SECTION 10

Effects of Electromagnetic Fields From Wireless Communication upon the Blood-Brain Barrier

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I. INTRODUCTION

The Blood-Brain Barrier

Some organs of crucial importance for the function of our bodies are protected from exposure to potentially harmful compounds in the blood. Thus the brain, the eyes (which are protrusions of the brain), the testes and the follicles of the ovaries have special barriers between the capillaries and the tissue. In the normal brain, the passage of compounds over this barrier, the Blood-Brain Barrier (BBB), is highly restricted.

The BBB is a hydrophobic barrier formed by the vascular endothelial cells of the capillaries in the brain with tight junctions between them leaving no openings between the vessel lumen and the surrounding brain. The existence of the mammalian BBB was discovered in the late 19th century by the German bacteriologist Paul Ehrlich and his student, Edwin Goldman. Paul Ehrlich found, that when he injected dyes into the systemic blood circulation, the brain tissue did not take up any of the stain. A barrier surrounding the brain tissue at the site of the brain micro vessels seemed to be a logic explanation to these findings.

There is scientific evidence that the BBB exists not only in vertebrates, but also in insects (1), crustaceans and cephalopod molluscs (such as the cuttlefish) (2) and in elasmobranchs (cartilaginous fishes such as sharks) (3) and helices (landsnails) (4), maintaining ionic integrity of the neuronal bathing fluid.

The BBB seems to be present very early in the foetal development. Also, at an early stage, there seems to be a cerebrospinal fluid barrier, which excludes cerebrospinal fluid (CST) protein from the brain extracellular space (5).

BBB Anatomy and Physiology

The tight junctions of the BBB are composed of tight junction proteins (occludin, claudin and zonula occludens, where the zonula occludens is the intracellular peripheral membrane protein that anchors claudin and occludin to the actin cytoskeleton (6). An important part is

the binding of claudin proteins on opposing membranes, where claudin-5 in particular is crucial in the BBB (7). Astrocytes are surrounding the outer surface of the endothelial cells with protrusions, called end feet, and are implicated in the maintenance, functional regulation and repair of the BBB. The astrocytes form a connection between the endothelium and the neurons and constitute a second barrier to hydrophilic molecules (see Figure 1).

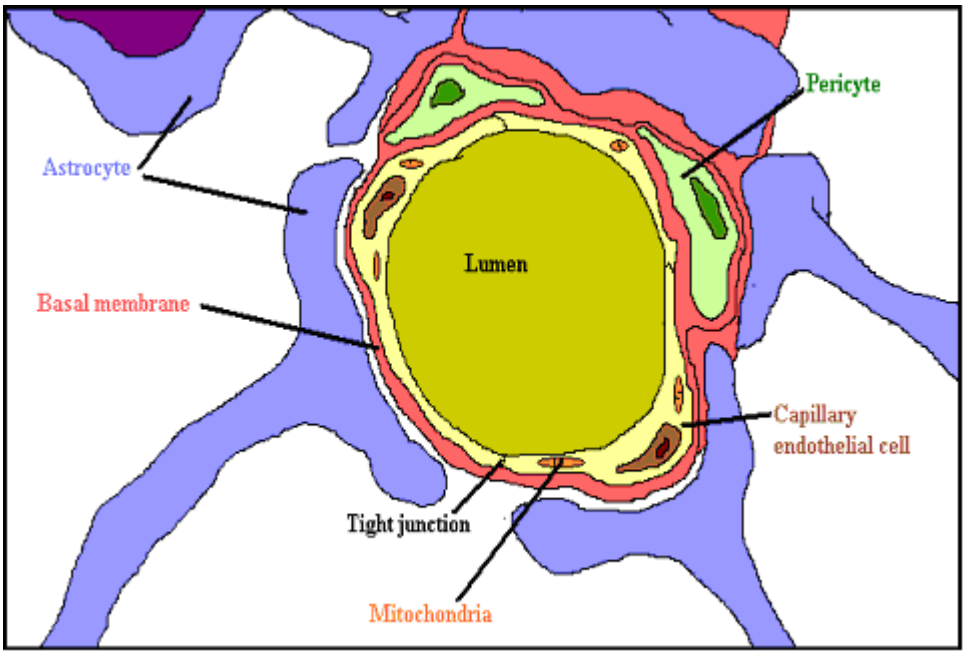

Fig. 1. The mammalian BBB

Other periendothelial accessory structures of the BBB include pericytes and a bilayer basal membrane which surrounds the endothelial cells and pericytes. The basement membrane (basal lamina) supports the ablumenal surface of the endothelium and may act as a barrier to passage of macromolecules. The pericytes are a type of macrophages, expressing macrophage markers with capacity for phagocytosis but also for antigen presentation. In fact, the pericytes, which cover about 25% o the capillary surface (8), seem to be in a position to significantly contribute to central nervous system (CNS) immune mechanisms (9). The pericytes also have other functional roles: with their capability for contractility they seem to serve as a smooth muscle equivalent, and through regulation of endothelial cells they maintain the stability of blood vessels (9). Additionally, the pericytes seem to be highly involved in many diseases, both infectious and autoimmune, and also in other diseases such as Alzheimer's by production

of amyloid. Also, by regulating their vascular permeability, the pericytes are supposed to play an important role in inflammatory diseases (9).

Physiologically, the microvasculature of the central nervous system (CNS) differs from that of peripheral organs. It is characterized not only by its tight junctions, which seal cell-to-cell contacts between adjacent endothelial cells, but also by the low number of pinocytotic vesicles for nutrient transport through the endothelial cytoplasm and its lack of fenestrations, and the five-fold higher number of mitochondria in BBB endothelial cells compared to muscular endothelia in rat (10). All this speaks in favour of an energy-dependent transcapillary transport. These above-described membrane properties of the BBB control the bidirectional exchange of molecules between the general circulation and the central nervous system. By at least four mechanisms, the endothelial cells directly control the flux of solutes into the brain parenchyma. Firstly, the tight junctions and low number of pinocytotic vesicles guarantee that proteins cannot pass freely into the brain parenchyma.
Secondly, solutes which are not highly lipid soluble, or which do not bind to selective transporters with high affinity, are excluded from free exchange. By means of this lipid solubility, carbon dioxide and oxygen, among many others, are able to enter the brain interstitial fluid passively, whereas the passage of, for example sugars and many amino acids, depends on other, active mechanisms. Thirdly, the BBB has a capacity to metabolize certain solutes, such as drugs and nutrients (11). Fourthly, active transporters maintain the levels of certain solutes at specific values within the brain interstitial fluid, made possible by active transport against the concentration gradients. These enzyme systems are differently distributed between the luminal and the ablumenal membranes of the endothelial cells, thus gaining the BBB polarity properties. For example, Na^+-K^+-ATPase is located on the antilumenal membrane (12).

It has been proposed that the active transport across the brain capillaries might be the most important mechanism for the regulation of the internal milieu within the brain parenchyma. Also, it has been proposed that this mechanism, requiring energy to function properly, might be the one most sensitive to disease and that interference with this active transport could play an important part in the neurological dysfunction seen in many metabolic disorders (12).

It is important to have information on possible differences between homo and other mammals. The mammalian brain at large seems to have a uniform anatomy of its BBB constituents

preserved through the evolution, and very little information about differences between mammalian species has been available. However, recently very interesting observations have been published. Humans have evolved protoplasmic astrocytes that are both larger (27-fold greater volume) and far more elaborate than their rodent counterparts. These astrocytes reside near blood vessels, and their processes contribute to the BBB (13). When the end feet of human and rodent protoplasmic astrocytes are compared, it is shown that nearly all astrocytes in both species contact the vasculature, but in the human brain, the end feet completely encompass the vessels while the rodent astrocytes form rosettes of end feet around the vasculature. The number of mithochondria is however equally abundant in human and rodent end feet (14).

Comparisons between mammalian species concerning enzymatic functions in the BBB are few in number. Similarities are described: mouse *vs* human (15) and rat *vs* human (16), while differences are demonstrated between rodent and dog BBB leading to the conclusion that the canine BBB may be preferable to that of the rat as a model for studies of glucose transport relevant to human brain (17).

In summary, the BBB serves as a regulatory system that stabilizes and optimizes the fluid environment of the brain's intracellular compartment (18-20). The intact BBB protects the brain from damage, whereas the dysfunctioning BBB allows influx of normally excluded hydrophilic molecules into the brain tissue. This might lead to cerebral oedema, increased intracranial pressure, and in the worst case, irreversible brain damage.

II. DISRUPTION OF THE BLOOD-BRAIN BARRIER

The normal selective permeability of the BBB can be altered in several pathological conditions such as epileptic seizures (21) or extreme hypertension (22)and also transient openings of the BBB might lead to permanent tissue damage (22). Considering the ensuing leakage of substances from the blood circulation into the brain tissue, harmful substances might disrupt the cellular balance in the brain tissue and in the worst case, even carcinogenic substances might pass into the brain tissue. It has also been shown that an increased permeability of the BBB is seen in cases of oxidative stress (23), where BBB dysfunction and

neurodegeneration were shown to be mediated through an excitotoxicity mechanism by the serine protease tissue plasminogen activator, with NO and $ONOO^-$ as downstream mediators (23).

Opening of the BBB thus can have detrimental effects and since it has been shown for a few decades that EMFs have the potency to increase the permeability of this barrier, a major debate is going on in society with increasing intensity. In the following, we try to clarify the actual status of the available evidence in the field.

Early Studies

In early studies on the effects of low-intensity EMFs on the BBB, various compounds were injected intravenously, followed by EMF exposure and comparisons of the penetration into the brain tissue between sham and exposed animals.

Frey et al. (25) found increases in the BBB permeability of rats to fluorescein after 30 min of exposure to both pulsed and continuous waves (CWs) at 1.2GHz with average power densities of $0.2mW/cm^2$. Similar observations were made in a study with 180 animals by Oscar and Hawkins (26). Exposure of anaesthetized rats for 20 min to 1.3GHz of pulsed EMFs with average power densities of $0.3mW/cm^2$ resulted in leakage of 14C-mannitol, dextran, and inulin into the cerebellar brain tissue, as well as inulin and dextran leakage from capillaries into hypothalamic and medullar tissue. Also, BBB permeability to mannitol was investigated in un-anaesthetised rats, which were exposed to pulsed radiation or sham exposed for 20 min. The animals were sacrificed at different time intervals after the exposure. BBB permeability was seen in the groups sacrificed 8 min and 4 h after exposure, but to a much lesser extent in those sacrificed after 8 h. Finally, the permeation of mannitol through the BBB was found to be a very definite function of exposure parameters such as power density, pulse width, and the number of pulses per second. However, in later studies, Oscar et al. (27) emphasised that changes of BBB permeability after microwave exposure partly could be explained by an increase of local cerebral blood flow. In accordance with this, they concluded that their initial findings (26) might be of less magnitude than originally thought (Table 1).

Effects of Radiofrequency/Microwave Radiation upon the BBB – A summary of Previous Studies

Table 1. BBB permeability after EMF exposure. (From Nittby et al. (24))

Reference	EMF Frequency (MHz)	Modulation, pulses per second (pps)	Duration of exposure	SAR (W/kg)	Effect on BBB permeability?	Total number of animals included in the study	Tracer or studied effect	Remark
Findings by the Lund Group								
Salford et al. 1994	915	CW and pulse-modulated with repetition rates of 8, 16, 50 and 200 /s	2 hours	0.016-5 W/kg	Yes	246 Fischer 344 rats	Albumin extravasation	
Persson et al. 1997	915	217, 50 Hz and CW	2-960 min	0.0004-0.95 W/kg	Yes	1002 Fischer	Albumin extravasation	

				average whole-body		344 rats		
Salford et al. 2003	915	GSM	2 hours	0.002-0.2 W/kg	Yes		Albumin extravasation and dark neurons	Effect was seen 50 days after the exposure
Eberhardt et al. 2008	915	GSM	2 hours	0.0002-0.2 W/kg	Yes	96 Fischer 344 rats	Albumin extravasation and dark neurons	Albumin extravasation 14 days after exposure, dark neurons 28 days after exposure
Mobile phone exposure								
Fritze et al. 1997	900	GSM	4 hours	0.3 to 7.5 W/kg	Yes		Albumin	Albumin extravasation only reported for SAR-values of 7.5 W/kg
Töre et al. 2001	900	GSM	2 hours	0.12; 0.5 and 2.0 W/kg	Yes	70 Sprague-Dawley	Albumin leakage, seen with fluorescein-labelled proteins	Albumin extravasation at SAR-values

								of 0.5 and 2.0 W/kg
Neubauer et al. 1990	2450	100 pps	30-120 min	Average 2 W/kg	Yes		Rhodamine-ferritin complex	No leakage at 1 W/kg at short-term exposure of 15 min
Tsurita et al. 2000	1439	TDMA	1 hour daily, for 2 or 4 weeks	Average whole-body 0.25 W/kg; peak in the brain of 2 W/kg	No	36 Sprague-Dawley rats	Evans blue, albumin	
Kuribayashi et al. 2005	1439	TDMA, 50 pps	90 min daily, for 1 to 2 weeks	Average brain power densities of 2 or 6 W/kg; average whole-body 0.29 or 0.87 W/kg	No	40 Fischer 344 rats	Three BBB-related genes; FICT-dextran and albumin extravasation	

Finnie et al. 2001	898.4	GSM	1 hour	Whole-body of 4 W/kg	No	60 mice	Albumin extravasation	
Finnie et al. 2002	900	GSM	1 hour daily, 5 days a week for 104 weeks	Average whole-body 0.25; 1.0; 2.0 and 4.0 W/kg	No	207 mice	Albumin extravasation	
Franke et al. 2005b	1800	GSM	1 to 5 days	Average 0.3 W/kg	No		Sucrose permeation	In vitro model of BBB
Schirmacher et al. 2000	1800	GSM	4 days	Average 0.3 W/kg	No		Sucrose permeation	In vitro model of BBB
Franke et al. 2005a	1966	UMTS	1 to 3 days	Average 1.8 W/kg	No		Sucrose and albumin permeation	In vitro model of BBB
Cosquer et al. 2005	2450	500 pps	45 min	Average whole-body 2 W/kg	No	Rats	Scopolamine methylbromide extravasation	Indirect investigation of BBB opening by performance in radial arm maze

RF exposure of other kinds								
Frey et al. 1975	1200	1000 pps and CW	30 min	0.2 mW/cm^2	Yes	Rats	Fluorescein	
Oscar and Hawksins 1977	1300	50-1000 pps	20 min	0.3 mW/cm^2	Yes	180 Wistar rats	Leakage of mannitol, dextran and inulin	
Preston et al. 1979	2450	CW	30 min	0.1 – 30 mW/ cm^2	No	Rats	Mannitol	
Merritt et al. 1978	1200 and 1300	1000 pps and CW	30 min	2-75 mW/ cm^2 and 0.1-50 mW/cm^2	No	Sprague Dawley rats	Fluorescein, mannitol, serotonin	Tried to replicate findings by Frey et al. (1975) and Oscar and Hawkins (1977)
Ward et al. 1982	2450	CW	30 min	10-30 mW/ cm^2	No	Rats	Sucrose and inulin	
Ward and Ali 1985	1700	CW and 1000 pps	30 min	0.1 W/kg	No	Rats	Sucrose and inulin	
Albert and	2450	CW	2 hours	2.5 W/kg	Yes	80 Chinese	Horseradish peroxidase	Reversible

Kerns 1981						hamsters		process with no HRP permeation after 1-2 recovery
Gruenau et al 1982	2800	CW and 500 pps	30 min	1-40 mW/cm^2	No	31 rats	Sucrose	
Lin and Lin 1980	2450	500	20 min	0.04-80 W/kg	No	Wistar rats	Evans blue and sodium fluorescein	
Lin and Lin 1982	2450	25-500	5-20 min	0.04-240 W/kg	No	51 Wistar rats	Evans blue	BBB permeability only at SAR of 240 W/kg, which is a thermal effect
Goldman et al. 1984	2450	500		240 W/kg	No		Rubidium-86	Hyperthermia induced BBB permeability
Williams et al. 1984a	2450	CW	30-180 min	4-13 W/kg	No	32 Fischer 344 rats	Fluorescein	BBB permeability only at

								hyperthermic levels > 41°C
Williams et al. 1984b	2450	CW	30-180 min	4-13 W/kg	No	20 Fischer 344 rats	HRP	
Williams et al. 1984c	2450	CW	30-90 min	13 W/kg	No	24 Fischer 344 rats	Sucrose	
Williams et al. 1984d	2450	CW	30-180 min	4-13 W/kg	No	66 Fischer 344 rats	Fluorescein, HRP, sucrose	BBB permeability only at brain temperatures > 40°C
Quock et al. 1986	2450	CW	10 min	24 W/kg		Mice	Domperidone	BBB permeability due to temperature increase
Quock et al. 1987	2450	CW	10 min	24 W/kg		Mice	Domperidone	BBB permeability due to temperature increase

Moriyama et al. 1991	2450	CW			21 Sprague Dawley rats	HRP	BBB permeability due to temperature increase
Nakagawa et al. 1994	2450	CW			Japanese monkeys		BBB permeability due to temperature increase

MRI exposure			**Magnetic field**				
Shivers et al. 1987		23 min	0.15 T static magnetic field	Yes		HRP	Standard MRI procedure
Preston et al. 1989		23 min	4.7 T static magnetic field	No	Rats	Sucrose	Standard MRI procedure
Prato et al.	65	23 min x 2	0.15 T static	Yes	43	Diethylenetriaminepentaacetic	Standard MRI

1990			magnetic field		Sprague Dawley rats	acid (DTPA)	procedure
Prato et al. 1994		23 min x 2	1.5 T static magnetic field	Yes	50 rats		Standard MRI procedure
Garber et al. 1989			0.3-0.5 T static magnetic field	Yes	Rats	Mannitol	Standard MRI procedure
Adzamli et al. 1989				No			Standard MRI procedure
ELF exposure							
Öztas et al. 2004	50	8 hours daily for 21 days	0.005T	Yes	34 Wistar rats	Evans-blue	BBB disruption in diabetic rats, but not in normoglycemic rats

In an attempt to repeat the findings of Oscar and Hawkins (26), Preston et al. (28) found no increase in the uptake of 14C-mannitol in anaesthetised rats after 2450MHz CW exposure for 30 min at power densities of 0.1 to 30mW/cm^2. Preston et al. further concluded that the increased BBB permeability, which had been observed by Oscar and Hawkins (26) in cerebellum and medulla, possibly had been misinterpreted and was not due to the EMF exposure. Rather, changes in blood flow and water influx or egress were supposed to be responsible for the BBB permeability in these caudal parts of the brain. Also, further attempts, made by Merritt et al. (1978) (29), to replicate the findings of Oscar and Hawkins from 1977, resulted in the conclusion that no repetition of the initial findings could be made. Merritt et al. (29) tried to replicate also the findings of Frey et al. (25), but reported that no changes were seen.

However, Frey commented upon this in an article in 1998, where he pointed out that, in fact, statistical analysis by the editor and reviewer of the data from the study by Merritt et al. provided a confirmation of the findings of Frey et al. (25) (30).

No alteration of BBB permeation of 14C-sucrose and 3H-inulin was found by Ward et al. (31)after exposure of anaesthetised rats to CW at 2450MHz for 30 min at power densities of 0, 10, 20, or 30 mW/cm^2 after correction for thermal effects. Similarly, Ward and Ali (32) observed no permeation after 1.7GHz exposure at SAR of 0.1 W/kg, using the same exposure duration and injected tracers as Ward et al. (31). Absence of EMF induced BBB permeability was also reported by Gruenau et al. (33), after injection of 14C-sucrose in conscious rats and exposure 30 min pulsed energy (2.8GHz at 0, 1, 5, 10, or 15mW/cm^2) or continuous wave (2.8 GHz, 0, 10, or 40 mW/cm^2).

Proof of EMF-induced BBB permeability was put forward by Albert and Kerns (34), who exposed un-anaesthetised Chinese hamsters to 2,450MHz CWs for 2 h at SARs of 2.5 W/kg. In one-third of the exposed animals there was an increased permeability of the BBB to horseradish peroxidase (HRP) and the endothelial cells of these irradiated animals had a 2–3-fold higher number of pinocytotic vesicles with HRP than the sham animals. The mechanism of BBB permeability seemed to be reversible, since animals allowed to recover for 1 or 2 h after the EMF exposure had almost no HRP permeation. A total number of 80 animals were included in this study.

Temperature Dependence

In further studies, more attention was directed towards the effects of hyperthermia, resulting from exposure at high SAR-levels, on BBB permeability.

A study correlating changes of BBB permeability with the quantity of absorbed microwave energy by Lin and Lin (35), using Evans blue and sodium fluorescein as indicators of BBB permeation, showed that 20 min of 2,450MHz exposure of anaesthetised Wistar rats caused no alteration of BBB permeability even at SAR values of 80 W/kg. Notably, the same lack of alteration was observed also at lower SAR-values, down to 0.04 W/kg. In further studies by the same group (36), no permeation of Evans blue could be observed after exposure to 2,450MHzB RFs for 5–20 min when the SAR-values ranged from 0.04–200 W/kg. Not until a SAR-value of 240 W/kg, with ensuing rise in brain temperature to 43ºC, was applied, the BBB permeability increased. These observations of demonstrable increases of BBB permeability associated with intense, microwave-induced hyperthermia were supported by another study by the same group (37).

In a series of EMF exposures at 2,450MHz CW, Williams et al. (38-40) concluded that increase of BBB permeability might not be explained by microwave exposure, but rather temperature increases and technically derived artefacts such as increase of the cerebral blood volume and a reduction in renal excretion of the tracer. Significantly elevated levels of sodium fluorescein (38) were found only in the brains of conscious rats made considerably hyperthermic by exposure to ambient heat for 90 min or 2,450MHz CW microwave energy for 30 or 90 min, but this was at high SAR values, 13 W/kg—far beyond the ICNIRP limit of 2 W/kg (41) —and not comparable to the experiments performed by, among others, our group, as described below.

With more research into the area of EMF induced BBB permeability, it became evident that with high-intensity EMF exposure resulting in tissue heating, the BBB permeability is temperature dependent (42). Thus, the importance of differentiating between thermal and non-thermal effects on the integrity of the BBB was realized. This is the reason why studies with increases of BBB permeability due to exposure to SAR-values well above recommended

exposure levels (43-46) need to be considered from another point of view, as compared to those focusing on the non-thermal effects of EMFs.

Continued Studies—MRI and BBB Permeability

Following the increasing use of magnetic resonance imaging (MRI), the effects of MRI radiation upon BBB permeability were investigated more thoroughly. MRI entails the concurrent exposure of subjects to a high-intensity static field, a radiofrequency field, and time-varying magnetic field. Shivers et al. (47) observed that exposure to a short (23 min) standard (of those days) clinical MRI procedure at 0.15 Tesla (T) temporarily increased the permeability of the BBB to horseradish peroxidase (HRP) in anaesthetised rats. This was revealed by electron microscopy (EM), to be due to an amplified vesicle-mediated transport of HRP across the microvessel endothelium, to the ablumenal basal lamina and extracellular compartment of the brain parenchyma. This vesicle-mediated transport also included transendothelial channels. However, no passage of the tracer through disrupted interendothelial tight junctions was present.

During the next few years, more groups studied the effects of MRI exposure on the BBB permeability by injection of radioactive tracers into rats. One supported (48)while others contradicted (49, 50) the initial findings made by Shivers et al. (47). Garber et al. exposed rats to MRI procedures at 1.5, 0.5, and 0.3 T with RFs of 13, 21, and 64 MHz, respectively (48). Brain mannitol concentration was significantly increased at 0.3 T and 0.5 T but not at 1.5 T. No decrease in plasma mannitol concentration of MRI exposed animals was found and thus the authors concluded that effects of MRI associated energies on mannitol transport do not occur measurably in the body, and might be more specific to brain vasculature. Preston et al. (50) found no significant permeation of blood-borne 14C-sucrose into brain parenchyma in anesthetized rats subjected to 23 min of MRI at 4.7 T and RFs at 12.5 kHz. However, the authors pointed out that if the MRI effect was focal and excess tracer counts were found only in restricted sites, there could have been MRI induced extravasation of sucrose that was not detected, due to the preponderance of normal tissue counts. When Preston et al. (50) compared the lack of BBB leakage in their study to the MRI induced leakage which had been observed by Shivers et al. (47), they also concluded that certain characteristics of electric and

magnetic fields, which were present in the study by Shivers et al. but not in their own work, could have been critical to the observed effects.

In 1990, further studies by the Shivers-Prato group were presented (51) and the group could now quantitatively support its initial findings, in a series of 43 Sprague-Dawley rats. The BBB permeability to diethylenetriaminepentaacetic acid (DTPA) increased in rats after two sequential 23 min MRI exposures at 0.15 T. It was suggested that the increased BBB permeability could result from a time-varying magnetic field mediated stimulation of endocytosis. Also, the increased BBB permeability could be explained by exposure-induced increases of intracellular Ca^{2+} in the vascular endothelial cells. Since the Ca^{2+} is an intracellular mediator, increases of BBB permeability could possibly be initiated in this way. A few years later, in a series of 50 rats, the Shivers - Prato group also found that the BBB permeability in rats is also altered by exposure to MRI at 1.5T for 23 min in 2 subsequent exposure sessions (52).

Studies by the Lund Group

Two of us found these observations highly interesting:

- the neurosurgeon (LGS) in the hope to utilize possible applications of EMF to make the blood-brain barrier (BBB) more penetrable to chemotherapy, in order to treat brain cancers more effectively. An intact BBB keeps out chemotherapy agents, allowing cancer cells to hide behind the BBB.

- the radiophysicist (BRRP) interested in possible adverse effects of the MRI technique.

After a visit to Shivers' group in London Ontario in 1988, we started work in Lund in 1988, studying the effects of MRI on rat brain and we found, by the use of Evans Blue, the same increased permeability over BBB for albumin (53).

This work was continued by separating the constituents of the MRI field: RF, undulant magnetic field, and static magnetic field. Since RF turned out to be the most efficient component of the MRI, the following studies focused mainly on the RF effects. Striving for

investigating the actual real-life situation, endogenous substances, which naturally circulate in the vessels of the animals, were used. In line with this, albumin and also fibrinogen leakage over the BBB were followed after identification of albumin with rabbit antibodies (see Figure 2 and 3) and rabbit anti-human fibrinogen.

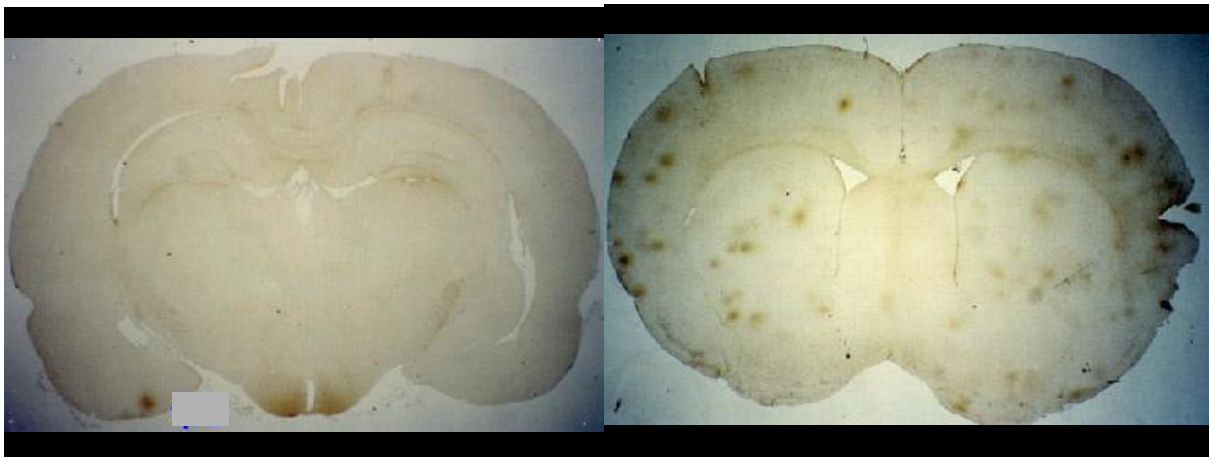

Figure 2. Albumin extravasation in rat brain (material from Persson et al. 1997)(54).
Left: control brain with albumin staining in hypothalamus, which serves as an inbuilt-control of the staining method, since the hypothalamus lacks BBB, and one occasional staining.
Right: Brain of EMF exposed rat, with multiple albumin positive foci.

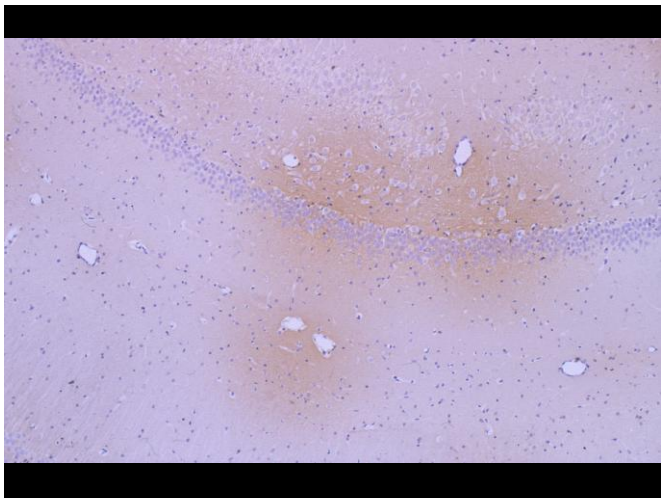

Figure 3. Albumin extravasation around vessels in the brain of an EMF exposed rat.

The work by Blackman et al. (55, 56) ~~made the ground~~ laid the groundwork for studies on the frequency modulation 16 Hz and its ~~harmonies~~ harmonics 4 and 8 Hz. A carrier wave of 915 MHz was used. At the suggestion of Östen Mäkitalo (Telia), a pioneer in mobile phone

development, who introduced 50 Hz (DUX) and 217 Hz (GSM) modulation in new digital wireless communication systems, we also included theses frequencies. This paralleled the first BBB study results that were published in 1992-1994 (57-59).

The result of our continued work, comprising more than 1000 animals, with exposure to both CWs and pulsed modulated waves, in the most cases lasting for 2 h, showed that there was a significant difference between the amount of albumin extravasation in the exposed animals as compared to the controls. In the exposed group 35–50% of the animals had a disrupted BBB as seen by the amount of albumin leakage, while the corresponding leakage in the sham exposed animals was only 17% (for results see Figure 4) (54).

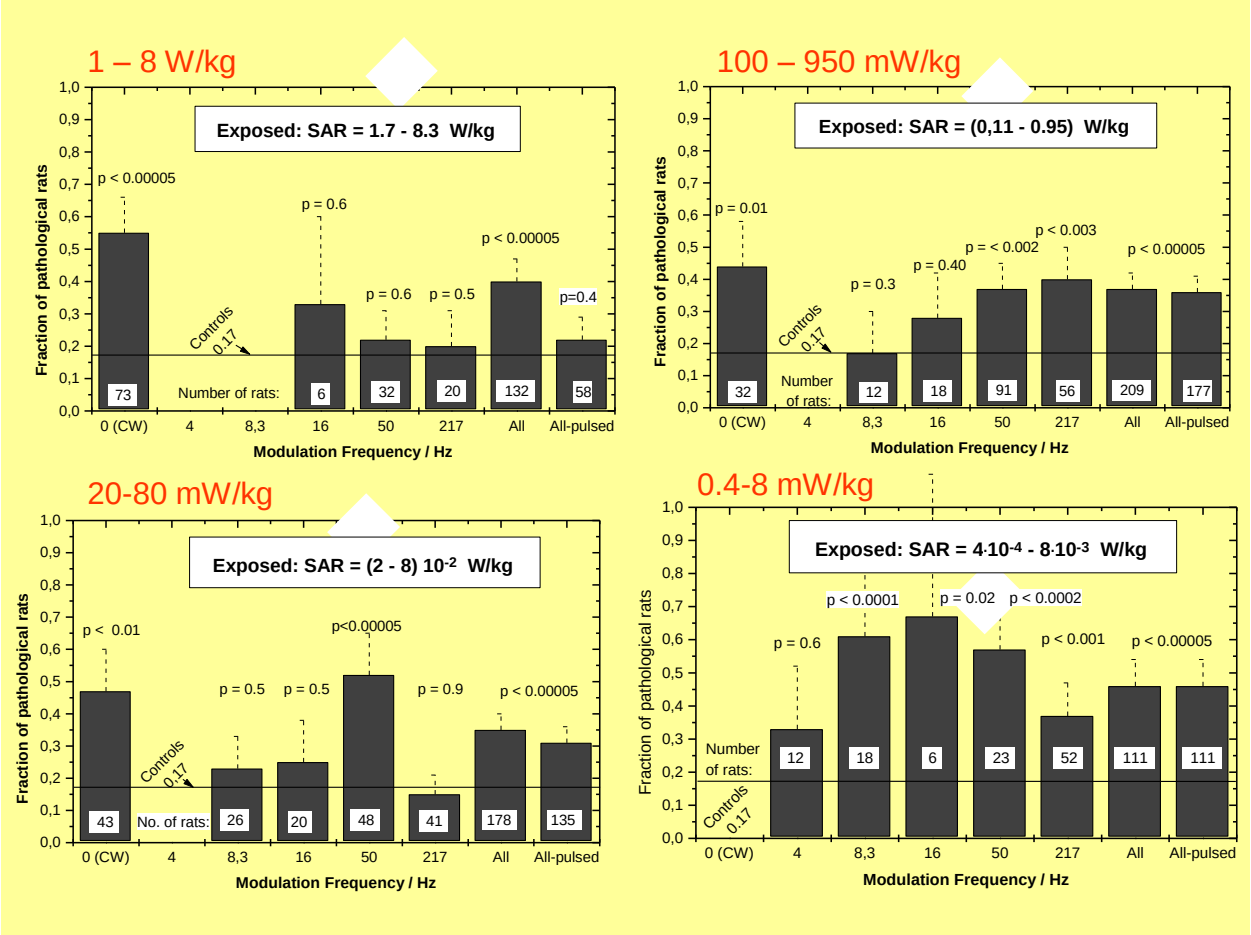

Figure 4. Albumin extravasation score as a result of EMF exposure (results from the study by Persson et al. (54)).

The fact that sham-exposed control animals also show some amount of albumin extravasation (see Figure 4), is most likely due to our very sensitive methods for immune histological examination. However, it is hard to explain the fact that although all animals in the 1997 series were inbred Fischer 344 rats, only every second animal, at the most, showed albumin leakage after EMF exposure. The question, what might protect the remaining 50% of the exposed animals from BBB disruption, is highly intriguing. It should be noted that in our large series, only in one single animal fibrinogen leakage has been observed (54).

Another conclusion from the 1997 study is that the number of pathological leakages in exposed animals is more frequent, and also more severe, per animal compared to the controls. This is an interesting observation as the prevailing opinion is that pulse modulated electromagnetic fields are more potent in causing biological effects.

In a statistical re-evaluation of our material published in 1997, where only exposed rats with a matched unexposed control rat are included, we found for the most interesting modulation frequency 217 Hz, i.e. that of GSM, that at SAR-values of 0.2 to 4 mW/kg 48 exposed rats had a significantly increased albumin leakage ($p < 0.001$) as compared their 48 matched controls. On the other hand, SAR-values of 25-50 mW/kg, gave no significant difference between 22 exposed rats *vs* their matched controls (Wilcoxon´s Rank Test, 2-sided p-value) (60).

In all our earlier studies we showed albumin extravasation immediately after exposure as described above. In later years we have performed a series of experiments where the animals were allowed to survive for 7 days (61), 14 days, 28 days (62) or 50 days (63) after one single 2-hour exposure to the radiation from a GSM mobile phone. All were exposed in TEM-cells to a 915 MHz carrier wave as described below. The peak power output from the GSM mobile phone fed into the TEM-cells was 1 mW, 10 mW, 100 mW and 1000 mW per cell respectively for the 7-14-28-days survival animals, resulting in average whole-body SAR of 0.12 mW/kg, 1.2 mW/kg, 12 mW/kg and 120 mW/kg for four different exposure groups SAR-values of 2, 20 and 200 mW/kg mW/kg for 2 hours for the 50-days survival animals.

Albumin extravasation over the BBB after GSM exposure seemed to be time-dependent, with significantly increased albumin in the brain parenchyma of the rats, which had survived for 7 and 14 days, but not for those surviving 28 days. After 50 days, albumin extravasation was

significantly increased again, with albumin-positive foci around the finer blood vessels in white and gray matter of the exposed animals.

In connection to the albumin passage over the BBB, albumin also spread in the surrounding brain tissue. A significantly increased uptake of albumin in the cytoplasm of neurons could be seen in the GSM exposed animals surviving 7 and 14 days after exposure, but not in those surviving 28 or 50 days.

Neuronal uptake

Extravasated albumin rapidly diffused down to, and beyond, concentrations possible to demonstrate accurately immunohistologically. However, the initial albumin leakage into the brain tissue (seen within hours in ~40% of exposed animals in our previous studies) most likely started a vicious circle of further BBB opening.

It has been postulated that albumin is the most likely neurotoxin in serum (64). Hassel et al. (65) have demonstrated that injection of albumin into the brain parenchyma of rats gives rise to neuronal damage. When 25 µl of rat albumin is infused into rat neostriatum, 10 and 30, but not 3 mg/ml albumin causes neuronal cell death and axonal severe damage. It also causes leakage of endogenous albumin in and around the area of neuronal damage. Albumin in the dose 10 mg/ml is approximately equivalent to 25% of the serum concentration.
It is less likely that the albumin leakage demonstrated in our experiments locally reaches such concentrations. However, we have seen that in the animals surviving 28 and 50 days after 2 hours of GSM exposure, there was a significantly increased incidence of neuronal damage as compared to the sham controls. In the 7-days and 14-days survival animals, on the other hand, no such increase of neuronal damage was seen.

In the 50-days post-exposure survival study, a 2 h exposure to GSM at SAR values 200, 20, and 2 mW/kg resulted in a significant ($p = 0.002$) neuronal damage in rat brains of the exposed animals as compared to the controls 50 days after the exposure occasion (Salford et al., 2003)(63). We have followed up this observation, as mentioned above, in a study where 96 animals were sacrificed 14 and 28 days respectively after an exposure for 2 h to GSM mobile phone electromagnetic fields at SAR values 0 (controls), 0.12, 1.2, 12 and 120 mW/kg. Significant neuronal damage is seen after 28 days and albumin leakage after 14. Our

findings may support the hypothesis that albumin leakage into the brain is the cause for the neuronal damage observed after 28 and 50 days (62).

The damaged neurons in the above mentioned studies took the shape of so-called dark neurons. Three main characteristics of the damaged dark neurons have been proposed (66): (i) irregular cellular outlines, (ii) increased chromatin density in the nucleus and cytoplasm and (iii) intensely and homogenously stained nucleus. The damaged dark neurons found in the 50 days-survival animals were investigated regarding signs of apoptotic markers, but we found no positive staining for Caspase-3, a marker for apoptosis (Bexell et al. unpublished results). However, the albumin leakage out in the neuropil in connection to EMF exposure might start other deleterious processes, leading to the formation of the dark neurons.

A group in Turkey performed similar experiments. However, also the presumed protective effects of the antioxidant Ginko biloba (Gb) were examined by Ilhan et al. (67). About 22 female Wistar rats were exposed to a 900 MHz electromagnetic GSM near-field signal for 1 h a day for 7 days. In the GSM only group, the pathological examination revealed scattered and grouped dark neurons in all locations, but especially in the cortex, hippocampus and basal ganglia, mixed in among normal neurons. A combined non-parametric test for the four groups revealed that the distributions of scores differed significantly between the control and the GSM only exposure group ($p < 0.01$).

Long-term study, including studies of memory and behaviour

In a recent long-term study from our laboratory, rats were exposed to GSM radiation 2 hours weekly during 55 weeks (two different exposure groups with 0.6 mW/kg and 60 mW/kg at the initiation of the exposure period). After this protracted exposure, behaviour and memory of the exposed animals were tested. Whereas the behaviour of the animals was not affected, the GSM exposed rats had significantly impaired episodic memory as compared to the sham controls (68). After the finalization of these tests, that is 5-7 weeks after the last exposure, the animals were sacrificed by perfusion fixation. Albumin extravasation, an indicator of BBB leakage, was increased in about 1 animal in each group of low GSM exposed, high GSM exposed, sham exposed and cage control rats. About 40 % of the animals had neuronal damage. GFAP staining, as an indicator of glial reaction, revealed positive results in 31-69 % of the animals for different groups and the aggregation product lipofuscin was increased in

44-71 % of the animals for different groups. With the Gallyas staining (aiming at cytoskeletal structures), no changes were seen. When comparing the results between the different groups, it turned out that there was no statistically significant difference for any of these parameters due to GSM exposure (69). When comparing these findings to those from animals which had been exposed only once for 2 hours, it seems likely that during the 55 weeks of repeated exposure, albumin leakage at an initial stage of the experimental period might have been absorbed after some time, and that at a certain, but unknown, time point during this protracted, more than 1 year long-exposure period, some adaptation process might have been activated. However, this could not compensate for cognitive alterations, demonstrated by the episodic memory tests.

TEM-cells

In the majority of our studies, EMF exposure of the animals has been performed in transverse electromagnetic transmission line chambers (TEM-cells, see Figure 5) (53, 54, 59, 61-63, 68-71). These TEM-cells are known to generate uniform electromagnetic fields for standard measurements. Each TEM-cell has two compartments, one above and one below the center septum. Thus, two animals can be exposed at a time. The animals are un-anaesthetized during the whole exposure. Since they can move and turn in the TEM-cells as they like, the component of stress-induced immobilization (described by Stagg et al. (72)) is effectively minimized. Through our studies, we have concluded that the amount of albumin leakage is neither affected by the sex of the animals, nor their placement in the upper or lower compartments of the TEM-cells.

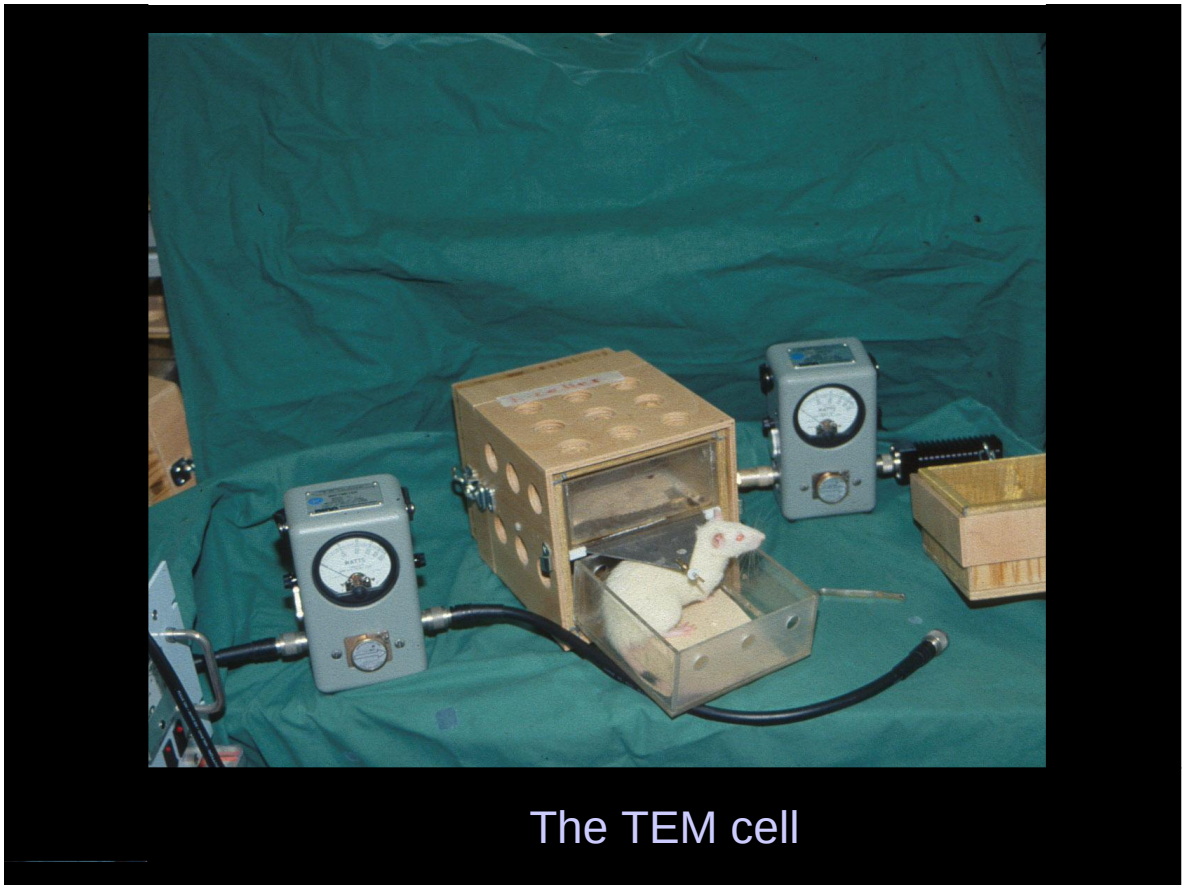

Figure 5. TEM-cells for EMF exposure.

GSM-1800 modulated and CW microwaves in an anechoic chamber

In Lund we have also utilized an anechoic chamber for studies on microwaves from a real GSM-1800 mobile telephone, which were amplified and transferred to a dipole antenna in the anechoic chamber. The output power was varied to study the effect of various SAR values.
In a series of 65 rats exposed for 2 h with 1800-GSM at SAR: 0.027 mW/kg, and 12 rats exposed for 2 h with continuous wave, we found significantly increased albumin leakage (see figure 6) as compared to 103 control rats ($p<0,03$ and $p<0,02$, respectively). (Unpublished results).

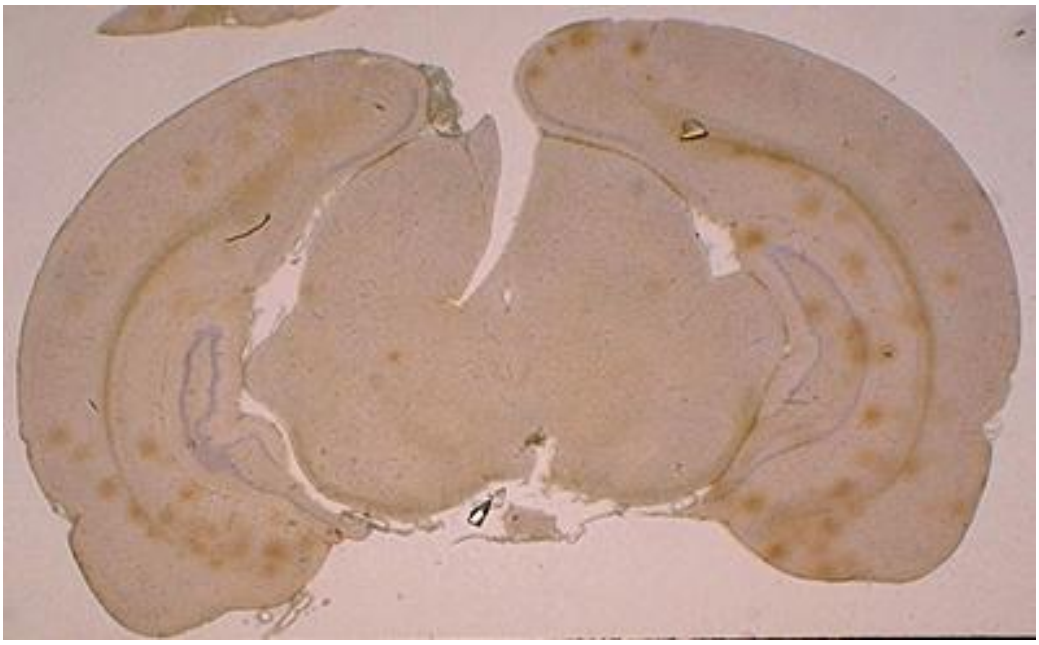

Figure 6.
Pathological leakage around vessels demonstrated by immunostaining against albumin.
Fischer 344 rat exposed for 2 h with 1800-GSM at SAR: 0.027 mW/kg

Other Studies on BBB Permeability, Focusing on the Effects of RF EMFs of the Type Emitted by Mobile Phones

With the increasing use of mobile phones, much attention has been directed towards the possible effects on BBB permeability, after exposure to the type of RF EMFs emitted by the different sorts of mobile phones.

Repetitions of our initial findings of albumin leakage have been made by Fritze et al. (73), with 900 MHz exposure of rats for 4 h at brain power densities ranging from 0.3–7.5 W/kg. Albumin extravasation into the brain tissue was seen, with significant difference between controls and rats exposed reported for 7.5 W/kg, which is a thermal level. However, Fisher exact probability test (two-tailed) performed on the reported results, reveals significant ($p < 0.01$, Fisher exact probability test) difference for the subthermal level group (SAR 0.3 W/kg plus 1.3 W/kg, compared to sham exposed and cage control animals) where in total 10 out of 20 animals showed one or more extravasations direct after exposure (Salford et al. (20)).

Another group, working in Bordeaux, and led by Prof Pierre Aubineau, has also demonstrated evidence of albumin leakage in rats exposed for 2 h to 900 MHz at non thermal SAR-values, using fluorescein-labeled proteins. The results were presented at two meetings by Töre et al. (74, 75). The findings are very similar to those of our group, described above.
At the BEMS meeting in 2002 in Quebec City in Canada, the Aubineau-Töre group presented results from exposure GSM-900 EMFs at SAR values of 0.12, 0.5, and 2.0 W/kg. Seventy Sprague-Dawley rats were included in the study. In addition to normal sham and normal GSM exposed rats, also rats subjected to chronic dura mater neurogenic inflammation, induced by bilateral sympathetic superior cervical ganglionectomy, were included. Arterial blood pressure was measured during the exposure, and Töre et al. (74, 75) concluded that the pressure variations (100–130mm Hg) were well below those limits, which are considered to be compatible with an opening of the BBB of rats. In order to induce opening of the BBB in rats, arterial blood pressure needs to reach values of 170 mmHg, according to Töre et al. (74, 75). At SAR of 2 W/kg a marked BBB permeabilization was observed, but also at the lower SAR-value of 0.5 W/kg, permeabilization, although somewhat more discrete, was present around intracranial blood vessels, both those of the meninges and of the brain parenchyma. Comparing the animals, which had been subjected to ganglionectomy, to the other animals, Töre et al. made an interesting observation: as expected, albumin extravasation was more prominent in the sympathectomised sham-exposed rats as compared to normal exposed rats. This was due to the fact that the sympathectomised rats were in a chronic inflammation-prone state with hyper-development of pro-inflammatory structures, such as the parasympathetic and sensory inputs as well as mast cells, and changes in the structure of the blood vessels. Such an inflammation-prone state has a well-known effect on the BBB leakage. However, when comparing sham-exposed sympathectomised rats to GSM-exposed sympathectomised rats, a remarkable increase in albumin leakage was present in the GSM exposed sympathectomised rats compared to the sham rats. In the GSM-exposed sympathectomised rats, both brain areas and the dura mater showed levels of albumin leakage resembling those observed in positive controls after osmotic shock. Indeed, more attention should be paid to this finding, since it implicates that the sensitivity to EMF-induced BBB permeability depends not only on power densities and exposure modulations, but also on the initial state of health of the exposed subject.

In rats, uptake of a systemically administered rhodamine-ferritin complex through the BBB also has been observed, after exposure to pulsed 2.45GHz EMFs at average power densities of

2 W/kg by Neubauer et al. (76). The authors observed that the magnitude of BBB permeability depended on power density and duration of exposure. Exposure to a lower power density (1 W/kg) and shorter duration of the exposure (15 min) did not alter the BBB permeability, as compared to higher power densities (SAR 2 W/kg) and longer duration of exposure (30–120 min). The microtubules seemed to play a vital role in the observed BBB permeability, since treatment with colchicine, which inhibits microtubular function, resulted in near-complete blockade of rhodamine-ferritin uptake. The mechanism underlying the observed leakage was presumed to be correlated to pinocytotic-like transport.

In other studies, no effect of EMF exposure has been observed on the BBB integrity. With exposure to 1,439MHz EMFs, 1 h daily during 2 or 4 weeks (average whole-body energy doses of 0.25 W/kg) no extravazation of serum albumin trough the BBB was observed in a series of 36 animals by Tsurita et al.(77). However, in this small material only 12 animals in total were EMF exposed (6 rats exposed for 2 weeks and 6 rats exposed for 4 weeks). Also, lack of interference with the BBB function of rats was found after 1,439MHz exposure for 90 min/d for 1–2 weeks at average brain power densities of either 2 or 6W/kg by Kuribayashi et al.(78). A total number of 40 animals were included in the study.

Finnie et al. (79) came to the conclusion that no increase in albumin leakage over the BBB resulted from EMF exposure in a series of 60 mice. With whole body exposure of mice to GSM-900 EMFs for 1 h at a SAR of 4 W/kg or sham exposure, no difference in albumin extravazation was observed between the different groups. Also, free-moving cage controls were included in the study, and interestingly, there was no significant difference between these non-restrained mice as compared to the sham and EMF-exposed animals. Thus, the authors concluded that there were no stress-related exposure module confinement effects on the BBB permeability.

Finnie et al. (80) continued to investigate more long-lasting exposure effects. In a series of experiments, a total of 207 mice were exposed 60 min daily, 5 days per week for 104 weeks at average whole body SARs of 0.25, 1.0, 2.0, and 4.0W/kg. This led to a minor disruption of the BBB, as seen by the use of endogenous albumin as a vascular tracer. However, it should be added that the authors performed no statistical analyses to evaluate the albumin leakage through the small vessels in the brain. In an answer to correspondence in the same journal (81), the authors presented the original data from the long-term study in one table, from which

one can conclude that non-leptomeningeal albumin leaking vessels were seen in few sham-exposed animals, and in one-third of the animals in the 0.25 W/kg group and to a lesser extent in the higher SAR groups.

The fact that some research groups observe albumin leakage/transport over the BBB after EMF exposure and others do not, has led to a rather intense debate between the researchers but also in society, which is puzzled by the divergent findings. A major concentration of the involved research groups took place at Schloss Reisensburg in Germany in 2003, where the technical approaches in the studies of BBB effects were discussed. Two world-renowned researchers in the BBB field, Dr. David Begley of Kings College, London, and Prof. Olaf Poulsen of Copenhagen, Denmark, chaired the FGF/COST 281 Reisensburg, November 2–6 meeting. They made the final statement as a summary of the meeting: ‘‘It seems clear that RF fields can have some effects on tissues’’. The statement was made to a large extent on the basis of the concordant findings of the Bordeaux group, represented by Prof. Aubineau, and the Lund group, represented by Prof. Salford and Prof. Persson.

The histopathological examinations of the brains are not uncomplicated. Some laboratories that have tried to replicate our studies have not been able to demonstrate the albumin leakage. We have recently had problems with the albumin staining due to change of suppliers of avidin, biotin, serum and antibodies. The lateral hypothalamic nuclei in the immediate vicinity of the third ventricle are well known for their normally insufficient BBB. This has served as an inbuilt control of adequate albumin staining in all our experiments since 1990. In our study on combined effects of RF- and ELF-EMF, for the first time, we could not demonstrate albumin extravasation in basal hypothalamus. Not until our third attempt with new staining material, we got our positive control and could also demonstrate albumin leakage in the exposed brains (61).

The biological effects of RF exposure depend on many parameters, such as mean power level and the time variations of the power (82) and whether in vivo or in vitro experiments are performed. In the in vivo situation, different kinds of animals, and also the same kind of animals but of different breeds, might react differently. It might not necessarily be the strongest RF fields that give rise to the most obvious biological effects (54, 63). In many cases, the weak and precisely tuned EMFs have the most important biological function; two examples of this are cellular communication and protein folding. It seems quite likely that in

different experimental set-ups, and in different living organisms, the signal has to be tuned to different properties in order to cause any effect. This could perhaps in some part explain why, in some cases, there are quite obvious effects of RF exposure, whereas in others, no such effects can be seen.

Other Studies on BBB permeability and neuronal damage

As has been mentioned above (p. 26) Ilhan et al. (67), in 2004 reported neuronal damage in female Wistar rats, which had been exposed to a 900 MHz electromagnetic GSM near-field signal for 1 h. a day for 7 days. They found scattered and grouped dark neurons in the cortex, hippocampus and basal ganglia, mixed in among normal neurons. A combined non-parametric test for the four groups revealed that the distributions of scores differed significantly between the control and the GSM only exposure group ($p < 0.01$).

Later, Masuda et al. (83) tried to replicate the findings by our group of albumin extravasation and dark neurons. F344 rats (n=64) were exposed to 915 MHz signals for 2 hours (SAR of 0, 0.02, 0.2 and 2 W/kg), and albumin extravasation and dark neurons were investigated 14 and 50 days after the exposure. No albumin extravasation was seen, neither in control or exposed rats, and no difference in the occurrence of dark neurons could be found due to EMF exposure. An interesting difference as compared to the studies by Salford et al. mentioned above, was that animals, after perfusion fixation, were left in a 4ºC storage for 18 hours before the brains were removed. The question is whether this might have led to dilution of the very sensitive albumin extravasation, which is often more pronounced in the circumventrical organs as compared to the brain extravasates (personal communications with our neuropathologist Arne Brun). This might explain the fact, that no albumin extravasation could be seen in neither the cage control animals, the shams or the GSM exposed animals.

Another study by Mason and his group at Brooks Airforce Resarch Laboratory, San Antonio, also tried to confirm our findings of albumin extravastion by using the same type of TEM-cells for EMF Exposure (84), although the exposure parameters where somewhat different with only 30-min exposure, including only male rats of the Fischer 344 CD-VAF strain and utilizing only the upper compartment of the TEM cells. Exposure was at whole-body SAR values of 0.002 to 20 W/kg. Regarding extracellular albumin accumulation, the results were

not formally analyzed, as motivated by too low scores of albumin. Regarding intracellular albumin uptake, no significant difference between the different groups was reported. However, as presented in the paper by McQuade et al.(84), at the lowest SAR of 1.8 mW/kg at 16 Hz, of 33 exposed rats, 11 had 2 or 3 positivities (33% of the animals) and 22 had none or 1 positivity. In the sham animals, 18% were positive and among the cage controls only 12%. These results are reminiscent of prior work by the Lund group reporting that 17% of the sham animals had some albumin leakage, while only at the most 50% of the identical and equally handled, but RF exposed animals displayed albumin extravasation (60).

In a third study aiming to replicate the Lund findings of dark neurons, a group in Bordeaux (85) exposed 14 weeks old Fischer 344 rats (which, however, were restrained in a rocket-type exposure setup), to the GSM-900 signal for 2 h at various brain-averaged SARs (0, 0.14 and 2.0 W/kg). Eight rats were included in each of these groups.
Albumin leakage and neuronal degeneration was evaluated 14 and 50 days after exposure.
It was reported that no statistically significant albumin leakage was observed and that neuronal degeneration assessed using cresyl-violet or the more specific marker Fluoro-Jade B, was not significantly different among the tested groups. Here we want to point out that the Bordeaux group makes a major deviation from the way we have evaluated the occurrence of dark neurons in the tissue slices. While we counted the overall number of dark neurons, de Gannes et al. (85) chose to subdivide the slices into 12 different small regions, which were compared individually to each other (fig 3 in the publication). This gave the effect that a clear overall difference in number of observed dark neurons between animals 50 days after exposure to 2 W/kg for two hours versus sham exposed, disappeared in the statistics. On the contrary, if all the numerical values for the bars representing the scored dark neurons observed in each brain zone and region 50 days after exposure to 2 W/kg are compared to all those of the sham animals, a highly significant difference (Kruskall-Wallis) between animals exposed to 2 W/kg and sham is demonstrated (Mann-Whitney) $p = 0.003$! This is in concordance with the Lund experience!

Indirect studies and studies on the blood cerebrospinal fluid barrier

The integrity of the BBB has also been investigated indirectly. Cosquer et al. (86) treated rats with the muscarinic antagonist scopolamine methylbromide, which is known to induce

memory impairments, followed by EMF exposure at 2.45GHz for 45 min at average whole body SARs of 2W/kg. Opening of the BBB after EMF exposure was hypothesised to affect the performance in a radial arm maze. However, no such alterations were observed and the authors concluded that no BBB opening seemed to have occurred. In agreement with this, no albumin extravasation was noticed.

Ushiyama et al. (87) investigated the effects on the blood cerebrospinal fluid barrier after RF-EMF exposure. With a microperfusion method, cerebrospinal fluid from rat brain was collected in vivo. Fluorescent intensity of FITC-albumin in perfusate was measured. Rats exposed to 1.5GHz RFs during 30 min at SAR-values of 0.5, 2.0, 9.5W/kg for adult rats and 0.6, 2.2, 10.4W/kg for juvenile rats, respectively, were compared to sham-exposed controls. Under these conditions, no increase in FITC-albumin was seen in the cerebrospinal fluid of exposed rats as compared to sham exposed controls. It was concluded that no effect on the function of the blood cerebrospinal fluid barrier was seen.

In a recent study, the permeability of the human BBB after mobile phone exposure was assessed measuring blood levels of S100B and transthyretin in human volunteers by Söderqvist et al. (88). S100B is a calcium-binding protein, and it has been shown to be increased in serum after damage to the BBB. Transthyretin, also known as pre-albumin, is synthesised both in the liver and the choroid plexus. 30 min of GSM-900-like exposure at SAR-values of 1 W/kg was used. No difference was seen regarding S100, but transthyretin was increased 60 min after the termination of exposure as compared to the control situation. The concentrations of S100B and transthyretin were also analysed 30 min prior to provocation and after 30 min rest, showing a decrease after 30 min rest, which was suggested, might be due to less stress after the 30 min rest. Thus, it is interesting that despite this decline, which might be due to relaxation, still an increase in thransthyretin could be measured 30 min after exposure. It was also put forward, that it could not be excluded that the thransthyretin rise might be a compensation to the previous decrease, and that new studies including more participants and also a sham group would be needed.

We have in the past investigated whether MW exposure, CW and at different SAR levels might enhance S-100 protein levels in the blood of a large proportion of our rats. We could conclude that no significant differences were seen (see Figure 7 below) (to be published).

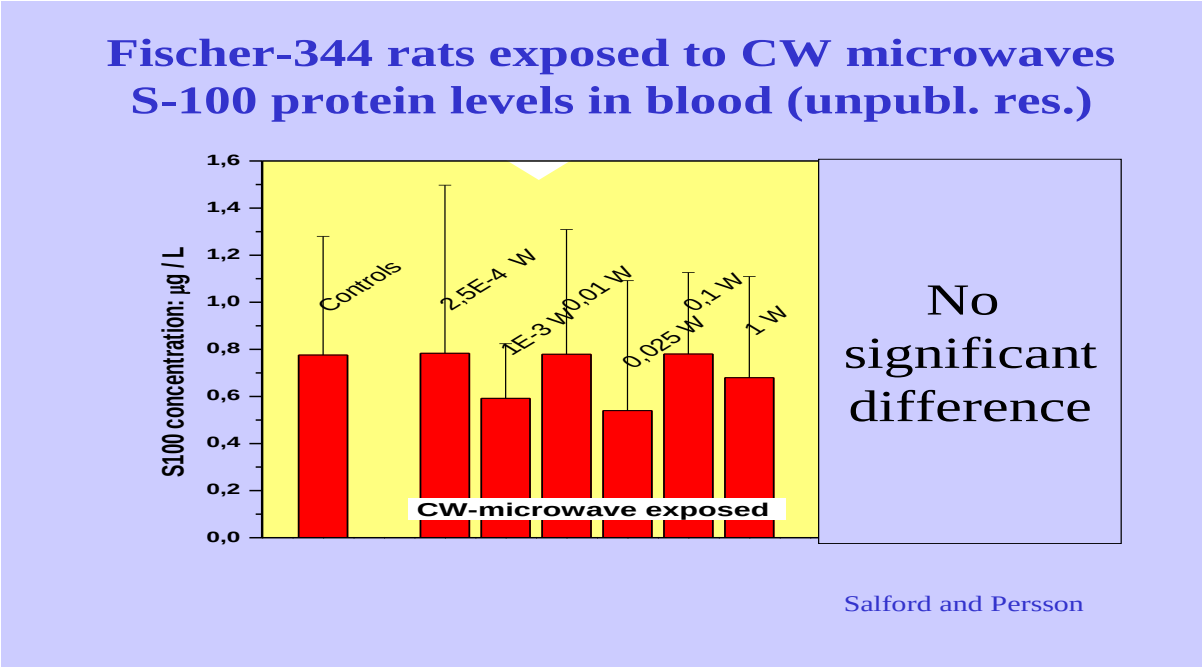

Figure 7. S-100 in the blood of rats after EMF exposure (to be published in Acta Scientiarum Lundensia).

In another study, by Sirav and Seyhan (89), exposure to CW EMFs at 900 and 1,800 MHz for 20 min, increased the BBB permeability of male but not female rats. Evans blue dye, which binds to serum albumin after injection, was used to quantitatively measure BBB permeability. A strength of this study, was the ability to objectively quantify the Evans blue uptake in the brain. The finding that only male, and not female rats, are affected, is however not fully addressed.

In Vitro Models

In recent years, there has been an increasing use of in vitro models in the search for BBB effects of EMF exposure. In vitro models of the BBB have been studied, as by Schirmacher et al. (90), with co-cultures consisting of rat astrocytes and porcine brain capillary cells. Exposure to GSM-1800 for 4 d with average SAR of 0.3 W/kg increased the permeability of 14C-sucrose significantly compared to unexposed samples in the studied BBB model. These findings were not repeated in experiments performed later by the same group, after modifications of their in vitro BBB model (91). The modified BBB model had a higher general tightness. It was speculated that at a higher original BBB permeability, which was

present in the first study by Schirmacher et al. (90), the cultures were more susceptible to the RF EMFs. Using porcine brain microvascular-endothelial cell cultures as an in vitro model of the BBB, no effects on barrier-tightness, transport behavior, and integrity of tight junction proteins were observed-after exposure to UMTS EMFs at 1.966 GHz for 1–3 d at different field strengths at 3.4–34 V/m, generating a maximum SAR of 1.8 W/kg (92).

In the search after the mechanism underlying non thermal EMF effects, Leszczynski et al. (93) observed human endothelial cells, with the interesting finding that GSM-900 exposure for 1 h with SAR-values of 2 W/kg resulted in changes in the phosphorylation status of many proteins. Among the affected pathways, the hsp27/p38MAPK stress response pathway was found, with a transient phosphorylation of hsp27 as a result of the mobile phone exposure. This generated the hypothesis that the mobile-phone induced hsp27-activation might stabilize stress fibers and in this way cause an increase in the BBB permeability. Furthermore, it was also suggested that several brain-damaging factors might all contribute to the mobile phone-induced effects observed in the brain and other structures as well.

Further perspectives of the importance of the BBB including the human situation

BBB in the Context of Alzheimer's Disease and the findings by the Zlokovic Group

The BBB, as mentioned previously, is of essential role for maintaining an accurate brain function. As described by Zlokovic (94), in a review regarding BBB in correlation to neurodegenerative disorders, BBB breakdown can be due to tight junction disruption, alterations of angiogenesis or vessel regression, hypoperfusion, inflammatory response and alterations of the transport of molecules across the BBB (94). Further, as Zlokovic hypothesises, this might contribute to neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis.

In the review by Zlokovic (94), a neurovascular disease pathway is presented, regarding possible genesis of AD, where it is suggested that changes in vascular genes and receptors in brain capillaries and small arteries might disrupt BBB functions, leading to an accumulation

of amyloid beta (Aβ), a neuroinflammatory response and BBB breakdown and further on accumulation of Aβ, loss of the BBB to clear Aβ (due to affected synaptic transmission, neuronal injury and recruitment of microglia) and secretion of proinflammatory cytokines. Ultimately, this is suggested to lead to disappearance of the capillary unit, increasing Aβ deposits and synaptic and neuronal loss (94).

This observation might explain how vascular disease contributes to Alzheimer's disease (AD) risk; the heterogeneity of AD; and supports the idea that exclusively focusing on amyloid is likely to be disappointing.

Neuronal injury resulting from vascular defects that are not related to amyloid-beta but is related to damage results from a breakdown of the blood-brain barrier and a reduction in blood flow (94). Although Amyloid beta definitely has an important role in Alzheimer's disease it's very important to investigate other leads, perhaps where amyloid-beta isn't as centrally involved.

Human apolipoprotein E has three isoforms: APOE2, APOE3 and APOE4. APOE4 is a major genetic risk factor for Alzheimer's disease and is associated with Down's syndrome dementia and poor neurological outcome after traumatic brain injury and haemorrhage. Neurovascular dysfunction is present in normal APOE4 carriers and individuals with APOE4-associated disorders. In mice, lack of APOE leads to blood-brain barrier (BBB) breakdown, whereas APOE4 increases BBB susceptibility to injury. How APOE genotype affects brain microcirculation remains elusive. Using different APOE transgenic mice, including mice with ablation and/or inhibition of cyclophilin A (CypA), it has been shown show that expression of APOE4 and lack of murine APOE, but not APOE2 and APOE3, leads to BBB breakdown by activating a proinflammatory CypA-nuclear factor-kappa B-matrix-metalloproteinase-9 pathway in pericytes. These findings suggest that CypA is a key target for treating APOE4-mediated neurovascular injury and the resulting neuronal dysfunction and degeneration. The data reviewed above support an essential role of neurovascular and BBB mechanisms in contributing to both, onset and progression of AD (95, 96).

BBB in the context of Alzheimer's Disease – Importance of EMF Exposure

In this context, the findings of Arendash et al., that long-term EMF reduced brain Aβ deposition through Aβ anti-aggregation actions in AD mice, are highly interesting (97). It was also found, by Mori and Arendash et al., that long-term exposure to high frequency EMF treatment prevented cognitive impairment in AD transgenic (Tg) mice and improved memory in normal mice and that an increase in neuronal activity could be observed in the EMF exposed groups (98). Furthermore, it was found by the group that EMF treatment enhances brain mitochondrial functions in AD Tg as well as normal mice and that no increase in brain temperature could be found in connection to the EMF exposure (99). An interesting aspect in this context, is the role of mitochondria for many cellular functions, including reactive oxygen species generation, apoptosis, and $Ca2^{+}$ homeostasis as was mentioned by Dragicevic et al. and reviewed by Nicholls (99, 100).

In the first mentioned study by Arendash et al. (97), mice were EMF exposed with start at young age or at adult age. In the young-age group, 24 mice were divided into 4 subgroups: n=6 were Tg controls, n=6 were Tg animals treated with EMF, n=6 were non-transgenic (NT) controls and n=6 were NT animals treated with EMF. 2.5, 4-5 and 6-7 months after daily GSM-900 EMF exposure (two 1-hour sessions daily, at SAR 0.25 W/kg), the animals were evaluated by cognitive tests. At the end of the study, Aβ in the brains was evaluated by immunohistochemistry. No effect on cognitive functions was observed after 2 months of exposure. However, for the Tg+EMF mice with start of EMF exposure at young age, the cognitive function was maintained after 6-7 months of exposure, while it deteriorated in the Tg group. In a final task for NT mice after 7 months of EMF, the EMF actually improved the mnemonic function. In the adult-age group, Tg animals had impaired cognitive functions at the age of 4 months. 28 Tg and NT mice were included. After long-term EMF exposure (2, 5 and 8 months) the memory was tested. While 2 months of EMF exposure had no effect, 5 months of exposure had positive effects only on NT mice, and 8 months of exposure had beneficial effects for the Tg mice, with better results in the Tg+EMF group as compared to the Tg controls. Also the NT+EMF mice had an improved function as compared to NT controls after 8 months. Staining for Aβ revealed lower values on both hippocampus and the entorhinal cortex in the Tg+EMF group as compared to the Tg control group. Hippocampal

tissue from Tg mice were then exposed to EMF for 4 days, after which it was shown that the Aβ amount had decreased as compared to non-exposed control tissue. It was also reported that a ~1° temperature increase was observed in EMF exposed animals during exposure, but not in between exposure sessions (97).

In the study by Mori and Arendash (98), n=6 mice were Tg controls, carrying the mutant APPK670N , n=10 mice were Tg treated with EMF, n=4 mice were NT controls and n=5 mice were NT treated with EMF. EMF exposed animals were placed in a Faraday cage, receiving two 2-hour periods of EMF treatment at GSM-900 frequencies, pulse modulated at SAR 0.25-1.05 W/kg. The neuronal expression of c-Fos was taken as an indicator of neuronal activity. With immunohistochemistry, it was found that c-Fos was increased in both the NT+EMF group, as well as in the Tg+EMF group in the entorhinal cortex. However, only this one brain region was analyzed, since c-Fos expression was too low in other regions, which the authors hypothesised might be due to that c-Fos in an early response gene, and that at a certain time after stimulation, when the animals were sacrificed, the expression had already declined in other regions, such as hippocampus. In a cognitive test (Y-maze), it was found that EMF improved the performance in both NT and Tg group as compared to untreated controls. It should also be noted, that despite the very interesting findings, the number of included animals is quite small (98).

EMF and ^{18}FDG Uptake – Recent Studies

The question whether EMF exposure from mobile phones has neuronal effects in the human situation was recently addressed by an American research group led by Volkow et al., conducting a PET study on ^{18}F-fluorodeoxyglucose (^{18}FDG) uptake (101). Though PET-studies on humans in correlation to EMF exposure have also been previously made, the purpose of this study was to extend the study material and use the more direct measure of brain glucose metabolism by the uptake of ^{18}FDG instead of the previously used CBF (cerebral blood flow) measure, which might be a more indirect sign of neuronal activity and also reflect short-term alterations (60s) as compared to the more long-lasting ones observed with ^{18}FDG (suggested to be in the range of 30 min). ^{18}FDG is actively transported across the BBB into the cells, where it is phosphorylated, and is, among others, used as a prognostic value for following low-grade brain tumours, where an increased uptake in previously low-

grade tumours is an indicator of anaplastic transformation (for review into the topic of ^{18}FDG and brain tumours (102).

(space)

In the study by Volkow et al. (101), in total, 47 persons were involved, and effects upon brain glucose metabolism of EMF exposure were evaluated using PET with injection of ^{18}FDG. PET scans were performed both with and without EMF exposure (50 min of GSM-900 with maximum SAR of 0.901 W/kg), and the participants were blinded to the exposure situation. Whereas whole-brain metabolism was not affected, there were regional differences, in the right orbitofrontal cortex and the lower part of the right superior temporal gyrus (that is, the same side as the mobile phone was placed at) with increased metabolism in the exposure situation of about 7% as compared to control. There was a positive correlation between the strength of the E-field from the phones and the brain activation. Interestingly, it was hypothesized that RF-EMF exposure might increase the excitability of brain neurons.

Following the study by Volkow et al. (101), Kwon et al. (103) also investigated effects of GSM-900 exposure upon brain ^{18}FDG uptake. Thirteen persons were exposed to GSM-900 for 30 minutes to the right side of the head, and all subjects were also sham-exposed, and blinded to the exposure situation (SAR-values of maximum 0.74 W/kg in the head and 0.23 W/kg in the brain tissue). Contrary to the findings of Volkow et al. (101), the study by Kwon et al. (103) demonstrated a decrease in brain ^{18}FDG uptake after GSM-900 exposure, with decreased uptake values in the temporoparietal junction. A volume-of-interest analysis focused upon the right temporal lobe, showed a decreased ^{18}FDG uptake in the anterior inferior temporal cortex. No effects on task performance were found, and no correlation between temperature or ^{18}FDG uptake (a temperature increase of <0.21°C was found on the skin on the exposed side of the head) (103).

In the animal situation, Frilot et al. investigated the effect of ELF magnetic field exposure (2.5 G at 60 Hz) upon ^{18}FDG uptake in rats, comparing uptake with and without EMF exposure. An increased glucose uptake was found in the hindbrain when the field was orthogonally to the sagittal plane, but not when the angle varied randomly between the field and sagittal plane. These effects were hypothesized to be coupled to induction of electric field on the gate of ion channels (104).

Possible connection between BBB leakage and nerve cell injury

It has been suggested that BBB leakage is the major reason for nerve cell injury, such as that seen in dark neurons in stroke-prone spontaneously hypertensive rats (105). Much speaks in favour of this possibility. The parallel findings in the Lund material of neuronal uptake of albumin and dark neurons may support the hypothesis that albumin leakage into the brain is the cause for the neuronal damage observed after 28 and 50 d. It should, however, be pointed out that the connection is not yet proven (Figure 8).

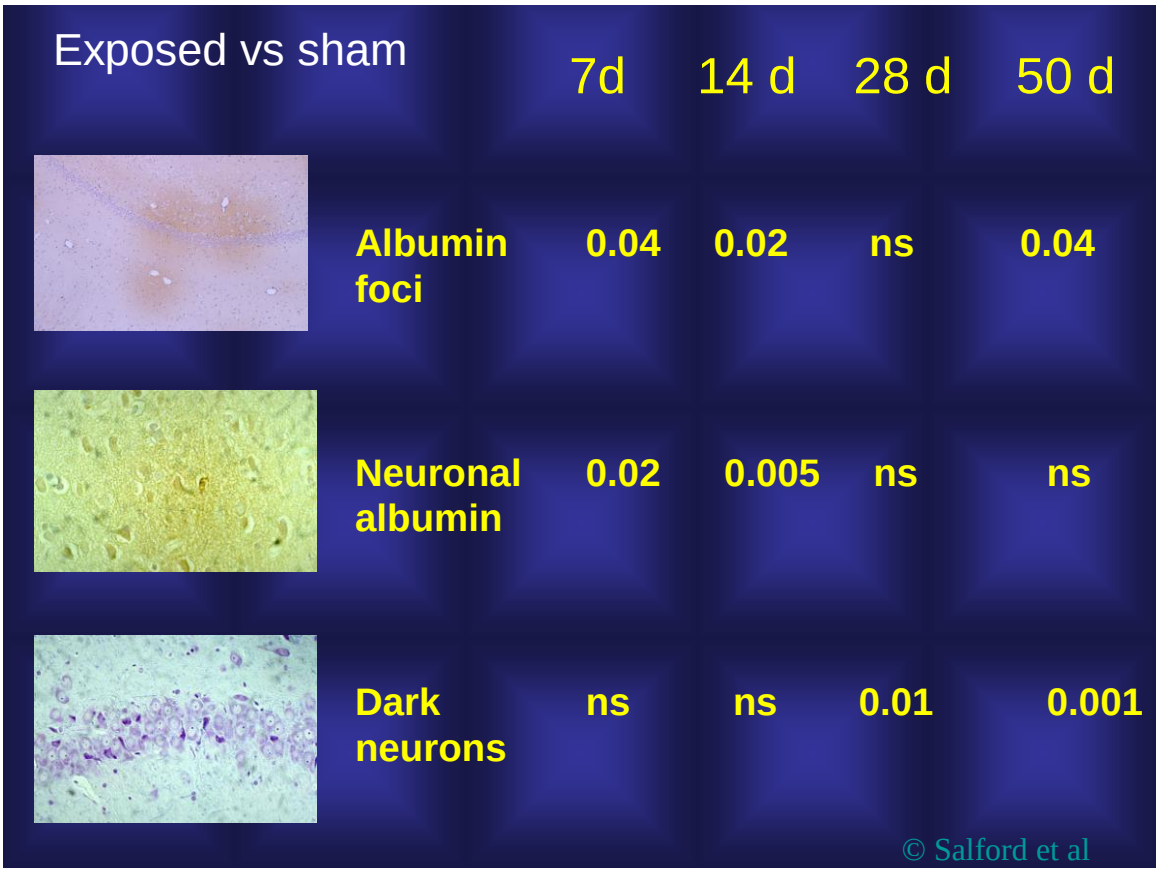

Figure 8. Results from the Lund group (61-63)

Also, other unwanted and toxic molecules in the blood may leak into the brain tissue in parallel with the albumin, and concentrate in and damage the neurons and glial cells of the brain. In favour of a causal connection between albumin and neuronal damage is a series of experiments performed in rats by another group at Lund University; albumin leaks into the brain and neuronal degeneration is seen in areas with BBB disruption in several circumstances: after intracarotid infusion of hyperosmolar solutions in rats (106) in the stroke

prone hypertensive rat (105); and in acute hypertension by aortic compression in rats (22). Furthermore, it has been shown in other laboratories that epileptic seizures cause extravasation of plasma into brain parenchyma (21), and in the clinical situation the cerebellar Purkinje cells are heavily exposed to plasma constituents and degenerate in epileptic patients . There are indications that an already disrupted BBB is more sensitive to the RF fields than an intact BBB (74, 91). It has been stated by other researchers that albumin is the most likely neurotoxin in serum (64). It has been demonstrated that injection of albumin into the brain parenchyma of rats gives rise to neuronal damage. When 25 micro-litres of rat albumin is infused into rat neostriatum, 10 and 30, but not 3 mg/ ml albumin causes neuronal cell death and axonal severe damage (65). It also causes leakage of endogenous albumin in and around the area of neuronal damage. However, it is still unclear whether the albumin leakage demonstrated in our experiments locally reaches such concentrations.

Possible mechanisms

Microarray analysis of the expression of all the rats' genes in cortex and hippocampus, after exposure to GSM RFs or sham exposure for 6 h, has shown interesting differences between exposed animals and controls as described by Nittby et al. (107). Genes of interest for membrane transport show highly significant differences. This may be of importance in conjunction with our earlier findings of albumin leakage into neurons around capillaries in exposed animals. It can be noted here that among the significantly altered genes from these evaluations, two variants of the gene RGS4 are up-regulated in hippocampal tissue from exposed rats as compared to the sham-exposed rats (unpublished results). RGS is a regulator of G protein signalling, and it has been proposed that RGS4 might regulate BBB permeability in mammals, in a way corresponding to the role of its Loco homolog G protein coupled receptor (GPCR) in developing and maintaining the BBB permeability of Drosophila (7).

It has also been suggested in other connections that manifestations of BBB disruption might also be mediated by the formation of free radicals, such as O_2^-, H_2O_2, and hydroxyl radical, which are supposed to oxidize cell membrane lipids by virtue of the high concentration of polyunsaturated fatty acids in these membrane constituents (108). As an example of this, it was reported by Chan et al.(109), that treatment of the brain of rats with a free-radical

generating system resulted in lipid-peroxidation, and an increased permeation of Evans blue due to barrier breakdown.

Recently, a detailed molecular mechanism, by means of which mobile phone radiation might exert its effects, has been proposed (110). By using Rat1 and HeLa cells, it was shown that EMF exposure resulted in rapid activation of ERK/ MAPKs (mitogen-activated protein kinase). The activation of these ERKs was mediated by reactive oxygen species (ROS), resulting in a signalling cascade ultimately affecting transcription, by the central key role of ERKs in signalling pathways.

In the continued search for the mechanisms behind EMF mediated effects, their interaction with calcium-45 transport in bio-membranes has been studied (111) and $Ca2^{+}$-efflux over plasma membranes has been observed in plasma vesicles from spinach exposed to ELF magnetic fields (112). With this model, quantum mechanical theoretical models for the interaction between magnetic fields and biological systems are tested. The model proposed by Blanchard and Blackman (113), in which it is assumed that biologically active ions can be bound to a channel protein and in this way alter the opening state of that channel, could in this way be quantitatively confirmed. Thus, the membrane is one site of interaction between the magnetic fields and the cell, and more specifically, the $Ca2^{+}$-channels, are one of the targets. More recently, new models for the interaction between magnetic fields and hydrogen nuclei also have been proposed.

EMF-induced $Ca2^{+}$-efflux over plasma membranes, understandably, can have many different effects on the target cells. Some agents that increase the BBB permeability act through a contractile mechanism that widens the intercellular junctions of the capillary endothelium. An increase of free $Ca2^{+}$ should mediate these changes, thereby resulting in measurable alterations of intracellular $Ca2^{+}$-levels in brain capillary cells after exposure to BBB-disrupting agents (108).

Another hypothesis is that EMF-induced intracellular $Ca2^{+}$-alterations might affect Ets genes, which are transcription factors expressed in different tissues (114). In this context, we could add that in our gene expression material from GSM-exposed rats vs., sham-exposed rats, one Ets variant gene is actually significantly up-regulated in hippocampus and one Ets1 gene is significantly up-regulated in cortex of the exposed animals.

EMF induced BBB permeability – with the aim of medical use

In the attempt to further try to understand the underlying mechanisms of the RF effects, we recently undertook a study upon snail nociception, with 1-hour GSM-1800 exposure of the land snail *H. pomatia*. This revealed, that the exposure induced analgesia in the snail model, with a significantly increased latency of reaction when placed on a hot plate, as compared to when only sham exposed. The vast knowledge about the physiology of the snail, its neurotransmission systems and it simplicity as compared the mammals may provide a tool for successful continued search for the mechanisms behind the effects of the GSM EMF upon biology (115).

In a recent study by Kuo et al (116), it was described how EMFs might be utilized to facilitate transport across the BBB. In an *in vitro* model, human micro-vascular endothelial cells were co-cultured with human astrocytes. Effects of EMF upon P-glycoprotein (P-gp) and multi-drug resistance -associated proteins (MRP) were tested in connection to treatment with anti-retroviral drugs, where the MRPs and P-gp are known to play an important role in multidrug resistance, which is encountered in carcinomas and therapies for acquired immune-deficiency (Kuo et al. 2012). With increasing EMF frequencies up to 900 MHz (both 715MHz and 900 MHz), the endocytotic uptake of calcein was increased (5mW, square wave with amplitude modulation at 20 MHz for 4 hours). Treatment with EMF could also inhibit expression of MRP and P-gp after treatment with anti-retroviral drugs, indicating that it might be useful in order to deliver antiretroviral proteins into the brain, by decreasing the efflux of the drugs due to the MRPs and P-gl.

Kuo et al. (117) also showed that EMF exposure (915 MHz EMFs at 5 mW with 20 MHz amplitude modulation for 4 hours) in combination with cationic solid lipid nanoparticles (CSLNs) could increase the transport of the antiretroviral drug Saquinavir 22-fold across human brain-microvascular endothelial cells (as compared to a 17-fold increase when only CSLNs were used).

Conclusions

In this review, we have reported the results of our group's research during the last 24 years, and the results of similar, but seldom identical, experiments of several other groups around the world. When summing up what we have described here, we are convinced that RF electromagnetic fields have effects upon biology, and we believe that it is more probable than unlikely, that non-thermal electromagnetic fields from mobile phones and base stations do have effects also upon the human brain. However, in this context, it is also important to point out, that the studies from our laboratory, as well as most studies presented above and available in literature, have been performed using animals and not humans. Thus no definitive conclusions can be drawn regarding effects of mobile phone use upon the human BBB.

However, studies in humans utilizing radiopharmaceuticals have been performed by Volkow et al. (101) upon brain glucose metabolism, and as was described by Saha et al. (118) already in 1994, studies with PET or SPECT and radiopharmaceuticals are used in brain imaging.

Further, a tool to directly study the human BBB has recently been described (119). It is based upon a non-radioactive methodology for *in vivo* non-invasive, real-time imaging of BBB permeability for conventional drugs, using nitroxyl radicals as spin-labels and MRI. In this connection, it should be mentioned though, that MRI has the drawback of possibly itself influence upon the results.

Based upon what has been presented here, we feel that the WHO IARC classification of RFR at the level 2B is adequate at present.

The question whether existing FCC/IEE and/or ICNIRP public safety limits and reference levels are adequate to protect the public is not easily answered. The reported studies on EMF induced BBB disruption have shown partially contradictory results from different laboratories. However, the fact that an abundance of studies do show effects is an important warning. This is true even if it can be summarized that the effects most often are weak and are seen in about 40% of the exposed animals.

However, we have stressed the following opinion in several publications during the past years: - "*The intense use of mobile phones, not least by youngsters, is a serious memento. A neuronal damage may not have immediately demonstrable consequences, even if repeated. It may, however, in the long run, result in reduced brain reserve capacity that might be unveiled by other later neuronal disease or even the wear and tear of ageing. We can not exclude that after some decades of (often), daily use, a whole generation of users, may suffer negative effects such as autoimmune and neuro-degenerative diseases maybe already in their middle age*".

One remarkable observation, which we have made in our studies throughout the years, is that exposure with whole-body average power densities below 10 mW/kg gives rise to a more pronounced albumin leakage than higher power densities, all at non-thermal levels. These very low SAR-values, such as 1 mW/kg, exist at a distance of more than one meter away from the mobile phone antenna and at a distance of about 150–200 m from a base station. Further, when a mobile phone operating at 915 MHz (and its antenna) is held 1.4 cm from the human head, the very low SAR levels of 10 mW/kg exist in deep-lying parts of the human brain such as the basal ganglia, and the power density of 1 mW/kg and less is absorbed in thalamus bilaterally.

With this information as a background, it is difficult to recommend safety limits as the function of existing mobile systems might not allow for limits that produce SAR levels below 1 or 0,1 mW/kg in the human brain, which are reported to cause a pathological leakage of the BBB and to neuronal damage.

Demonstrated effects on the BBB, as well as a series of other effects upon biology (120) have given rise to scientific concern and to public anxiety. It is up to the society and our politicians and also the providers of the radiofrequency-emitting technologies to support continued research in order to understand the nature of the effects, thereby neutralizing or at least reducing them. Also, it should be kept in mind that proven effects on biology also means that positive potentials might be revealed. This might be useful in medical applications, for example a controlled opening of the BBB would enable previously excluded pharmaceuticals to reach their targets within the brain tissue.

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SECTION 11

Use of Wireless Phones and Evidence for Increased Risk of Brain Tumors

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I. INTRODUCTION

In May 2011 the International Agency for Research on Cancer (IARC) at WHO categorised the radiofrequency electromagnetic fields (RF-EMF) from mobile phones, and from other devices that emit similar non-ionising electromagnetic fields, as a Group 2B, i.e. a 'possible', human carcinogen (Baan et al., 2011, IARC, 2011). Nine years earlier IARC had also classified extremely low frequency (ELF) magnetic field as Group 2B carcinogen (IARC, 2002).

The IARC decision on mobile phones was based mainly on case-control studies from the Hardell group in Sweden and the IARC Interphone study. Both provided supportive results on positive associations between two types of brain tumors; glioma and acoustic neuroma, and exposure to RF-EMF from wireless phones.

The final IARC decision was confirmed by voting of 29 scientists (one not present during voting) at the meeting. A large majority of participants voted to classify RF-EMF radiation as 'possibly carcinogenic' to humans, Group 2B. The decision was also based on occupational studies. We present in this paper an updated review of evidence of the association between use of wireless phones and brain tumors including also papers published after the IARC evaluation.

The Nordic countries were among the first countries in the world to widely adopt the wireless telecommunications technology. Analogue phones (NMT; Nordic Mobile Telephone System) were introduced in the early 1980s using both 450 and 900 Megahertz (MHz) frequencies. NMT 450 was used in Sweden from 1981-2007, NMT 900 operated during 1986-2000.

The digital system (GSM; Global System for Mobile Communication) using dual band, 900 and 1800 MHz, started to operate in 1991 and dominates now the market. The third generation of mobile phones, 3G or UMTS (Universal Mobile Telecommunication System), using 1 900/2 100 MHz RF fields has been introduced worldwide in recent years, in Sweden in 2003. Currently the fourth generation, 4G (Terrestrial 3G), operating at 800/2600 MHz and Trunked Radio Communication (TETRA 380-400 MHz) are being established in Europe. 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). Worldwide, an estimate of 5.9 billion mobile phone subscriptions was reported at the

end of 2011 by the International Telecommunication Union (ITU; http://www.itu.int/ITU-D/ict/facts/2011/material/ICTFactsFigures2011.pdf).

Desktop cordless phones (DECT) have been used in Sweden since 1988, first using analogue 800-900 MHz RF fields, but since early 1990s using a digital 1900 MHz system. These cordless phones are becoming more common than traditional landlines. They emit RF-EMF radiation similar to that of mobile phones. Thus when human health risks are evaluated it is also necessary to consider the use of cordless phones along with mobile phones.

The real increase in use and exposure to radiation fields from wireless phones (mobile phones and cordless phones) in most countries has occurred since the end of the 1990s. The brain is the main target organ during use of the handheld phone (Cardis et al., 2008). Fear of an increased risk for brain tumors has dominated the debate during the last one or two decades. While RF-EMFs do not have sufficient energy to break chemical bonds like ionising radiation, at least not directly, they can nevertheless have harmful effects on biological tissues. Plausible biological mechanisms for these effects include DNA damage, impairment of DNA repair mechanisms, and epigenetic changes to DNA (see also chapters by H. Lai (Genotoxicity) and I. Belyaev (Physical and Biological Mechanisms).

Primary brain tumors (central nervous system; CNS) constitute of a heterogeneous group of neoplasms of different histological types depending on tissue of origin with different growth patterns, molecular markers, anatomical localisations, and age and gender distributions. The clinical appearance, treatment and prognosis are quite different depending on tumor type.

There are few established risk factors for brain tumors besides ionising radiation (Preston Martin et al., 2006). Higher socio-economic status tends to be related to higher incidence and some rare inherited cancer syndromes account for a small fraction of tumors (Preston Martin et al., 2006). Familial aggregation of glioma has also been reported (Scheurer et al., 2010).

We base this review primarily on the Hardell group papers and the WHO Interphone study (Interphone Study Group, 2010, 2011, Cardis et al., 2011). More discussion of the results and responses, agreements and disagreements of the findings for the Hardell group and Interphone studies can be found in Hardell et al., (2012, 2013).

II. MATERIALS AND METHODS

The PubMed database (www.ncbi.nlm.nih.gov) was used for an up-dated search of published studies in this area using mobile/cellular/cordless telephone and brain tumour/neoplasm/acoustic neuroma/meningioma/glioma as searching terms. Personal knowledge of published studies was also used in order to get as up-to-date review as possible.

III. RESULTS

Brain tumors overall

Exposure to the radiation from the phones is generally higher in the temporal lobe, the part of the brain that is near to the ear (Cardis et al., 2008). For tumors located in the temporal, occipital or temporoparietal lobe areas of the brain an increased risk was found for ipsilateral exposure, that is the telephone was mostly used on the same side of the head as the tumor appeared, yielding OR = 2.42, 95 % CI = 0.97-6.05 (Hardell et al., 2001). This was the first study in the world that indicated an association between use of mobile phones and an increased risk for brain tumors. However, the results were based on low numbers of exposed subjects and different histopathological types of brain tumors so no firm conclusions could be drawn. Furthermore, this first study did not include use of cordless phones, see also Hardell et al., (1999).

Glioma

Glioma is the most common malignant brain tumor and represents about 60 % of all central nervous system tumors. The most common glioma subtype is astrocytoma. Astrocytic tumors are divided in two groups depending on the malignant potential; low-grade (WHO grades I-II) and high-grade (WHO grades III-IV). Low-grade astrocytoma has a relatively favourable prognosis, whereas survival is shorter for patients with high-grade glioma. Glioblastoma multiforme (WHO grade IV) accounts for 60-75 % of all astrocytoma.

The Hardell group in Sweden studied the association between use of mobile and cordless phones and brain tumors diagnosed during 1997-2003. First, cases diagnosed during 1 January 1997 to 30 June 2000 were included (Hardell et al., 2002, 2003). The next study period included 1 July 2000 to 31 December 2003 (Hardell et al., 2005, 2006a). The methods were the same with the same inclusion criteria and an identical questionnaire in both studies.

In short, both men and women aged 20-80 years at the time of diagnosis were included and all were alive at the time of inclusion in the study. They were reported from cancer registries and had all a brain tumor verified by histopathology. The Swedish Population Registry was used for identification of matched controls. In addition to other exposures use of wireless phones was carefully assessed by a self-administered questionnaire supplemented over the phone. The ear that had mostly been used during calls with mobile phone and/or cordless phone was assessed by separate questions. This information was checked during the supplementary phone calls and finally also by a separate letter with good agreement between these three methods.

Use of the wireless phone was defined as ipsilateral ($\geq$ 50 % of the time), or contralateral (< 50 % of the time) in relation to tumor side. The matched control was assigned the same side as the tumor of the respective case. Use of hands free devices was also assessed as well as use in a car with external antenna. Such use was not included in the calculation of cumulative number of hours for life time use. Latency time was defined as the period from the year of first use until diagnosis (corresponding year for the matched control).

Medical records including computer tomography (CT) and/or magnetic resonance imaging (MRI) were used to define tumor localisation in the brain. Further details can be found in the publications.

As a response to a critique from Boice and McLaughlin (2002) that the exclusion of deceased cases was a source of bias in our studies we performed a study on the cases with a malignant brain tumor that had died before inclusion in the case-control studies 1997-2003. These cases represented patients with a poor prognosis, mostly with astrocytoma WHO grade IV (glioblastoma multiforme). Controls were selected from the Death Registry in Sweden. The study encompassed 464 cases and 464 controls that had died from a malignant disease and 463 controls with other causes of death. Exposure was assessed by a questionnaire sent to the next of kin to each deceased case and control. The questionnaire was similar as in previous studies. This investigation confirmed the previous results of an association between use of mobile phones and malignant brain tumors (Hardell et al., 2010).

We have previously published pooled analysis of malignant brain tumors diagnosed during the period 1997-2003 (Hardell et al., 2006b). These results were updated including also results for the deceased cases with malignant brain tumors (Hardell et al., 2011a, Carlberg, Hardell 2012). The results on use of wireless phones were based on 1,251 cases with malignant brain tumor (response rate 85%) and 2,438 controls (response rate 84%). Most cases had glioma (n=1,148) so we present in the following results for that type of tumor. Latency was divided in three categories, >1-5 years, >5-10 years, and > 10 years from first use of a wireless phone until diagnosis of glioma.

Both use of mobile and cordless phone gave an increased risk overall, highest in the latency group >10 years, increasing further for ipsilateral use yielding for mobile phone OR = 2.9, 95 % CI = 1.8-4.7 and for cordless phone OR = 3.8, 95 % CI = 1.8-8.1 (Table 1). Highest ORs were found in the > 10 year latency group for total wireless phone use as well, OR = 2.1, 95 % CI = 1.6-2.8.
OR increased statistically significant for glioma for cumulative use of wireless phones per 100 h; OR = 1.014, 95 % CI = 1.008-1.019, and per year of latency; OR = 1.056, 95 % CI = 1.037-1.075 (Carlberg and Hardell, 2012). Separate calculations of mobile phone and cordless phone use yielded similar results with statistically significant increasing risks.

The Interphone study was conducted at 16 research centres in 13 countries during varying time periods between 2000 and 2004 under the guidance of IARC. An increased risk for brain tumor was found in some separate country studies and decreased risk in other studies as we have discussed elsewhere (Hardell et al., 2008, 2009). After several years of delay the overall Interphone results were finally published in May 2010 (Interphone Study Group, 2010).

In total 4,301 glioma cases were included in Interphone and the final results were based on 2,708 participating cases (response rate 64 %, range by centre 36-92 %). In total 14,354 potential controls were identified and interviews were completed with 7,658 (53 %, range 42-74 %). The low participation rates in some centres may have created selection bias, see Hardell et al., (2008).

Regular use of mobile phone in the past $\geq$ 1 year gave for glioma OR = 0.81, 95 % CI = 0.70-0.94 (Table 1). Subgroup analyses showed statistically significant increased risk in the highest

exposure group, i.e. those with cumulative mobile phone use ≥ 1,640 hours, OR = 1.40, 95 % CI = 1.03-1.89. The risk increased further for glioma in the temporal lobe yielding OR = 1.87, 95 % CI = 1.09-3.22. In the same exposure category, cumulative use ≥ 1,640 hours and ipsilateral exposure produced OR = 1.96, 95 % CI = 1.22-3.16 in total (no data given for temporal lobe).

In Appendix 2 (Interphone Study Group, 2010, available on the web) analysis was restricted to ever-regular users of mobile phones. Cumulative call time ≥ 1,640 hours gave OR = 1.82, 95 % CI = 1.15-2.89 compared with use < 5 hours. Time since start of regular use (latency) ≥ 10 years produced OR = 2.18, 95 % CI = 1.43-3.31; reference entity 1-1.9 years.

The Interphone study group concluded: "*However, biases and errors limit the strength of the conclusions we can draw from these analyses and prevent a causal interpretation.*" In an editorial accompanying the Interphone results the main conclusion of the Interphone results was described as "*both elegant and oracular…(which) tolerates diametrically opposite readings"* (Saracci and Samet 2010). Several methodological reasons why the Interphone results were likely to have underestimated the risks were discussed including 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"*.

Estimated RF-EMF dose in the tumor area from mobile phone use was associated with an increased risk of glioma in parts of the Interphone study (Cardis et al., 2011). OR increased with increasing total cumulative dose of specific energy (J/kg) absorbed at the estimated tumor centre for more than 7 years before diagnosis giving OR = 1.91, 95 % CI = 1.05-3.47 (p trend = 0.01) in the highest quintile of exposure. A similar study based on less clear methods was later published by another part of the Interphone study group (Larjavaara et al., 2011). The results seemed not to support the findings of Cardis et al., (2011). However, only 42 cases had used a mobile phone for more than 10 years and no analysis was made of the most exposed group with longest duration of use.

Based on Hardell et al (2011b) and Interphone Study Group (2010) we made meta-analysis of glioma and use of mobile phones. Random-effects model was used based on test for heterogeneity in the overall (≥10 years and ≥1,640 hours) groups. We used published results in

Interphone since we do not have access to their database. Our results were recalculated to these groups of exposure. The meta-analysis yielded for mobile phone use OR = 1.71, 95 % CI = 1.04-2.81 for glioma in the temporal lobe in the ≥ 10 years latency group. Ipsilateral mobile phone use ≥ 1,640 h in total gave the highest risk, OR = 2.29, 95 % CI = 1.56-3.37 (Hardell et al 2012). This meta-analysis strengthens a causal association between use of mobile phones and glioma.

Meningioma

Meningioma is the most common benign brain tumor. It develops from the pia and arachnoid that covers the central nervous system. Meningioma is an encapsulated and well-demarked tumor more common in women than in men. It is rarely malignant.

A pooled analysis of benign brain tumors from the two case-control studies from the Hardell group as discussed above (Hardell et at., 2006c, Hardell and Carlberg, 2009) gave regarding meningioma and use of mobile phone OR = 1.1, 95 % CI = 0.9-1.3, and cordless phone OR = 1.1, 95 % CI = 0.9-1.4 (Table 2). Using > 10 year latency period OR increased; for mobile phone to OR = 1.5, 95 % CI = 0.98-2.4, and for cordless phone to OR = 1.8, 95 % CI = 1.01-3.2. Ipsilateral mobile phone use in the > 10 years latency group yielded OR = 1.6, 95 % CI = 0.9-2.9, and cordless phone OR = 3.0, 95 % CI = 1.3-7.2. These results were based on rather low numbers of exposed cases, however.

Regular use of mobile phone produced in the Interphone study (2010) a statistically significant decreased risk for meningioma, OR = 0.79, 95 % CI = 0.68-0.91, Table 2. The risk increased somewhat with cumulative use ≥ 1,640 hours and ipsilateral mobile phone use to OR = 1.45, 95 % CI = 0.80-2.61. Analysis restricted to tumors in the temporal lobe or to the group of ever-regular use did not change the overall pattern of no increased risk.

We performed meta-analysis of meningioma for use of mobile phone based on results in the Hardell group and Interphone results similarly as for glioma. No statistically significant decreased or increased risk was found (Hardell et al., 2012). These results support the conclusion that up to latency ≥ 10 years or cumulative use ≥1,640 hours there is no consistent pattern of an association between use of mobile phones and meningioma.

Acoustic neuroma

Acoustic neuroma or Vestibular Schwannoma is a slow growing benign tumor located in the eighth cranial nerve in the auditory canal. It grows gradually out into the cerebellopontine angle with potential compression of vital brain stem centres. Tinnitus and hearing problems are usual first symptoms of acoustic neuroma. The eighth cranial nerve is located close to the handheld wireless phone when used, so there is particular concern of an increased risk for neuroma development due to exposure to EMF-RF emissions during use of these devices.

The pooled analysis of the Hardell group studies yielded regarding use of mobile phones for acoustic neuroma OR = 1.7, 95 % CI = 1.2-2.3 increasing to OR = 2.9, 95 % CI = 1.6-5.5 with > 10 years latency period, Table 3. Ipsilateral use increased the risk further; in the > 10 years latency group to OR = 3.0, 95 % CI = 1.4-4.2 (Hardell and Carlberg, 2009). Cordless phone use gave OR = 1.5, 95 % CI = 1.04-2.0 increasing to OR = 1.7, 95 % CI =1.2-2.5 for ipsilateral use in the > 1 year latency group.

In the Interphone study (2011) 1,121 (82 %) acoustic neuroma cases participated, range 70-100 % by centre. Of the controls 7,658 (53 %) completed the interviews, range 35-74 % by centre. The final matched analysis (1:1 or 1:2) consisted of 1,105 cases and 2,145 controls. Overall no increased risk was found censoring exposure at one year or at 5 years before reference date, OR = 0.85, 95 % CI = 0.69-1.04 and OR = 0.95, 95 % CI = 0.77-1.17, respectively (Table 3).

Cumulative number of hours of ipsilateral mobile phone use $\geq$ 1,640 hours up to 1 year before reference date gave OR = 2.33, 95 % CI = 1.23-4.40 and contralateral use OR = 0.72, 95 % CI = 0.34-1.53 for acoustic neuroma, see Table 3 (Interphone Study Group, 2011). For cumulative number of hours of ipsilateral mobile phone use $\geq$ 1,640 hours up to 5 years before reference date OR = 3.53, 95 % CI = 1.59-7.82, and for contralateral use OR = 1.69, 95 % CI = 0.43-6.69 were obtained. The risk increased further for cumulative ipsilateral use $\geq$ 1,640 hours with start $\geq$ 10 years before reference date to OR = 3.74, 95 % CI = 1.58-8.83. Contralateral use in that group yielded OR = 0.48, 95 % CI = 0.12-1.94, however based on only 4 exposed cases and 9 exposed controls. Overall OR = 1.93, 95 % CI = 1.10-3.38 was obtained for long-term use with start $\geq$ 10 years before reference date and cumulative call time $\geq$ 1,640 hours.

Similar analyses of the data as in Appendix 2 for glioma (see Interphone Study Group, 2010) yielded highest OR for acoustic neuroma in the shortest latency group, 2-4 years before reference date, OR = 1.41, 95 % CI = 0.82-2.40. Lower OR was calculated in the ≥ 10 years group, OR = 1.08, 95 % CI = 0.58-2.04. Somewhat higher risk than in total, OR = 1.32, 95 % CI = 0.88-1.97, was found for cumulative mobile phone use ≥ 1,640 hours; OR = 1.74, 95 % CI = 0.90-3.36, in this analysis restricted to only regular users. No results were given for ipsilateral use.

We performed meta-analysis of the results for use of mobile phone and the association with acoustic neuroma based on results by the Hardell group and Interphone study (Hardell et al 2012). For the latency group ≥ 10 years highest risk was obtained for ipsilateral use, OR = 1.81, 95 % CI = 0.73-4.45. The risk increased further for cumulative use ≥ 1,640 hours yielding OR = 2.55, 95 % CI = 1.50-4.40 for ipsilateral use. The meta-analysis strengthens a causal association between use of mobile phones and acoustic neuroma.

A case-case study was performed in Japan (Sato et al., 2011). The cases were identified during 2000-2006 at 22 participating neurosurgery departments. The diagnosis was based on histopathology or CT/MRI imaging. Of 1,589 cases 816 (51 %) agreed to participate and answered a mailed questionnaire. The final analysis included 787 cases, Cases with ipsilateral use were regarded as exposed and those with contralateral use were assumed to be unexposed and were used as the reference category. Overall no increased risk was found. However, for average daily call duration > 20 minutes with reference date 1 year Risk Ratio (RR) = 2.74, 95 % CI = 1.18-7.85 was found increasing to OR = 3.08, 95 % CI = 1.47-7.41 with reference date 5 years before diagnosis (Table 3). Unfortunately no results were given for cumulative number of hours for use over the years. For cordless phones no increased risk was found but the analysis was not very informative.

Risks to children and adolescents

The developing brain is more sensitive to toxins (Kheifets et al., 2005) and it is still developing until about 20 years of age (Dosenbach et al., 2010). Children have smaller head and thinner skull bone than adults. Their brain tissue has also higher conductivity and these circumstances give higher absorption from RF-EMF than for adults (Cardis et al., 2008, Christ et al., 2010, Gandhi et al., 2012). Use of wireless phones is widespread among children and adolescents

(Söderqvist et al., 2007, 2008). The greater absorption of RF energy per unit of time, the greater sensitivity of their brains, and their longer lifetimes with the risk to develop a brain tumor leaves children at a higher risk than adults from mobile phone radiation.

We have published results regarding brain tumor risk for different age groups at the time of diagnosis (Hardell et al., 2004) or age at first use of wireless phones (Hardell and Carlberg, 2009, Hardell et al., 2011a, 2012, 2013). Three age groups for first use of a wireless phone were used: <20 years, 20-49 years and 50-80 years. Highest risk for glioma was found for first use of mobile phone or cordless phone before the age of 20 years (Table 4). Thus, mobile phone use yielded for glioma OR = 3.1, 95 % CI = 1.4-6.7 and cordless phone OR 2.6, 95 % CI = 1.2-5.5.

Also for acoustic neuroma the risk was highest in the youngest age group with OR = 5.0, 95 % CI = 1.5-16 for use of mobile phone. Only one case had first use of cordless phone before the age of 20, so no conclusions could be drawn for cordless phones. Regarding meningioma no clear pattern of age-dependent increased risk was seen.

A multi-centre case-control study was conducted in Denmark, Sweden, Norway, and Switzerland, CEFALO (Aydin et al., 2011). It included children and adolescents aged 7–19 years and has been commented elsewhere in detail since serious methodological problems exist in the study design and interpretation of the results (Söderqvist et al., 2011). In CEFALO a statistically non-significant increased risk for brain tumors among regular users (one call per week for at least 6 months) of mobile phones was found; 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). No data for long-term use were given; the longest latency period was 5 years. 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).

Use of cordless phones was covered only in the first 3 years of use. No explanation was given for this most peculiar definition. Wireless phone use was not considered, that is use of both mobile phones and cordless phones as the relevant exposure category, as used by the Hardell group and adopted by IARC (Baan et al., 2011). Instead Aydin et al., (2011) included use of

cordless phones in the 'unexposed' category when risk estimates were calculated for mobile phone use. Similarly, regarding use of cordless phones RF-EMF emissions from mobile phones were regarded as 'no exposure'. Thus, an increased risk was potentially concealed.

The authors summarised that they "*did not observe that regular use of a mobile phone increased the risk for brain tumors*." An editorial in the same journal accompanied that conclusion by stating by that the study showed "*no increased risk of brain tumors*" (Boice and Tarone, 2011). This was echoed by a news release from the Karolinska Institute in Stockholm claiming that the results of no increased risk were 'reassuring' (Karolinska Institute, 2011). However the results 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, see Söderqvist et al., (2011).

Danish cohort study on mobile phone subscribers

An attempt to establish a cohort of mobile phone users was made in Denmark in co-operation between the Danish Cancer Society and the International Epidemiology Institute (IEI), Rockville, MD, USA. It was financed by grants from two Danish telecom operation companies (TeleDenmark Mobil and Sonafon), IEI, and the Danish Cancer Society. The source of money for IEI has not been disclosed.

The Danish study on brain tumor risk among mobile phone subscribers has so far resulted in four publications (Johansen et al., 2001, Schüz et al., 2006, Frei et al., 2011, Schüz et al., 2011). It included subjects from January 1, 1982 until December 31, 1995 identified from the computerised files of the two Danish operating companies, TeleDenmark Mobil and Sonofon. A total of 723,421 subscribers were initially identified but the final cohort consisted of only 58 % of these subjects. Due to lack of names of individual users 200,507 corporate users were excluded.

We have discussed elsewhere several shortcomings in the Danish cohort study such as exclusion of corporate users, no individual exposure data, users of cordless phones are included in the reference category, no control for use of mobile phones in the population after the establishment of the cohort, and no operator-verified data on years of subscription is available (Söderqvist et al., 2012). These limitations are likely to have led to an underestimate of any risk in this study.

One would also expect considerable misclassification of mobile phone use both among subscribers and the reference population since no new subscribers were included in the exposed cohort after 1995.

The IARC working group concluded that the methods used could have resulted in considerable misclassification in exposure assessment in the Danish cohort study on mobile phone subscribers (Baan et al., 2011).

After the outcome of the IARC-evaluation was made public in June 2011 (Baan et al., 2011) two additional reports on the Danish cohort were published (Frei et al., 2011, Schüz et al., 2011). Both were new up-dates of the initial cohort and included more information on risk related to longer follow-up. One focused on acoustic neuroma (Schüz et al., 2011) while the other gave results both for all cancers and separately for glioma and meningioma (Frei et al., 2011). This time the number of the cohort was reduced to 358,403 (49.5 %) of the initially identified subscribers (n=723,421). The major additional exclusion (n=54,350) was due to record linkage with the Danish so-called CANULI cohort on socioeconomic factors (Dalton et al., 2008).

The authors of the Danish study have themselves pointed out the main causes of considerable exposure misclassifications (Frei et al., 2011). While at least non-response and recall bias can be excluded the study has serious limitations related to exposure assessment (Söderqvist et al., 2012). In fact, these limitations cloud the findings of the four reports to such an extent they are uninformative at best. At worst, they may be used in a seemingly solid argument against an increased risk; as reassuring results from a large nationwide cohort study.

Brain tumor incidence

It has been suggested that overall incidence data on brain tumors for countries show no increasing trends and may be used to disqualify the association between mobile phone use and brain tumors observed in the case-control studies (Aydin et al., 2011; Ahlbom, and Feychting, 2011; Deltour et al., 2012; Little et al., 2012).

However, by now several studies show increasing incidence of brain tumors. In Denmark a statistically significant increase in incidence rate per year for brain and central nervous system

tumors (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). Updated results for brain and central nervous system tumors have been released in Denmark. The age-standardized incidence of brain and central nervous system tumors increased with 40 % among men and 29 % among women during 2001-2010 (Sundhedsstyrelsen, 2010). A more recent news release based on the Danish Cancer Register stated that during the last 10 years there has been an increasing number of cases with the most malignant glioma type, glioblastoma multiforme (astrocytoma WHO grade IV), especially among men (http://www.cancer.dk/Nyheder/nyhedsartikler/2012kv4/Kraftig+stigning+i+hjernesvulster.htm).

Little et al., (2012) studied the incidence rates of glioma during 1992-2008 in the United States and compared with ORs for glioma associated with mobile phone use in the 2010 Interphone publication (Interphone Study Group, 2010) and our pooled results published in 2011 (Hardell et al., 2011a). Since our results are discussed and questioned by Little et al their study needs to be reviewed in more detail. Our response to the journal (BMJ) was never accepted for publication in the journal and cannot be found via PubMed, only on the web (http://www.bmj.com/content/344/bmj.e1147/rr/578564).

First, one important methodological issue that was not stated in the abstract or in the article [Figures 2-4] by Little et al., (2012), 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 $\geq$ 18 years and all 12 SEER registries. Thereby numerous assumptions were made as pointed out by Kundi (2012) and Davis et al., (2012).

Using only men, as Little et al., did, ignores the fact that women had less frequent use of mobile phones than men in our studies (Table 5). Overall 31 % of women reported such use *versus* 57 % of men. Furthermore, use varies with age group with a large difference according to age, as we have explored in our publications (Hardell and Carlberg, 2009, Hardell et al., 2011a). Thus, the age group 60-64 year old men is not valid to use for these calculations.

There are several other points that may be added. Another example is that the results for anatomical localisations and tumor grade [in Table 5 in the article] by Little et al are based on numerous assumptions from SEER data, Interphone and the Hardell group studies. The authors seem not to have paid attention to the fact that the fraction of mobile phone users differs for gender and age, see Table 5.

One interesting result that was not commented further by Little et al., (2012) was the finding of a statistically significant yearly increasing incidence of high-grade glioma (WHO grades III-IV) in the SEER data for 1992-2008, +0.64%, 95% CI = +0.33 to 0.95 %. On the contrary, the incidence of low-grade glioma (WHO grades I-II) decreased with –3.02 %, 95 % CI = –3.49 to –2.54 %. Little et al., (2012) found also a statistically significant increasing yearly trend for glioma in the temporal lobe, +0.73 %, 95 % CI = +0.23 to 1.23 %.

Zada et al., (2012) studied incidence trends of primary malignant brain tumors in the Los Angeles area during 1992-2006. The overall incidence of primary malignant brain tumors decreased over the time period with the exception of glioblastoma multiforme (astrocytoma WHO grade IV). The annual age adjusted incidence rate of that tumor type increased statistically significant in the frontal lobe with Annual Percentage Change (APC) +2.4 % to +3.0 % ($p \leq 0.001$) and temporal lobe APC +1.3 % to +2.3 % ($p \leq 0.027$) across all registries. In the California Cancer Registry the incidence of glioblastoma multiforme increased also in cerebellum, APC +11.9 % ($p < 0.001$). For lower grade astrocytoma decreases of annual age adjusted incidence rates were observed. The authors concluded that there was a real increase in the incidence of glioblastoma multiforme in frontal and temporal lobes and cerebellum, areas of the brain with the highest absorbed dose of RF-EMF emissions from handheld mobile phones (Cardis et al., 2008).

Of interest is also the report by de Vocht et al., (2011) from England that showed for the time period 1998 to 2007 a statistically significant increasing incidence of brain tumors, the majority glioma, in the temporal lobe for men and women ($p < 0.01$), and frontal lobe for men ($p < 0.01$). The incidence increased also for women in the frontal lobe, although not statistically significant ($p = 0.07$). The incidence decreased in other parts of the brain.

Deltour et al., (2012) reported increasing glioma incidence rates in Denmark, Finland, Norway, and Sweden for the time period 1979-2008. APC increased for men with +0.4 %, 95 % CI +0.1 to 0.6 % and for women with +0.3 %, 95 % CI +0.1 to 0.5 %. A study from Australia for the time period 2000-2008 showed that APC for malignant brain tumors increased statistically significant +3.9 %, 95 % CI +2.4 to 5.4 % (Dobes et al., 2011). An increase was seen among both men and women. The APC for benign tumors increased with +1.7 %, 95 % CI -1.4 to +4.9 %, thus not statistically significant.

From urban Shanghai an increasing incidence of brain and nervous system tumors for the time period 1983-2007 was reported with APC +1.2 %, 95 % CI +0.4 to 1.9 % in males and APC +2.8 %, 95 % CI +2.1 to 3.4 % in females (Ding and Wang, 2011).

We reported increasing incidence of astrocytoma WHO grades I-IV during 1970-2007 in Sweden. In the age group > 19 years the annual change was +2.16 %, 95 % CI +0.25 to 4.10 % during 2000-2007, for further details see Hardell and Carlberg (2009).

IV. DISCUSSION

As pointed out by IARC (Baan et al., 2011) the most comprehensive results on use of wireless phones and the association with brain tumors come from the Hardell group in Sweden and the international Interphone study. Results for latency time of 10 years or more have been published from both study groups.

Both were case-control studies and the cases were recruited during similar time periods, 1997-2003 in the Hardell group and during 2000-2004 in Interphone, with somewhat different years in the varying study regions. There was no overlapping of cases in the Hardell group studies and the Swedish part of Interphone.

The Hardell group included cases aged 20-80 years whereas eligible cases in Interphone were aged 30-59 years at diagnosis. One control subject matched on age, gender and geographical area (region) to each case in the Hardell group studies was drawn from the national population register. In Interphone one control was selected for each case from a ‘locally appropriate population-based sampling frame’. In Germany two controls were selected and the centres used

individual matching or frequency matching. Regarding the Interphone study on acoustic neuroma some centres sampled special controls to the cases, other draw controls from the pool of controls in the glioma and meningioma studies, or used a mixture of both methods. In UK general practioners' lists (Hepworth et al 2006) and in Japan random digit dialling were used (Takebayashi et al., 2006, 2008). Certainly the methods used in Interphone may introduce selection bias.

Use of wireless phones and other exposures were carefully assessed by a self-administered questionnaire in the Hardell et al., studies. The information was supplemented over the phone by trained interviewers thereby using a structured protocol. This was done blinded as to case or control status. After the interviews all personal data like names and addresses were removed from the questionnaires so that only an id-number that did not disclose if it was a case or a control was shown. Thus, coding of the data for statistical analysis was performed without personal data of the individual.

On the contrary information on past mobile phone use was collected during face-to-face interviews in Interphone obviously disclosing if it was a case or a control that was interviewed. These interviews were performed by a large number of interviewers at different participating centres. Experienced interviewers were defined as those who conducted at least 20 interviews. In fact, in the sensitivity analysis the risk increased for glioma for cumulative mobile phone use $\geq$ 1,640 hours from OR = 1.40, 95 % CI 1.03-1.89 to OR = 1.50, 95 % CI = 1.10-2.06 if 'experienced interviewers only' were considered. The higher risk restricting analysis to 'experienced interviewers' in Interphone indicates observational bias during assessment of exposure decreasing the risk.

In the Hardell group studies few persons conducted all interviews of the 1,251 participating cases with malignant brain tumor, 1,254 cases with benign brain tumor, and 2,438 controls (total 4,942; note one case had both a malignant and a benign brain tumor). All interviewers were first educated; they used a defined protocol and gained considerable experience as interviewers. In fact, they were obliged to carry out the interviews extensively to fulfil the quality in data assessment according to the structured protocol. It is obvious that the few interviewers in the Hardell group study must have been much more experienced than the diversity of interviewers in Interphone.

In the personal interviews in Interphone a computer program that guided the interview with questions read by the interviewer from a laptop computer screen was used. The answers were entered directly into the computer by the interviewer. Using computer based face-to-face interviews may be a stressful situation for the patients. In fact patients scored significantly lower than controls due to recalling of words (aphasia), problems with writing and drawing due to paralysis in the Danish part of Interphone (Christensen et al., 2005). Furthermore, it has not been disclosed how the personal interviews were performed in sparsely populated areas, e.g. in the Northern Sweden. Did the interviewers travel long distances for interviews of controls in rural areas or were all controls living in the largest cities thereby creating selection bias?

In the Hardell group studies the response rate was 85 % (n=1,251) for cases with malignant brain tumor, 88 % (n=1,254) for cases with benign brain tumor, and 84 % (n=2,438) for controls (Hardell et al., 2006c, Carlberg and Hardell, 2012). Lower response rates were obtained in Interphone study, 64 %, range by centre 36-92 %, (n=2,765) for glioma cases, 78 %, range 56-92 %, (n=2,425) for meningioma cases, 82 %, range 70-100 % (n=1,121) for acoustic neuroma cases, and 53 %, range 42-74 %, (n=7,658) for controls (Interphone Study Group, 2010; 2011). These low response rates may have created the possibility of considerable selection bias (Hardell et al., 2008). Not responding controls in Interphone tended to be less frequent users of mobile phone than participating controls leading to underestimation of the risk.

The Hardell group studies included subjects aged 20-80 years, versus 30-59 years in Interphone. We have shown that restricting the age group to 30-59 years and considering subjects that used a cordless phone as unexposed in the Hardell group studies reduced the ORs and produced results quite similar to Interphone (Hardell et al., 2011b). Latency time > 10 years for glioma in the temporal lobe yielded OR = 1.40, 95 % CI = 0.70-2.81 in the Hardell group studies and OR = 1.36, 95 % CI = 0.88-2.11 in Interphone (latency $\geq$ 10 years). Thus, excluding exposure to RF-EMFs from cordless phones as in the Interphone study as well as excluding the younger and older subjects biased the ORs towards unity in Interphone, which likely dilutes the ability to see health risks.

By placing a strong emphasis on incidence data an association between use of wireless phones and brain tumors has been challenged (Swerdlow et al., 2011). The authors considered that if the

increased risks seen in case-control studies reflect a causal relationship, there would already be an increase in incidence of brain and central nervous system tumors. As discussed above by now increasing incidence rates, especially for certain brain tumor types and anatomical localisations of relevance, have been reported. The natural history of most glioma from earliest events to clinical manifestation is unknown, but most likely several decades. The exposure duration in most studies is thus incompatible with a tumor initiating effect. If the exposure on the other hand acts as a promoter, this would decrease latency time for already existing tumors, giving a temporary but not a continuous increase in incidence (Kundi, 2010).

The first case in the world on worker's compensation for a brain tumor after long-term use of wireless phones was the ruling 12 October 2012 by the Italian Supreme Court. A previous ruling that the Insurance Body for Work (INAIL) must grant compensation to a businessman who had used wireless phones for 12 years and developed a neurinoma in the brain was affirmed (http://www.applelettrosmog.it/public/news.php?id_news=44 ; www.microwavenews.com). 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 same area of the brain. No further appeal of the Supreme Court decision is possible.

V. CONCLUSIONS

Based on epidemiological studies there is a consistent pattern of increased risk for glioma and acoustic neuroma associated with use of mobile phones and cordless phones. The evidence comes mainly from two study centres, the Hardell group in Sweden and the Interphone Study Group. No consistent pattern of an increased risk is seen for meningioma. A systematic bias in the studies that explains the results would also have been the case for meningioma. The different risk pattern for tumor type strengthens the findings regarding glioma and acoustic neuroma. Meta-analyses of the Hardell group and Interphone studies show an increased risk for glioma and acoustic neuroma. Supportive evidence comes also from anatomical localisation of the tumor to the most exposed area of the brain, cumulative exposure in hours and latency time that all add to the biological relevance of an increased risk. In addition risk calculations based on estimated absorbed dose give strength to the findings.

In summary:

- There is reasonable basis to conclude that RF-EMFs are bioactive and have a potential to cause health impacts.
- There is a consistent pattern of increased risk for glioma and acoustic neuroma associated with use of wireless phones (mobile phones and cordless phones) mainly based on results from case-control studies from the Hardell group and Interphone Final Study results.
- Epidemiological evidence gives that RF-EMF should be classified as a human carcinogen.
- Based on our own research and review of other evidence the existing FCC/IEE and ICNIRP public safety limits and reference levels are not adequate to protect public health.
- New public health standards and limits are needed.

Authors' contributions

Lennart Hardell was responsible for drafting of the manuscript and Michael Carlberg made all statistical calculations. Michael Carlberg and Kjell Hansson Mild read and gave valuable comments on the manuscript. All authors have read and approved the final version. No conflicts of interest reported. Supported by grants from Cancer- och Allergifonden, Cancerhjälpen, and Örebro University Hospital Cancer Fund.

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Table 1. Summary of studies on the use of wireless phones and glioma risk

Study	Years Study Type	Age	Tumour type	No. of exposed cases	Odds ratio, 95 % confidence interval	Comments
Hardell et al (2006b, 2010, 2011a) Carlberg, Hardell (2012) Sweden	1997-2003 Case-control	20-80 years	Glioma (n=1148)	123	OR **2.5** (1.8-3.3)	>10 year latency, mobile phone
				57	OR **2.9** (1.8-4.7)	>10 year latency, mobile phone, *ipsilateral*, only living
				50	OR **2.6** (1.7-4.1)	>10 year latency, *mobile phone only*
				45	OR **1.7** (1.1-2.6)	>10 year latency, cordless phone
				20	OR **3.8** (1.8-8.1)	>10 year latency, cordless phone, *ipsilateral*, only living
				9	OR 1.2 (0.5-2.9)	>10 year latency, *cordless phone only;* >5-10 year latency OR **1.9** (1.3-2.9; n=55)
				150	OR **2.1** (1.6-2.8)	>10 year latency, wireless phone (mobile and cordless phone)
			Astrocytoma, high grade (n=820)	102	OR **3.0** (2.1-4.2)	>10 year latency, mobile phone
				47	OR **3.9** (2.3-6.6)	>10 year latency, mobile phone, ipsilateral, only living
				37	OR **2.8** (1.7-4.6)	>10 year latency, *mobile phone only*
				36	OR **2.0** (1.2-3.2)	>10 year latency, cordless phone
				15	OR **5.5** (2.3-13)	>10 year latency, cordless phone, ipsilateral, only living
				6	OR 0.9 (0.3-2.6)	>10 year latency, *cordless phone only;* >5-10 year latency OR **2.4** (1.6-3,7; n=44)
				121	OR **2.5** (1.8-3.4)	>10 year latency, wireless phone (mobile and cordless phone)

Table 1. cont.

Study	Years Study Type	Age	Tumour type	No. of exposed cases	Odds ratio, 95 % confidence interval	Comments
Interphone Study Group (2010) 13 countries; Australia, Canada, Denmark, Finland, France, UK, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden	2000-2004, 2-4 years depending on study region. Case-control	30-59 years	Glioma (n=2708)	1666	OR **0.81** (0.70-0.94)	Regular use of mobile phone in the past ≥1 year
				210	OR **1.40** (1.03-1.89)	Cumulative hours mobile phone ≥ 1640 hours
				78	OR **1.87** (1.09-3.22)	Cumulative hours mobile phone ≥ 1640 hours, tumors in *temporal lobe*
				100	OR **1.96** (1.22-3.16)	Cumulative hours mobile phone ≥ 1640 hours, *ipsilateral* mobile phone use
Interphone Study Group (2010) Appendix 2			Glioma (n=1211)	460	OR **1.68** (1.16-2.41)	Restricted to *ever regular use* time since start 2-4 years; 1-1.9 years as reference entity
				468	OR **1.54** (1.06-2.22)	Restricted to *ever regular use* time since start 5-9 years; 1-1.9 years as reference entity
				190	OR **2.18** (1.43-3.31)	Restricted to *ever regular use* time since start 10+ years; 1-1.9 years as reference entity
				160	OR **1.82** (1.15-2.89)	Restricted to *ever regular use* ≥1640 hours, <5 hours as reference entity

Table 2. Summary of studies on the use of wireless phones and meningioma risk

Study	Years Study Type	Age	Tumour type	No. of exposed cases	Odds ratio, 95 % confidence interval	Comments
Hardell et al (2006c), Hardell, Carlberg (2009) Sweden	1997-2003 Case-control	20-80 years	Meningioma (n=916)	347	OR 1.1 (0.9-1.3)	> 1 year latency, mobile phone use
				38	OR 1.5 (0.98-2.4)	> 10 years latency of mobile phone use
				18	OR 1.6 (0.9-2.9)	> 10 years latency of ipsilateral mobile phone use
				294	OR 1.1 (0.9-1.4)	> 1 year latency, cordless phone
				23	OR 1.8 (1.01-3.2)	> 10 years latency of cordless phone use
				11	OR **3.0** (1.3-7.2)	> 10 years latency of ipsilateral cordless phone use
Interphone Study Group (2010) 13 countries; Australia, Canada, Denmark, Finland, France, UK, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden	2000-2004, 2-4 years depending on study region. Case-control	30-59 years	Meningioma (n=2409)	1262	OR **0.79** (0.68-0.91)	Regular use of mobile phone in the past ≥1 year
				130	OR 1.15 (0.81-1.62)	Cumulative hours mobile phone ≥ 1640 hours
				21	OR 0.94 (0.31-2.86)	Cumulative hours mobile phone ≥ 1640 hours, tumors in *temporal lobe*
				46	OR 1.45 (0.80-2.61)	Cumulative hours mobile phone ≥ 1640 hours, *ipsilateral* mobile phone use

Table 2. cont.

Study	Years Study Type	Age	Tumour type	No. of exposed cases	Odds ratio, 95 % confidence interval	Comments
Interphone (2010) Appendix 2	2000-2004, 2-4 years depending on study region. Case-control	30-59 years	Meningioma (n=842)	362	OR 0.90 (0.62-1.31)	Restricted to *ever regular use* time since start 2-4 years; 1-1.9 years as reference entity
				288	OR 0.75 (0.51-1.10)	Restricted to *ever regular use* time since start 5-9 years; 1-1.9 years as reference entity
				76	OR 0.86 (0.51-1.43)	Restricted to *ever regular use* time since start 10+ years; 1-1.9 years as reference entity
				96	OR 1.10 (0.65-1.85)	Restricted to *ever regular use* ≥1640 hours, <5 hours as reference entity

Table 3. Summary of studies on the use of wireless phones and acoustic neuroma risk

Study	Years Study Type	Age	Tumour type	No. of exposed cases	Odds ratio, 95 % confidence interval	Comments
Hardell et al (2006c), Hardell, Carlberg (2009) Sweden	1997-2003 Case-control	20-80 years	Acoustic neuroma (n=243)	130	OR **1.7** (1.2-2.3)	> 1 year latency of mobile phone use
				20	OR **2.9** (1.6-5.5)	> 10 years latency of mobile phone use
				13	OR **3.0** (1.4-6.2)	> 10 years of *ipsilateral* mobile phone use
				4	OR 1.3 (0.4-3.8)	> 10 years latency of cordless phone use
				3	OR 2.3 (0.6-8.8)	> 10 years latency of *ipsilateral* cordless phone use
Sato et al (2011) Japan	2000-2006 Case-case	All ages	Acoustic neuroma (n=787)	97	RR 1.08 (0.93-1.28)	Mobile phone, reference date 1 year before diagnosis, *ipsilateral*
				86	RR 1.14 (0.96-1.40)	Mobile phone, reference date 5 years before diagnosis, *ipsilateral*
				18	RR **2.74** (1.18-7.85)	Mobile phone, reference date 1 year before diagnosis, average daily call duration >20 min, *ipsilateral*
				28	RR **3.08** (1.47-7.41)	Mobile phone, reference date 5 years before diagnosis, average daily call duration >20 min, *ipsilateral*
				45	RR 0.93 (0.79-1.14)	Cordless phone, reference date 1 year before diagnosis, *ipsilateral;* mobile phone non-users
				125	RR 1.02 (0.91-1.17)	Cordless phone, reference date 5 years before diagnosis, *ipsilateral;* mobile phone non-users

Table 3 cont.

Study	Years Study Type	Age	Tumour type	No. of exposed cases	Odds ratio, 95 % confidence interval	Comments
Interphone Study Group (2011) 13 countries; Australia, Canada, Denmark, Finland, France, UK, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden	2000-2004, 2-4 years depending on study region. Case-control	30-59 years	Acoustic neuroma (n=1105)	643	OR 0.85 (0.69-1.04)	Mobile phone regular use up to 1 year before reference date
				304	OR 0.95 (0.77-1.17)	Mobile phone regular use up to 5 years before reference date
				77	OR 1.32 (0.88-1.97)	Cumulative hours mobile phone ≥ 1640 hours up to 1 year before reference date
				36	OR **2.79** (1.51-5.16)	Cumulative hours mobile phone ≥ 1640 hours up to 5 years before reference date
				47	OR **2.33** (1.23-4.40)	Cumulative hours mobile phone ≥ 1640 hours up to 1 year before reference date; *ipsilateral* use
				27	OR **3.53** (1.59-7.82)	Cumulative hours mobile phone ≥ 1640 hours up to 5 years before reference date; *ipsilateral* use
				37	OR **1.93** (1.10-3.38)	Cumulative hours mobile phone ≥ 1640 hours in the past start ≥10 years before reference date
				28	OR **3.74** (1.58-8.83)	Cumulative hours mobile phone ≥ 1640 hours in the past start ≥10 years before reference date, *ipsilateral*
				225	OR 1.41 (0.82-2.40)	Restricted to *ever regular use* time since start 2-4 years; 1-1.9 years as reference entity
				209	OR 1.38 (0.80-2.39)	Restricted to *ever regular use* time since start 5-9 years; 1-1.9 years as reference entity
				64	OR 1.08 (0.58-2.04)	Restricted to *ever regular use* time since start 10+ years; 1-1.9 years as reference entity
				72	OR 1.74 (0.90-3.36)	Restricted to *ever regular use* ≥1640 hours, <5 hours as reference entity

Table 4. Odds ratio (OR) and 95 % confidence interval (CI) for glioma, meningioma and acoustic neuroma in different age groups for first use of the wireless phone (Hardell et al 2006b,c, 2010, 2011a). Numbers of exposed cases (Ca) and controls (Co) are given. Adjustment was made for age, gender, SEI-code, year of diagnosis. For glioma adjustment was also made for vital status.

	Glioma (n=1148)		**Meningioma (n=916)**		**Acoustic neuroma (n=243)**	
	Ca/Co	OR, CI	Ca/Co	OR, CI	Ca/Co	OR, CI
Mobile phone	529/963	**1.3** (1.1-1.6)	347/900	1.1 (0.9-1.3)	130/900	**1.7** (1.2-2.3)
< 20 years old	17/14	**3.1** (1.4-6.7)	5/14	1.9 (0.6-5.6)	5/14	**5.0** (1.5-16)
20-49 years old	315/581	**1.4** (1.1-1.7)	210/555	1.3 (0.99-1.6)	86/555	**2.0** (1.3-2.9)
≥ 50 years old	197/368	**1.3** (1.01-1.6)	132/331	1.0 (0.8-1.3)	39/331	1.4 (0.9-2.2)
Cordless phone	402/762	**1.3** (1.1-1.6)	294/701	1.1 (0.9-1.4)	96/701	**1.5** (1.04-2.0)
< 20 years old	16/16	**2.6** (1.2-5.5)	2/16	0.5 (0.1-2.2)	1/16	0.7 (0.1-5.9)
20-49 years old	206/437	1.2 (0.9-1.5)	167/416	1.3 (0.98-1.6)	65/416	**1.7** (1.1-2.5)
≥ 50 years old	180/309	**1.4** (1.1-1.7)	125/269	1.1 (0.8-1.4)	30/269	1.3 (0.8-2.1)

Table 5. Gender and age distribution for use of mobile phones among cases aged 20-80 years in the Hardell group studies. Glioma (n=1148).

	Men		Women		Total	
Age, diagnosis	No use/≤1 year latency, mobile phones	Use >1 year latency, mobile phones	No use/≤1 year latency, mobile phones	Use >1 year latency, mobile phones	No use/≤1 year latency, mobile phones	Use >1 year latency, mobile phones
20-24	8	7 (47 %)	3	8 (73 %)	11	15 (58 %)
25-29	10	15 (60 %)	5	10 (67 %)	15	25 (63 %)
30-34	11	26 (70 %)	19	8 (30 %)	30	34 (53 %)
35-39	9	23 (72 %)	8	13 (62 %)	17	36 (68 %)
40-44	10	26 (72 %)	16	11 (41 %)	26	37 (59 %)
45-49	14	37 (73 %)	12	16 (57 %)	26	53 (67 %)
50-54	22	61 (73 %)	26	27 (51 %)	48	88 (65 %)
55-59	35	65 (65 %)	59	20 (25 %)	94	85 (47 %)
60-64	41	51 (55 %)	53	15 (22 %)	94	66 (41 %)
65-69	55	46 (46 %)	57	13 (19 %)	112	59 (35 %)
70-74	43	16 (27 %)	41	5 (11 %)	84	21 (20 %)
75-80	27	8 (23 %)	35	2 (5 %)	62	10 (14 %)
All	**285**	**381 (57 %)**	**334**	**148 (31 %)**	**619**	**529 (46 %)**

SECTION 11

Evidence for Brain Tumors (Epidemiological)
Supplement 2012

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I. INTRODUCTION

Primary central nervous system (CNS) tumors are a heterogeneous group of benign and malignant neoplasms localized in the brain, the spinal cord and their coverings. They differ in histological type, tissue of origin, anatomic site, growth pattern, age distribution, sex ratio, clinical appearance and many other features including molecular neuropathological markers. These features are not independent but little is known about the etiology of these tumors and the reason for the observed epidemiological patterns. The rapidly developing field of molecular neuropathology may provide clues to solve these problems in the future.

Annually about 57,000 new cases of CNS tumors are diagnosed in the US. The age distribution has two peaks: incidence is about 4.7 cases per 100,000 per year below 10 years of age (which is mainly due to astrocytoma of the juvenile pilocytic type, malignant glioma, medulloblastoma and tumors originating from mesodermal and embryonic tissues), and after age 15 there is a steady increase of incidence with increasing age reaching its second peak of about 68 cases per 100,000 per year at an age around 75 to 80 years (CBTRUS, 2011). The burden of CNS cancers is distinctly higher in children making up around 20% of all childhood malignancies, while in adults less than 2% of all cancers are primary brain cancers.

There are some rare cases of inherited cancer syndromes (e.g. von Hippel-Lindau disease, Li-Fraumeni syndrome) that are related to brain tumor risk, accounting for a small fraction of cases. Except for therapeutic x-rays no environmental or lifestyle factor has unequivocally been established as risk factor for brain tumors. Non-whites seem to have lower risk, and incidence tends to be higher with increasing socio-economic status. However, because of the rather advanced age of 75-80 years of peak incidence, such differences may partly be due to differences in life-expectancy. During the last decades of the 20th century some types of brain tumors show a steady increase of a few percent per year, which might to some extent be related to the introduction of computed tomography and other high-resolution neuroimaging methods. For most CNS tumors except meningioma and pituitary tumors the incidence is higher in males than females.

Since the report of Wertheimer and Leeper in 1979 of an increased incidence of brain tumors in children living in homes with an expected higher exposure to power-frequency electric and magnetic fields, exposure to electromagnetic fields have become an area of interest in the study of factors affecting brain tumor risk.

This review focuses on the radio frequency (RF) part of the electromagnetic spectrum (3 kHz to 300 GHz). However, because the epidemiology of mobile phone use is covered in another section, it will be restricted to RF exposure conditions other than microwaves from mobile phone use. Exposure to ELF magnetic fields and childhood brain tumors is covered in the chapter about childhood cancers.

II. MATERIAL AND METHODS

Published articles of relevant studies restricted to the years 1987 to 2012 were obtained by searching PubMed using the following terms:

("radio frequency" OR electromagnetic* OR microwaves) AND ("brain cancer" OR brain tumor* OR "CNS cancer" OR CNS tumor* OR glioma* OR meningioma* OR neuroma*) NOT ("power frequency" OR "low frequency") AND epidemiolog*

The search resulted in 137 hits. After removing reviews and animal or in vitro studies as well as studies of mobile phone use, 10 articles remained. A hand search in review papers (Krewski et al. 2001; Elwood 2003; Ahlbom et al. 2004; Kundi et al. 2004) and reference lists of the articles found in PubMed revealed another 9 papers; hence the final body of evidence consists of 19 studies of exposure to various types of RF fields.

Of the 19 studies 8 were cohort studies, 5 case-control studies and 6 of an ecological type. The majority of studies (11) were occupational studies, four studies investigated children, and one ecological study investigated both, adults and children.

III. EPIDEMIOLOGICAL STUDIES OF RF FIELDS AND BRAIN TUMORS

Table 10A-1 gives an overview of the 17 studies obtained by the literature search with respect to study type, assessment of exposure and outcome, confounders considered and matching variables used, number of cases included and selection method of study participants. Results are summarized in Table 10A-2.

Table 10A- 1: Synopsis of epidemiologic studies of or including brain tumors (1987 – 2007)

Study	Country/Period/Study Type	Exposure assessment	Outcome assessment	Confounders considered & matching variables(m)	Number of cases/controls or cases (cohort studies)	Selection of participants
Thomas et al. 1987	Northern New Jersey, Philadelphia, gulf coast of Lousiana/1979-1981/Case-control	Interviews with next-of-kin about occupational history – response rates: cases 74%, controls 63%; JEM (2 methods)	Death certificates verified through review of hospital records	age(m), (only males), year of death(m), area of residence(m), educational level, (lead, soldering fumes)	435/386	Cases: deaths of brain tumor or CNS tumors of white males (age>30) from death certificates Controls: deaths from other causes than brain tumors, epilepsy, etc.
Milham 1988	Washington, California/1979-1984/Cohort	Amateur radio operator license within 1/1979 to 6/1984	Mortality records	age, (only males), race, year of death	29	67829 operators, search of deaths in state registry through 1984
Selvin et al. 1992	San Francisco/1973-1988/Spatial cluster	Distance of center of census tract to microwave tower (Sutro tower)	SEER records	-	35	Search of cancer deaths of white individuals (age<21)

Study	Country/Period/Study Type	Exposure assessment	Outcome assessment	Confounders considered & matching variables(m)	Number of cases/controls or cases (cohort studies)	Selection of participants
Tynes et al. 1992	Norway/1961-1985 /Occupational cohort	Job title in 1960 and 1970 censuses and expert categorization	Cancer registry	age, (only males)	119 overall, 6 in subgroup with possible RF exposure	Cohort of 37945 male workers identified that had jobs in 1960 with possible EMF exposure. among these 3017 with possible RF exposure
Grayson 1996	US Air Force/1970-1989/Nested case-control	Detailed job history and classification based on JEM (RF/MW exposure from frequent measurements)	Screening of hospital discharge records	age(m), race(m), military rank, (ELF and ionizing radiation exposure)	230/920	Cohort of ~880000 US Air Force members with at least one completed year of service within the study period, no follow up after subjects left service
Szmigielski 1996	Poland (military)/1971 -1985/Occupational cohort	Allocation to RF/MW exposure group based on service records, documented measurements of military safety groups	Incident cases from central and regional military hospitals and military health departments	age, (only males)	~46	Annual number of ~127800 military career personnel, ~3720 RF/MW exposed per year

Study	Country/Period/Study Type	Exposure assessment	Outcome assessment	Confounders considered & matching variables(m)	Number of cases/controls or cases (cohort studies)	Selection of participants
Hocking et al. 1996	Sydney (Australia)/ 1972-1990/Ecological	Municipalities within ~4 km of 3 TV broadcasting towers considered higher exposed as compared to 6 further away	Incident and death cases from cancer registry	age, sex, calendar period	740 (incident) 606 (mortality) 64 age<15 (incident) 30 age<15 (mortality)	Study population: inner area ~135000, outer area ~450000
Tynes et al. 1996	Norway/1961-1991/ Occupational cohort	Certified radio and telegraph operators 1920-1980 (98% worked on merchant ships); spot measurements on ships with old-fashioned equipment	Cancer registry	age, (only females)	5	2619 women certified as radio or telegraph operators by Norwegian Telecom
Dolk et al. 1997a	Birmingham (GB)/ 1974-1986/Ecological	Living near a TV/FM radio transmitter (Sutton Coldfield)	Cancer registry	age, sex, calendar year, SES	332	Population (age≥15) ~408000 within 10 km of the transmitter
Dolk et al. 1997b	GB/1974-1986/	Living near a	Cancer registry	age, sex,	244	Population (age<15)

Study	Country/Period/Study Type	Exposure assessment	Outcome assessment	Confounders considered & matching variables(m)	Number of cases/controls or cases (cohort studies)	Selection of participants
	Ecological	high power (≥500 kW erp) transmitter (overall 21)		calendar year, SES		within 10 km of one of 20 high power transmitters
Lagorio et al. 1997	Italy/1962-1992/ Occupational cohort	Working as RF heat-sealer operator	Cancer deaths from registry	age, (only females), calendar period, region	1	302 women employed 1962-1992 in a plastic-ware manufacturing plant as RF sealers
Finkelstein 1998	Ontario (Canada)/ 1964-1995/ Occupational cohort	Working as a police officer (possible handheld radar exposure)	Cancer registry	age, (only males), calendar year	16	20601 male officers of Ontario Police
Morgan et al. 2000	USA/1976-1996/ Occupational cohort	Jobs classified according to work with RF emitting devices with different output power	Death certificates from states' statistics offices	age, sex, period of hire	51	All U.S. Motorola employees with at least 1 day employment 1976-1996 (195775 workers, 2,7 million person-years)

Study	Country/Period/Study Type	Exposure assessment	Outcome assessment	Confounders considered & matching variables(m)	Number of cases/controls or cases (cohort studies)	Selection of participants
Groves et al. 2002	USA/1950-1997/ Occupational cohort	6 occupational groups 3 with assumed low radar exposure (radar-, radio operator, aviation electrician's mate) and 3 with assumed high exposure (aviation electronics -, electronics -, fire control technician)	Death certificate from a state vital statistics office or National Death Index Plus	age at entry, (only males), attained age	88	40581 Navy Korean War veterans graduated 1950-54 from Navy technical schools; follow-up from graduation through 1997
Ha et al. 2003	South Korea/1993-1996/Ecological	Area <2 km around 11 high power and 31 low power AM radio transmitter and control areas >2 km from any transmitter	Cancer cases from insurance records	age, sex (direct and indirect standardization)	45/not specified	Census and residents registration data 1995 (population size between 3152 and 126523 at the different sites)
Park et al. 2004	South Korea/1994-1995/Ecological	10 areas with a AM radio transmitter ≥100kW	Cancer deaths from death certificates	age, sex (direct standardization)	30/100	Census data from 1990

Study	Country/Period/Study Type	Exposure assessment	Outcome assessment	Confounders considered & matching variables(m)	Number of cases/controls or cases (cohort studies)	Selection of participants
Berg et al. 2006	Germany/2000-2003/ Case-control	JEM from occupational history collected in interview	Histological verified cases of glioma and meningioma	age(m), sex(m), region(m), SES, urban/rural, smoking, ionizing rad. exposure	Glioma 366/732 Meningioma 381/762	All histological confirmed cases of glioma and meningioma from 4 neurosurgical clinics (age: 30-69) (part.rate 84%); frequency matched controls from population registry (part.rate 63%)
Schüz et al. 2006	Germany/2000-2003/ Case-control	Questionnaire about DECT cordless phone base station near the bed	Histological verified cases of glioma and meningioma	age(m), sex(m), region(m), SES, urban/rural, smoking, ionizing rad. exposure	Glioma 366/732 Meningioma 381/762	All histological confirmed cases of glioma and meningioma from 4 neurosurgical clinics (age: 30-69) (part.rate 84%); frequency matched controls from population registry (part.rate 63%)
Ha et al. 2007	South Korea/1993-1999/Case-control	Distance from 31 AM radio transmitters and 49 radio antennas, measurements and calculation of	Cases of brain cancer from verified by entry into cancer registry	age(m), sex(m), year of diagnosis(m), SES, population density	956/1020	All cases of brain cancer (age<15) from 14 hospitals and matched hospital controls with respiratory diseases

Study	Country/Period/Study Type	Exposure assessment	Outcome assessment	Confounders considered & matching variables(m)	Number of cases/controls or cases (cohort studies)	Selection of participants
		total RF electric field strength				

SES…socio-economic status, JEM…job exposure matrix, erp…equivalent radiation power, RF/MW…radio frequency/microwaves, CNS…central nervous system, ELF…extremely low frequency

Table 10A- 2: Synopsis of main results of brain tumor studies (1987 – 2007)

Study	Endpoint	Exposure category	Meas.	Outcome [95% CI]
Thomas et al. 1987	Brain tumor deaths (ICD not specified)	Ever exposed to RF	OR	1.6 [1.0 – 2.4]
		Electrical/electronics job	OR	2.3 [1.3 – 4.2]
		Unexposed*		
		Ever exposed < 5 y	OR	1.0
		5-19 y	OR	2.3
		20+ y	OR	2.0
Milham 1988	Brain cancer deaths (ICD-8: 191)	All	SMR	1.39 [0.93 – 2.00]
		Novice[a]	SMR	0.34
		Technician	SMR	1.12
		General	SMR	1.75
		Advanced	SMR	1.74
		Extra	SMR	1.14
Selvin et al. 1992	Brain cancer deaths (ICD-O: 191.2)	> 3.5 km distance from tower*		
		≤ 3.5 km[b]	RR	1.16 [0.60 – 2.26]
Tynes et al. 1992	Incident brain cancer (ICD-7: 193)	All with possible EMF exposure	SIR	1.09 [0.90 – 1.41]
		Subgroup possible RF exposure[c]	SIR	0.49 [0.18 – 1.06]
Grayson 1996	Incident brain cancer (ICD-9: 191)	Never RF/MW exposed*		
		Ever exposed	OR	1.39 [1.01 – 1.90]
Szmigielski 1996	Incident nervous system & brain tumors	RF/MW exposed	OER	1.91 [1.08 – 3.47]
Hocking et al. 1996	Brain cancer (ICD-9: 191)	Outer area*		
		Inner area (incident, overall)	RR	0.89 [0.71 – 1.11]
		Inner area (mortality, overall)	RR	0.82 [0.63 – 1.07]
		Inner area (incident, age<15)	RR	1.10 [0.59 – 2.06]
		Inner area (mortality, age<15)	RR	0.73 [0.26 – 2.10]
Tynes et al. 1996	Incident brain cancer (ICD-7: 193)	All	SIR	1.0 [0.3 – 2.3]
Dolk et al. 1997a	Incident brain tumors (ICD-8/9: 191, 192)	0-2 km from transmitter	OER	1.29 [0.80 – 2.06]
		0-10 km from transmitter	OER	1.04 [0.94 – 1.16]
Dolk et al. 1997b	Incident brain tumors (ICD-8/9: 191, 192)	0-2 km from transmitter	OER	0.62 [0.17 – 1.59]
		0-10 km from transmitter	OER	1.06 [0.93 – 1.20]

Study	Endpoint	Exposure category	Meas.	Outcome [95% CI]
Lagorio et al. 1997	Brain cancer deaths (ICD-9: 191)	RF sealer operator	OER	1 : 0.1
Finkelstein 1998	Incident brain cancer (ICD-9: 191)	All police officers	SIR	0.84 [0.48 – 1.36]
Morgan et al. 2000	Incident brain cancer (ICD-9: 191)	No RF exposure*		
		Low[d]	RR	0.92 [0.43 – 1.77]
		Moderate	RR	1.18 [0.36 – 2.92]
		High	RR	1.07 [0.32 – 2.66]
Groves et al. 2002	Brain cancer deaths (ICD-9: 191)	Low radar exposure*		
		High radar exposure	RR	0.65 [0.43 – 1.01]
Ha et al. 2003	Brain cancer (ICD-10:C70-C72)	Low power transmitters*		
		High power transmitters	SIR	1.8 [0.8 – 11.1]
		Control sites (>2 km)*		
		100 kW transmitter	OER	2.27 [1.30 – 3.67]
		250 kW	OER	0.86 [0.41 – 1.59]
		500 kW	OER	1.47 [0.84 – 2.38]
		1500 kW	OER	2.19 [0.45 – 6.39]
Park et al. 2004	Brain cancer deaths (ICD-10:C69-C72)	Control area*		
		≥100 kW transmitter	SMR	1.52 [0.61 – 3.75]
Berg et al. 2006	Incident glioma (ICD-O3: C71)	No occup. RF/MW exposure*		
		Probably no exposure	OR	0.84 [0.48 – 1.46]
		Probable exposure	OR	0.84 [0.46 – 1.56]
		High exposure	OR	1.22 [0.69 – 2.15]
		No high exposure*		
		High exposure <10 y	OR	1.11 [0.48 – 2.56]
		High exposure ≥ 10 y	OR	1.39 [0.67 – 2.88]
	Incident meningioma (ICD-O3: C70.0)	No occup. RF/MW exposure*		
		Probably no exposure	OR	1.11 [0.57 – 2.15]
		Probable exposure	OR	1.01 [0.52 – 1.93]
		High exposure	OR	1.34 [0.61 – 2.96]
		No high exposure*		
		High exposure <10 y	OR	1.15 [0.37 – 3.48]

Study	Endpoint	Exposure category	Meas.	Outcome [95% CI]
		High exposure ≥ 10 y	OR	1.55 [0.52 – 4.62]
Schüz et al. 2006	Incident glioma (ICD-O3: C71)	DECT near bed	OR	0.82 [0.29 – 2.33]
	Incident meningioma (ICD-O3: C70.0)	DECT near bed	OR	0.83 [0.29 – 2.36]
Ha et al. 2007	All brain cancers (ICD-10: C70-C72)	≤2 km	OR	1.42 [0.38 – 5.28]
		2-4 km	OR	1.40 [0.77 – 2.56]
		4-6 km	OR	1.02 [0.66 – 1.57]
		6-8 km	OR	1.08 [0.73 – 1.59]
		8-10 km	OR	0.94 [0.67 – 1.33]
		10-20 km	OR	1.01 [0.77 – 1.34]
		>20 km*		

* Reference
[a] From Milham 1988b, license classes as proxy for exposure duration
[b] Based on the assumption that exposure is higher near the microwave tower
[c] Computed based on Table 5 in Tynes et al. 1992
[d] Classification according to power output of equipment used for longest period of employment

OR…odds-ratio, SIR…standardized incidence ratio, SMR…standardized mortality ratio, RR…relative risk (rate ratio), OER…observed/expected ratio

In the following paragraphs each study is briefly discussed with respect to its strengths and weaknesses.

A. Thomas et al. 1987

This case-control study included 435 deaths from brain or CNS tumors and 386 deaths from other causes as controls. Only adult males were included. Basis of data collection on occupational history were interviews with next-of-kin. Two methods of classification were used: one method assigned subjects to one of three categories (never exposed to RF/ever exposed to RF in an electrical or electronics job/ever exposed to RF but not in an electrical or electronics job), the other method consisted of a classification of each job by an industrial hygienist for presumed exposure to RF, soldering fumes, and lead. Both methods revealed significantly increased brain tumor risks of presumed occupational exposure to RF fields. This increase was due to an association in electronics and electrical jobs with astrocytic tumors as the predominant outcome associated with employment in these categories. In addition a significant increase of brain tumor risk was found for increasing duration of exposure.

Although relying on information of next-of-kin could be a source of misclassification, one strength of this study is it's relying on occupational history only that could be assumed to be more accurate than recall of exposure to various agents. The two methods of classification led to almost the same results, which lends support to the hypothesis that indeed exposure in electrical and electronics jobs is associated with an increased brain tumor risk. Due to the relationship between RF exposure and exposure to lead, solvents or soldering fumes in these jobs, it is not possible to separate effects of these exposures. Soldering fumes were never investigates with respect to brain tumors, and the hypothesis of an association with sinonasal cancer could not be corroborated so far. However, analysis of exposure to lead did not show a consistent relationship with brain tumor risk, indicating that it may not confound the relationship to RF exposure.

Because this study is of dead cases only it is likely over-representing high grade brain tumors that may not all be associated with exposure leading to an effect dilution. Exposure misclassification, if it is non-differential in cases and controls, also reduces effect estimates.

A weakness of this study is obviously its lack of an exposure indicator other than the occupational category. While there is no doubt that in these jobs some exposure to RF fields occur quite regularly, specific characteristics including frequency ranges, modulation, intensity, duration and distance from the source vary considerably. Overall the study (as well as two earlier ones outside the search window: Lin et al. 1985 and Milham 1985) are sufficient to formulate a research hypothesis that can be tested in appropriately designed subsequent investigations. Unfortunately such studies have never been conducted.

B. Milham 1988

In this cohort study of 67,829 amateur radio operators holding a license within 1/1979 to 6/1984 in Washington and California 29 brain tumor deaths occurred during the follow up period with 21 expected.

It should be noted that there was a substantial and statistically significant lower number of overall deaths of less than three quarters of deaths expected from country mortality rates. This could be due to both a 'healthy-worker' effect as well as an effect of socio-economic status. In lieu of computing standardized mortality ratios (SMR) it may be instructive to look at the proportional mortality rates in the reference population and the amateur radio operators: 0.6% of all deaths are expected to be due to brain tumors in the reference population while in amateur radio operators twice as many occurred (1.2%). Whether or not this is an indication of an increased brain tumor risk due to RF exposure is difficult to assess. First of all, this study is a register only investigation and no information on intensity, frequency and duration of engagement in amateur radio operations were available. In a later analysis the author reported about results using a proxy of intensity and duration of exposure: the license class. In this analysis indications of an increase of risk with increasing license class were obtained.

This study could and should have started off a thorough follow up of amateur radio operators and nested case-control studies to address the problem of potential confounders and to narrow down the conditions that may be responsible for the increased mortality from some cancers. It is another loose end that leaves us without a clear message.

Although no risk factor for brain cancer except therapeutic ionizing radiation is known, there are some indications that risk increases with social class. The reason for this association is unknown but life-style factors may play a role as well as concomitant causes of death that

could lead to a spurious reduction of risk in lower class populations because brain tumors have their peak close to life-expectancy.

C. Selvin et al. 1992

The objective of this investigation was not primarily to study the relationship between RF exposure and childhood cancer but to address the general problem of how to assess disease incidence or mortality in relation to a point source. As the point source the Sutro Tower in San Francisco, the only microwaves emitting tower in this county, was chosen. A total of 35 brain tumor deaths occurred among 50,686 white individuals at risk aged less than 21 in the years 1973-88 in an area of approximately 6 km around the tower. The exact location of residence could not be obtained; therefore each case was located in the center of the census tract. Different methods of analysis were applied to assess a potential relationship between distance from the tower and brain tumor risk. Relative risk for brain tumors for a distance less than 3.5 km from Sutro Tower compared to more than 3.5 km was 1.162 and not significant.

The study explored different methodological procedures and has its merits from a methodological point of view. However, it starts from the wrong assumption: that distance to a point source is a valid proxy for intensity of exposure. Under ideal conditions of spherical symmetry of an emission this assumption holds, however, there are almost no real life situations where this assumption is sufficiently close to actual exposure levels. And it is definitely not true for the Sutro Tower. Radiations from the antennae are directed towards the horizon and the complex pattern of emission with main and side lobes results in a complex pattern of RF exposure at ground level. Furthermore, the area is topographically structured with hills and valleys such that areas of high exposure at the vertices are in close proximity to areas of low exposure at the shadowed side downhill.

Studying the relationship between a point source and disease is not only difficult due to the complex relationship between distance and exposure but also because of the fact that humans are not stable at a certain location. This is of greater importance for adults who may commute from and to work places and have generally a greater radius of activity as compared to children. Nevertheless, there is at least a high chance of one long-lasting stable location that is when people sleep in their beds. Therefore, studies in relation to a point source should attempt to assess exposure at the location of the bed. Because the objective of this study was not the

assessment of a potential brain tumor risk but the application of methods for the analysis of spatial data, no attempts were made to measure actual exposure.

D. Tynes et al. 1992

In this study information on occupations obtained for all Norwegians every 10 years was used to assess cancer incidence in relation to job titles. In 1960 37,945 male workers were identified that had jobs with possible exposure to EMFs and among these 3,017 with possible RF exposure. Overall 119 brain tumor cases were found in the cancer registry between 1961 and 1985. Of these cases 6 occurred in the subgroup of workers possibly exposed to RF fields. The overall expected number of brain tumor cases was 109 and 12 for the subgroup with possible RF exposure. Hence no increased brain tumor risk could be detected.

Despite the long follow-up period of 25 years with an accumulated number of 65,500 person-years the expected number of brain tumors diagnosed during that period is too low to detect a moderately elevated risk of 1.3 to 1.5. Furthermore, the follow up period just reaches the median induction period for brain tumors as delineated from studies on ionizing radiation.

As mentioned above, all studies solely relying on job titles lead to exposure misclassification and, therefore, to a dilution of risk. For dichotomous exposure variables (exposed/not exposed) and assuming a negligibly small proportion of exposed in the reference population standardized incidence ratios (SIR) are biased by a factor (1+f*(SIR-1))/SIR, if f denotes the fraction of true exposed and SIR is the true incidence ratio. Hence a true SIR of 2.0 is reduced to 1.5 if only 50% in the cohort are actually exposed. The observed SIR is further reduced if the assumption of a negligible fraction of exposed in the reference population is wrong. In this case the bias factor given above is further divided by (1+g*(SIR-1)), where g is the fraction of exposed in the general population.

While a cohort study that is based on registry data has the advantage of independence from recall errors and selection bias due to possible differential participation, it has the disadvantage that registry data are generally insufficient to provide reliable exposure indicators. While no association with brain tumors could be detected in this study it revealed an increased number of leukemia cases in occupations with possible RF exposure. This could

be due to the higher incidence of leukemia or to a stronger association or to the shorter latency and various other reasons including chance.

E. Grayson 1996

In this case-control study nested within approx. 880,000 US Air Force personnel with at least one years of service during the study period of 1970-89, primary malignant brain tumor cases were ascertained by screening hospital discharge records. The study included only males and only as long as they were on Air Force records. From 246 cases detected 16 were dropped due to incomplete or ambiguous data. For each case four controls were randomly selected from the case's risk set matching it exactly on year of birth and race. Controls that were diagnosed with diseases possibly associated with EMF exposure (leukemia, breast cancer, malignant melanoma) were excluded from the risk set.

A strength of this study is the detailed job history filed for each cohort member that could be used for retrospective exposure assessment. Furthermore, Air Force files contained detailed data from personal dosímetry on ionizing radiation for the different posts and jobs. Classification of RF field exposure was based on a detailed job exposure matrix with over 1,950 entries, indexing 552 different job titles. One source of classification was recorded events of exposure to RF fields above 100 W/m^2. By this method probable exposure was assigned if for a job such events were recorded in the past as well as for closely related jobs. Possible exposure was assigned for jobs that required operation of RF emitters but without recorded overexposure.

A further strength is the thorough consideration of possible confounders. Because of the possible relationship of brain tumor risk with socio-economic status (SES), military rank was used as a surrogate for SES and included in the analysis as well as ionizing radiation exposure that has previously been shown to increase brain tumor risk.

Exposure to RF fields was associated with a moderate but statistically significant increased risk of OR=1.39. Investigation of duration of exposure was compromised by an ambiguity introduced due to the calculation of an exposure score as the product of exposure and months. Nevertheless, for those ever exposed there were indications of an increasing risk with increasing exposure duration.

A weakness of this investigation is its incomplete follow-up of cohort members. This could have resulted in an underestimation of the true risk. Leaving the Air Force could have been more likely in those exposed to RF fields and developing a brain tumor. Some malignant brain tumors have early signs that could be incompatible with the Air Force job especially if involving operation of RF equipment (like seizures, severe headaches, somnolence, and absences). Because the study did not involve personal contact it is free of other selection biases.

F. Szmigielski 1996

In this military cohort study of cancer morbidity Polish military career personnel was assessed for occupational exposure to RF fields based on service records. The study covered 15 years (1971-85) including approx. 128,000 persons per year. Expected rates for 12 cancer types were calculated based on the age specific morbidity in those classified as unexposed.

For brain and nervous system tumors a significantly increased ratio of observed to expected (OER=1.91) was found. Other malignancies with significantly increased incidence in exposed were: esophageal and stomach cancers, colorectal cancers, melanoma, and leukemia/lymphoma.

A strength of this study is its substantial size with almost 2 million person-years of follow-up. Furthermore, accurate military records on job assignment and on exposure from military safety groups gives a unique opportunity to assess long-term exposure effects based on already filed data.

Some important data are missing because they were military classified information that could not be provided in the paper. This includes the exact number of cases of the different neoplasms. However, from the data presented an observed number of brain tumors of about 46 can be calculated.

The study has been criticized for an alleged bias because more information on risk factors was available for cancer cases. It is true that military medical boards collected data for cases such as life style factors and exposure to possible carcinogens during service, however, at no stage this information entered the analysis. Therefore, this criticism is unfounded. Such information could have been utilized within a nested case-control study applying the same methods of assessment of risk factors for controls as has been done for cases. Because some findings,

such as the increased risk for esophagus/stomach cancer, that are rarely reported in relation to RF exposure warrant further study, such a nested case-control approach is recommended. It could, albeit with some difficulties, even be successfully conducted retrospectively.

G. Hocking et al. 1996

In an ecological study cancer incidence and mortality in nine municipalities of northern Sydney during 1972-90 three of which surround three TV towers were assessed. Population size in the three municipalities located within a radius of approx. 4 km around the TV towers amounts to 135,000, while population size in the six municipalities further away was 450,000. High-power transmission commenced in 1956, an additional 100 kW transmission started in 1965 and another 300 kV broadcast in 1980. Carrier frequencies varied between 63 and 533 MHz for TV broadcasting and were around 100 MHz for FM radio broadcast.

During the study period 740 primary malignant brain tumors were diagnosed in adults and 64 in children, 606 deaths due to brain cancer occurred in adults and 30 in children. While incidence of lymphatic leukemia was significantly higher in adults as well as in children inhabiting the three municipalities surrounding the transmission towers compared to the six districts further away, brain tumor incidence was not significantly elevated (RR=0.89 in adults and 1.10 in children).

As has been stated above, distance from a transmitter is a poor proxy for exposure. Some measurements done in the study area obtained levels much lower than those calculated from the power emitted and antenna gain. Several factors are responsible for this effect: multiple reflections, attenuation by buildings and vegetation, ground undulations, non-coincidence of maxima for the different signals as well as complex radiation characteristics of the broadcast antennae.

The exact location of the residence of cases could not be provided which reduces the potential of the study to relate incidences to measurements or calculations of RF fields. Authors discussed some potential sources of bias such as migration and other exposures in the different regions. However, the most important disadvantage in such studies is that individual risk factors cannot be adjusted for. Both spurious positive as well as false negative results can be obtained by disregarding such individual variables.

H. Tynes et al. 1996

In a historical cohort study 2,619 Norwegian female radio and telegraph operators certified between 1920 and 1980 were followed from 1961 through 1991 for entries in the cancer registry. During this period a total of 140 cases of cancer occurred which are about 20% more than expected from the Norwegian population. Among these were 5 brain tumor cases closely matching the number expected.

An excess for breast cancer was found in this study that may be related to a combination of RF field exposure and night work. For other cancers including brain cancer numbers of cases were too low to address exposure risk.

In this very thoroughly conducted study including a nested case-control approach for breast cancer, measurements at historical transmitters on ships, comparison with women at other jobs on sea, brain tumors were not distinctly higher than expected from the reference population. However, because of the limited cohort size a moderately increased risk cannot be excluded.

I. Dolk et al. 1997a

This ecological small area study of cancer incidence 1974-86 near the Sutton Coldfield TV/radio transmitter at the northern edge of the city of Birmingham (England) was initiated by an unconfirmed report of a ‘cluster’ of leukemias and lymphomas. The transmitter came into service in 1949. Transmission at 1 megawatt (effective radiated power erp) began in 1964, at 3 MW in 1969, and at 4 MW in 1982. The tower has a height of 240 m with no big hills in the surrounding area. The study area was defined by a circle of 10 km radius centered at the transmitter. The population within this area was about 408,000. All cancers, excluding non-melanoma skin cancer, were considered focusing on hematopoietic and lymphatic cancers, brain and nervous system cancers, eye cancer, and male breast cancer. Childhood cancers were restricted to all cancers and all leukemias.

In the study area a small but significant excess of all cancers was observed in adults. All leukemias and non-Hodgkin’s lymphoma were particularly elevated and incidence within 2 to 4 km from the tower was about 30% higher than expected. Brain tumors were only analyzed for distances of within 2 km and the whole study area. Within 2 km an increased OER of 1.29

for all brain tumors and 1.31 for malignant brain tumors was calculated based on 17 and 12 cases, respectively.

Also this investigation suffers from using distance from the tower as proxy for intensity of exposure. The wrong assumption that exposure decreases with increasing distance invalidates the statistical trend test applied. Measurements conducted in the study area revealed the poor relationship with distance but without consequences on the evaluation of the data. Overall the study is consistent with a moderately increased risk of hematopoietic and lymphatic cancers as well as some other cancers including brain cancer in the vicinity of high-power transmitters that, if related to RF fields, must be substantially higher for actual exposure.

The Sutton Coldfield study was later continued (Cooper & Saunders 2001) to cover the period 1987-94. The study revealed, compared to the earlier period, an almost unchanged increase of leukemias and non-Hodgkin's lymphoma in adults and a slight increase in children.

J. Dolk et al. 1997b

Because the Sutton Coldfield study was triggered by a cluster report and to provide independent test of hypotheses arising from that study, similar methods as applied in the previous study were used to study all high-power TV/radio transmitters (≥ 500 kW ERP) in Great Britain. In adults leukemias, bladder cancer, and skin melanoma, and in children, leukemias and brain tumors were studied. The study period was 1974-86 for England and somewhat shorter in Wales and Scotland.

Although population density around transmitters was not always as high as in the case of the Sutton Coldfield tower, with an average population density of only about one third of that around Sutton Coldfield tower within 2 km from the towers, in the most important range of 2 to 4 km from the transmitters, where in many cases the maximum of radiated RF at ground level is reached, population density was similar. The study of all high-power transmitters essentially corroborated the findings for adult leukemias with an increase of incidence between 10 and 50% in the distance band of 2 to 4 km from the transmitters for the different transmitter types. Most of these increased incidences were statistically significant.

For children only the incidence in the whole study area and within a distance of 2 km was calculated, which is unfortunate because the area close to the towers is sparsely populated and

exposure is low. Number of brain tumors in children was slightly above expectation (244 observed and 231 expected).

In contrast to the interpretation by the authors, the study of all high power transmitters essentially replicated and supported the findings of an excess incidence of leukemias in relation to RF emission from TV/radio towers. Because the different heights and radiation characteristics of the transmitters result in different exposure patterns at ground level, the consistent increase in an area that is likely close to the maximum of exposure supports the hypothesis of an association.

K. Lagorio et al. 1997

A mortality study of a cohort of 481 female plastic-ware workers employed between 1962 and 1992 in an Italian plant, 302 of which were engaged in the sealing department with exposure to RF fields, was reported by Lagorio et al. (1997). For RF-sealers 6,772 person-years of follow-up were accumulated and overall 9 deaths occurred, 6 of which were from malignant neoplasms (which are twice as many as expected from comparison with the local reference population). In the 31 years only one brain cancer occurred but only 0.1 were expected.

Although the small size of the cohort and the potential exposure to other agents except RF fields such as solvents and vinyl chloride prohibit far reaching conclusion, much more of such thorough follow-up studies of exposed cohorts are needed to accumulate a body of evidence that can provide a useful basis for analysis.

L. Finkelstein 1998

A preliminary study intended to form the basis for an assessment of cancer risks associated with handheld radar devices was conducted among a cohort of 20,601 male Ontario police officers. The retrospective follow up covered the period of 1964-95. By linkage with the cancer registry and mortality database 650 cases of cancer were detected.

Testicular cancer and melanoma showed an excess incidence while overall cancer incidence was reduced as expected from a working cohort. Overall 16 cases of primary malignant brain tumors occurred which is slightly less than expected.

The author had difficulties to build up a proper cohort because some departments refused to participate and others couldn't spare the time to provide lists of all officers employed during the target period. Furthermore, while cancer sites of primary interest showed actually an increased incidence calling for a nested case-control approach, this study was never conducted due to lack of interest and support of the authorities.

M. Morgan et al. 2000

In an occupational cohort study all US Motorola employees with at least 6 months cumulative employment and at least 1 day of employment in the period 1976-96 were included. A total of 195,775 workers contributing about 2.7 million person-years were available for the study. The cohort was compared to the SSA Master Mortality File and the National Death Index to obtain vital status. Death certificates were obtained by states' vital statistics offices and company records. Exposure was assessed by expert opinion. Four RF exposure groups were defined with increasing level of estimated RF exposure. Only about 5% of the total cohort was classified as highly exposed and more than 70% with only background exposure. Neither private nor occupational mobile phone use was included.

Overall 6,296 deaths occurred in the cohort in 21 years, which were only two thirds of deaths expected from mortality data of the four countries where most Motorola facilities are located. This reduction is too pronounced to be solely due to a healthy worker effect, other factors such as higher SES must have contributed, an interpretation supported by the substantial reduction of mortality from all life-style associated causes of death. Internal comparisons were done for mortality from brain cancer and hematopoietic and lymphatic cancers. Brain tumor mortality was slightly but insignificantly elevated in high and moderately high exposed workers as compared to those with no or low RF exposure.

This study of a huge cohort demonstrates the limitations of such a study design. The majority of the cohort (58%) consisted of retired or terminated workers that may or may not have accumulated further RF exposure at other companies. Furthermore, it can be assumed that Motorola employees were among the first that used mobile phones at the workplace and

privately. Neglecting mobile phone use may diminish the gradient of exposures between occupational groups studied. It would have been better to conduct nested case-control studies instead of using internal comparison that may be compromised by mobility bias, exposure misclassification and use of mobile phones.

N. Groves et al. 2002

In this military cohort study of 40,581 men followed from the year of graduation (1950-1954) from Navy technical schools through 1997, known as the Korean War Veterans study, groups of sailors with imputed difference in likelihood and amount of exposure to radar waves were compared with respect to mortality. The original study, with a follow up through 1974, (Robinette et al. 1980) reported increased risks of cancer of the hematopoietic and lymphatic system, of the lung and digestive system for the high exposure group but was handicapped by the lack of information on date of birth of the cohort members. For the extended follow up study many missing birth dates were found in the Veterans Administration Master Index. Nevertheless, birth date remained unknown for over 8% of the cohort. Based on expert opinion low RF exposure was assigned to job classifications of radioman, radarman, and aviation electrician's mate, high exposure stratum included men with job classifications of electronics technician, aviation electronics technician, and fire control technician.

By matching against the Social Security Administration's Death Master File and the National Death Index 8,393 deceased subjects were identified through 1997. This number is substantially and significantly lower as expected from the male white US population. A healthy soldier effect may have been responsible for a lower mortality rate in the 1950ies but cannot explain the reduced mortality after 40 years. It has not been reported how long the cohort members stayed in service nor were life-style factors investigated; however, of more than 40% of the cohort no social security number could be obtained suggesting possible under-estimation of deaths.

Comparison of high- with low-exposure groups revealed significantly lower mortality from life-style associated causes of death (lung cancer, vascular diseases, diabetes mellitus, chronic obstructive pulmonary disease, and liver cirrhosis) and significantly higher mortality from all leukemias and external causes of death. Increased mortality from leukemias was found in all high exposure groups but the most pronounced increase was observed in aviation electronics

technicians. Brain cancer was less frequent in all high exposure groups compared to the low exposure category.

The long period of follow up of this large cohort with start of follow up almost at the same time (1950-54) and at a time when exposure commenced is a great advantage of this investigation. However, there are a number of shortcomings: follow up was possibly incomplete by unknown social security number of a substantial proportion of the cohort; almost half of all deaths in the first 20 years were from external causes which could have obscured an effect of exposure; duration and intensity of exposure is unknown as well as potential exposure after leaving the Navy; classification into low and high exposure groups may introduce substantial misclassification. In the earlier report, inspection of Navy records for a sample from the high exposure group revealed that 24% had no exposure to radar waves at all.

Concerning brain tumors, assuming an effect of radar exposure on tumor growth rate, exposure during the Korean War and no exposure afterwards would be expected to result in only a slightly increased risk during a period of about 10 years after the war. Sailors were about 20 to 25 years at that time. The fraction with an already initiated brain tumor during this age range is estimated to be less than 3 in 100,000 per year. Increase of growth rate even if substantial cannot result in an effect observable in a cohort of that size. If radar exposure increases the likelihood of malignant transformation this could increase the incidence during a time window of 10 to 30 years after the exposure period. Results of the Israeli study of x-ray treated tinea capitis (Sadetzki et al. 2005) suggests an average latency of about 20-25 years, however, risk decreased with increasing age at first exposure to x-rays. Taking the data on ionizing radiation as a guiding principle for brain tumor initiation, radar exposure of sailors during their twenties might result in an increase of brain tumor mortality of about 10 to 15%, i.e. a maximum of 8 additional cases among 20,000. Considering the biases of the study such a low risk is easily obscured. Hence neither tumor promotion nor initiation may be detected in this study even if there is an increased risk. Because of the mentioned limitation to a certain time window with possibly increased incidence due to exposures during service in the Korean War, it would have been instructive to compute Kaplan-Meier estimates for cumulative brain tumor mortality.

O. Ha et al. 2002

An ecological study around 11 high-power AM transmitter study sites (i.e., 100–1,500-kW transmission power) and 31 low-power study sites (i.e., 50-kW transmission power) used for comparison was conducted in South Korea. For each high-power site four control areas located in the same or nearest adjacent province as the high-power site, but were at least 2 km from any of the transmitters were chosen. The incidence of cancer within a 2-km radius of each transmitter and within control districts was obtained from Korean medical-insurance records for the years 1993 through 1996. Standardized incidence ratios (SIR) of high- against low-power transmitter areas were reported and additionally observed-to-expected ratios for each type of transmitter. SIRs were elevated for all cancers and for female brain cancer. Concerning transmitter types, for all types except 250 kW elevated OER for brain cancer were obtained (statistically significant for 100 kW).

Due to the complex relationship between distance and field strength, depending on antenna type and characteristics, height above ground level, orographic conditions, electrical properties of the terrain, etc., choice of a 2-km radius for all transmitters might not have been the best option to select the highest exposure group.

P. Park et al. 2004

A similar design as in the study of Ha et al. (2003) was applied in this ecological investigation of cancer deaths. Ten high-power (i.e., 100–1,500-kW transmission power) sites were chosen and compared to four control districts as in the previous study. Standardized mortality ratios were elevated for all single cancer sites but significant only for total cancer deaths. For brain cancer the ratio was 1.52 and statistically not significant.

The same criticism as for the study of Ha et al. (2003) applies to this study. Both studies share the limitations inherent in the ecological study design.

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Q. Berg et al. 2006

In the German part of the Interphone study special attention was paid to occupational history and exposure to RF fields at workplaces. Incident meningioma (n=381, response rate 88%) and glioma cases (n=366, response rate 80%) aged 30-69 years were selected from four

neurological clinics. Overall 1,535 (participation rate 63%) were randomly selected from population registries matched to the cases by sex, age, and region. Most cases were interviewed during their stay in hospitals, controls were interviewed at home. The interview contained several screening questions about occupations that are probably associated with RF exposure. If any of these screening questions were marked additional questions were asked about the job. Based on the literature and the evaluation by two industrial hygienists a classification into the following categories was performed: no RF exposure/not probably RF exposed/probably RF exposed/highly RF exposed. In total about 13% (299 cases and controls) were classified with at least possible RF exposure at the workplace. Analyses were adjusted for region, sex, age, SES, urban/rural residence, ionizing radiation exposure in the head/neck region. Mobile phone use was not considered as a confounder.

While overall RF exposure at workplaces showed no increased odds-ratios, high exposure and especially for durations of 10 years or more resulted in elevated risk estimates that were, however, not significant. This result was similar for meningioma (OR=1.55 for high exposure for 10 years or more) and glioma (OR=1.39).

The study tried to assess potential workplace exposure as precisely as possible in a personal interview, but still misclassification may have occurred especially in the probable and not probable categories while the high exposure group is likely to have had at least occasionally above average RF exposure. Odds ratios are in the range expected if exposure results in a substantial increase of growth rate. The small number of highly and long-term exposed cases (13 glioma and 6 meningioma) prohibit, however, far reaching conclusions.

R. Schüz et al. 2006

In the same study as mentioned above also exposure to emissions from DECT (Digital Enhanced Cordless Telecommunications) base stations near the bed were analyzed. Both, for glioma and meningioma, not significantly decreased odds ratio were reported. There was also no increasing risk observed with duration of exposure to DECT cordless phone base stations. The study was limited due to the small number of exposed subjects and the short exposure duration. It is unlikely that after these short exposures periods an increased risk can be observed.

S. Hu et al. 2007

The study from South Korea that was a major improvement in investigating the possible association between RF EMF exposure and cancer risk applied not only instead of an ecological approach the case-control paradigm but also used an interesting method to estimate individual exposure. This method seems a reasonable compromise between effort and precision. The study included leukemia and brain cancer patients under age 15 years and controls with respiratory illnesses matched to cases on age, sex, and year of diagnosis (1993–1999). All were selected from 14 South Korean hospitals using the South Korean Medical Insurance Data System. Residential addresses were obtained from medical records so that no direct contact with the participants was necessary. Authors developed an exposure prediction program incorporating a geographic information system that was modified by the results of actual measurements carried out systematically at defined locations and during driving along specific trajectories. Furthermore, electrical characteristics of the environment were considered. This method was used to estimate RF EMF exposure from 31 AM radio transmitters with a power of 20 kW or more. A total of 1,928 leukemia patients, 956 brain cancer patients, and 3,082 controls were included.

A significantly increased odds ratio was obtained for childhood leukemia at a distance of 2 km or less from the transmitters relative to a distance of >20 km. In response to a critical comment by Schüz et al. (2008) authors recalculated the risk estimates for total and peak RF EMF exposure (Hu et al. 2008) and reported for the highest quartile of peak RF EMF exposure a significantly increased risk of ALL. For childhood brain cancers insignificantly increased risks of about 1.4 for ≤2 km and 2-4 km from the transmitter were obtained.

It seems that there were problems with the RF EMF estimates since peak and total field strengths had quite different results and also the correlation with peak exposure and distance was much higher than with total exposure suggesting that more distant transmitters led to a decrease in the gradient of exposures. The measurements are not reported for the different transmitter types and therefore it is difficult to assess their validity. For very high power transmitters (1,500 kW) the relationship is known to be not monotonous which cannot be discriminated in the figure shown in the article. Overall the study has an improved methodology due to the case-control and registry approach. However, the methods to assess actual exposure need to be further improved.

IV. EVALUATION OF THE EVIDENCE

Due to the varying endpoints, methods used and populations included the meta-analysis shown in fig.1 applied the random effects model and DerSimonian-Laird estimate of the overall risk and confidence interval. Only few studies found clear indications of an association between RF exposure and brain tumors: one cohort study (Szmigielski 1996) and two case-control studies (Thomas et al. 1987, Grayson 1996). None of the ecological studies except for Ha et al. (2003) for one of the AM transmitter types demonstrated a significantly increased risk in the vicinity of RF antennas.

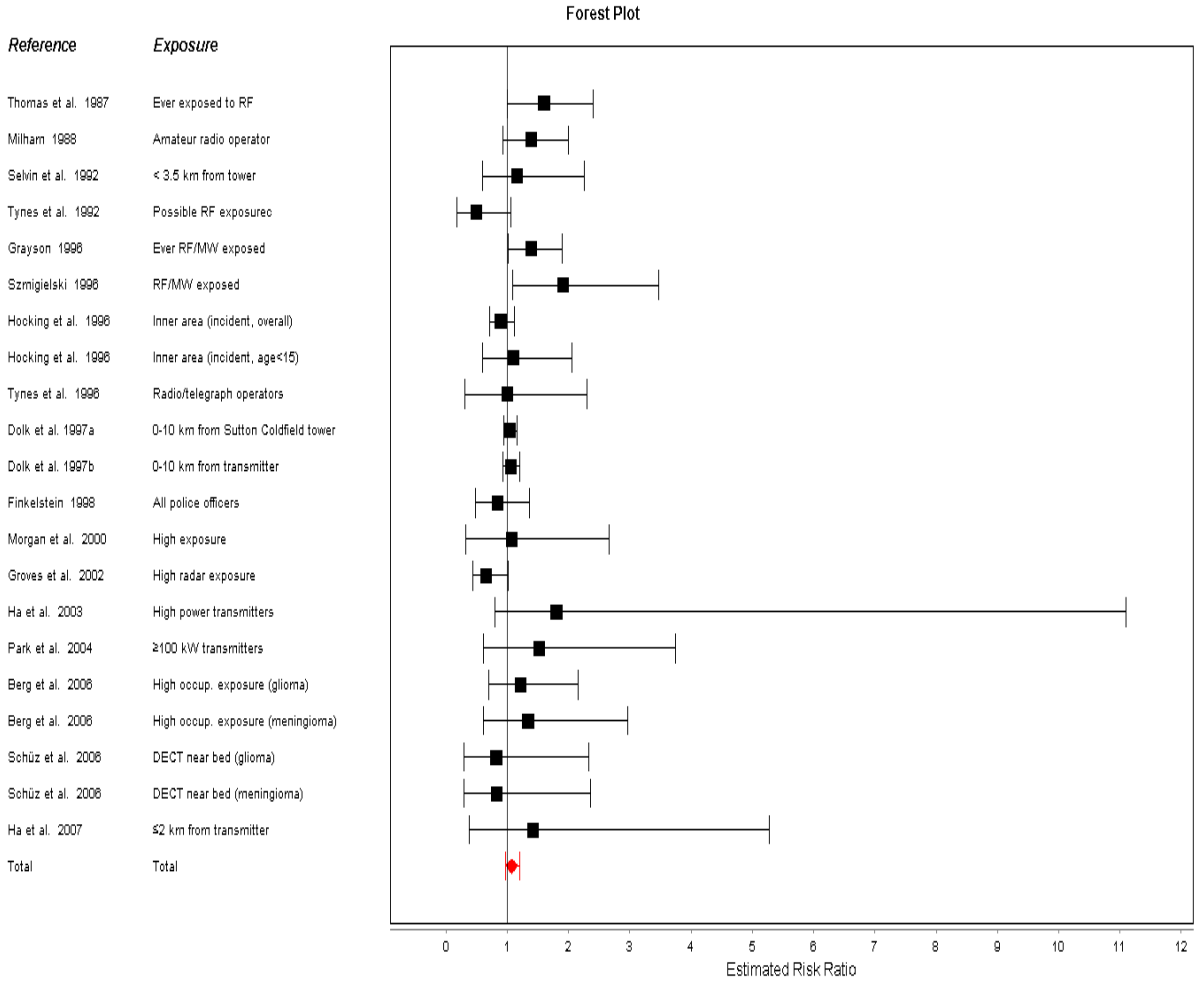

Fig. 1: Forest plot of risk estimates for RF exposure with respect to brain tumors and DerSimonian-Laird overall estimate

The meta-analytical estimate of the risk was 1.08 (95% confidence interval: 0.97 – 1.20). The discussion of the 19 published investigations revealed shortcomings in all studies. The

greatest problem was encountered in the difficulties to reliably assess actual exposure. Even if we don't know the relevant aspect of the exposure, if any, that is responsible for an increased risk, the type, duration and amount of exposure must be determined in order to use the studies in derivations of exposure standards. None of the studies included a useful quantitative indicator of intensity of exposure and even duration of exposure was rarely addressed. Concerning type of exposure only quite crude and broad categories were used.

In ecological studies, although for the studied population the exposure - despite considerable variations in time - is similar with respect to carrier frequency, modulation etc. it is quite different between various types of transmitters and hence results are not easily generalized. The ecological studies are not conclusive with respect to brain tumors but provide some evidence for hematopoietic malignancies that need to be further pursued. Investigating residential exposure to RF EMFs from broadcasting stations poses severe methodological problems mainly due to the small size of the exposed population because high exposure levels occur only in a small band around the radiation sources. Due to the transition to digital television many TV broadcasting antennas with high power are or will be disconnected leaving us with changing exposure conditions. Because brain tumors have long latencies it is hardly possible to produce conclusive evidence in the near future.

Considering the discussion of the different investigations and the fact that most biases encountered tend to dilute a potential risk, the compiled evidence from occupational cohorts is compatible with a moderately increased risk of RF exposure. Because of the lack of actual measurements but observing that exposure above guideline levels must have been a rare event a precautionary approach must result in a reduction of occupational exposure levels and organizational measures to avoid over-exposure and also environmental exposure levels should be given greater attention. Although brain tumors are rare and the population attributable risk is low (assuming 13% of adults being occupationally exposed to RF fields as inferred from Berg et al. 2006, and assuming a relative risk of 1.3, about 4% of brain tumors can be attributed to RF exposure, i.e. 2,200 cases per years in the US).

CONCLUSIONS

- Only few studies of long-term exposure to low levels of RF fields and brain tumors exist, all of which have methodological shortcomings including lack of quantitative exposure assessment. Given the crude exposure categories and the likelihood of a bias towards the null hypothesis of no association the body of evidence is consistent with a moderately elevated risk.

- Occupational studies indicate that long term exposure at workplaces may be associated with an elevated brain tumor risk.

- Although in some occupations and especially in military jobs current exposure guidelines may have sometimes been reached or exceeded, overall the evidence suggest that long-term exposure to levels generally lying below current guideline levels still carry the risk of increasing the incidence of brain tumors.

- Although the population attributable risk is low (likely below 4%), still more than 2,000 cases per year in the US can be attributed to RF exposure at workplaces alone. Due to the lack of conclusive studies of environmental RF exposure and brain tumors the potential of these exposures to increase the risk cannot be estimated. However, these figures are theoretical as long as the evidence is as weak as it is for the time being.

V. ASSESSMENT OF EPIDEMIOLOGICAL EVIDENCE BY IEEE (C95.1 REVISION)

Introduction

Before 1988 C95 standards were developed by Accredited Standards Committee C95, between 1988 and 1990, the committee was converted to Standards Coordinating Committee 28 (SCC 28) under the sponsorship of the IEEE Standards Board. In 2001 IEEE approved the name "International Committee on Electromagnetic Safety (ICES)" for SCC 28. Subcommittee 4 of ICES Technical Committee 95 is responsible for the revision of standard C95.1 "IEEE Standard for Safety Levels with Respect to Human Exposure to Radio Frequency Electromagnetic Fields, 3 kHz to 300 GHz". There are five TC95 subcommittees: 1) Techniques, Procedures, and Instrumentation; 2) Terminology, Units of Measurements and Hazard Communication; 3) Safety Levels with Respect to Human Exposure, 0-3 kHz; 4) Safety Levels with Respect to Human Exposure, 3 kHz-300 GHz; 5) Safety Levels with Respect to Electro-Explosive Devices.

The recommendations in standard C95.1 are intended to protect against scientifically established adverse health effects in human beings resulting from exposure to radio frequency electromagnetic fields in the frequency range of 3 kHz to 300 GHz. A "scientifically established adverse health effects" is defined as: "A biological effect characterized by a harmful change in health that is supported by consistent findings of that effect in studies published in the peer-reviewed scientific literature, with evidence of the effect being demonstrated by independent laboratories, and where there is consensus in the scientific community that the effect occurs for the specified exposure conditions." It is interesting that this definition does not only demand the effect being demonstrated by independent laboratories but also that a consensus must be reached in the scientific community. This is a strange definition. When is a consensus reached? If more than 50% of scientists in the scientific community agree? Or must all agree? Usually this term is used to describe a situation where there is no open or covert dissent. In decisions theory demanding consent is criticized as a policy that results in the preservation of the status-quo.

It might be instructive to contrast this definition with IARCs (International Agency for Research on Cancer) characterization of sufficient evidence for carcinogenicity in experimental animals: "The Working Group considers that a causal relationship has been established between the agent or mixture and an increased incidence of malignant neoplasms

or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols", and the characterization of sufficient evidence in humans: "The Working Group considers that a causal relationship has been established between exposure to the agent, mixture or exposure circumstance and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence." Clearly these definitions are incompatible with the definition by IEEE.

The scientific rationale for the derivation of the exposure standard of IEEE is presented in Annex C and Annex B "Identification of levels of RF exposure responsible for adverse effects: summary of the literature" which is based on "critical reviews of studies within the IEEE/WHO RF literature database". In this commentary I will address chapter 9) Epidemiological Studies of RF Exposures and Human Cancer.

Evaluation of Cancer-Related Endpoints (RF Exposure)

In their 2006 revision of the standard C95.1 IEEE has assessed the evidence from epidemiology for cancer related endpoints in chapter B.7.3. The assessment relies mainly on the reviews of Bergqvist (1997), Moulder et al. (1999) and Elwood (2003). These reviews and the IEEE overview share the same deficiencies. The main lines of argumentation would be impossible in any other field of environmental health and closely resemble the strategy used to dismiss a power frequency exposure/childhood leukemia association. In the following paragraphs the assessment by IEEE will be discussed. The text of IEEE C95.1 is presented in italics as blocked citation. References within the text of the citations are found by the Rnnn and Bnnn numbers in the Annexes F and G of the standard document, but are also included in the reference section of this overview.

> *Cluster studies, such as the one performed in Sutton Coldfield in the U.K. in response to a cluster of leukemia and lymphoma in adults living close to an RF broadcasting transmitter (Dolk et al. [R624]), are inherently difficult to interpret because of the impossibility of assessing all of the effects that chance variation might have contributed to the cluster. In the initial Sutton Coldfield study, the authors correctly concluded that no causal association could be drawn between the presence of the cluster and RF exposure from broadcasting towers (Dolk et al. [R625]) (Cooper et al. [R760]). (IEEE C 95.1 – 2005, p.75)*

First of all the Sutton Coldfield study was no cluster study but an ecological investigation. It only was initiated by an unconfirmed report of a cluster of leukemia and lymphoma in the vicinity of this broadcasting transmitter but it proceeded independently of this initial report and used registry data of the population living within a radius of 10 km around the transmitter. The statement that such studies are "inherently difficult to interpret because of the impossibility of assessing all of the effects that chance variation might have contributed to the cluster" is ridiculous not only because the study is no cluster study but because it is impossible for any study to "assess all effects that chance variation might have contributed" to the endpoint under investigation. It is not mentioned that the study was supplemented by a larger investigation of another 20 high-power transmitters in Great Britain. The difficulties of interpreting ecological studies is related to the fact that potential confounders can only be related to a segment of the population but not to individuals and that in general duration and intensity of exposure are not known for individual members of the different strata. While evidence for an effect on brain tumor incidence from both studies (Dolk et al. 1997a, 1997b) is weak, there is consistent evidence for a relation to hematopoietic cancers. This evidence has been overlooked by the authors due to their wrong assumption about the relation between proximity to the transmitter and exposure.

> *Inconsistent effects have been reported between residential proximity to other RF broadcast towers and adverse health endpoints (Bielski [R267]) (Maskarinec et al. [R579]) (Selvin and Merrill [R823]) (Michelozzi et al. [R858]) (Altpeter et al. [R977]) (Hallberg and Johansson [R995], [R996]) (Boscolo [R1012]), although many of these studies have significant flaws in their study design (making them difficult to interpret). (IEEE C 95.1 – 2005, p.75)*

Although it is not stated what these "inconsistent effects" might be, the statement is flawed in more than this respect. First of all the study by Bielski (1994) is an occupational investigation and not about residential proximity to RF broadcast towers, second three of these investigations (Selvin et al. 1992; Maskarinec et al. 1994; Michelozzi et al. 2002) included leukemia as an endpoint with indications of an increased incidence consistent with the studies from Great Britain (Dolk et al. 1997a, 1997b) and Australia (Hocking et al. 1996). Note that the study by Selvin et al. (1992), as stated in section 10, intended to compare different methods to assess the relationship between a point source and diseases and did erroneously assume a monotonous relationship between exposure and distance from a transmitter. Correcting this error there seems to be an increased probability of childhood leukemia in areas receiving the highest exposure from the Sutro tower. The other three investigations (Altpeter

et al. 1995; Boscolo 2001; Hallberg & Johansson 2002) have nothing in common and hence cannot be inconsistent.

> *An increased incidence and mortality rate of childhood leukemia was reported in Australia with residential proximity to a specific RF broadcasting tower (Hocking et al. [R633]), although subsequent reanalysis of the data showed the results may have been influenced by other confounding variables within the study location (McKenzie et al. [R669]). (IEEE C 95.1 – 2005, p.75)*

This is another example how carelessly and sloppy the evidence is dealt with by the IEEE committee. The study of Hocking et al. (1996) was not about "proximity to a specific RF broadcasting tower" but about an area where three broadcasting towers are located. While there is always the possibility of confounders influencing results of an epidemiologic investigation, the 'reanalysis' of McKenzie et al. (1998) is seriously flawed and cannot support the cited statement. Hocking et al. (1996) combined the districts near the broadcasting area and those further away based on homogeneity analyses, while McKenzie et al. (1998) omitted one area with high incidence (and highest exposure) based on inspection of data. Any statistical analysis subsequent to such data picking is useless.

> *While scattered reports of adverse health effects associated with occupational exposure to RF do exist (Demers et al. [R36]) (Kurt and Milham [R68]) (Pearce [R110]) (Speers et al. [R125]) (Thomas et al. [R128]) (Pearce et al. [R199], [R211]) (Hayes et al. [R207]) (Cantor et al. [R268]) (Davis and Mostofi [R563]) (Tynes et al. [R570], [R605]) (Grayson [R592]) (Richter et al. [R747]) (Holly et al. [R838]) these studies are largely inconsistent with each other in terms of the adverse health endpoints affected, and often show no clear dose response with RF exposure. Many have serious flaws in their study design, contain limited or insufficient RF exposure assessment, and are generally inconsistent with the absence of findings of an association from other occupational studies (Tornqvist et al. [R131]) (Coleman [R142]) (Lilienfeld et al. [R146]) (Robinette and Silverman [R147], [R148]) (Siekierzynski et al. [R151], [R152]) (Wright et al. [R213]) (Coleman et al. [R214]) (Muhm [R506]) (Czerski et al. [R542]) (Hill [R568]) (Lagorio et al. [R616]) (Kaplan et al. [R647]) (Morgan et al. [R701]) (Gallagher et al. [R822]) (Groves et al. [R853]) (Wiklund [R1013]) (Armstrong et al. [R1014]). (IEEE C 95.1 – 2005, p.75)*

Even allowing for restrictions of space for a discussion of the evidence, greater nonsense has not been produced so far in this field as condensed in these two sentences. Putting higgledy-piggledy all sorts of studies together and then wondering about endpoints being inconsistent is an intellectual masterpiece. Of the occupational studies mentioned, three (Thomas et al. 1987; Speers et al. 1988; Grayson 1996) were about brain cancer, three about hematopoietic cancers

(Pearce et al. 1985; Kurt & Milham 1988; Pearce 1988), two about testicular cancer (Hayes et al. 1990; Davis & Mostofi 1993), one about male (Demers et al. 1991) and two about female breast cancer (Cantor et al. 1995, Tynes et al. 1996) the latter including other cancers as well, and one about intraocular melanoma (Holly et al. 1996). Three further studies (Pearce et al. 1989; Tynes et al. 1992; Richter et al. 2000) investigated several or all malignancies. These studies differ not only in endpoints, study type (cohort, case-control, and cluster) but also in the methods of exposure assessment. Ignorance of the IEEE reviewers is underlined by the compilation of studies characterized by an "absence of findings of an association". Not only did several of these studies indeed indicate an association of cancer risk with EMF exposure (Lilienfeld et al. 1978; Robinette et al. 1980; Tornqvist et al. 1991; Armstrong et al. 1994; Lagorio et al. 1997; Groves et al. 2002) but two were no epidemiologic studies at all (Siekierzynski et al. 1974; Czerski et al. 1974) and several were rather addressing ELF exposure (Tornqvist et al. 1991; Wright et al. 1982; Coleman et al. 1983; Gallagher et al. 1991) and one (Wiklund 1981) was a cluster study in the telecommunication administration with uncertain type of exposure. Simply confronting studies finding an effect with others that were 'negative' is scientifically flawed and permits neither the conclusion that there is nor that there is no association between exposure and cancer risk. Even if all studies would have applied the same method, assessed the same endpoint and used the same exposure metric, studies reporting a significantly increased cancer risk are not outweighed by others that did not.

> *While micronuclei formation in workers occupationally exposed from broadcast antennas has been reported (Garaj-Vrhovac [R757]) (Lalic et al. [R791]), these findings were not verified in a larger study of more than 40 Australian linemen exposed under similar conditions (Garson et al. [R186]). (IEEE C 95.1 – 2005, pp.75-76)*

It goes without saying that also this statement is wrong. Garson et al. (1991) did not investigate micronuclei formation, their workers were considerably shorter exposed and it were not more than 40 linemen but 38 radio-lineman.

> *No clear association could be established between occupational exposures of parents to a number of agents, including RF, and effects (neuroblastoma) in their offspring (Spitz and Johnson [R289]) (De Roos et al. [R798]). (IEEE C 95.1 – 2005, p.76)*

What is meant by 'no clear association' is obscure. Spitz and Johnson (1985) found a significantly increased risk after paternal occupational exposure to electromagnetic fields, and also De Roos et al. (2001) found several jobs with paternal as well as maternal exposure to

EMFs associated with an elevated risk for neuroblastoma in their children. However, broad groupings of occupations with ELF, RF EMF, as well as ionizing radiation (!) exposure did not reveal an increased risk.

> *One study reported a slight excess in brain tumors associated with combined exposure to RF and other exposures associated with electrical or electronic jobs, but not with RF alone (Thomas et al. [R128]). A study of a Polish military cohort reported a substantial excess of total cancer and several cancer sub-types with jobs associated with RF exposure (Szmigielski [R578]), (Szmigielski and Kubacki [R982]), although questions have been raised about severe bias in the exposure assessment of this study (Elwood [R665]) (Bergqvist [R1015]) (Stewart [R1133]). Studies by Milham of U.S. amateur radio operators reported an excess in one of nine types of leukemia assessed (see [R101], [R102], [R209], [R215], and [R569]), but not for total tumors, total leukemia, or brain tumors, and potential confounding factors might have included exposure to soldering fumes, degreasing agents and over-representation of a particular social class. (IEEE C 95.1 – 2005, p.76)*

Again the evidence is incorrectly summarized for all cited investigations. Thomas et al. (1987) found a significantly elevated risk for brain tumors among all men exposed to RF fields and in particular in those exposed for 20 or more years. There were indications that this elevated risk is due to a subgroup with electrical or electronics jobs. The group of those exposed in other jobs is heterogeneous and may contain subjects with low or no exposure (e.g. some groups of welders) and therefore lack of an association could be due to a dilution effect from exposure misclassification.

As mentioned in section 10 criticism of the Polish military cohort study about exposure assessment is unfounded. Bergqvist (1997), Elwood (1999) and Stewart (2000) criticized that the military health board assessed a number of potential risk factors only for cancer cases. However, they overlooked that the study was a cohort and not a case-control study and that at no stage information about these factors entered the analysis and therefore couldn't affect the results in any way.

The study by Milham (1988a, 1988b) of radio amateur operators revealed a significantly increased standardized mortality ratio (SMR) for acute myeloid leukemia while the overall mortality and cancer mortality was significantly reduced relative to the country mortality rates. As mentioned in section 10 this points to a 'healthy worker' effect as well as to an influence of life-style factors (mortality related to smoking and overweight were reduced). From the mentioned nine types of leukemia three with expectancies below one and no case observed couldn't be assessed, from the six remaining types five had elevated SMRs with AML, the most frequent type in adults, being significantly elevated.

The last portion of the IEEE review of epidemiology studies is dedicated to mobile phone investigations that are discussed in another contribution.

The following citation presents the IEEE summary in its full length:

> *The epidemiological evidence to date does not show clear or consistent evidence to indicate a causal role of RF exposures in connection with human cancer or other disease endpoints. Many of the relevant studies, however, are weak in terms of their design, their lack of detailed exposure assessment, and have potential biases in the data. While the available results do not indicate a strong causal association, they cannot establish the absence of a hazard. They do indicate that for commonly encountered RF exposures, any health effects, if they exist, must be small. Even though epidemiological evidence cannot rule out a causal relationship, the overall weight-of-evidence is consistent with the results of the long term animal studies showing no evidence of physiological, pathological or disease-specific effects. (IEEE C95.1 - 2005; pp.76-77)*

As already pointed out earlier (Kundi 2006) there is an intolerable tendency in the past years that confronted with an undeniable epidemiologic evidence of an association between an agent and adverse health effects such as cancer, interested parties take their resort to the concept of causality based on the wrong assumption evidence to "indicate a causal role" is a lot more difficult to provide. Unprecedented, however, is the notion of "a strong causal association". Whatever the meaning of this exceptional statement, the conclusion that, if health effects of commonly encountered RF exposures exist, they must be small, is wrong. To the contrary: considering the "lack of detailed exposure assessment" and other potential biases that predominantly lead to an underestimation of the risk, the evidence points to a quite substantial risk. While the animal studies reviewed in another section of the IEEE standard document cannot be discussed here it should be underlined that they are generally insufficient to support either an increased risk or the lack of health relevant effects. Therefore they cannot be used in a weight-of-evidence statement as has been made by IEEE, that there is no evidence for adverse health effects of RF exposure.

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