.8–3.4) was found in the group with more than 2000 hours cumulative use. This investigation confirmed the previous results of an association between mobile phones and malignant brain tumours (Hardell et al., 2010). It was concluded that the critique made by Boice and McLaughlin (2002) was scientifically unfounded.

21.6 Some Swedish responses to the Hardell group studies

The first publication on mobile phone use and brain tumour risk (Hardell et al., 1999a) was quickly followed by a letter to the journal (Ahlbom and Feychting, 1999). They suggested that selection bias of cases might have created the high response rate in the Hardell study. However, the critique was unfounded and easy to rebut (Hardell et al., 1999b). In all of the Hardell et al. studies there has usually been a high response rate to the oncologists who have been trained in cancer epidemiology. This applies as well to studies not related to mobile phone use.

Interestingly in the Swedish part of the Interphone studies, one of the authors (Anders Ahlbom) had stated, even before the study started, that an association between cellular telephones and brain tumours was *biologically bizarre* in an 'opinion' letter (Adami et al., 2001). Ahlbom's own work provided evidence for an association between exposure to magnetic fields from overhead power lines and childhood leukemia: an association that would also have to be regarded as *biologically bizarre* (Feychting and Ahlbom, 1993).

Maria Feychting, who participated in the Swedish part of the Interphone studies, queried whether *'the questions really were placed in the same way to cases and controls'* (Björkstén, 2006). Indeed they were in the Hardell studies, however, different methods do seem to have been used for the interviews with cases and controls in the Interphone study, for example, when bed-side interviews were done of cases only.

Meanwhile, the Hardell studies and other evidence of possible health risks from EMF inspired a group of scientists to summarise this evidence in their BioInitiative Report (BioInitiative Working Group, 2007). This had considerable impact in alerting many people to the emerging evidence of risks and to the presence of a small but growing minority of experts who did not agree with the WHO EMF Project statements and other reports that there was no evidence of risk (e.g. of SCENIHR 2007).

The European Environment Agency (EEA), having produced a report *Late lessons from early warnings* (EEA, 2001) was invited by the Biointiative group to submit a chapter about the relevance of the 14 well known 'Late lessons' case studies to the emerging issue of EMF. Having considered the published evidence, the EEA decided it was timely to issue a guarded early warning about the possible risk of brain tumours from mobile phones in September 2007 (see Box 21.2).

21.7 A pooled analysis of the Hardell group studies

Pooled analysis of the two case-control studies on brain tumour cases (glioma, meningioma and acoustic neuroma ([7]), Table 21.1) diagnosed for the whole time period 1997–2003 was made and results were reported for both malignant (Hardell et al., 2006b) and benign (Hardell, 2006c) tumours. This was possible since the same methods were used in both studies with an identical questionnaire. In this presentation results for glioma in the fourth study were added (Hardell et al., 2010; Hardell et al., 2011a).

Latency was divided in three categories, > 1–5 year, > 5–10 year, and > 10 year from first use of a wireless phone until diagnosis. Both use of mobile and cordless phones gave an increased risk overall for **glioma**, highest in the latency group > 10 years, increasing further for *ipsilateral* use; mobile phone OR of 2.9 (95 % CI = 1.8–4.7) and cordless phone OR of 3.8 (95 % CI = 1.8–8.1). Highest OR was found in the > 10 year latency group for total wireless phone use as well.

Table 21.1 gives the same calculations for **meningioma** (n = 916). There was no consistent pattern of an increased risk, although highest risk was found for ***ipsilateral*** exposure in the > 10 year latency period, mobile phone OR = 1.6 (95 % CI = 0.9–2.9). Also ipsilateral use of cordless phone in the same latency category yielded an increased risk, OR = 3.0 (95 % CI = 1.3–7.2).

Regarding **acoustic neuroma** (n = 243) wireless phone use gave OR = 2.2 (95 % CI = 1.3–3.7) in the > 10 y latency period. *Ipsilateral* use gave higher risks than contralateral use for both mobile phone and cordless phone use.

([7]) Studying especially long-term use and laterality.

21.8 Risks to children

Use of wireless phones is widespread among children and adolescents (Söderqvist et al., 2007, 2008). Children's brain absorbs higher radiation from RF-EMF emissions than adults (Cardis et al., 2008; Christ et al., 2010; Gandhi et al., 2012). This is due to the smaller head, thinner skull bone and higher conductivity of the brain tissue. The developing brain is more sensitive to toxins (Kheifets et al., 2005) and the brain is still developing until about 20 years of age (Dosenbach et al., 2010). The greater absorption of RF energy per unit of time, the greater sensitivity of their brain, and the longer lifetimes within which to develop a brain tumour leaves children at a higher risk than adults from mobile phone radiations.

Analyses of the Hardell group results revealed that first use before age of 20 is associated with the highest risk for glioma and acoustic neuroma, see Table 21.2 (Hardell, Carlberg, 2009).

Three age groups for first use of a wireless phone were used; < 20 years, 20–49 years and 50–80 years. For glioma, first use of a mobile phone < 20 y of age gave OR = 3.1 (95 % CI = 1.4–6.7). A similar pattern was found also for cordless phone use (data not shown). Also for acoustic neuroma the risk was highest in the youngest age group; OR = 5.0 (95 % CI = 1.5–16), but no conclusions could be drawn regarding cordless phones since only 1 case had first use before the age of 20 years. These ORs increased further for *ipsilateral* mobile phone use in the youngest age group; glioma OR = 4.4 (95 % CI = 1.3–15), acoustic neuroma OR = 6.8 (95 % CI = 1.4–3.4). No clear age dependent pattern of increased risk was found for meningioma.

There have been very few other studies of children and mobile phone use except the CEFALO study (Aydin et al., 2011) and that of the EU, Mobikids ([8]), which is ongoing.

The multi-centre case–control study CEFALO, conducted in Denmark, Sweden, Norway, and Switzerland has been commented in detail by Söderqvist et al. (2011) since serious methodological problems exist as exemplified below.

In the summary of the study the authors wrote that they *did not observe that regular use of a mobile phone increased the risk for brain tumors.* This conclusion was accompanied by an editorial stating that the study showed *no increased risk of brain tumors* (Boice and Tarone, 2011) as well as by a news release from the Karolinska Institute in Stockholm that the results of no increased risk were 'reassuring' (Karolinska Institute, 2011). However, the statements go far beyond what the study really showed.

For example the data collection and analyses of use of cordless phones was not valid. Use of cordless phones was assessed only *in the first 3 years* of use, a most peculiar definition for which the authors gave no explanation for or reference to. Furthermore, the study never considered wireless phone use, including both mobile and cordless phones, as an exposure category. IARC categorised wireless phone use as a relevant exposure group (Baan et al., 2011). Instead, Aydin et al. (2011) included use of cordless phones in the 'unexposed' category, so risk estimates for mobile phone use might therefore be underestimated. Similarly mobile phone use was included among the 'unexposed' when considering use of cordless phones and thereby potentially concealing an increased risk.

The study yielded a statistically non-significant increased risk for brain tumours among regular users of mobile phones, OR = 1.36 (95 % CI = 0.92–2.02). This OR increased somewhat with cumulative duration of subscriptions and duration of calls (Aydin et al., 2011). Only latency time of 5 years or more was presented with very few cases within this category. Further support of a true association was found in the results based on operator-recorded use for 62 cases and 101 controls, which for time since first subscription > 2.8 years yielded a statistically significant OR of 2.15 (95 % CI = 1.07–4.29) with a statistically significant trend (p = 0.001).

Although the authors do not emphasize that the results yielded an increased risk, the data indicate a moderately increased risk, in spite of low exposure, short latency period and limitations in study design and analyses. Certainly it cannot be used as reassuring evidence *against* an association, as discussed in the commentary (Söderqvist et al., 2011).

Unfortunately, the CEFALO study (Aydin et al., 2011) was published after the IARC meeting in May 2011. Had it been available at the IARC meeting it would have provided additional evidence to support the IARC conclusion that human exposure to RF-EMF is a group 2B carcinogen.

([8]) Contact: ecardis@creal.cat for details.

Box 21.2 The EEA early warnings on brain tumour from mobile phones, 2007–2011

'There are many examples of the failure to use the precautionary principle in the past, which have resulted in serious and often irreversible damage to health and environments. Appropriate, precautionary and proportionate actions taken now to avoid plausible and potentially serious threats to health from EMF are likely to be seen as prudent and wise from future perspectives' (EEA, 2007).

This early warning was updated in 2009 to include:

'The evidence for a head tumour risk from mobile phones, although still very limited, and much contested, is, unfortunately, stronger than two years ago when we first issued our early warning'.

The evidence is now strong enough, using the precautionary principle, to justify the following steps (EEA, 2009):

1. For governments, the mobile phone industry, and the public to take all **reasonable measures to reduce exposures to EMF, especially to radio frequencies from mobile phones, and particularly the exposures to children and young adults who seem to be most at risk from head tumours**. Such measures would include stopping the use of a mobile phone by placing it next to the brain. This can be achieved by the use of texting; hands free sets; and by the use of phones of an improved design which could generate less radiation and make it convenient to use hands free sets ([9]).

2. **To reconsider the scientific basis for the present EMF exposure standards which have serious limitations** such as reliance on the contested thermal effects paradigm; and simplistic assumptions about the complexities of radio frequency exposures.

3. To provide **effective labelling and warnings** about potential risks for users of mobile phones. Across the European Union, the vast majority (80 %) of citizens do not feel that they are informed on the existing protection framework relating to potential health risks of electromagnetic fields. 65 % of citizens say that they are not satisfied with the information they receive concerning the potential health risks linked to EMF. (Special Euro barometer report on EMF, Fieldwork Oct/Nov 2006, published 2007).

4. To **generate the funds needed to finance and organise the urgently needed research** into the health effects of phones and associated masts (base stations). **Such funds could include grants from industry and possibly a small levy on the purchase and or use of mobile phones**. This idea of a research levy is a practice that we think the US pioneered in the rubber industry with a research levy on rubber industry activities in the 1970s when lung and stomach cancer was an emerging problem for that industry. The research funds would be used by independent bodies ([10]) (http://latelessons.ew.eea.europa.eu/fol572324/statements/Benefits_of_mobile_phones_and_potential_hazards_of_EMF.doc).

This was updated in 2011 when evidence was presented to the Council of Europe hearing on mobile phones, February 2011 (EEA, 2011a).

([9]) The EEA has since noted, with some relief, what appears to be an increased use of hands free devices, particularly in the younger generation, due to enhanced applications.

([10]) The EEA has noted the increasing evidence of 'funding bias' in scientific research whereby results outcomes are strongly linked to source of funding. This observation is based on evidence from pharmaceuticals, tobacco, lead, asbestos, BPA and EMF, as well as on evidence from other fields such as cost-benefit analysis and transport construction project cost estimations.

Table 21.1 Odds ratio (OR) and 95 % confidence interval (CI) for glioma, meningioma and acoustic neuroma and use of wireless phones (mobile phones and/or cordless phones)

	Ipsilateral, > 10 year latency	> 10 year latency	Total, > 1 year latency
	OR, CI	OR, CI	OR, CI
Glioma (n = 1148)			
Wireless phone	-	**2.1** **1.6–2.8**	**1.3** **1.1–1.5**
Mobile phone	**2.9** **1.8–4.7**	**2.5** **1.8–3.3**	**1.3** **1.1–1.6**
Cordless phone	**3.8** **1.8–8.1**	**1.7** **1.1–2.6**	**1.3** **1.1–1.6**
Meningioma (n = 916)			
Wireless phone	-	1.4 0.97–2.0	1.0 0.9–1.2
Mobile phone	1.6 0.9–2.9	1.4 0.9–2.1	1.1 0.9–1.3
Cordless phone	**3.0** **1.3–7.2**	1.6 0.9–2.8	1.1 0.9–1.4
Acoustic neuroma (n = 243)			
Wireless phone	-	**2.2** **1.3–3.7**	**1.5** **1.1–2.0**
Mobile phone	**3.0** **1.4–6.2**	**2.6** **1.5–4.6**	**1.7** **1.2–2.3**
Cordless phone	2.3 0.6–8.8	1.0 0.3–2.9	**1.5** **1.04–2.0**

Note: Bold = statistically significant. Number of controls = 2438 in analyses of glioma (living and deceased controls), 2162 for meningioma and acoustic neuroma (only living controls). Only living cases and controls included in analyses of ipsilateral use of mobile and cordless phones.

Adjustment was made for age, gender, socioeconomic-code and year of diagnosis. For glioma adjustment was also made for vital status.

Source: Hardell et al., 2006b, 2006c, 2010, 2011a.

Table 21.2 Odds ratio (OR) and 95 % confidence interval (CI) for glioma, meningioma and acoustic neuroma in different age groups for age at first use of a mobile phone

	Glioma (n = 1148)	Meningioma (n = 916)	Acoustic neuroma (n = 243)
	OR, (CI)	OR, (CI)	OR, (CI)
Mobile phone	**1.3** **(1.1–1.6)**	1.1 (0.9–1.3)	**1.7** **(1.2–2.3)**
< 20 years old	**3.1** **1.4–6.7**	1.9 0.6–5.6	**5.0** **1.5–16**
20–49 years old	**1.4** **1.1–1.7**	1.3 0.99–1.6	**2.0** **1.3–2.9**
≥ 50 years old	**1.3** **1.01–1.6**	1.0 0.8–1.3	1.4 0.9–2.2

Note: Bold = statistically significant. Number of controls=2438 in analyses of glioma (living and deceased controls), 2162 for meningioma and acoustic neuroma (only living controls).

Adjustment was made for age, gender, socioeconomic-code, year of diagnosis. For glioma adjustment was also made for vital status.

Source: Hardell et al., 2006b, 2006c, 2010, 2011a.

21.9 The Interphone study 2000–2010: disagreements and delays

The Interphone study was an international collaboration on brain tumour risk and mobile phone use conducted under the guidance of IARC, which is an independent agency of WHO. The investigation was inititated by recommendations from several expert groups to study possible health effects of exposure to RF-fields (McKinlay, 1997; Cardis et al., 2007). It was conducted at 16 research centres in 13 countries during varying time periods between 2000 and 2004. It cost nearly EUR 20 million of which industry contibuted 5.5 million (IARC, 2010) ([11]).

Some of the separate country analyses of the Interphone study produced different results, with some being positive i.e. finding increased brain tumour risks, and some negative i.e. finding decreased risks, i.e. seemingly a 'protective' effect of the radiation.

The authors therefore found it hard to come to an agreed conclusion and there was a 4 year delay between publication of the country results and of the overall study results. One group reportedly thought that the Interphone study overall had found indications of a positive link between mobile phone use and brain tumours, especially when the results of the 10+ year exposure group were analysed separately. Another group thought that they had found no indication of a risk and that the apparent excess of brain tumour was an artifact of the study design and methodology. A third group could agree to neither position.

The publication of the overall Interphone results was finally initiated by the Director of IARC, Christopher Wild, who brokered sufficient agreement between the scientists to finally get the results published in May 2010.

No association between mobile phone use and meningioma was found in the overall Interphone results whereas subgroup analyses showed statistically significant increased risk for glioma in the highest exposure group, i.e. those who had used their mobile phones for 1 640 hours or more, which corresponds to about half an hour of use per day for ten years (Interphone Study Group, 2010), OR = 1.40 (95 % CI = 1.03–1.89). The risk increased further for ipsilateral exposure (OR = 1.96, 95 % CI = 1.22–3.16) and for tumours in the most exposed part of the brain, the temporal lobe, (OR = 1.87, 95 % CI = 1.09–3.22) in the highest exposure group for glioma.

However, the compromise reached between the opposing scientists involved the juxtaposition of two contrasting sentences that were pointing in different directions: *There were suggestions of an increased risk of glioma, and much less so meningioma, at the highest exposure levels, for ipsilateral exposures and, for glioma, for tumours in the temporal lobe* followed by *…biases and errors limit the strength of the conclusions we can draw from these analyses and prevent a* ***causal*** [our emphasis] *interpretation* (Interphone Study Group, 2010).

There was no explanation about how the strength of a link between a cause and an effect can vary from a 'scientific suspicion of risk' to a 'strong association' through 'reasonable certainty' and on to 'causality' which requires the strongest of evidence. This continuum in strengths of evidence, which was illustrated in Bradford Hill's paper written at the height of the tobacco and lung cancer controversy (Hill, 1965), was not explained in the Interphone paper. This meant that the media and the public could assume that 'not causal' meant 'no link' between mobile phones and brain tumours. Other epidemiologists did pick up this rather significant nuance.

In an Editorial accompanying the Interphone results (Saracci and Samet, 2010), published in the International Journal of Epidemiology, the main conclusion of the Interphone results, was described as *both elegant and oracular…(which) tolerates diametrically opposite readings*. They also pointed out several methodological reasons why the Interphone results were likely to have underestimated the risks, such as the short latency period since first exposures became widespread: less than 10 % of the Interphone cases had more than 10 years exposure.

None of the today's established carcinogens, including tobacco, could have been firmly identified as increasing risk in the first 10 years or so since first exposure.

The 'oracular' concluding sentences from the Interphone study therefore allowed the media to report opposite conclusions. For example, on 17 May, 2010 the UK Daily Telegraph reported that the Interphone study provided evidence of a brain tumour risk from mobile phones (http://

([11]) The Hardell studies cost approximately EUR 410 000 and were financed by the Swedish Work Environment Fund, Cancer- och Allergifonden, Cancerhjälpen, Telia, Fondkistan, and the Örebro University Hospital Cancer Fund.

www.telegraph.co.uk/health/7729676/Half-an-hour-of-mobile-use-a-day-increases-brain-cancer-risk.html) whilst the BBC News reported on the same day that there was no risk (http://news.bbc.co.uk/2/hi/health/8685839.stm). This conflicting media reporting pattern was widely repeated elsewhere ([12]).

Further confusion for the public and policymakers followed as a result of the differences in the statements of the Interphone scientists reported in the media. For example, Microwave News reported on 17 May that Elisabeth Cardis, the coordinator of the Interphone study, thought that *Overall...the results show a real effect*; Bruce Armstrong, the Australian Interphone participant, thought that *It shows some indication of an increased risk of gliomas, but I cannot say this with certainty;* and Siegal Sadetzki from Israel thought the results had consistency in indicating a risk but, whilst not *strong enough for a* ***causal*** [our emphasis] *interpretation, they are sufficient to support precautionary policies* (http://www.microwavenews.com/Interphone.Main.html).

In contrast, another co-author, Feychting, thought, *the use of mobile phones for over ten years shows no increased risk of brain tumours* (http://www.i-sis.org.uk/EEA_Highlight_Mobile_Phone_Cancer_Risks.php) and Ahlbom, also from the Swedish Interphone part, told Chinese Television that *there is nothing in these data or in previous data, really, to indicate that there is any risk involved in this* (http://www.youtube.com/watch?v=TllmreWZdoA).

In later publications of Interphone data the estimated RF dose from mobile phone use in the tumour area was also associated with an increased risk for glioma in parts of the Interphone group. The OR increased with increasing total cumulative dose of specific energy (J/kg) absorbed at the estimated tumour centre for more than 7 years before diagnosis with an OR of 1.91 (95 % CI = 1.05–3.47) in the highest quintile of exposure (Cardis et al., 2011).

This important result, which for the first time linked amount of radiation absorbed (rather than just its proxy which is years of exposure/cumulative hours of use) to tumour induction, received very little media attention.

A similar study based on less sound methods was later published by another part of the Interphone study group, see below (Larjavaara et al., 2011).

Results have also now been published for **acoustic neuroma** (Interphone study group, 2011). An increased risk was found for start of *ipsilateral* mobile phone use ≥ 10 year before reference date and cumulative use ≥1 640 h; OR = 3.74 (95 % CI = 1.58–8.83).

The total Interphone results for tumours of the parotid gland ([13]) have never been published. Since the IARC has now terminated the Interphone study ([14]) only the results from Sweden (Lönn et al., 2006) and Israel (Sadetzki et al., 2008) are available. Subgroup analyses that considered laterality (side of use and risk of tumour) and/or amount of use (cumulative hours) indicated increased risks. However, results from other studies do not indicate a consistent pattern of increased risk (Auvinen et al., 2002; Hardell et al., 2004; Duan et al., 2011; Söderqvist et al., 2012a). Results on long-term use are, however, scarce.

21.10 Some reviews and discussions of the Hardell group and Interphone studies

There are by now several meta-analyses and reviews on mobile phones and cancer and they describe the challenges of doing epidemiology on this issue, the methodological limitations of the major studies published so far and the difficulties of interpreting their results.

For example, several of the Interphone findings display differential misclassification of exposure due to observational and recall bias which would tend to underestimate the risk. There were low participation rates for both cases and controls in the Interphone studies, for example in some countries only about 50 % of the cases and about 40 % of the controls participated. This is to be compared with 90 % response rate for cases with malignant brain tumours, 88 % for benign and 89 % for controls in the Hardell-group studies on living subjects (Hardell et al., 2006b, 2006c). Deceased cases were included in the calculations of participation in Interphone, but in

([12]) The EEA had anticipated this confusion and had earlier proposed to IARC that the conflicting opinions of the different Interphone groups should be published alongside each other, with their different arguments and data interpretations clearly illustrated in the same scientific article. This would have helped the media and the public to better understand the reasons for the divergent views amongst the Interphone scientists. However, this suggestion was not adopted.
([13]) A tumour in a gland on the cheek in front of the ear.
([14]) According to the official website (http://interphone.iarc.fr/) the Interphone Study was completed in February 2012.

the Hardell studies deceased cases were included in a separate sub-study on malignant brain tumours.

About 40 % of the cases were interviewed at hospitals in the Interphone studies. Further, it was always known to the interviewer if it was a case or a control that was interviewed. Use of cordless phones was not properly assessed in the Interphone study, or at least not reported. Further discussion on these methodological points may be found elsewhere (Hardell et al., 2008; Kundi, 2009).

Myung et al. (2009) subsequently compared methods and results in all the published studies on the use of mobile phones and the risk for brain tumours. They concluded that the Hardell studies were of higher quality compared with the Interphone study based on the Interphone results from different countries that were then available.

However, one important issue was not covered in the Myung et al. (2009) review, namely that the Hardell group also assessed use of cordless phones in contrast to the Interphone study group. RF-EMF emissions from a cordless phone are of the same magnitude as that from a digital mobile phone, something that has been pointed out several times (Hardell et al., 2006d; Kundi, 2009; Redmayne et al., 2010). Moreover cordless phones are typically used for longer calls than mobile phones (Hardell et al., 2006b, 2006c). Including cordless phone use in the 'unexposed' group, as was done in the Interphone study, would bias estimates against a risk.

The use of bedside interviews of cases, as in the Interphone study, can be a major disadvantage and is ethically questionable. At that time the patient has not fully recovered from e.g. surgery, may not have been fully informed about the diagnosis, treatment and prognosis and may even be under sedation by drugs. In fact patients scored significantly lower than controls due to problems in recalling words (aphasia), problems with writing and drawing due to paralysis in the Danish part of Interphone (Christensen et al., 2005). Obviously observational bias could have been introduced thereby during these bedside interviews.

In contrast, the Hardell group cases received a postal questionnaire approximately 2 months after diagnosis and could give the answers in a relaxed manner, a situation similar to the controls. All cases and controls were later interviewed over the phone to verify and clarify different exposures. This was done blinded as to case or control status.

The possibility of recall and observational bias was investigated in the second case-control study by Hardell et al. (2002). Use of a wireless phone was similar among cases and controls regardless if they reported a previous cancer or if a relative helped to fill in the questionnaire. Potential observational bias during phone interviews was analysed by comparing change of exposure in cases and controls after these interviews. No significant differences were found, showing that the results could not be explained by observational bias: for further details see discussion in that publication (Hardell et al., 2002). All interviews were performed by trained persons using structured instructions and protocols.

The article by Myung et al. was commented on by e.g. Rowley and Milligan (2010) representing the mobile phone industry. They claimed that the Interphone studies were independent of industry influence. However, the mobile phone industry provided 5.5 million euro for the Interphone study and additional funding was provided by the industry in some countries. Furthermore, according to the study protocol *Other parties may also be involved in the Study Group as observers or consultants. These may include representatives of industry, other concerned organisations...* In addition, *representatives of industry and other concerned organisations… shall be informed shortly (maximum of seven days) before publication,* and before the scientific community and laymen have access to the study results (IARC, 2001).

Rowley and Milligan claim that there is *evidence of selection, information, and recall bias, and unusually high reported participation rates* in the Hardell studies (Rowley and Milligan, 2010). These ad hoc statements are not substantiated by the authors or in their references. A high participation rate is a pre-requiste for high quality in case-control studies.

Other scientists have analysed the Hardell results more favourably (Kundi, 2009; Myung et al., 2009; Mead, 2009; Cardis and Sadetzki, 2011; Levis et al., 2011) and IARC relied mainly on the Hardell group and Interphone study group results for its evaluation of the RF evidence.

The Cardis review was particulary interesting as she was the coordinator of the Interphone study. In the review with Sadetzki, another Interphone study participant, they concluded, after a full discussion of the methodological strengths and weaknesses of the Hardell and Interphone studies, that:

> *It is not possible to evaluate the magnitude and direction of the different possible biases on the study results and to estimate the net effect of mobile phones on the risk of brain tumours. The overall balance of the above mentioned arguments,*

> *however, suggest the existence of a possible association* (i.e. between mobile phones and brain tumour).

They ended by concluding that:

> *Simple and low cost measures, such as the use of text messages, handsfree kits and/or the loudspeaker mode of the phone could substantially reduce exposure to the brain from mobile phones. Therefore, until definitive scientific answers are available, the adoption of such precautions, particularly among young people, is advisable* (Cardis and Sadetzki, 2011, p. 170).

21.11 IARC evaluation of the carcinogenicity of RF-EMFs 2011

In 2011 IARC evaluated the carcinogenic effect to humans for RF-EMF emissions during a 8 days (24–31 May) meeting at Lyon in France. This included all sources of radiofrequency radiation, not only mobile and cordless phones. Regarding use of wireless phones all of the published studies by the Hardell group were included as well as overall results for Interphone (Interphone Study Group, 2010, 2011; Cardis et al., 2011). The results on glioma are similar in the Hardell group and Interphone studies if the same inclusion and exclusion criteria are used (Hardell et al., 2011b). This is in contrast to widespread claims that the results of the two sets of studies differed significantly.

The IARC Working Group consisted of 30 scientists ([15]) representing four areas: 'animal cancer studies', 'epidemiology', 'exposure' and 'mechanistic and other relevant data'. The different expert groups had initially a draft written before the meeting by some of the experts. Further work was done in the expert groups and a final agreement, sentence by sentence, was obtained during plenary sessions with all experts participating.

The Working Group concluded that there is 'limited evidence in humans' for the carcinogenicity of RF-EMF, based on positive associations between glioma and acoustic neuroma and exposure to RF-EMF from wireless phones. This conclusion was based on the Interphone study and the Hardell group studies. No conclusions could be drawn from the Danish cohort study on mobile phone subscribers due to considerable misclassification in exposure assessment (Baan et al., 2011).

The final conclusion was obtained by voting by all 30 scientists and there was a very large majority for the conclusion that RF-EMF radiation is 'possibly carcinogenic' to humans, Group 2B, based also on occupational studies.

21.12 Some responses to the IARC conclusion

It is interesting to see that even the authoritative IARC evaluation has been interpreted very differently by different groups.

To date, no adverse health effects have been established as being caused by mobile phone use. This was stated in a fact sheet in June 2011 from WHO EMF Program after the IARC decision (http://www.who.int/mediacentre/factsheets/fs193/en/), and furthermore that *Tissue heating is the principal mechanism of interaction between radiofrequency energy and the human body* without acknowledging any of the non-thermal effects that could explain the evidence on brain tumours (Guiliani and Soffriti, 2010).

Michael Milligan from the Mobile Manufacturers Forum (MMF) said:

> *…After reviewing the available scientific evidence, it is significant that IARC has concluded that RF electromagnetic fields are not a definite nor a probable human carcinogen…* (http://www.mmfai.org/public/docs/eng/MMF_PR_310511_IARC.pdf).

Jack Rowley from GSM Association (GSMA) said:

> *…The IARC classification suggests that a hazard is possible but not likely…* (http://www.gsma.com/articles/gsma-statement-on-the-iarc-classification/17567/).

([15]) David Gee of the EEA had been invited by IARC to join the group as 'a representative of your organization, rather than as an observer' (for a definition of representatives and observers, please see the Preamble: http://monographs.iarc.fr/ENG/Preamble/currenta5participants0706.php). However, a few days before the IARC meeting began the EEA wrote to IARC to say they were withdrawing because of further delays in publishing the full Interphone results and because of the intellectual bias of Ahlbom who was then the Chair of the epidemiology group for the meeting. The day before the meeting began Ahlbom was removed from the Chair by IARC as a result of a reported conflict of interest: and the meeting was also given part of the unpublished Interphone data. However, this was too late for the EEA to then participate.

Patrick Frostell from the Federation of Finnish Technology Industries (FFTI) said:

> *…IARC's classification is in line with the dominant interpretation of current research data, according to which radiofrequency electromagnetic fields are neither carcinogenic to humans nor probably carcinogenic to humans…* (http://www.teknologiateollisuus.fi/en/news/announcements/2011-6/no-change-in-international-assessment-of-the-health-effects-of-mobile-phones).

Professor **Dariuz Leszczynski** from the Finnish Radiation and Nuclear Safety Authority (STUK) and member of the IARC expert panel wrote:

> *Recent IARC evaluation of mobile phone radiation potential to cause cancer and classification of it as a 2B carcinogen has caused a stir of pro and contra opinions among the scientists, industry and news media. Unfortunately, the only outcome of this broad attention leads to only one — **confusion**. Regular mobile phone user, whether highly or not so highly educated, can only be **confused** by this flurry of contradictory opinions and spin-statements* (http://betweenrockandhardplace.wordpress.com/2011/06/29/%e2%80%a2viva-confusion/).

The Economist wrote:

> *..your correspondent thinks the whole brouhaha over mobile phones causing brain cancer is monumentally irrelevant compared with all the other things there are to worry about* (http://www.economist.com/blogs/babbage/2011/06/mobile-phones-and-health).

Microwave News has followed this area for a long time. Much of the whole IARC story and the aftermath can be found at its website, for example regarding ICNIRP's standpoint:

> *ICNIRP is a self-perpetuating group that declines to disclose its finances. Its Standing Committee on Epidemiology, which wrote the new commentary, has only welcomed the like-minded. Its previous chairman, Anders Ahlbom, has also registered his opinion that cell phone tumor risks are nonexistent. (He was the lead author of the last ICNIRP review of cell phones and cancer.) Another former member, Maria Blettner, was the lone dissenting voice in the final vote of the IARC working group. Both Blettner and Ahlbom worked on Interphone* (http://www.microwavenews.com/ICNIRP.Interphone.html).

Perhaps even IARC has contributed to this confusion by seeming to agree with the largely non-positive but much criticized Danish cohort study, see below (http://www.microwavenews.com).

No doubt the IARC decision started a world-wide spinning machine perhaps similar to the one launched by the tobacco industry when IARC was studying and evaluating passive smoking as a carcinogen in the 1990s (Ong and Glanz, 2000) ([16]). Sowing confusion and 'manufacturing doubt' is a well known strategy used by the tobacco and other industries (Michaels, 2008; McGarity and Wagner, 2008; Oreskes and Conway, 2010).

21.13 Some further studies published since the IARC conclusion

The Nordic part of Interphone published a study relating brain tumour location to mobile phone radiation (Larjavaara et al., 2011). The results seemed to contradict the findings by Cardis et al. (2011) as discussed above, but used a different, less clear method. Only 42 cases had used the mobile phone for more than 10 years and no analysis was made of the highest exposed group with longest duration of use. Thus, this study is much less informative and less sophisticated that the one by Cardis et al. (2011).

In Denmark a cohort of mobile phone subscribers was designed and started in cooperation between The International Epidemiology Institute (IEI), Rockville, MD, USA, and the Danish Cancer Society. The cohort was established by grants from two Danish telecom operation companies (TeleDenmark Mobil and Sonafon), by IEI, and by the Danish Cancer Society. The source of money for the IEI has not been disclosed.

([16]) In the early 1990s the Philip Morris tobacco company feared that an IARC study and a possible IARC monograph on second-hand smoke would lead to increased restrictions in Europe so they spearheaded an inter-industry, three-prong strategy to subvert IARC's work. The scientific strategy attempted to undercut IARC's research and to develop industry-directed research to counter the anticipated findings. The communications strategy planned to shape opinion by manipulating the media and the public. The government strategy sought to prevent increased smoking restrictions. The IARC study cost USD 2 million over ten years; Philip Morris planned to spend USD 2 million in one year alone and up to USD 4 million on research (Ong and Glanz, 2000).

Box 21.3 IARC and its classifications of carcinogens

IARC evaluates the *hazard* from potential carcinogens, i.e. 'an agent that is capable of causing cancer under some circumstances', while a cancer *risk* is an estimate of the carcinogenic effects expected from an exposure to a cancer hazard. The IARC monographs are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title.

IARC has categorised nearly 1000 potentially carcinogenic **hazardous** agents, that it has studied over the last 40 years, into 5 classifications. These are differentiated by different strengths of evidence. In *descending order of strengths of evidence* they are: **Group 1**, which are '**established'** human carcinogens, such as asbestos, diesel engine exhaust, tobacco, and X-rays (*108 agents*); **Group 2A**, which are **probable** carcinogens, such as perchloroethylene (*64 agents*); **Group 2B,** which are **possible carcinogens,** such as other traffic fumes, lead, DDT and now radiofrequency electromagnetic fields, including mobile phones (*272 agents*); **Group 3**, where the agent is **not classifiable** because the evidence is inadequate and does not permit another classification *(508 agents);* and **Group 4**, where the agent is **probably not carcinogenic to humans,** based on fairly strong evidence *against* a cancer effect in both humans and animals (*1 agent*) (IARC, 2012).

It may be helpful to clarify the meaning of the particularly contentious groups. i.e. 2A and 2B.

IARC chooses 3 main different strengths of evidence when it is evaluating the different types of cancer evidence that may be available. The evidence evaluated comes mainly from humans; from animals; and from consideration of the biological mechanisms for cancer causation: this last can provide understanding about *how* carcinogens cause cancer, in contrast to *whether* they cause cancer.

The main strengths of evidence groups used by IARC are: 'sufficient', 'limited', and 'inadequate'. For example, while Group 1 consists of those agents where there is 'sufficient evidence of carcinogenicity' in humans; Group 2A includes those agents where there is 'limited evidence of cancer in humans' but 'sufficient evidence of cancer in animals'; and Group 2B, which is the radiofrequency EMF category, is those agents where there is 'limited evidence of cancer in humans and less than sufficient evidence in animals' and where 'chance, bias or confounding cannot be ruled out with reasonable confidence'. 'Evidence suggesting lack of carcinogenicity' is used for Group 4 (IARC, 2006, p. 19–20).

Different agents in the same classification group are evaluated on the basis of very different kinds of evidence and exposure conditions that are specific for each substance. Some 2B agents will be at the lower end of the probability range, others will be close to the nearly one in two probability and the rest are somewhere in between, depending on their very specific characteristics. By loosely lumping together several randomly chosen carcinogens from the 271 in Group 2B such as dry cleaning fumes and coffee, which invites comparison to mobile phones, journalists and others help to complicate the already difficult discussion about the likelihood of cancer risks. Each agent needs to be considered on its own evidence.

The first results from the Danish study on brain tumour risk among mobile phone subscribers were published in 2001 and updated in 2006 and 2011 (Johansen et al., 2001; Schüz et al., 2006, 2011; Frei et al., 2011). It included subjects from 1 January, 1982 until 31 December, 1995 identified from the computerized files of the two Danish operating companies, TeleDenmark Mobil and Sonafon. A total of 723 421 subscribers were identified but the initial cohort consisted of only 58 % of these subscribers.

The IARC working group's main reason for not using the Danish study as evidence for its evaluation was that it *could have resulted in considerable misclassification in exposure assessment* (Baan et al., 2011).

The authors of the Danish study have themselves pointed out the main causes of such considerable exposure misclassification (Frei et al., 2011): mobile phone subscription holders not using the phone were classified as 'exposed'; non-subscribers using the mobile phone were classified as 'unexposed'; corporate subscribers of mobile phones (200 507 people), which are likely to have been heavy users, were classified as 'unexposed'; persons with a mobile phone subscription later than 1995 (which is over 80 % of the Danish population) were classified as 'unexposed'; and many users of cordless phones, which Hardell et al. have linked to excess risks of brain cancers, were also classified as 'unexposed'.

Other limitations are the absence of analysis by laterality (the side of head were the phone is used in relation to the side of the tumour) and the complete absence of actual exposure data. These and other shortcomings in this cohort study have been discussed elsewhere in more detail (Ahlbom et al., 2007; Söderqvist et al., 2012b).

It is clear from these limitations that the authors conclusion that 'In this update of a large nationwide cohort study of mobile phone use, there were no increased risks of tumours of the central nervous system, providing little evidence for a causal association' is not soundly based (Frei et al., 2011).

21.14 Need for monitoring long term trends in country wide nervous system tumours

It has been suggested that overall incidence data on brain tumours for countries may be used to qualify or disqualify the association between mobile phones and brain tumours observed in the case-control studies (Aydin et al., 2011; Ahlbom and Feychting, 2011; Deltour et al., 2012; Little et al., 2012). In support of the findings that Frei et al. (2011) presented for Denmark, Ahlbom and Feychting (2011) refer to data on overall brain tumour incidence from the Swedish Cancer Registry (which does not show an overall increase in brain tumour incidence since the 1990s) rather than from the Danish Cancer Registry which would have been more relevant.

The quality of the Swedish Cancer Registry in reporting of central nervous system tumours, particularly high grade glioma, has been seriously questioned (Bergenheim et al., 2007; Barlow et al., 2009). In the Deltour et al. paper (2012) Sweden accounted for about 40 % of the population and cases. Thus, underreporting of brain tumour cases to the Swedish Cancer Register would make the conclusions in the Deltour et al. study less valid.

In Denmark a statistically significant increase in incidence rate per year for brain and central nervous system tumours (combined) was seen during 2000–2009, in men +2.7 % (95 % CI = 1.1 to 4.3) and in women + 2.9 % (95 % CI = 0.7 to 5.2) (NORDCAN). Recently updated results for brain and central nervous system tumours were released in Denmark. The age-standardized incidence of brain and central nervous system tumours increased by 40 % among men and by 29 % among women between 2001–2010 (Sundhedsstyrelsen, 2010).

A more recent news release based on the Danish Cancer Register states that during the last 10 years there has been an almost 4-fold increase in the incidence of the most malignant glioma type, glioblastoma (http://www.cancer.dk/Nyheder/nyhedsartikler/2012kv4/Kraftig+stigning+i+hjernesvulster.htm). So far these incidence data are not generally available.

Little et al. (2012) studied the incidence rates of glioma during 1992–2008 in the United States and compared the results with odds ratios for glioma associated with mobile phone use in the 2010 Interphone publication (Interphone Study Group, 2010) and the Hardell group pooled results published in 2011 (Hardell et al., 2011a). However, an important methodological issue that was not stated in the abstract or in Figures, but can be found in the web appendix, is that observed rates were based on men aged 60–64 years from the Los Angeles SEER registry as the baseline category. These data were used to estimate rates in the entire dataset, men and women aged ≥ 18 years and all 12 SEER registries. Thereby numerous assumptions were made. The conclusion by Little et al. that 'Raised risk of glioma with mobile phone use, as reported by one (Swedish) study … are not consistent with observed incidence trends in the US population data...' goes far beyond scientific evidence and what would be possible to show with the faulty methods used in the study. On the contrary, it is of interest that they in fact showed statistically significant yearly increasing incidence of high-grade glioma in the SEER data for 1992–2008, + 0.64 %, 95 % CI 0.33 to 0.95, a result not commented further by the research group.

Much care is needed when using *descriptive* data, as in Aydin et al. (2011), Deltour et al. (2012) and Little et al. (2012), to dismiss results from *analytical* epidemiology. In addition to methodological shortcomings, there might be other factors that influence the overall incidence rate such as changes in exposure to other risk factors for brain tumours that are unknown in descriptive studies. Cancer incidence depends on initiation, promotion and progression of the disease (Hazleton et al., 2005). As the mechanism for RF-EMF carcinogenesis is unclear it supports the view that descriptive data on brain tumour incidence is of limited value.

21.15 Concluding remarks

It is sometimes claimed by the telecommunications industry and others that:

- the scientific basis for the current ICNIRP limits for exposure to EMF is adequate to protect the public from cancer risks;
- that children are no more sensitive than adults to the RF from mobile phones;
- that there are no biologically significant effects from **non-thermal** levels of EMF, and
- that, if there are such effects, there are no acceptable mechanisms of action that could explain these effects.

However the recent 400-page review by the Ramazzini Institute and The International Commission for Electromagnetic Safety (ICEMS) provides a wealth of evidence on the non–thermal biological and ecological effects of EMF (Giuliani and Soffritti, 2010). The EEA summarised the main findings of this report in its evidence to the Council of Europe' hearing on RF and mobile phones in 2011 (EEA, 2011a, 2011b).

Results from the Hardell-group as well as from the Interphone group show an increased risk for glioma and acoustic neuroma associated with long term mobile phone use. Also use of cordless phones increases the risk when properly assessed and analysed. The risk is highest for ipsilateral exposure to the brain of RF-EMF emissions. Adolescents seem to be at higher risk than adults. For meningioma there is no consistent pattern of increased risk.

Furthermore, of interest is that in the same studies different results were obtained for different tumour types. This strongly argues against systematic bias as an explanation of the findings. In that case the results would have been similar regardless of tumour type.

The IARC conclusion that RF-EMF emissions overall, e.g. occupational and from wireless phones, are possibly carcinogenic to humans, Group 2B (Baan et al., 2011) has been questioned by e.g. members of ICNIRP (Swerdlow et al., 2011). That article appeared online 1 July, 2011, one month after the IARC decision, and concluded that *the trend in the accumulating evidence is increasingly against the hypotheses that mobile phone use can cause brain tumors in adults*. There has also been unfounded attacks on individual researchers as exemplified in this article, a pattern that repeats similar experiences in the asbestos, lead and tobacco histories. Published results on health effects are questioned by using obscure methods and citing single results out of context without considering the overall pattern.

There is a lack of investigating journalists who can produce nuanced reports in the media. Most journalists seem to make only reference to news reports or press releases without making their own evaluations or without seeming to have read the original articles. Many limitations of epidemiological studies are to be found in the text, but rarely in the abstract which is most often all that is read. Without accurate and reliable reporting in the media the public do not get a robust and consistent information on potential health risks to make their own judgements about how precautionary they should be.

It is remarkable that the IARC carcinogenic classification does not seem to have had any significant impact on governments' perceptions of their responsibilities to protect public health from this widespread source of radiation, especially given the ease with which exposures can be reduced (i.e. texting, handsfree devices and better phone design).

Independent research into the many unknowns about the biological and ecological effects of RF radiations are urgently needed, given the global exposure of over 5 billion people and many other species, especially those, like bees and some birds whose navigation systems are possibly being affected by such radiations (Balmori, 2005, 2009; Sharma and Kumar, 2010), and effects on breeding of wild birds (Everaert and Bauwens, 2007). Research could be in part funded by relevant industries from levies on phones and masts but used independent from their influence.

The benefits of mobile telecommunications are many, but, as with other case studies in the *Late lessons from early warnings* Volume 1 (EEA, 2001) and the present report, such benefits need not to be accompanied by the possibility of widespread harms. Precautionary actions now to reduce head exposures, as pointed out by the EEA in 2007, and many others since, would limit the size and seriousness of any brain tumour risk that may exist. Reducing exposures may also help to reduce the other possible harms that are not considered in this case study.

21.16 Epilogue

The Italian Supreme Court affirmed a previous ruling that the Insurance Body for Work (INAIL) must grant worker's compensation to a businessman who had used wireless phones for 12 years and developed a neurinoma in the brain (http://www.applelettrosmog.it/public/news.php?id_news=44;

http://microwavenews.com/news-center/italian-supreme-court-affirms-tumor-risk). He had used both mobile and cordless phones for five to six hours per day preferably on the same side as the tumour developed. The neurinoma was located in the trigeminal Gasser's ganglion in the brain. This 5th cranial nerve controls facial sensations and muscles. It is the same type of tumour as the acoustic neuroma in the 8th cranial nerve located in the similar area of the brain. Although neurinoma is a benign tumour it causes persistent disabling symptoms after treatment with neurological impairment that severely affects the daily life. The Italian case fulfils the criteria for a causal association; more than 10 years use of wireless phones, high cumulative exposure on the same side as the tumour appeared, and a tumour type that would be predicted based on previous research on use of wireless phones and brain tumour risk. No further appeal of the Supreme Court decision is possible.

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