

- of culture flasks. *Bioelectromagnetics*, 20: 65–80. doi:10.1002/(SICI)1521-186X(1999)20:2<65::AID-BEM1>3.0.CO;2-W PMID:10029133
- Nagaoka T, Kunieda E, Watanabe S (2008). Proportion-corrected scaled voxel models for Japanese children and their application to the numerical dosimetry of specific absorption rate for frequencies from 30 MHz to 3 GHz. *Phys Med Biol*, 53: 6695–6711. doi:10.1088/0031-9155/53/23/004 PMID:18997264
- Nagaoka T, Togashi T, Saito K *et al.* (2007). An anatomically realistic whole-body pregnant-woman model and specific absorption rates for pregnant-woman exposure to electromagnetic plane waves from 10 MHz to 2 GHz. *Phys Med Biol*, 52: 6731–6745. doi:10.1088/0031-9155/52/22/012 PMID:17975294
- Nagaoka T, Watanabe S (2009). *Estimation of variability of specific absorption rate with physical description of children exposed to electromagnetic field in the VHF band*. International conference of the IEEE EMBS.
- Narda STS (2005). *Electric Field Probe For EMR-200 and EMR-300*. (December 16, 2005). Available at: <http://www.narda-sts.com>.
- NASA (2011). *Sun FactSheet*. National Aeronautics and Space Administration. Available at: <http://nssdc.gsfc.nasa.gov/planetary/factsheet/sunfact.html>
- NCRP; National Council on Radiation Protection and Measurements (1986). *Biological Effects and Exposure Criteria for Radiofrequency Electromagnetic Fields*. NCRP Report 86, Recommendations of the National Council on Radiation Protection and Measurements.
- Neubauer G, Preiner P, Cecil S *et al.* (2009). The relation between the specific absorption rate and electromagnetic field intensity for heterogeneous exposure conditions at mobile communications frequencies. *Bioelectromagnetics*, 30: 651–662. PMID:19551765
- Nielsen (2010). *Media industry fact sheet*. Available at: <http://blog.nielsen.com/nielsenwire/press/nielsen-fact-sheet-2010.pdf>
- Nikoloski N, Fröhlich J, Samaras T *et al.* (2005). Reevaluation and improved design of the TEM cell in vitro exposure unit for replication studies. *Bioelectromagnetics*, 26: 215–224. doi:10.1002/bem.20067 PMID:15768424
- NOAA (2011). *Science on a Sphere: Annual lightning flash rate*. Available at: <http://www.srh.noaa.gov/>
- Olivier C & Martens L (2005). Optimal settings for narrow-band signal measurements used for exposure assessment around GSM base stations. *IEEE Trans Instrum Meas*, 54: 311–317. doi:10.1109/TIM.2004.838114
- Olivier C & Martens L (2006). Theoretical derivation of the stochastic behavior of a WCDMA signal measured with a spectrum analyzer. *IEEE Trans Instrum Meas*, 55: 603–614. doi:10.1109/TIM.2006.870330
- Petersen RC & Testagrossa PA (1992). Radio-frequency electromagnetic fields associated with cellular-radio cell-site antennas. *Bioelectromagnetics*, 13: 527–542. doi:10.1002/bem.2250130608 PMID:1482416
- Peyman A, Gabriel C (2002). *Variation of the dielectric properties of biological tissue as a function of age*. Final Technical Report, Department of Health, UK.
- Peyman A & Gabriel C (2007). Development and characterization of tissue equivalent materials for frequency range 30 – 300 MHz *Electron Lett*, 43: 19–20 doi:10.1049/el:20073455
- Peyman A, Gabriel C, Grant EH *et al.* (2009). Variation of the dielectric properties of tissues with age: the effect on the values of SAR in children when exposed to walkie-talkie devices. *Phys Med Biol*, 54: 227–241. doi:10.1088/0031-9155/54/2/004 PMID:19088390
- Peyman A, Holden SJ, Watts S *et al.* (2007). Dielectric properties of porcine cerebrospinal tissues at microwave frequencies: in vivo, in vitro and systematic variation with age. *Phys Med Biol*, 52: 2229–2245. doi:10.1088/0031-9155/52/8/013 PMID:17404466
- Peyman A, Khalid M, Calderon C *et al.* (2011). Assessment of exposure to electromagnetic fields from wireless computer networks (Wi-Fi) in schools; results of laboratory measurements. *Health Phys*, 100: 594–612. doi:10.1097/HP.0b013e318200e203
- Peyman A, Rezazadeh AA, Gabriel C (2001). Changes in the dielectric properties of rat tissue as a function of age at microwave frequencies. *Phys Med Biol*, 46: 1617–1629. doi:10.1088/0031-9155/46/6/303 PMID:11419623
- Poković K (1999). *Advanced Electromagnetic Probes for Near-Field Evaluations*. PhD thesis, Diss. ETH Nr. 13334, Zurich.
- Poković K, Schmid T, Fröhlich J, Kuster N (2000b). Novel probes and evaluation procedures to assess field magnitude and polarization. *IEEE Trans Electromagn Compat*, 42: 240–245. doi:10.1109/15.852419
- Poković K, Schmid T, Kuster N (2000a). Millimeter-resolution E-field probe for isotropic measurement in lossy media between 100 MHz and 20 GHz. *IEEE Trans Instrum Meas*, 49: 873–878. doi:10.1109/19.863941
- Porter SJ, Capstick MH, Faraci F, Flintoft ID (2005). *AR testing of hands-free mobile telephones*. Mobile Telecommunications and Health Research Programme. Available at: [http://www.mthr.org.uk/research_projects/dti_funded_projects/porter\(sar\).htm](http://www.mthr.org.uk/research_projects/dti_funded_projects/porter(sar).htm)
- SProhofsky EW (2004). RF absorption involving biological macromolecules. *Bioelectromagnetics*, 25: 441–451. doi:10.1002/bem.20013 PMID:15300730
- Redmayne M, Inyang I, Dimitriadis C *et al.* (2010). Cordless telephone use: implications for mobile phone research. *J Environ Monit*, 12: 809–812. doi:10.1039/b920489j PMID:20383359
- Repacholi MH (2001). Health risks from the use of mobile phones. *Toxicol Lett*, 120: 323–331. doi:10.1016/S0378-4274(01)00285-5 PMID:11323191
- Ritz T, Wiltshko R, Hore PJ *et al.* (2009). Magnetic compass of birds is based on a molecule with optimal directional sensitivity. *Biophys J*, 96: 3451–3457. doi:10.1016/j.bpj.2008.11.072 PMID:19383488

- Rudge AW (1970). An electromagnetic radiation probe for near-field measurements at microwave frequencies. *J Microw Power*, 5: 155–174.
- Samaras T, Kalampaliki E, Sahalos JN (2007). Influence of Thermophysiological Parameters on the Calculation of Temperature Rise in the Head of Mobile Phone Users *IEEE Trans Electromagn Compat*, 49: 936–939. doi:10.1109/TEMC.2007.908257
- Schmid G, Lager D, Preiner P *et al.* (2007b). Exposure caused by wireless technologies used for short-range indoor communication in homes and offices. *Radiat Prot Dosimetry*, 124: 58–62. doi:10.1093/rpd/ncm245 PMID:17566000
- Schmid G, Neubauer G, Illievich UM, Alesch F (2003). Dielectric properties of porcine brain tissue in the transition from life to death at frequencies from 800 to 1900 MHz. *Bioelectromagnetics*, 24: 413–422. doi:10.1002/bem.10122 PMID:12929160
- Schmid G, Preiner P, Lager D *et al.* (2007a). Exposure of the general public due to wireless LAN applications in public places. *Radiat Prot Dosimetry*, 124: 48–52. doi:10.1093/rpd/ncm320 PMID:17562659
- Schmid G & Überbacher R (2005). Age dependence of dielectric properties of bovine brain and ocular tissues in the frequency range of 400 MHz to 18 GHz. *Phys Med Biol*, 50: 4711–4720. doi:10.1088/0031-9155/50/19/019 PMID:16177499
- Schönborn F, Burkhardt M, Kuster N (1998). Differences in energy absorption between heads of adults and children in the near field of sources. *Health Phys*, 74: 160–168. doi:10.1097/00004032-199802000-00002 PMID:9450585
- Schubert M, Bornkessel C, Wuschek M, Schmidt P (2007). Exposure of the general public to digital broadcast transmitters compared to analogue ones. *Radiat Prot Dosimetry*, 124: 53–57. doi:10.1093/rpd/ncm337 PMID:17617635
- Schuderer J, Schmid T, Urban G *et al.* (2004a). Novel high-resolution temperature probe for radiofrequency dosimetry. *Phys Med Biol*, 49: N83–N92. doi:10.1088/0031-9155/49/6/N04 PMID:15104331
- Schuderer J, Spät D, Samaras T *et al.* (2004b). In Vitro Exposure Systems for RF Exposures at 900 MHz. *IEEE Trans Microw Theory Tech*, 52: 2067–2075. doi:10.1109/TMTT.2004.832010
- Schüz J (2009). Lost in laterality: interpreting “preferred side of the head during mobile phone use and risk of brain tumour” associations. *Scand J Public Health*, 37: 664–667. doi:10.1177/1403494809341096 PMID:19581357
- Schüz J & Mann S (2000). A discussion of potential exposure metrics for use in epidemiological studies on human exposure to radiowaves from mobile phone base stations. *J Expo Anal Environ Epidemiol*, 10: 600–605. doi:10.1038/sj.jea.7500115 PMID:11140443
- Seibersdorf Research (2011). *Precision Conical Dipole PCD 8250*. Available at: <http://www.seibersdorf-laboratories.at>
- Sektion NIS (2002). *BUWAL und Sektion Hochfrequenz, EMV und Verkehr*. Mobilfunk-Basisstationen (GSM). Messempfehlung. February 2002.
- Sheppard AR, Swicord ML, Balzano Q (2008). Quantitative evaluations of mechanisms of radiofrequency interactions with biological molecules and processes. *Health Phys*, 95: 365–396. doi:10.1097/01.HP.0000319903.20660.37 PMID:18784511
- Shum M, Kelsh MA, Sheppard AR, Zhao K (2011). An evaluation of self-reported mobile phone use compared to billing records among a group of engineers and scientists. *Bioelectromagnetics*, 32: 37–48. doi:10.1002/bem.20613 PMID:20857456
- Singal T (2010). *Wireless communications*. New Delhi: Tata McGraw Hill Education Private Limited.
- Smith GS (1981). Analysis of miniature electric field probes with resistive transmission lines. *IEEE Trans Microw Theory Tech*, MTT-29: 1213–1224. doi:10.1109/TMTT.1981.1130534
- Stuchly MA (1979). Interaction of radiofrequency and microwave radiation with living systems. A review of mechanisms. *Radiat Environ Biophys*, 16: 1–14. doi:10.1007/BF01326892 PMID:382232
- Taurisano MD & Vander Vorst A (2000). Experimental thermographic analysis of thermal effects induced on a human head exposed to 900 MHz fields of mobile-phones. *IEEE Trans Microw Theory Tech*, 48: 2022–2032. doi:10.1109/22.884191
- Thurai M, Goodridge VD, Sheppard RJ, Grant EH (1984). Variation with age of the dielectric properties of mouse brain cerebrum. *Phys Med Biol*, 29: 1133–1136. doi:10.1088/0031-9155/29/9/009 PMID:6483977
- Thurai M, Steel MC, Sheppard RJ, Grant EH (1985). Dielectric properties of developing rabbit brain at 37 degrees C. *Bioelectromagnetics*, 6: 235–242. doi:10.1002/bem.2250060304 PMID:3836667
- Timmel CR, Till U, Brocklehurst B *et al.* (1998). Effects of weak magnetic fields on free radical recombination reactions. *Mol Phys*, 95: 71–89. doi:10.1080/00268979809483134
- Tinniswood AD, Furse CM, Gandhi OP (1998). Power deposition in the head and neck of an anatomically based human body model for plane wave exposures. *Phys Med Biol*, 43: 2361–2378. doi:10.1088/0031-9155/43/8/026 PMID:9725610
- Togashi T, Nagaoka T, Kikuchi S *et al.* (2008). TDTD calculations of specific absorption rate in fetus caused by electromagnetic waves from mobile radio terminal using pregnant woman model. *IEEE Trans Microw Theory Tech*, 56: 554–559. doi:10.1109/TMTT.2007.914625
- Togo H, Shimizu N, Nagatsuma T (2007). Near-field mapping system using fiber-based electro-optic probe

- for specific absorption rate measurement *IEICE Trans Electron*, 90: C436–442. doi:10.1093/ietele/e90-c.2.436
- Tomitsch J, Dechant E, Frank W (2010). Survey of electromagnetic field exposure in bedrooms of residences in lower Austria. *Bioelectromagnetics*, 31: 200–208. PMID:19780092
- Uusitupa T, Laakso I, Ilvonen S, Nikoskinen K (2010). SAR variation study from 300 to 5000 MHz for 15 voxel models including different postures. *Phys Med Biol*, 55: 1157–1176. doi:10.1088/0031-9155/55/4/017 PMID:20107250
- Valberg PA (1995). Designing EMF experiments: what is required to characterize “exposure”? *Bioelectromagnetics*, 16: 396–401, discussion 402–406. doi:10.1002/bem.2250160608 PMID:8789071
- Van Leeuwen GM, Lagendijk JJ, Van Leersum BJ *et al.* (1999). Calculation of change in brain temperatures due to exposure to a mobile phone. *Phys Med Biol*, 44: 2367–2379. doi:10.1088/0031-9155/44/10/301 PMID:10533916
- Vermeeren G, Gosselin MC, Kühn S *et al.* (2010). The influence of the reflective environment on the absorption of a human male exposed to representative base station antennas from 300 MHz to 5 GHz. *Phys Med Biol*, 55: 5541–5555. doi:10.1088/0031-9155/55/18/018 PMID:20808028
- Vermeeren G, Joseph W, Olivier C, Martens L (2008). Statistical multipath exposure of a human in a realistic electromagnetic environment. *Health Phys*, 94: 345–354. doi:10.1097/01.HP.0000298816.66888.05 PMID:18332726
- Viel JF, Clerc S, Barrera C *et al.* (2009). Residential exposure to radiofrequency fields from mobile phone base stations, and broadcast transmitters: a population-based survey with personal meter. *Occup Environ Med*, 66: 550–556. doi:10.1136/oem.2008.044180 PMID:19336431
- Vrijheid M, Armstrong BK, Bédard D *et al.* (2009b). Recall bias in the assessment of exposure to mobile phones. *J Expo Sci Environ Epidemiol*, 19: 369–381. doi:10.1038/jes.2008.27 PMID:18493271
- Vrijheid M, Cardis E, Armstrong BK *et al.* Interphone Study Group (2006). Validation of short term recall of mobile phone use for the Interphone study. *Occup Environ Med*, 63: 237–243. doi:10.1136/oem.2004.019281 PMID:16556742
- Vrijheid M, Mann S, Vecchia P *et al.* (2009a). Determinants of mobile phone output power in a multinational study: implications for exposure assessment. *Occup Environ Med*, 66: 664–671. doi:10.1136/oem.2008.043380 PMID:19465409
- Wainwright P (2000). Thermal effects of radiation from cellular telephones. *Phys Med Biol*, 45: 2363–2372. doi:10.1088/0031-9155/45/8/321 PMID:10958200
- Wang J & Fujiwara O (2003). Comparison and evaluation of electromagnetic absorption characteristics in realistic human head models of adult and children for 900-MHz mobile telephones. *IEEE Trans Microw Theory Tech*, 51: 966–971. doi:10.1109/TMTT.2003.808681
- Wang J, Fujiwara O, Kadera S, Watanabe S (2006). FDTD calculation of whole-body average SAR in adult and child models for frequencies from 30 MHz to 3 GHz. *Phys Med Biol*, 51: 4119–4127. doi:10.1088/0031-9155/51/17/001 PMID:16912372
- Whiteside H & King RWP (1964). The loop antenna as a probe. *IEEE Trans Antenn Propag*, AP-12: 291–297. doi:10.1109/TAP.1964.1138213
- WHO (2010a). *Radio frequency (RF) fields - new 2010 research agenda*. Available at: http://whqlibdoc.who.int/publications/2010/9789241599948_eng.pdf.
- WHO (2010b). Fact Sheet N°193
- Wiat J, Dale C, Bosisio AD, Le Cornec A (2000). Analysis of the Influence of the Power Control and Discontinuous Transmission on RF Exposure with GSM Mobile Phones. *IEEE Trans Electromagn Compat*, 42: 376–385. doi:10.1109/15.902307
- Wiat J, Hadjem A, Gadi N *et al.* (2005). Modeling of RF head exposure in children. *Bioelectromagnetics*, 26: Suppl 7S19–S30. doi:10.1002/bem.20155 PMID:16142772
- Wiat J, Hadjem A, Gadi N *et al.* (2007). *RF Exposure assessment in children head: Present questions and future challenges*. International Conference on Electromagnetics in Advanced Applications (ICEAA), Sept. 17–21, Torino, pp. 1034–1035.
- Wiat J, Hadjem A, Wong MF, Bloch I (2008). Analysis of RF exposure in the head tissues of children and adults. *Phys Med Biol*, 53: 3681–3695. doi:10.1088/0031-9155/53/13/019 PMID:18562780
- Wickersheim K-A & Sun M-H (1987). Fiberoptic thermometry and its applications. *J Microw Power*, 22: 85–94.
- Willett JC, Bailey JC, Leteinturier C, Krider EP (1990). Lightning electromagnetic radiation field spectra in the interval from 0.2 to 20 MHz. *J Geophys Res*, 95: D1220367–20387. doi:10.1029/JD095iD12p20367
- World Bank; International Monetary Fund (2009). *Global Monitoring Report 2009: A Development Emergency*. Washington DC, USA. Available at: <https://openknowledge.worldbank.org/handle/10986/2625>
- Wu T, Tan L, Shao Q *et al.* (2011). Chinese adult anatomical models and the application in evaluation of RF exposures. *Phys Med Biol*, 56: 2075–2089. doi:10.1088/0031-9155/56/7/011 PMID:21386138

2. CANCER IN HUMANS

This section is a review of the large body of epidemiological evidence from studies of exposure of occupational groups and the general population to radiofrequency (RF) radiation from diverse sources, including from the use of mobile telephones. The results of these studies comprise a large amount of data, which could not be fully reproduced here. The Working Group included studies that assessed specific sources of RF radiation or job titles that were specifically linked to RF radiation. Studies that were excluded used job titles only for classification, or source surrogates only, without specifically addressing RF exposure. The Tables in this section summarize the main findings, but do not uniformly capture the results for all exposure metrics or all subgroups given in the original publications. In the text, the Working Group provides comments on those findings that are of greatest relevance to the evaluation, e.g. risk in the overall exposed group, patterns of change in risk with increasing exposure (such as a monotonic increase in risk with increasing exposure), and changes in risk with duration of exposure or latency.

2.1 Occupational exposure

The occupational environment is one domain in which humans are exposed to RF radiation. Many occupational circumstances entail regular or occasional exposure to RF radiation from fixed or mobile sources. A wide variety of workers are involved, including military and security personnel using walkie-talkie devices, radar operators, radio and television antenna maintenance and repair workers, welders performing dielectric (high-frequency) welding and sealing of plastics, workers using RF radiation for drying or testing operations, and physiotherapists employing medical diathermy equipment. Only a limited number of studies have assessed the risk of cancer in relation to either measured or inferred levels of exposure. There have been

a large number of epidemiological studies of workers who were not evaluated in terms of their exposure to RF radiation, but rather with respect to their exposure to electric or magnetic fields (EMF), extremely low-frequency (ELF) fields, i.e. < 300Hz ([IARC, 2002](#)), or microwaves (MW), and an even larger number of studies in which it might be suspected that some workers were likely to have been exposed to RF radiation. The Working Group did not include these studies in the present review because it was not certain that sizable fractions of the workers in such studies were actually exposed to RF radiation, or at what levels they were exposed. This review is therefore limited to occupational studies in which the investigators made an effort to specifically document or assess exposures to RF radiation in the workers considered to be exposed.

2.1.1 Cancer of the brain

(a) Case-control studies

[Thomas et al. \(1987\)](#) conducted a death-certificate-based case-control study in selected counties of the north-eastern and southern United States of America (USA). The cases were men who had died from tumours of the brain or other parts of the central nervous system (CNS) at age ≥ 30 years between 1978 and 1981. Diagnoses were verified in hospital records. One control decedent, whose cause of death was not brain cancer, epilepsy, stroke, suicide or homicide, was selected for each case, and matched by age and year of death, and usual area of residence. The next-of-kin of the study subjects were interviewed: participation rates were 74% for cases and 63% for controls. For each job held since age 15 years, the job title and a brief description of the work, the industry, the location, the employment dates, and the hours worked per week were obtained. Two methods were used to classify men according to their occupational exposure to MW or RF radiation: one was based on a selection of broad job titles [most of which would have had mixed or predominant exposure to EMF frequencies other than RF], while in the other an industrial hygienist classified each job according to exposure to RF radiation, lead and soldering fumes. Data from 435 cases and 386 controls were analysed. Only results based on the industrial hygienist's classification are reviewed here. [While controls were individually matched to cases, there was a deficit of controls, possibly due to poorer participation, but no mention was made of adjusting for the matching variables in the analysis; thus there may have been uncorrected bias due to study design in the calculated odds ratios (ORs).] Risk of brain tumours was increased in those ever occupationally exposed to RF radiation (OR, 1.7; 95% CI, 1.1–2.7) adjusted for educational level ([Table 2.1](#)); however, the odds ratio decreased when men also exposed to soldering fumes or lead were removed from

the exposed group, and dropped even further when those who might also have had exposure to organic solvents were removed from the exposed group. [This study was one of the few to directly attempt to address possible confounding of occupational exposure to RF radiation with coexposure to soldering fumes, lead and organic solvents. It was limited by the fact that it was based on death certificates (the dead controls were unlikely to accurately represent the population from which the dead cases came) and on an analysis that may not have controlled for bias due to the matched design.]

[Berg et al. \(2006\)](#) analysed data obtained from cases (glioma and meningioma) and controls using a detailed questionnaire on occupational exposure to what the authors described as RF/MW/EMF, which formed part of the data collected in the German component of the INTERPHONE study (as described in Section 2.2.2 in relation to [Schüz et al., 2006a](#)). Participants were asked screening questions about use of industrial heating equipment to process food, to bond, seal, and weld materials, or to melt, dry, and cure materials. Questions were also asked about manufacturing semiconductor chips or microelectronic devices; using radar; maintaining electromagnetic devices used to treat or diagnose diseases; working with or nearby to broadcasting and telecommunications antennae and masts; using different kinds of transmitters; and using amateur (“ham”) radio. When a participant screened positive for one of these activities, further questions were asked to determine whether the occupation entailed exposure to RF/MW/EMF. Each person was classified as having: no exposure (responded negatively to the screening questions, or were positive for some activities thought not to entail exposure); no probable exposure (exposure existed but probably not exposed continuously during working hours in any activity); probable exposure (probably exposed continuously during working hours in at least one activity); or high exposure

Table 2.1 Case-control studies on cancer of the brain and occupational exposure to radiofrequency radiation

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Comments
Thomas et al. (1987) USA, 1979-81	435	386	Death certificates of residents who had died from a cause other than brain tumour, epilepsy, stroke, suicide or homicide, matched to cases by age and year at death, and area of residence	Next-of-kin interviews regarding employment history and other risk factors for brain tumours. Exposure classified according to job title and results of previous studies, and by an industrial hygienist	Brain	<i>Occupational exposure to MW or RF based on assessment by the industrial hygienist</i> Never exposed Ever exposed Ever exposed, excluding those with co-exposure to soldering fumes or lead Ever exposed, excluding those with co-exposure to organic solvents	 2	 1.0 1.7 (1.1-2.7) 1.4 (0.7-3.1) 0.4 (NR)	Restricted to white men aged > 30 yr. Methods of statistical analysis were not described. Covariates: matched by age and year at death, and area of residence, but not included as covariates in the unmatched analysis

Table 2.1 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Comments
Berg et al. (2006) Germany, 2000–03	381 cases of meningioma, 366 cases of glioma	1494, of whom 732 matched to glioma and 762 to meningioma cases	2449 controls frequency-matched on age, sex and centre, were derived from population registries, 63% participated. Subsequently, controls were matched to cases on a 2:1 basis	CAPI mostly in hospital for cases, and at home for controls. Interview included questions about job title and specific occupational activities followed by expert assessment of exposure to RF/MW	Glioma (C71.0–71.9; 9380–9383, 9390–9393, 9400–9401, 9410–9411, 9420–9421, 9440–9442, 9450–9451) and meningioma (C70.0; 9530–9539)	<i>Exposure to RF</i> <i>Glioma</i> Total exposure: No/not probable Probable/high exposure Probable exposure: No exposure Not probable Probable High Duration of high exposure: Not highly exposed Highly exposed for < 10 yr Highly exposed for ≥ 10 yr	328 38 308 20 16 22	1.00 1.04 (0.68–1.61) 1.00 0.84 (0.48–1.46) 0.84 (1.46–1.56) 1.22 (0.69–2.15)	Aged 30–69 yr Covariates: SES, urban or rural, exposure to ionizing radiation, smoking history, age at diagnosis

Table 2.1 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Comments
Berg et al. (2006) (contd.)	<i>Meningioma</i>								
	Total exposure:								
	No/not probable						355	1.00	
	Probable/high exposure						26	1.12 (0.66–1.87)	
	Probable exposure:								
	No exposure						340	1.00	
	Not probable						15	1.11 (0.57–2.15)	
	Probable						15	1.01 (0.52–1.93)	
	High						11	1.34 (0.61–2.96)	
	Duration of high exposure:								
	Not highly exposed						370	1.00	
	Highly exposed for < 10 yr						5	1.14 (0.37–3.48)	
	Highly exposed for ≥ 10 yr						6	1.55 (0.52–4.62)	

Table 2.1 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Comments
Karipidis et al. (2007) Australia, 1987–91	416	422	Population of four major centres as recorded by the electoral rolls for the Australian state of Victoria	Comprehensive job history, including self-reported RF exposure in each job, expert assessment by occupational hygienist and application of a community-based job-exposure matrix, FINJEM	Glioma (ICD-O codes 938–946)	<i>Total cumulative exposure to RF given by FINJEM ($W/m^2 \cdot yr$)</i>	396	1.00	Covariates: age, sex, and year of education
						Unexposed			
						> 0–11			
						> 11–52			
						> 52			
						<i>P</i> trend			
						<i>Self-reported duration of exposure (yr) to RF</i>			
						Unexposed			
						> 0–3			
						> 3–8			
						> 8			
						<i>P</i> trend			
						<i>Expert assessment of duration of exposure (yr) to RF</i>			
						Unexposed			
> 0–3									
> 3–6									
> 6									
<i>P</i> trend									
							381	1.00	
							10	1.20 (0.48–3.04)	
							12	1.65 (0.66–4.17)	
							11	1.57 (0.62–4.02)	
								0.17	

Table 2.1 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Comments
Baldi <i>et al.</i> (2011) France, 1999–2001	221	442	Population selected from local electoral rolls and individually matched on age, sex and department of residence	Interviewer-administered face-to-face questionnaire, which included a lifetime occupational history documenting for each job held for ≥ 6 mo: job title, industry, begin and end dates, and details of tasks performed. Occupational hygienists assessed probability of exposure to RF and duration for each job.	CNS (70.0–70.9, 71.0–71.9, 72.2–72.9)	Occupational exposure to RF All brain tumours ($n = 221$): Unexposed Exposed Glioma ($n = 105$): Unexposed Exposed Meningioma ($n = 67$): Unexposed Exposed Acoustic neurinoma ($n = 32$): Unexposed Exposed <i>Amateur radio practice</i> All brain tumours ($n = 221$): No Yes	148 7 71 7 61 0 31 1 NR NR	1.00 1.50 (0.48–4.70) 1.00 1.44 (0.50–4.13) 1.00 - 1.00 0.40 (0.05–3.42) 1.00 1.39 (0.67–2.86)	95 males, 126 females. 70% of eligible cases participated and 69% of eligible and contactable controls. Covariates: exposure to pesticides, smoking, educational level

CAP1, computer-assisted personal interview; FINJEM, FIN(nish) job-exposure matrix; mo, month; MW, microwave; NR, not reported; RF, radiofrequency radiation; SES, socioeconomic status; W, watt; yr, year

(certainly exposed continuously during working hours and sometimes at levels $> 0.08\text{W/kg}$ in at least one activity). Analyses included data from proxy interviews, and results were not sensitive to removal of proxy interview data. There was weak evidence that risk of glioma and of meningioma increased with increasing duration of high occupational exposure to RF/MW/EMF. For glioma, the odds ratio for < 10 years of high exposure relative to no exposure was 1.11 (95% CI, 0.48–2.56) and that for ≥ 10 years of high exposure was 1.39 (95% CI, 0.67–2.88); the analysis controlled for centre, sex, age at diagnosis, socioeconomic status, urban or rural area, exposure to ionizing radiation, and smoking history. The corresponding odds ratios for meningioma were 1.14 (95% CI, 0.37–3.48) and 1.55 (95% CI, 0.52–4.62) ([Table 2.1](#)). [The strengths of this study were its large size and evaluation of exposure at the job-activity level. Its main weaknesses included the small numbers of cases with high exposure and lack of associated consideration of other sources of exposure to RF radiation.]

[Karipidis *et al.* \(2007\)](#) reported on risk of glioma in relation to occupational exposure to RF radiation in a case-control study in five major population centres in the Australian state of Victoria. Cases were patients aged 20–70 years with glioma, newly diagnosed between July 1987 and December 1991, who were ascertained by screening the medical records of 14 major Melbourne (capital of Victoria) hospitals that together provided most of the neurosurgical services in the state. Completeness of ascertainment was checked against cancer-registry records of Victoria. Controls were randomly selected from the electoral rolls and frequency-matched to cases by age and sex; the electoral rolls covered about 85% of citizens at that time. Controls were excluded if they had a history of brain tumour, stroke or epilepsy. Participants completed a self-administered work-history questionnaire, which included queries about occupation, employer, industry, main tasks and duties, equipment used,

start and finish dates, number of hours worked per day, number of days worked per week and whether or not they had been exposed to RF radiation, for all jobs undertaken since age 12 years that had lasted ≥ 3 months. Work histories were checked for completeness at a subsequent face-to-face interview. For 44% of cases and 2% of controls, a next-of-kin proxy completed the work history. In addition to the self-report, exposure to RF radiation was assessed from the work history by use of the Finnish National Job-Exposure Matrix (FINJEM; a community-based job-exposure matrix developed by the Finnish Institute of Occupational Health) and by review of the work histories by an expert occupational hygienist. Four categories of cumulative exposure were created for each exposure measure: unexposed, and thirds of the ranked exposure distributions for all exposed subjects. Results were adjusted for age, sex and years of schooling (a surrogate for socioeconomic status). Data on occupational exposure were obtained for 414 cases and 421 controls, i.e. 66% and 65%, respectively, of those eligible and contactable [respective numbers not contacted were not given]. With FINJEM, 18 cases and 17 controls were classified as exposed to RF radiation, 29 and 48 by self-report and 33 and 25 by expert assessment. Only in the case of classification based on expert assessment of exposure was there any consistent indication that risk of glioma increased with exposure to RF radiation: relative to those who were not exposed, odds ratios were 1.20 (95% CI, 0.48–3.04) for > 0 –3 years of exposure, 1.65 (95% CI, 0.66–4.17) for > 3 –6 years and 1.57 (95% CI, 0.62–4.02) for > 6 years ([Table 2.1](#)). Analyses excluding participants with proxy information showed no major differences in results. [The use of multiple measures of occupational exposure to RF radiation, including expert assessment of a comprehensive occupational history, was a strength of the study. It was limited by lack of inclusion of non-contactable subjects when estimating participation rates, by the large proportion of

cases requiring proxy respondents and by the comparatively small number of subjects who were exposed to RF radiation. FINJEM provides a probably incomplete assessment of occupational exposure to RF radiation.]

[Baldi et al. \(2011\)](#) reported on a case-control study of people aged ≥ 16 years, newly diagnosed with cancer of the primary CNS between mid-1999 and mid-2001 in the administrative region of Gironde in south-western France. Patients with neurofibromatosis, Von Hippel-Lindau disease or AIDS were excluded. Controls were selected from local electoral rolls, which automatically register all French subjects, and individually matched to cases by age, sex and department of residence. Participation rates were 70% of eligible cases and 69% of eligible and contactable controls. Occupational exposure to RF radiation was assessed by two occupational hygienists from lifetime histories of jobs that had lasted ≥ 6 months (including job title, industry, dates each job began and ended, details of tasks performed), which were collected by face-to-face interview. Information on use of amateur radio was also collected. The odds ratio for occupational exposure to RF radiation and all tumours of the brain was 1.50 (95% CI, 0.48–4.70), while for use of amateur radio it was 1.39 (95% CI, 0.67–2.86) ([Table 2.1](#)). [The Working Group noted the comparatively small size of the study and the small number of exposed subjects, which appeared to have precluded analysis at multiple exposure levels; the exposure assessment based on a comparatively limited occupational history, and an estimated participation rate for controls that was not based on all potentially eligible participants.]

(b) *Cohort studies*

[Lilienfeld et al. \(1978\)](#) reported on a retrospective cohort study of USA employees and their dependents who had worked or lived at the United States embassy in Moscow during 1953–1976 and, for comparison, employees and their

dependents at other United States embassies in eastern Europe who had not served in Moscow over the same period. There were unusual levels of background exposure to MW in the embassy in Moscow. The maximum measured levels were $5 \mu\text{W}/\text{cm}^2$ for 9 hours per day, $15 \mu\text{W}/\text{cm}^2$ for 18 hours per day, and $< 1 \mu\text{W}/\text{cm}^2$ thereafter for non-overlapping time periods between 1953 and 1975 and between 1975 and 1976. Only background levels of exposure to MW were recorded in other eastern-European embassies. Relevant health information and follow-up data were obtained from the medical records of employees and their dependents (held by the Department of State) and a health-history questionnaire sent to each employee or dependent who could be located. Death certificates were sought for all decedents. The analysis was based only on subjects who could be traced ($> 90\%$): 1719 Moscow employees and 1224 dependents known to have lived with them in the embassy, and 2460 employees at other embassies and 2072 dependents known to have lived with them. For embassy employees, 194 deaths were ascertained; of these, there was sufficient information for 181 for inclusion in the analysis, and death certificates were available for 125. There were no deaths from tumours of the brain or other parts of the CNS in Moscow employees, compared with 0.9 expected on the basis of comparable mortality rates in the USA [standardized mortality ratio, SMR, 0; 95% CI, 0–4.1]. For other embassy employees, there were five deaths from tumours of the brain or other parts of the CNS, with 1.5 expected (SMR, 3.3; 95% CI, 1.1–7.7). For dependents known to have lived in the relevant embassy, $> 90\%$ were traced, 67 deaths were ascertained, 62 death certificates were available. There were no observed deaths from tumours of the brain or other parts of the CNS (0.15 expected) [SMR, 0; 95% CI, 0–24.6] for the Moscow embassy and 1 death was observed (0.19 expected) for the other embassies ([Table 2.2](#)). [This study was available only in a United States government report; it was not published in the

peer-reviewed literature. Its main weaknesses were the small sizes of the two cohorts and the small number of deaths from cancer of the CNS observed. The long and continuous exposure to high background levels of MW in the Moscow Embassy was a strength. Possible confounding factors were not addressed.]

[Milham \(1988a, b\)](#) followed a cohort of people who were licensed as amateur radio-operators between 1 January 1979 and 16 June 1984 (a licence was valid for 5 years) and had addresses in Washington State or California. The full names and dates of birth of male cohort members (67 829 people; there were few females) were matched with deaths in Washington State and California. Only exact matches were accepted. Person-years at risk started on the effective current registration day and ended on the day of death, or on 31 December 1984. There were 232 499 person-years at risk and 2485 deaths; 29 deaths from cancer of the brain (International Classification of Disease Revision 8 [ICD-8] code 191) were observed and 20.8 expected [the death rates used to estimate the expected numbers were not specified], SMR for deaths from cancer of the brain was 1.39 (95% CI, 0.93–2.00) ([Table 2.2](#)). Licensees were further subdivided by licence class, i.e. Novice, Technician, General, Advanced and Extra. Novices were limited in their use of transmitter power and transmission frequencies; these conditions became more liberal as licence class rose. The average age increased with rising licence class; those holding higher-level licences may have generally been amateur radio operators for longer than those holding lower-level licences. Deaths from cancer of the brain were more frequent than expected for each licence class after Novice, but with little evidence of progressive increases as licence class rose ([Table 2.2](#)). [The main strength of this study was its clear and straightforward execution. Its weaknesses included lack of information about erroneous or missed links of cohort members to deaths, lack of consideration of possible migration of cohort

members from Washington State and California, limited validation of licence class as a surrogate for intensity and duration of exposure to RF radiation, and the small number of observed deaths from cancer of the brain. Possible confounding factors were not addressed.]

[Armstrong *et al.* \(1994\)](#) carried out a nested case-control analysis of the association of several cancers, including tumours of the brain, and exposure to pulsed electromagnetic fields (PEMFs; frequency range, 5–20 MHz) in two cohorts of electrical-utility workers in Quebec, Canada (21 749 men; follow-up, 1970–1988), and France (170 000 men; follow-up, 1978–1989), among whom 2679 cases of cancer were identified, 84 malignant tumours of the brain and 25 benign tumours of the brain. Utility-based job-exposure matrices were created with information obtained from surveys of samples of 466 (Quebec) and 829 (France) workers wearing exposure meters in 1991–1992. For malignant tumours, the odds ratios were 0.84 (95% CI, 0.47–1.50) for above-median exposure to PEMFs and 1.90 (95% CI, 0.48–7.58) for exposure at or above the 90th percentile, while for astrocytoma – the most common type of glioma – the odds ratio for exposure at or above the 90th percentile was 6.26 (95% CI, 0.30–132). For benign tumours, the odds ratio was 1.58 (95% CI, 0.52–4.78) for above-median exposure. None of the odds ratios for other subtypes of cancer of the brain were elevated ([Table 2.2](#)).

[Grayson \(1996\)](#) reported on risk of brain cancer related to exposure to equipment producing RF or MW (RF/MW) radiation in a case-control study conducted within a cohort of male members of the United States Air Force in 1970–89 ([Table 2.2](#)). Four matched controls were randomly selected for each case from all cohort members. Controls were not eligible if they had been diagnosed with leukaemia, cancer of the breast or melanoma “...because excess risks of these tumours have been associated with EMF exposures in other studies” [this exclusion was

not appropriate in a nested case-control study as if the excluded tumours were associated with EMF exposure, this could bias exposure in controls downwards, though probably only to a very small degree given the relative rarity of these cancers]. An expert panel assessed each job title-time couplet for probability of exposure to RF/MW radiation, which was recorded as “unexposed,” “possibly exposed” and “probably exposed.” Incident cases of cancer of the brain (ICD-9 code 191) were identified from hospital discharge records of serving personnel; confirmatory data (imaging or histopathology records) were not sought. Conditional logistic regression was used for the analysis; no potential confounders were included as covariates in the models. The odds ratio for cancer of the brain with ever-exposure to RF/MW was 1.39 (95% CI, 1.01–1.90). There was only weak evidence of a trend towards increasing odds ratio with increase in the value of the product of a score for probable intensity of exposure and duration of exposure. [The strengths of this study included its basis within a cohort, the careful design and the probably complete ascertainment of brain cancers occurring within the study period. It is limited by its lack of confirmation of diagnosis through access to diagnostic records, the reliance on occupational title to identify instances of potential exposure to RF/EMF radiation, and the uncertain accuracy of exposure quantification. Any bias due to these weaknesses would probably be towards the null and would weaken a dose-response relationship, if there were one.]

[Szmitowski \(1996\)](#) studied the incidence of cancer in the whole population of career military personnel in Poland from 1971 to 1985, averaging about 127 800 men over these 15 years. [This study appeared to be a cross-sectional study rather than a cohort study ([Table 2.2](#)).] Annual data were obtained on all career servicemen from personnel and health departments, and included numbers of servicemen, types of service posts and exposure to possible

carcinogenic factors during service, while military safety groups provided information on the number of personnel exposed to RF radiation. On average, 3720 men were considered to have been exposed to RF radiation each year. It was estimated that of these, 80–85% were exposed at $< 2 \text{ W/m}^2$ and the remainder at $2\text{--}6 \text{ W/m}^2$, but individual exposure levels could not be assigned. Exposure was largely to pulse-modulated RF radiation at 150–3500 MHz. Annual data on all men newly diagnosed with cancer were collected from records of military hospitals and the military medical board; in addition to type of cancer, they included duration and type of service and exposure to possible carcinogenic factors during service, including whether or not they were exposed to RF radiation. [It was unclear from the text whether information in individual health records may have been used, in addition to information applicable to all servicemen, in allocating a man diagnosed with cancer to the group exposed to RF radiation.]

[It appeared to the Working Group that these data were insufficient to permit calculation of annual age-specific rates of all cancers (in age groups of 10 years) and individual types of cancer in men exposed to RF radiation and men not exposed and thus to calculate ratios of incidence in the exposed group to that in the unexposed group for each year and for the whole period. The methods were described in limited detail and it was not stated how the rates or rate ratios were summarized across age groups and years and, in particular, whether cancer-incidence rate ratios based on all exposed and all unexposed men were age-standardized. The observed numbers of cases of all cancers or individual types of cancer were not presented, but could be approximated from average annual rates of incidence, from which it appeared that two to three cases of cancer of the nervous system and brain (ICD codes not specified) were diagnosed in men exposed to RF radiation over the 15 years, and about 54 cases in men not exposed.]

Table 2.2 Cohort studies of cancer of the brain and occupational exposure to radiofrequency radiation

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Covariates	Comments
Lilienfeld et al. (1978) United States embassies in eastern Europe	7475	1953–76	Worked or lived in the United States embassy in Moscow during study period. The maximum measured levels were 5 $\mu\text{W}/\text{cm}^2$ for 9 h/d, 15 $\mu\text{W}/\text{cm}^2$ for 18 h/d, and < 1 $\mu\text{W}/\text{cm}^2$ thereafter for non-overlapping periods between 1953 and 1975 and between 1975 and 1976	Brain and CNS (ICD-7 code 193)	<i>Role and location in eastern Europe</i> Employed in the United States embassy in Moscow Dependent of a Moscow United States embassy employee Employed in a different United States embassy in eastern Europe	0 0 5	SMR 0 [0–4.1]* 0 [0–24.6]* 3.3 [1.1–7.7]*	Sex, age	SMRs are relative to the corresponding mortality rates in the USA. Contract report is available through the National Technical Information Service of the USA.
Milham (1988a, b) USA	67 829	1979–84	Licensing as an amateur radio operator	Brain (191)	<i>Amateur radio operator licence class</i> Novice Technician General Advanced Extra All	1 4 11 11 2 29	SMR 0.34 1.12 1.75 1.74 1.14 1.39 (0.93–2.00)		

Table 2.2 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Covariates	Comments
Armstrong et al. (1994) Canada and France	191 749	1970–89	Exposure assessed through a job-exposure matrix based on about 1000 person-weeks of measurements from exposure meters worn by workers to derive estimates of short-duration PEMFs, or high-frequency transient fields.	Brain (191)	PEMFs Malignant cancer of the brain: < Median > Median ≥ 90th percentile Astrocytoma: < Median > Median ≥ 90th percentile Glioblastoma: < Median > Median ≥ 90th percentile Other cancers: < Median > Median ≥ 90th percentile Benign tumours of the brain: < Median > Median ≥ 90th percentile	49 35 9 22 12 3 16 13 5 7 6 1 9 16 1	OR 1.00 0.84 (0.47–1.50) 1.90 (0.48–7.58) 1.00 0.89 (0.29–2.67) 6.26 (0.30–132) 1.00 0.49 (0.19–1.28) 0.57 (0.08–3.91) 1.00 2.67 (0.43–16.71) – 1.00 1.58 (0.52–4.78) –	SES	Nested case-control analysis. Controls for each case were selected at random from the cases risk set and matched by utility and year of birth. Exposure was counted only up to the date of diagnosis of the case.

Table 2.2 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Covariates	Comments
Grayson (1996) USA	230 cases, 920 controls	1970–89	Job title-time-exposure matrix. Census of control histories was carried out at time of matched case's diagnosis. Exposure score was the sum of the products of duration of deployment in each job and the assessed probability of RF exposure in that job at that time.	Brain (191)	RF/MW Never exposed Exposed RF/MW exposure score None 2–48 49–127 128–235 236–610	94 136 136 15 29 25 25	OR 1.00 1.39 (1.01–1.90) 1.00 1.26 (0.71–2.24) 1.50 (0.90–2.52) 1.26 (0.71–2.22) 1.51 (0.90–2.51)	Controls exactly matched to case on year of birth, race and presence in the cohort at the time when the case was diagnosed. Matching retained in analysis. Age, race, rank (senior or other) included as covariates.	United States Air Force personnel Nested case-control analysis within cohort study. All male members of United States Air Force. Rank associated with risk; senior officers at increased risk.
Szmigielski (1996) Poland	Average of 127 800 men, yearly during 15 yr	1971–85	Military safety (health and hygiene) groups classified military service posts as having exposure, or not, to RF	Nervous system, including brain	Occupational exposure to RF Not exposed Exposed P value	[54]* [2–3]* < 0.05	1.00 1.91 (1.08–3.47) < 0.05	None specified	Cross-sectional study. Incidence rate ratio for all cancers, 2.07 (95% CI, 1.12–3.58) suggests possible upward bias in rate ratios.
Tynes et al. (1996) Norway	2619 women	1961–91	Radio and telegraph operators with potential exposure to RF and ELF	Brain (ICD-7 code 193)	Radio and telegraph operators with potential exposure to RF and ELF	5	SIR, 1.0 (0.3–2.3)	Age, time since certification, calendar year, age at first childbirth	Women certified as radio and telegraph operators 1920–80

Table 2.2 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Covariates	Comments
Lagorio et al. (1997) Italy	481 women	1962–92	Occupational history from plant records. RF generated by dielectric heat sealers. Exposure of 10 W/m ² equivalent power-density frequently exceeded.	Brain (191)	Job title			Sex, age, calendar period-specific regional person-year at risk	Mortality analysis restricted to women
					RF-sealer operators	1	10 [0.25–56]*		
					Other workers	0	0 [0–46]*		
					All female workers	1	5 [0.13–28]*		
Morgan et al. (2000) USA	195 775 Motorola employees	1976–96	Job-exposure matrix	Brain/CNS	Cumulative exposure to RF		Rate ratio	Age, sex, and race for external comparisons; and age, sex, and period of hire for internal comparisons	All employees of Motorola; exposure from cellular phones not assessed. Definition of exposure categories unclear.
					None	34	1.00		
					< Median	7	0.97 (0.37–2.16)		
					≥ Median	10	0.91 (0.41–1.86)		
					Usual exposure to RF				
					None	38	1.00		
					Low	7	0.92 (0.43–1.77)		
					Moderate	3	1.18 (0.36–2.92)		
					High	3	1.07 (0.32–2.66)		
					Peak exposure to RF				
					None	34	1.00		
					Low	10	0.98 (0.50–1.80)		
					Moderate	3	0.70 (0.21–1.77)		
					High	4	1.04 (0.36–2.40)		
					Duration of exposure				
					None	44	1.00		
					≤ 5 yr	3	0.74 (0.22–1.84)		
					> 5 yr	4	0.99 (0.35–2.26)		
					Cumulative exposure to RF				
					Males-low	23	1.00		
					Males-high	8	1.11 (0.38–2.78)		
					Females-low	18	1.00		
					Females-high	2	0.58 (0.03–3.30)		

Table 2.2 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Covariates	Comments
Groves et al. (2002) USA	40 581 men (271 women excluded)	1950–97	United States Navy personnel with potential for RF exposure; job classified as entailing low or high exposure	Brain (ICD-9 codes 191.0–191.9)	<i>Job-associated exposure to RF</i> Low High Total cohort Within-cohort comparison: Low exposure High exposure	51 37 88	SMR 1.01 (0.77–1.33) 0.71 (0.51–0.98) 0.86 (0.70–1.06)	Age at cohort entry, attained age	White United States Navy (male) veterans of Korean War (1950–54)
Degraeve et al. (2009) Belgium	Military personnel (4417 men) in battalions equipped with radar, and 2932 controls	1968–2003	Exposure levels on the site where the battalion lived and worked were characterized, individual exposure assessment could not be conducted.	Cancer of eye, brain and nervous system (190–192)	Control cohort Radar-exposed	2 8	1.00 2.71 (0.42–17.49)		Cause of death found for 71% of the men in the radar group and 70% in the control group.

* values calculated/deducted by the Working Group
d, day or days; ELF, extremely low-frequency electric and magnetic field; h, hour or hours; mo, month; MW, microwaves; OR, odds ratio; PEMFs, pulsed electromagnetic fields; RF, radiofrequency radiation; SES, socioeconomic status; SIR, standardized incidence ratio; SMR, standardized mortality ratio; W, watt; yr, year

The incidence rate ratio (IRR) for cancer of the nervous system and brain over the 15 years in those exposed to RF radiation was estimated to be 1.91 (95% CI, 1.08–3.47). The corresponding incidence rate ratio for all cancers was 2.07 (95% CI, 1.12–3.58). [The similarity of these two incidence rate ratios suggested the possibility of consistent upward bias in their estimation. It also appeared that the 95% confidence intervals had not been correctly calculated given their similar width and the large difference in the observed numbers on which they were based: 2–3 cancers of the nervous system and brain and about 32 cancers of all types.] Age-specific incidence rate ratios for all cancers ranged from 2.33 at age 20–29 years to 1.47 at age 50–59 years. [This was somewhat against the hypothesis that failure to standardize by age had increased the incidence rate ratios with exposure to RF radiation. The interpretation of this study was hampered by its cross-sectional design, in which risk of cancer was related only to current exposure to RF radiation; uncertainty about the accuracy of the classification of exposure; lack of a quantitative measure of exposure; lack of information on completeness of ascertainment of cancer incidence; lack of clarity concerning the analytical methods, including whether incidence rate ratios were age-standardized; and probable errors in the statistical analysis. Possible confounding factors were not addressed. The possibility that medical records accessed for men with cancer may have provided information that led them to being classified as exposed to RF radiation may explain the apparently high risks of cancer in men exposed to RF radiation in this study.]

[Tynes et al. \(1996\)](#) examined incidence of cancer in a cohort of 2619 Norwegian women who were certified as radio and telegraph operators between 1920 and 1980 ([Table 2.2](#)); 98% had worked on merchant navy ships. They were followed from 1961 to 1991 via the Norwegian cancer registry; 41 were lost to follow-up. Electric and magnetic fields were measured in the radio

rooms of three older Norwegian ships. They were below detection levels at radio-frequencies at the operators' desks and were considered to be comparable to those found at normal Norwegian workplaces. The age- and calendar period-adjusted standardized incidence ratio (SIR) for cancers of the brain and nervous system (ICD-7 code 193) was 1.0 (95% CI, 0.3–2.3; based on five cases) with reference to the national Norwegian female population. [The strengths of this study were its homogeneous cohort and near-complete follow-up; its principal weaknesses were the small number of cases of brain cancer and the probably low exposure of the cohort to RF radiation. Possible confounding factors were not addressed.]

[Lagorio et al. \(1997\)](#) reported on mortality from all causes and from specific cancers in a group of 201 men and 481 women employed in a plastic-ware manufacturing facility in Grosseto, Italy, from 1962 to 1992 and followed until death, or until the end of 1992 ([Table 2.2](#)). Those lost to follow-up were considered to be alive at the end of 1992. Vital status and cause of death were ascertained from the registry office of the municipality of residence and death. Workers were classified into three groups: RF-sealer operators, other labourers and white-collar workers. RF-sealer operators received the greatest exposure to RF radiation. They were also exposed to vinyl chloride monomer due to its volatilization from polyvinyl chloride (PVC) sheets during sealing. At the end of follow-up, 661 subjects were alive, 16 had died and 5 were lost to follow-up [details of tracing methods were not given]. The mortality analysis was restricted to women, who were mostly employed in the manufacturing department (6772 person-years in RF-sealer operators). There was one death ascribed to a tumour of the brain and 0.2 expected based on mortality rates in the regional population; this single death occurred in an RF-sealer operator (expected, 0.1). [The principal weakness of this study was its

small size. Possible confounding from exposure to vinyl chloride was not addressed.]

[Morgan et al. \(2000\)](#) studied a cohort of all employees of Motorola USA with at least 6 months of cumulative employment, who were employed for at least 1 day between 1976 and 1996, and followed to 31 December 1996. Deaths were ascertained through reference to the Social Security Administration Master Mortality File and the National Death Index. Death certificates were obtained from the state vital statistics offices and company benefits records, and causes of death were coded according to ICD-9. There were 195 775 workers, 2.7 million person-years of follow-up and 6296 deaths, 53 of which were attributed to cancer of the CNS [ICD-9 codes not stated]. No losses to follow-up were reported [it is probable that the 116 700 workers who had retired or whose employment had been terminated were assumed to be alive if no death record was found for them]. Exposure to RF radiation was assessed on the basis of a company-wide job-exposure matrix, developed through expert consultation, that categorized each of 9724 job titles into one of four exposure groups: background, low, moderate, and high, corresponding roughly to < 0.6 W, $0.6 - < 2.0$ W, $2.0 - < 5.0$ W, $5.0 - < 50$ W and ≥ 50 W. About 45 500 employees were thought to have had usual exposures of ≥ 0.6 W, 8900 employees had a high usual exposure (≥ 50 W) and 9000 employees had unknown usual exposure. Relative to mortality in the combined populations of Arizona, Florida, Illinois, and Texas, where most Motorola facilities were located, the SMR for tumours of the CNS was 0.60 (95% CI, 0.45–0.78). Internal comparisons between categories of estimated cumulative, usual and peak exposure to RF radiation; duration of exposure; (cumulative exposure lagged 5, 10 and 20 years) and cumulative exposure in males and females separately, showed no consistent evidence of an increase in risk of tumours of the CNS with increasing estimated exposure to RF radiation ([Table 2.2](#)). [The main

strength of this study was the clear and straightforward execution and comprehensive analyses. Its weaknesses included lack of measured exposure to RF radiation on which to base the exposure classification; inadequate description of the exposure-validation study; lack of detail on how the links between cohort members and death records were established, and therefore uncertainty about completeness and accuracy of death ascertainment; the comparatively small number of observed deaths from tumours of the CNS; and possible conservative bias due to exclusion of mobile-phone use from the estimate of exposure to RF radiation. Possible confounding factors were not addressed.]

[Groves et al. \(2002\)](#) reported on an extended follow-up to death or to the end of 1997 for 40 890 United States Navy personnel originally studied by [Robinette et al. \(1980\)](#). These men were graduates of Class-A Navy technical training schools who had served on ships in the Korean War during 1950–54, and who had potentially been exposed to high-intensity radar. They were divided into two occupational groups considered by a consensus of Navy personnel involved in training and operations to have had high exposure to RF radiation (electronics, fire-control and aviation-electronics technicians: 20 109 men) or low exposure (radiomen, radar men and aviation electricians' mates: 20 781 men). Potential exposure in each job category was evaluated from the records for 435 men who had died and those of a randomly selected 5% of living men as "the sum of all power ratings of all fire control radars aboard the ship or search radars aboard the aircraft to which the technician was assigned multiplied by the number of months of assignment." Ascertainment of death required use of Department of Veterans' Affairs and Social Security Administration records and the National Death Index. [Its completeness was uncertain.] It was necessary to impute moderate proportions of dates of entry into the cohort (1950–54) and dates of birth, because of missing

data. The analysis was limited to 40 581 men and SMRs were calculated with reference to all white men in the USA, standardized for age at entry to the cohort and attained age. Altogether, there were 51 deaths from cancer of the brain (ICD-9 codes 191.0–191.9); there was no evidence of any increase in risk of cancer of the brain associated with high exposure to RF radiation ([Table 2.2](#)). The SMRs for cancer of the brain were 0.86 (95% CI, 0.70–1.06) for the whole cohort, 1.01 (95% CI, 0.77–1.33) for the group with low exposure to RF radiation (usual exposures well below 1 mW/cm²) and 0.71 (95% CI, 0.51–0.98) for the group with high exposure to RF radiation (potential for exposures up to 100 kW/cm², but usually less than 1 mW/cm²). Within the cohort, the relative risk (RR) of death from cancer of the brain in the group with high exposure to RF radiation relative to the group with low exposure was 0.65 (95% CI, 0.43–1.01). [This appeared to have been an initially somewhat poorly documented cohort, for which follow-up was difficult and some missing data, including birth date, had to be imputed. While expert assessment permitted division of the cohort into groups with low and high exposure to RF radiation, no specific measurements of exposure were reported. Assessment of exposure appeared to have been limited to 1950–54. Possible confounding factors, such as occupational exposure to other agents, were not addressed.]

In a cohort of 4417 Belgian male professional military personnel who served in battalions equipped with radar for anti-aircraft defence, cause-specific mortality was compared with that of 2932 Belgian military personnel who served in battalions not equipped with radar ([Degraeve et al., 2009](#)). Administrative archives of the battalions were used to reconstruct a list of personnel serving in each battalion. Lists were matched to those of the Department of Human Resources of the Belgian Army to find the subjects' birthdays, which allowed retrieval of their Belgian national identity number. With this number, mortality

follow-up could be conducted. For military personnel who died before 1979, the registry only recorded month and year of birth, and thus for 35 dead military exact birth-dates were not available, matching was equivocal and the cause of death was not used. The registry was complete until 1997 and from 1998 to 2004, only for the northern, Dutch-speaking part of Belgium. In parallel, for all professional military personnel who died up to 31 December 2004, first-degree family members were sought and a questionnaire sent to enquire about likely cause of death. For the period of follow-up of this study, the Belgian cancer registry was incomplete, but the information on cases of cancer reported to the registry was reliable. Thus the cancer registry was used only for confirmation, but not for identification of cancer cases. The risk ratio for deaths from cancers of the eye, brain and nervous system in the cohort serving in battalions equipped with radar compared with the unexposed cohort was 2.71 (95% CI, 0.42–17.49) ([Table 2.2](#)). [The Working Group noted the difficulties in following-up the study population that may have affected the study results, as well the difficulty of attributing any possible increase in risk ratio to exposure to RF radiation, given possible confounding due to ionizing radiation also emitted by devices producing MW radiation.]

2.1.2 Leukaemia and lymphoma

(a) Case-control studies

No data were available to the Working Group.

(b) Cohort studies

[Lilienfeld et al. \(1978\)](#) reported on a retrospective cohort study of USA employees, and their dependents, who had worked or lived at the United States embassy in Moscow during 1953–76 (see Section 2.1.1 for details). The total risk ratio for leukaemia in the embassy employees was 2.5 (95% CI, 0.3–9.0).

[Milham \(1988a, b\)](#) followed a cohort of people who were licensed as amateur radio operators between 1 January 1979 and 16 June 1984 (see Section 2.1.1 for details). There was a borderline excess risk of death from lymphatic and haematopoietic neoplasms, from acute myeloid leukaemia, and from multiple myeloma and lymphoma ([Table 2.3](#)). There was no evidence for an increase in SMR for these neoplasms with higher license class (see Section 2.1.1. for discussion of the strengths and weaknesses of this study).

[Armstrong et al. \(1994\)](#) conducted a nested case-control study of cancers at different sites within cohorts of electrical workers in Quebec, Canada, and in France (see Section 2.1.1 for details). There were no excess risks for all haematological cancers, non-Hodgkin lymphoma (NHL) or for all leukaemias, or for any of the subtypes of leukaemia, associated with exposure to PEMF ([Table 2.3](#)). [The strengths and weaknesses of this study are described in Section 2.1.1.]

The study by [Szmigielski \(1996\)](#) is described in detail in Section 2.1.1. A significantly increased incidence rate ratio for cancers of the haematological system and lymphatic organs was reported ([Table 2.3](#)). [The results were difficult to interpret, as there were many methodological flaws in the design and analysis of the study. Main issues were that exact data on the age of the subjects in the cohort were missing and that collection of exposure data was potentially differential.]

[Tynes et al. \(1996\)](#) followed a cohort of 2619 Norwegian women who were certified as radio and telegraph operators between 1920 and 1980. There was no elevation in risk of lymphoma or leukaemia for those potentially exposed to RF radiation ([Table 2.3](#)). [The strengths of this study are discussed in Section 2.1.1; its principal weaknesses were the small number of cancer cases and the probably low exposure of the cohort to RF radiation. Possible confounding factors were not addressed.]

[Lagorio et al. \(1997\)](#) reported on mortality from all causes and from specific cancers in a group of plastic sealers in Italy (see Section 2.1.1 for details). There was one death (0.2 expected) ascribed to leukaemia in an RF-sealer operator ([Table 2.3](#)). [The principal weakness of this study was its small size. Possible confounding factors were not addressed.]

[Morgan et al. \(2000\)](#) reported on a 20-year follow-up of 195 775 employees of Motorola USA (described in Section 2.1.1) and considered death from lymphatic and haematopoietic malignancies ([Table 2.3](#)). Of these, there were 87 deaths from leukaemia, 19 from Hodgkin disease and 91 from NHL. Reduced odds ratios for lymphatic and haematopoietic malignancies and subtypes were seen among workers categorized as exposed (compared with non-exposed workers) in most categories of estimated exposure, duration of exposure and cumulative exposure lagged 5, 10 and 20 years. [The Working Group noted the small number of deaths from lymphoma and leukaemia in the exposed cohort, which, together with the other limitations mentioned in Section 2.1.1, complicated the interpretation of these findings.]

[Richter et al. \(2000\)](#) collected data on six patients claiming compensation for their cancer who visited the Unit of Occupational and Environmental Medicine at the Hebrew University-Hatlawah Medical School, Jerusalem in 1992–99. They were judged to have received high RF/MW radiation based on self-reports, information from manuals containing specifications of the equipment they had used and repaired, and results of sporadic measurements from their work and medical records. A study was then conducted of 25 co-workers of one of the patients and of other personnel with self-reported exposure to RF radiation. An increased risk of haematolymphatic malignancies was found (5 cases observed compared with 0.02 cases expected among Jewish men aged 20–54 years). [The Working Group noted that the results of

this study were very difficult to interpret, due to unclear definition of the study population, follow-up and exposure assessment.]

[Groves et al. \(2002\)](#) reported on mortality in a cohort of 40 890 male United States Navy personnel who had served on ships during the Korean War in 1950–54 in an extended follow-up to 1997 (described in more detail in Section 2.1.1). The cohort was divided into two subgroups on the basis of job title, with potential exposure to RF radiation based on expert assessment: 20 109 workers comprising a subcohort with high exposure to RF radiation (potential for exposures up to 100 kW/cm², but usually < 1 mW/cm²) and a subcohort of 20 781 workers with low exposure (usually well below 1 mW/cm²). A total of 182 deaths from lymphoma or multiple myeloma (91 each in the high- and low-exposure subcohorts) and 113 deaths from leukaemia (44 and 69 in the high- and low-exposure subcohorts, respectively) were identified in 1950–97. In both subcohorts, SMRs were not elevated for lymphoma and multiple myeloma, all leukaemias, lymphocytic leukaemia or non-lymphocytic leukaemia ([Table 2.3](#)). An internal comparison of high relative to low exposure to RF radiation elicited RRs of 0.91 (95% CI, 0.68–1.22) for lymphoma and multiple myeloma, 1.48 (95% CI, 1.01–2.17) for all leukaemias, 1.82 (95% CI, 1.05–3.14) for non-lymphocytic leukaemia and 1.87 (95% CI, 0.98–3.58) for acute non-lymphocytic leukaemia. An increased risk of all leukaemias was observed primarily in aviation-electronics technicians (RR, 2.60; 95% CI, 1.53–4.43, based on 23 deaths) and was highest for acute myeloid leukaemia (RR, 3.85; 95% CI, 1.50–9.84, based on 9 deaths). RRs for other job categories with high exposure were close to 1. This was interpreted as indicating a possible association, since aviation-electronics technicians who dealt primarily with mobile radar units may have had more potential to enter the beam path of an operating radar than members of other groups who worked with ship-mounted radars. [The limitations of this study

are discussed in Section 2.1.1, including limitations in the documentation of the cohort definition and difficulties in follow-up. Classification of exposure to RF radiation in the different groups was based on expert assessment. No measurement of RF radiation was provided.]

[Degraeve et al. \(2009\)](#) compared a cohort of 4417 Belgian male professional military personnel who served in battalions equipped with radars for anti-aircraft defence with 2932 Belgian male professional military personnel who served at the same time in the same place in battalions not equipped with radars. Attempts were made to characterize exposure levels on the site where the battalion lived and worked, but individual exposure assessment could not be conducted. Administrative archives of the battalions were used to reconstruct a list of personnel serving in each battalion. These archives only provided first name, family names, and a unique identification number. Lists were matched to those of the Department of Human Resources of the Belgian Army to find the subjects' birthdays, which allowed retrieval of their Belgian national identity number. With this number, mortality follow-up could be conducted. The first source of information on cause of death was the official Belgian death registry, which collects anonymous data. Linkage was conducted using date of birth and date of death as matching variables (cause of death could be found for 71% of persons in the radar group and 70% in the control group). For military personnel who died before 1979, the registry only recorded month and year of birth, and exact birth-dates were not available for 35 of the dead, while matching was equivocal and the cause of death was not used. The registry was complete until 1997 and from 1998 to 2004, only for the Northern, Dutch-speaking part of Belgium. In parallel, for all professional military personnel who died up to 31 December 2004, first-degree family members were sent a questionnaire to enquire about the likely cause of death. For the period of follow-up of this study,

Table 2.3 Cohort studies of leukaemia and occupational exposure to radiofrequency radiation

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Covariates	Comments
Lilienfeld et al. (1978)	7475	1953–76	Worked or lived in the United States embassy in Moscow during study period. The maximum measured levels were 5 µW/cm ² for 9 h/d, 15 µW/cm ² for 18 h/d, and < 1 µW/cm ² thereafter for non-overlapping periods 1953–1975 and 1975–1976	Leukaemia	Embassy employees		2.5 (0.3–9.0)	Sex, age	SMRs are relative to the corresponding mortality rates in the USA. Contract report is available through the National Technical Information Service of the USA.
Milham (1988a, b) USA	67 829	1979–1984	Licensing as an amateur radio operator	Lymphatic and haematopoietic cancers	All leukaemia AML Multiple myeloma and lymphoma All lymphatic and haematopoietic cancers <i>By licence class:</i> Novice Technician General Advanced Extra	89 36 15 43	SMR 1.23 (0.99–1.52) 1.24 (0.87–1.72) 1.76 (1.03–2.85) 1.62 (1.17–2.18)		The death rates used to estimate the expected numbers were not specified

Table 2.3 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Covariates	Comments
Armstrong et al. (1994) Canada and France	191 749	1970–89	Exposures assessed through a job-exposure matrix based on about 1000 person-weeks of measurements from exposure meters worn by workers to derive estimates of short-duration PEMFs, or high-frequency transient fields.	Haematological	PEMFs All haematological cancers: < Median > Median ≥ 90th percentile NHL: < Median > Median ≥ 90th percentile All leukaemias: < Median > Median ≥ 90th percentile	167 135 28 54 56 13 57 38 9	OR 1.00 0.90 (0.65–1.25) 0.96 (0.48–1.90) 1.00 1.41 (0.83–2.38) 1.80 (0.62–5.25) 1.00 0.69 (0.40–1.17) 0.80 (0.19–3.36)	SES	Nested case-control analysis Controls for each case were selected at random from the cases risk set, and matched to the case by utility and year of birth. Exposure was counted only up to the date of diagnosis of the case.
Szmigielski (1996) Poland	Average of 127 800 men, yearly during 15 yr	1971–85	Military safety (health and hygiene) groups classified military service posts as having exposure, or not, to RF	Cancer of the haematopoietic system and lymphatic organs	Occupational exposure to RF Not exposed Exposed	[131]* [24]*	Incidence rate ratios 1.00 6.31 (3.12–14.32)	None specified	Cross-sectional study
Tynes et al. (1996) Norway	2619 women	1961–91	Radio and telegraph operators with potential exposure to RF and ELF fields	Lymphoma (ICD-7 code 201) Leukaemia (ICD-7 code 204)	Potential exposure Lymphoma Leukaemia	5 2	SIR 1.3 (0.4–2.9) 1.1 (0.1–4.1)	Age, time since certification, calendar year, age at first childbirth	Women certified as radio and telegraph operators, 1920–80

Table 2.3 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Covariates	Comments
Lagorio <i>et al.</i> (1997) Italy	481 women	1962–92	Occupational history from plant records. RF generated by dielectric heat sealers. Exposure of 10 W/m ² equivalent power-density frequently exceeded.	Leukaemia (204–208)	<i>Job title</i> RF-sealer operators Other workers All female workers	1 1 2	SMR [5.0 (1.27–27.85)]* [11.1]* 8.0 (1.0–28.8)	Sex, age, calendar period-specific regional person-year at risk	Mortality analysis; restricted to women
Richter <i>et al.</i> (2000) Israel	Co-workers (n = 25) of one of the six patients claiming compensation for their cancer, and other personnel with self-reported exposure to RF	1992–99	Self-reports, information from manuals containing specifications of the equipment they had used and repaired, and results of sporadic measurements from their work and from medical records.	Haemato-lymphatic malignancies	Jewish men aged 20–54 yr	5	SIR [250 (81.17–583.42)]*	None	[The Working Group noted that the results of this study were very difficult to interpret, due to unclear definition of the study population, follow-up, and exposure assessment.]

Table 2.3 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Covariates	Comments
Morgan et al. (2000) USA	195 775	1976–96	Job-exposure matrix; developed through expert consultation that categorized each of 9724 job titles into different RF exposure groups: background, low, moderate, and high, corresponding roughly to < 0.6 W, 0.6 to < 2.0 W, 2.0 to < 5.0 W, 5.0 to < 50 W and ≥ 50 W, respectively	All lymphatic/haematopoietic cancers (n = 203)	Cumulative exposure to RF		Rate ratio	Age, sex, and race for external comparisons; and age, sex, and period of hire for internal comparisons	All employees of Motorola; exposure from cellular telephones not assessed. Definition of exposure categories unclear
					None	148	1.00		
					< Median	21	0.74 (0.39–1.28)		
					> Median	34	0.67 (0.40–1.05)		
					Usual exposure to RF				
					None	152	1.00		
					Low	28	0.94 (0.57–1.47)		
					Moderate	10	0.90 (0.39–1.78)		
					High	8	0.70 (0.27–1.47)		
					Peak exposure to RF				
					None	145	1.00		
					Low	34	0.79 (0.49–1.23)		
					Moderate	11	0.58 (0.25–1.13)		
					High	10	0.60 (0.49–1.23)		
					Duration of exposure				
					None	182	1.00		
					≤ 5 yr	5	0.29 (0.12–0.57)		
					> 5 yr	16	0.89 (0.55–1.35)		
					Cumulative exposure to RF				
					Males-low	109	1.00		
					Males-high	19	0.53 (0.39–0.72)		
					Females-low	60	1.00		
					Females-high	15	1.12 (0.22–3.90)		

Table 2.3 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Covariates	Comments
Groves <i>et al.</i> (2002) USA	40 581 men (271 women excluded)	1950 – 97	United States Navy personnel with potential exposure to RF; job classified as having low or high exposure by a consensus of Navy personnel involved in training and operation	All haematopoietic cancers (200–208)	<i>Job-associated exposure to RF</i>		SMR	Age at cohort entry and attained age	White (male) United States Navy veterans of Korean War (1950–54) Reference: all white men, USA Group of aviation-electronics technicians: RR 2.60 (1.53–4.43) for all leukaemias; RR 3.85 (1.50–9.84) for acute myeloid leukaemia
					Lymphoma and multiple myeloma:				
					Low	91	0.94 (0.77–1.16)		
					High	91	0.89 (0.72–1.09)		
					All leukaemias:				
					Low	44	0.77 (0.58–1.04)		
					High	69	1.14 (0.90–1.44)		
					Lymphocytic leukaemia:				
					Low	17	1.31 (0.81–2.11)		
					High	16	1.12 (0.69–1.83)		
					Non-lymphocytic leukaemia:				
					Low	20	0.67 (0.43–1.04)		
					High	39	1.24 (0.90–1.69)		

Table 2.3 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Covariates	Comments
Degraeve et al. (2009) Belgium	Military personnel (4417 men) in battalions equipped with radar, and 2932 controls	1968–2003	Exposure levels on the site where the battalion lived and worked were characterized; individual exposure assessment could not be conducted.	Cancer of lymphatic and haematopoietic tissue (200–208)	Control cohort Radar exposed	1 11	1.00 7.22 (1.09–48.9)		Cause of death found for 71% of the men in the radar group and 70% in the control group

* values calculated/deduced by the Working Group

AML, acute myeloid leukaemia; ELF, extremely low frequency electric and magnetic field; MW, microwaves; NHL, non-Hodgkin lymphoma; OR, odds ratio; PEMFs, pulsed electromagnetic fields; RF, radiofrequency radiation; SES, socioeconomic status; SIR, standardized incidence ratio; SMR, standardized mortality ratio; W, watt; yr, year

the Belgian cancer registry was extremely incomplete, but the information on cases of cancer reported to the registry was reliable. Thus, the cancer registry was used only for confirmation but not for identification of cancer cases. The relative risks were estimated, adjusting for age in 10-year categories with a Poisson regression model. There were 11 deaths from lymphatic and haematopoietic neoplasms in the radar battalion compared with 1 in the unexposed cohort (RR, 7.22; 95% CI, 1.09–48.9) (Table 2.3). [The Working Group noted the difficulties in following-up the study population, which may have affected the study results, as well the difficulty in attributing any possible increase in relative risk to exposure to RF radiation, given possible confounding due to ionizing radiation also emitted by devices producing MW radiation.]

2.1.3 Uveal (ocular) melanoma

Stang *et al.* (2001) conducted population-based and hospital-based case-control studies of uveal melanoma and occupational exposures to different sources of electromagnetic radiation, including RF radiation. For the population-based study, 37 cases were identified by a reference pathologist (response rate, 84%) and 327 controls were sampled and matched from the same region of residence, age and sex (response rate, 48%). For the hospital-based study, the 81 cases were patients treated at the University of Essen (response rate, 88%) and controls ($n = 148$) were patients with benign intra-ocular tumours (response rate, 79%). The results of these studies were pooled. The 118 female and male cases and 475 controls were interviewed by a trained interviewer with a structured questionnaire involving medical history, lifestyle, occupation and occupational exposure to RF radiation. Participants were specifically asked about exposure to radar and to other RF-emitting devices (“Did you use radio sets, mobile phones or similar devices at your workplace for at least several hours per

day?”) and more detail was obtained from those who reported exposure. Additional information provided by exposed participants was used by two of the authors, working independently and unaware of case or control status, to classify them as: exposed only to radio receivers that do not transmit RF radiation and therefore unexposed; exposed to RF radiation from walkie-talkies and radio sets; possibly exposed to RF radiation from mobile phones; and probably or certainly exposed to RF radiation from mobile phones. Few participants reported occupational exposure to radar. The odds ratio for uveal melanoma was 0.4 (95% CI, 0.0–2.6). For exposure to radio sets, the odds ratio was 3.3 (95% CI, 1.2–9.2) (Table 2.4). Adjustment for socioeconomic status or iris/hair colour did not alter these results. The results for reported occupational use of mobile phones are considered in Section 2.3. [This study was weakened by its poor assessment of occupational exposure to RF radiation, particularly the retrospective classification of exposure to other RF-emitting devices, although neither should be a source of positive bias. Confounding of occupational exposure to RF radiation with exposure to ultraviolet light from the sun or other sources was not considered and may have been important if, for example, much of the use of radio sets had entailed use of walkie-talkie radios for communication outdoors.]

2.1.4 Cancer of the testis

(a) Case-control studies

Interpretable results were available from only two case-control studies (Table 2.5). Both were limited by reliance on self-report for exposure classification.

Hayes *et al.* (1990) carried out a case-control study in the USA examining associations of testicular cancer with occupation and occupational exposures. Cases ($n = 271$) were aged 18–42 years and diagnosed between 1976 and 1981 in three medical institutions, two of which

treated military personnel, while the controls ($n = 259$) were men diagnosed in the same centres with a cancer other than of the genital tract. A complete occupational history was taken and participants were also asked about specific exposures, including to radar equipment and to MW radiation, MW ovens or other radio-waves. For all cancers of the testis combined, the odds ratio associated with exposure to MW radiation, MW ovens or other radio-waves was significantly increased, while the odds ratio for exposure to radar equipment was not elevated ([Table 2.5](#)). The participants were further classified by an industrial hygienist as to degree of exposure to MW radiation, MW ovens, and other radio-waves and no indication of an exposure–response relationship was found. [The Working Group noted that the exposure-classification approach was based on self-report and was probably subject to substantial misclassification.]

[Baumgardt-Elms et al. \(2002\)](#) carried out a case–control study examining the association of cancer of the testis with workplace exposures to EMF. The histologically confirmed cases ($n = 269$; including 170 seminomas and 99 non-seminomas) were recruited between 1995 and 1997 from five German regions (response rate, 76%). The controls ($n = 797$) were randomly selected from mandatory registries of residents, with matching on age and region (response rate, 57%). Occupational exposure to EMF was assessed in standardized face-to-face interviews with closed questions. For radar, job descriptions were selected for participants who had reported exposure to radar or had worked in occupations and industries involving such exposures. The participants were classified as to exposure to radar on the basis of expert review and measurements conducted in Germany. There was no excess risk of cancer of the testis associated with being classified as having exposure to radar. [A comparison of self-report of exposure with classification by the expert panel showed substantial misclassification from reliance on self-report.]

(b) Cohort study

[Davis & Mostofi \(1993\)](#) reported six cases of cancer of the testis in a cohort of 340 police officers who used hand-held radar guns in the state of Washington, USA. Only one case was expected, based on national data. [The Working Group noted that the finding of the six cases as a cluster had sparked the investigation. Exposure assessments were not made for the full cohort.]

2.1.5 Other cancers

[Armstrong et al. \(1994\)](#) carried out a nested case–control study of the association between exposure to PEMFs and various cancers, including lung (described in Section 2.1.1). An association was observed between exposure to PEMFs and cancer of the lung ([Table 2.6](#)). The highest excess risk was found in cases first exposed 20 years before diagnosis. [The relevance of the measured EMF parameters to exposure to RF radiation was unclear.]

No association of RF radiation with cancer of the lung has been reported in other studies ([Milham, 1988a](#); [Szmigielski, 1996](#); [Tynes et al., 1996](#); [Lagorio et al., 1997](#); [Morgan et al., 2000](#); [Groves et al., 2002](#); [Degraeve et al., 2009](#); described in Section 2.1.1, and [Table 2.6](#)). A later overview by [Szmigielski et al. \(2001\)](#) reported an incidence rate ratio of 1.06 in the population studied by [Szmigielski \(1996\)](#), based on 724 not-exposed cases and 27 exposed cases.

[Tynes et al. \(1996\)](#) (described in Section 2.1.1) studied the impact of exposure to RF radiation (405 kHz to 25 MHz) in an occupational cohort of Norwegian female radio/telegraph operators who had worked at sea for extended periods. There were increased standardized incidence ratios (SIR) for cancers of the breast and uterus ([Table 2.6](#)). A nested case–control analysis for cancer of the breast was performed within this cohort. To control for the possible confounding effect of reproductive history, the investigators linked the cohort to a unique database from

the Norwegian Central Bureau of Statistics that contained information on the reproductive histories of Norwegian women born between 1935 and 1969. After adjusting for duration of employment, the odds ratio for cancer of the breast was 4.3 (95% CI, 0.7–26.0) in women aged ≥ 50 years who had performed a large amount of shift-work (> 3.1 – 20.7 category–years). Adjustment for shift-work and relevant reproductive history reduced the odds ratio for cancer of the breast to 1.1 (95% CI, 0.2–6.1) in those with the longest duration of employment. [The apparent excess risk of cancer of the breast in this cohort, based on high-quality databases and linkage, was not explained by reproductive history and could be potentially attributed to exposure to light at night.]

2.2 Environmental exposure from fixed-site transmitters

Ecological studies are considered to provide a lower quality of evidence than case–control or cohort studies, as they reflect the possibility of uncontrolled confounding and possible misclassification of exposure. With regard to exposure to RF radiation and its association with cancers of the brain, there appears to be little possibility of confounding by anything other than socio-demographic factors associated with diagnostic opportunity. For other cancer sites, confounding may be of greater concern.

Individual measurements of distance from a transmitter as a proxy for exposure are effectively ecological measures, in which the ecological unit includes everyone living at the same distance, or within a restricted range of distances, from the transmitter. Spot measurements will only be partly correlated with total exposure and even a personal exposure meter provides only an approximation of the dose of radiation absorbed by a specific tissue. Measurement of lifetime exposure is problematic regardless of the study design, particularly when there is a high level of

population mobility and measurements of exposure are not readily available for previous areas of residence.

The crucial issue is to what extent the exposure surrogate is associated with the radiation absorbed, since this modulates the statistical power of the study. Some studies have validated correlations between proxy measures, based either purely on distance or on a more sophisticated propagation model. In some cases the correlation has been estimated at approximately 60%, in others it is $< 10\%$, especially when based upon self-report of exposures ([Schmiedel *et al.*, 2009](#); [Viel *et al.*, 2009](#); [Frei *et al.*, 2010](#)). Hence it is difficult to assume that exposure classification based on distance-based proxy measurements is useful, unless validation measurements are included. Detailed modelling of field propagation shows that several parameters are potentially required.

2.2.1 Cancer of the brain

(a) Ecological studies

In several ecological studies, incidence or mortality rates of brain tumours have been compared between defined populations living close to television or radio broadcast stations or other RF radiation fixed-site transmitters or transmission towers.

[Selvin *et al.* \(1992\)](#) undertook a cross-sectional analysis in which the proportion of people aged < 21 years with cancer of the brain diagnosed between 1973 and 1978 living ≤ 3.5 km or > 3.5 km from a large MW transmission tower (Sutro Tower) in San Francisco, USA ($n = 35$) was compared with corresponding proportions from the 1980 USA census. The odds ratio for cancer of the brain and living ≤ 3.5 km from the tower was 1.16 [95% CI, 0.56–2.39]. [No possible confounding factors were considered, nor were the ambient levels of RF radiation in the compared areas documented.]

Table 2.4 Case-control study of uveal melanoma and occupational exposure to radiofrequency radiation

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Stang <i>et al.</i> (2001) Germany, 1995–98	118 (37/81)	475	Population-based study: 327 controls sampled and matched from the same region of residence, age, and sex. Hospital-based study: controls were 148 patients with benign intraocular tumours.	Interviewer-administered structured questionnaire	Uveal melanoma	Radar units Radio set: Ever exposed Exposed ≥ 5 yr before Exposed for ≥ 3 yr	1 9 9 7	0.4 (0.0–2.6) 3.3 (1.2–9.2) 3.3 (1.2–9.2) 2.5 (0.8–7.7)	Age, sex, region, SES, colour of iris and hair	Results of the population-based study (37 cases) and the hospital-based study (81 cases) were pooled.

SES, socioeconomic status; yr, year

Table 2.5 Case-control studies of cancer of the testis and occupational exposure to radiofrequency radiation

[illegible]

Table 2.5 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Baumgardt-Elms <i>et al.</i> (2002) Germany, 1995–97	269	797	Controls were randomly selected from mandatory registries of residents, and matched on age and region (response, 57%).	Interviewer-administered standardized questionnaire	Testicular (170 seminoma and 99 non-seminoma)	Radar units	22	1.0 (0.60–1.75)		Exposure to RF weighted by duration and distance from source
						RF emitters	50	0.9 (0.60–1.24)		
						Radar units				
						0	251	1.0		
						> 0 to ≤ 45	7	1.4 (0.55–3.77)		
						> 45 to ≤ 135	4	0.5 (0.17–1.55)		
						> 135 to ≤ 2225	7	0.9 (0.36–2.19)		
						RF emitters				
						0	220	1.0		
						> 0 to ≤ 6	19	1.0 (0.56–1.74)		
						> 6 to ≤ 15	14	0.7 (0.38–1.35)		
						> 15 to ≤ 102	16	0.9 (0.46–1.56)		

MW, microwave; NR, not reported; RF, radiofrequency radiation

Table 2.6 Cohort studies of cancers of the lung and other sites and occupational exposure to radiofrequency radiation

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Covariates	Comments
Milham (1988a, b) USA	67 829	1979–84	Licensing as an amateur radio operator	Cancer of the respiratory system (160–163)	None	209	SMR, 0.66 (0.58–0.76)		The death rates used to estimate the expected numbers were not specified
Armstrong et al. (1994) Canada and France	191 749	1970–89	Exposures assessed through a job-exposure matrix based on about 1000 person-wks of measurements from exposure meters worn by workers to derive estimates of short-duration PEMFs, or high-frequency transient fields.	Lung cancer (162)	PEMFs < Median > Median ≥ 90th percentile First exposed 0–20 yr before diagnosis: < Median > Median ≥ 90th percentile First exposed > 20 yr before diagnosis: < Median > Median ≥ 90th percentile	200 308 84	OR 1.00 1.27 (0.96–1.68) 3.11 (1.60–6.04)	SES	Nested case-control analysis Controls for each case were selected at random from the cases risk set and matched to the case by utility and year of birth. Exposure was counted only up to the date of diagnosis of the case.
Szmigielski (1996) Poland	Average of 127 800 men, yearly during 15 yr	1971–85	Military safety (health and hygiene) groups classified military service posts as having exposure, or not, to RF	Cancer of the larynx and lung	Occupational exposure to RF Not exposed Exposed	[420]* [13]*	Incidence rate ratios 1.00 1.06 (0.72–1.56)	None specified	Cross-sectional study.
Tynes et al. (1996) Norway	2619 women	1961–91	Radio and telegraph operators with potential exposure to RF and ELF fields	Lung (ICD-7 code 162) Breast (ICD-7 code 170) Uterus (ICD-7 code 172)	Potential exposure Lung Breast Uterus	5 50 12	SIR 1.2 (0.4–2.7) 1.5 (1.1–2.0) 1.9 (1.0–3.2)	Age, time since certification, calendar year, age at first childbirth	Women certified as radio and telegraph operators 1920–80

Table 2.6 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Covariates	Comments
Lagorio et al. (1997) Italy	481 women	1962–92	Occupational history from plant records. RF generated by dielectric heat sealers. Exposure of 10 W/m ² equivalent power-density frequently exceeded.	Lung (162)	<i>Job title</i> RF-sealer operators Other workers All female workers	1 0 1	SMR [5 (1.27–27.85)]* - [3.3]*	Sex, age, calendar period-specific regional person-yr at risk	Mortality analysis; restricted to women
Morgan et al. (2000) USA	195 775	1976–96	Job-exposure matrix, developed through expert consultation that categorized each of 9724 job titles into different RF exposure groups: background, low, moderate, and high, corresponding roughly to < 0.6 W, 0.6 to < 2.0 W, 2.0 to < 5.0 W, 5.0 to < 50 W and ≥ 50 W, respectively.	Respiratory system cancer	<i>RF exposure</i> High and moderate	94	SMR [approx. 0.8]*	Age, sex, and race for external comparisons; and age, sex, and period of hire for internal comparisons	All employees of Motorola; exposure from cellular phones not assessed. Definition of exposure categories unclear

Table 2.6 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Covariates	Comments
Groves et al. (2002) USA	40 581 men (271 women excluded)	1950–97	United States Navy personnel with potential for RF exposure; job classified as having low or high exposure by a consensus of Navy personnel involved in training and operation	Trachea, bronchus and lung (162)	<i>Job-associated exposure to RF</i> Low High	 497 400	SMR 0.87 (0.79–0.94) 0.64 (0.58–0.70)	Age at cohort entry and attained age	White United States Navy (male) veterans of Korean War (1950–54) Reference: all white men, USA
Degraeve et al. (2009) Belgium	Military personnel (4417 men) in battalions equipped with radar, and 2932 controls.	1968–2003	Exposure levels on the site where the battalion lived and worked were characterized; individual exposure assessment could not be conducted.	Respiratory and intra-thoracic organs (160–169)	Control cohort Radar exposed	28 45	1.00 1.07 (0.66–1.71)		Cause of death found for 71% of the men in the radar group and 70% in the control group.

* Values calculated/deducted by the Working Group
ELF, extremely low frequency electric and magnetic field; MW, microwaves; OR, odds ratio; PEMFs, pulsed electromagnetic fields; RF, radiofrequency radiation; SES, socioeconomic status; SIR, standardized incidence ratio; SMR, standardized mortality ratio; W, watt; V, volt; wk, week; yr, year

[Hocking et al. \(1996\)](#) studied incidence and mortality attributable to cancer of the brain (ICD-9 code 191) near three television and FM-radio broadcasting antennae located close together in Sydney, Australia. Exposure from these towers was to amplitude modulation (AM) at 100 kW and frequency modulation (FM) at 10 kW for signals at 63–215 MHz. Calculated power densities of RF radiation ranged from 8.0 $\mu\text{W}/\text{cm}^2$ near the tower to 0.2 $\mu\text{W}/\text{cm}^2$ at a distance of 4 km and 0.02 $\mu\text{W}/\text{cm}^2$ at 12 km. For cancer of the brain at all ages in three “inner ring” municipalities relative to six “outer-ring” municipalities, the rate ratio for incidence was 0.89 (95% CI, 0.71–1.11; 740 cases) and the rate ratio for mortality was 0.82 (95% CI, 0.63–1.07; 606 deaths). [Municipality-specific incidence rates were only available in broad, sex-specific age groups: 0–14, 15–69 and ≥ 70 years]. For children aged 0–14 years, the corresponding rate ratios were 1.10 (95% CI, 0.59–2.06; 64 cases) and 0.73 (95% CI, 0.26–2.10; 30 deaths). All municipalities were said to have upper middle-class populations.

Prompted by reported clustering of leukaemia and lymphoma near a high-power television and FM-radio broadcast antenna in the West Midlands, England, [Dolk et al. \(1997a\)](#) studied the incidence of cancer within a radius of 10 km from the antenna. The authors noted that available field-strength measurements generally showed a decrease of the average field strength with increasing distance from the transmitter, although with undulations in predicted field strength up to about 6 km from the transmitter. The maximum total power-density equivalent summed across frequencies at any one measurement point was 0.013 W/m^2 for television, and 0.057 W/m^2 for FM radio. Observed numbers of cases within 0–2 km and 0–10 km of the antenna were compared with “national” incidence rates, adjusted for age, sex, year and deprivation quintile (calculated based on data on unemployment, overcrowding, and social class of head of

household). For all tumours of the brain (ICD-8/ICD-9 codes 191, 192, 225, and ICD-9 codes 237.5, 237.6, 237.9) in persons aged ≥ 15 years, the SIR was 1.29 (95% CI, 0.80–2.06) within 0–2 km and 1.04 (95% CI, 0.94–1.16) within 0–10 km. For malignant tumours of the brain only, these SIRs were 1.31 (95% CI, 0.75–2.29) and 0.98 (95% CI, 0.86–1.11), respectively.

[Dolk et al. \(1997b\)](#) undertook a similar analysis of cancer incidence in proximity to all 20 other high-power radio and television transmitter antennae in the United Kingdom. [With one exception, information about field distribution and strength in proximity to those antennae was not provided.] In this analysis, results for tumours of the brain were reported only for children aged 0–14 years and in proximity to all 21 such antennae (including that studied by [Dolk et al., 1997a](#)). At 0–2 km from the antenna, SIRs were 0.62 (95% CI, 0.17–1.59) for all tumours of the brain and 0.50 (95% CI, 0.10–1.46) for malignant tumours, while at 0–10 km SIRs were 1.06 (95% CI, 0.93–1.20) and 1.03 (95% CI, 0.90–1.18), respectively.

[Ha et al. \(2003\)](#) studied the incidence of cancer between November 1993 and October 1996 in people aged ≥ 10 years in populations of 11 administrative areas of the Republic of Korea within about 2 km of high-power (≥ 100 kW) AM transmitter antennae, 31 such areas within about 2 km of low-power AM transmitter antennae (50 kW), and 4 control areas near, but not within 2 km, of each high-power transmitter antenna (44 control areas in total). Incident cases of cancer were ascertained from medical insurance records [no information was given regarding the completeness and accuracy of these records]. Directly age-standardized incidence rate ratios for cancer of the brain (ICD-9 codes 191–192, and ICD-10 codes C70–C72) comparing people living near high-power transmitter antennae with people living near low-power antennae were 1.8 (0.9–11.1) in males and females combined. Indirectly age-standardized incidence rate

ratios for cancer of the brain comparing people living near high-power transmitter antennae at different levels of power output with those in control areas were 2.27 (95% CI, 1.30–3.67) for a power output of 100 kW, 0.86 (95% CI, 0.41–1.59) for 250 kW, 1.47 (95% CI, 0.84–2.38) for 500 kW, and 2.19 (95% CI, 0.45–6.39) for 1500 kW.

[Park et al. \(2004\)](#) reported the results of a similar study of cancer mortality in 1994–95 in people of all ages in the Republic of Korea. Mortality rates within an area of 2 km surrounding AM broadcasting towers with a power of > 100 kW were compared with those in control areas that had a similar population and were located in the same province as the matched exposed area. Information on deaths due to cancer was identified in Korean death certificates from 1994 to 1995. The resident population at that time was assumed to correspond to that recorded in the nationwide population census of 1990. To control for possible selection bias, four control areas ($n = 40$) were matched to each exposed area ($n = 10$). Based on six age groups, annual age-adjusted world population-standardized mortality rates were calculated per 100 000 residents. Mortality rate ratios (MRR) were calculated comparing 10 areas within about 2 km of high-power antennae with 40 areas situated > 2 km from high-power antennae in the same or neighbouring provinces. The directly standardized MRR for cancer of the CNS, comparing areas near high-power antennae with control areas, was 1.52 (95% CI, 0.61–3.75).

The incidence of cancer in relation to mobile-phone base-station coverage was investigated in 177 428 people living in 48 municipalities in Bavaria, Germany, between 2002 and 2003 ([Meyer et al., 2006](#)). Municipalities were classified on a crude three-level exposure scale based on the operating duration of each base station and the proportion of the population living within 400 m of the base station. Based on 1116 malignant tumours in 242 508 person-years, no indication of an overall increase in the incidence of cancer

was found in the populations of municipalities belonging to the highest exposure class. The Potthoff-Whittinghill test was used to examine the homogeneity of the case distribution among the communities. The following cancers were not found to be heterogeneously distributed: breast ($P = 0.08$); brain and CNS ($P = 0.17$); and thyroid ($P = 0.11$). For leukaemia, there were indications of underreporting and thus the test for homogeneity was not performed. [The exposure assessment in this study was very crude and likely to result in substantial random exposure misclassification. The number of organ-specific tumours was not reported, but is expected to be small given the total number of tumours. Thus, the observed absence of an association may be real, or due exposure misclassification, or to inadequate statistical power.]

(b) Case-control studies

[Schüz et al. \(2006b\)](#) reported on the association of proximity of a DECT (Digital Enhanced Cordless Telecommunications) cordless-phone base station to a person's bed (a proxy for continuous low-level exposure to RF radiation during the night) with the risk of brain glioma and meningioma in a case-control study in Germany that was a component of the INTERPHONE study. This was a subanalysis of the main study in which no association of either brain glioma or meningioma with use of cordless phones had been found ([Schüz et al., 2006a](#)). Cases were newly diagnosed with a histologically confirmed glioma or meningioma in 2000–03, aged 30–69 years, lived in the study region, had a main residence in the study region, and had a knowledge of German sufficient for interview. Proxy interviews were conducted if the cases or controls had died or were too ill for interview. Controls were selected randomly from compulsory population registers in the study regions, were required to meet relevant case-inclusion criteria, and were initially frequency-matched to the cases by age, sex and region. Participation rates were: patients

with glioma, 79.6%; patients with meningioma, 88.4%; and controls, 62.7%. Interview questions about cordless phones addressed the type of phone (DECT or analogue), make and model, the dates on which use started and stopped, and the location of the base station within the residence. Since many subjects could not recall whether their cordless phone was a DECT phone, information on the make, model and price of the phone and its technical features were used to classify phones into “definitely” or “possibly” DECT, or definitely analogue. Participants were considered definitely or possibly exposed if, in addition, the DECT base station was located 3 m or less from the bed (this was the case for 1.6% of participants). Information from proxy interviews (patients with glioma, 10.9%; patients with meningioma, 1.3%; and control participants, 0.4%) was used in the analysis, since most proxies lived with their index subjects and were users of the same cordless phones. For analysis, controls were individually matched 2 : 1 to cases by birth year, sex, region and date of diagnosis (case) or interview (control); 366 cases of glioma and 381 cases of meningioma were analysed. Risk of glioma or meningioma was not increased with definite or possible exposure to DECT base stations; nor was there any consistent trend with time since first exposure ([Table 2.7](#)). [This study was limited by the small proportion of people who were considered to be exposed, difficulty in classifying cordless phones as DECT or analogue, and lack of associated consideration of other sources of exposure to RF radiation.]

[Ha et al. \(2007\)](#) reported on risk of childhood cancers of the brain in relation to residential exposure to RF radiation from AM-radio fixed-site transmitters (power, > 20 kW) in the Republic of Korea. Cases were diagnosed with cancer of the brain (ICD-9 codes 191–192, and ICD-10 codes C70–C72) between 1993 and 1999, and controls were diagnosed over the same period with a respiratory disease (ICD-9 codes 469–519, and ICD-10 codes J20 and J40–J46). Both cases

and controls were identified through the national health insurance system of the Republic of Korea, and individually matched by age, sex and year of first diagnosis. Both were restricted to children diagnosed at one of fourteen large cancer or tertiary-care hospitals. Cancer diagnoses were confirmed by reference to the national cancer registry or hospital medical records [the basis for confirmation was not stated]. Cases were excluded if the diagnosis of cancer could not be confirmed; controls were excluded if they had a history of cancer recorded in the national cancer registry (which was 80% complete in 1998); and both were excluded if they had incomplete addresses (which were obtained from the medical records). The distance from each subject’s residence to the nearest AM-radio transmitter established before diagnosis was evaluated by means of a geographical information system, and total exposure to RF radiation from all AM-radio fixed-site transmitters was estimated with a flat-earth attenuation statistical-prediction model, which took into account features of the receiving point and the propagating pathway [intervening terrain, the output power of the fixed-site transmitters and their distance from the receiving point]. The prediction program was validated by taking measurements of field strength at sites around 11 fixed-site transmitters, and correction coefficients were calculated and applied to the prediction program. Twenty-nine of the thirty-one radio fixed-site transmitters were established between 1980 and 1995, and children in the study were born between 1978 and 1999. Socioeconomic status was classified according to the number of cars owned per 100 people in defined regions and population density in these regions was used as a surrogate for industrialization and environmental pollution. The odds ratio for cancer of the brain was not materially increased in those living closest (≤ 2 km) to a transmitter (OR, 1.42; 95% CI, 0.38–5.28) or in those with greatest estimated exposure (≥ 881 mV/m) to RF radiation (OR, 0.77; 95% CI, 0.54–1.10) ([Table 2.7](#)). [This

Table 2.7 Case-control studies of cancer of the brain and environmental exposure to radiation from transmitters of radiofrequency signals

Reference, study location and period	Total cases	Total controls	Control source (hospital, Population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Comments
Schüz et al. (2006b) Bielefeld, Heidelberg, Mainz, Mannheim, Germany, 2000–03	747	1494	Population	Interviewer-administered questionnaire	Brain (glioma and meningioma)	DECT cordless-phone base station ≤ 3m from bed			Covariates: age, sex, region, educational level
					Glioma				
					Definitely		342	1.00	
					No				
					Yes		3	0.50 (0.14–1.76)	
					Possibly or definitely				
					No		342	1.00	
					Yes		5	0.82 (0.29–2.33)	
					Time since first exposure (possibly or definitely)				
					No, < 1 yr		342	1.00	
					1–4 yr		3	0.95 (0.24–3.70)	
					≥ 5 yr		2	0.68 (0.14–3.40)	
					Meningioma				
					Definitely				
					No		360	1.00	
					Yes		5	1.09 (0.37–3.23)	
					Possibly or definitely				
					No		364	1.00	
					Yes		5	0.83 (0.29–2.36)	
					Time since first exposure (possibly or definitely)				
					No, < 1 yr		364	1.00	
					1–4 yr		1	0.33 (0.04–2.80)	
					≥ 5 yr		4	1.29 (0.37–4.48)	

Table 2.7 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, Population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Comments
Ha et al. (2007) Republic of Korea, 1993–99	956	1020	Hospital-based study. Controls had attended one of 14 large cancer or tertiary care hospitals where the cases had been diagnosed, for management of respiratory disease (ICD-9 469–519; ICD-10 J20 and J40–46). Controls were individually matched to a case by age, sex, and year of first diagnosis.	Based on locations of 31 AM transmitters of ≥ 20 kW and 49 associated antennae and locations of subjects' residences at time of diagnosis.	Brain (ICD-9 code 191–192; ICD-10 codes C70–C72)	Distance from nearest AM radio-transmitter established before subject's year of diagnosis (km) ≤ 2 $> 2-4$ $> 4-6$ $> 6-8$ $> 8-10$ $> 10-20$ > 20 Unknown <i>P</i> (trend)	All brain cancer (age < 15 yr) 10 32 59 90 114 244 400 7 0.76	 1.42 (0.38–5.28) 1.40 (0.77–2.56) 1.02 (0.66–1.57) 1.08 (0.73–1.59) 0.94 (0.67–1.33) 1.01 (0.77–1.34) 1.00 (reference) 4.30 (0.50–36.73) 0.76	Children aged < 15 yr. The use only of large hospitals for ascertainment of controls are not representative of population from which cases were drawn. Covariates: age, sex, residential location, population density, SES
<i>Total exposure to RF (mV/m)</i>									
< 532.55*							329	1.00 (reference)	*Quartiles of the distribution
532.55 – < 622.91							185	0.66 (0.47–0.92)	
622.91 – < 881.07							181	0.72 (0.51–1.01)	
≥ 881.07							254	0.77 (0.54–1.10)	
<i>P</i> (trend)								0.73	

Table 2.7 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, Population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Comments
Haefel et al. (2007) (cont.)						<i>Distance from nearest AM radio-transmitter established before subject's year of diagnosis (km)</i>	All brain cancer (age < 1 yr)		
						≤ 10	10	0.41 (0.05–3.10)	
						> 10–20	10	0.49 (0.06–3.80)	
						> 20	12	1.00 (reference)	
						<i>P</i> (trend)		0.78	
						<i>Total exposure to RF (mV/m)</i>			
Oberfeld (2008) Hausmannstätten & Vasoldsberg, Austria, 1984–97						< 485.85*	9	1.00 (ref.)	
						485.85 – < 632.96	7	3.56 (0.49–25.95)	
						632.96 – < 810.81	7	1.41 (0.12–17.11)	
						≥ 810.81	9	5.13 (0.44–60.26)	
						<i>P</i> (trend)		0.27	

The status of this study (printed version, German and English online versions) is controversial. It was therefore decided to remove the description of this study from text and tables.

Table 2.7 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, Population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Comments
Spinelli et al. (2010) Western Provence-Alpes-Côte d'Azur (PACA), France, 2005	122	122	Hospital-based	Self-administered questionnaire and face-to-face interview, including lifetime job history, job title, dates, tasks	Brain (glioma grades II–IV)	Residence within 500 m of: Cell-phone tower	19	0.49 (0.26–0.92)	Covariates: age, sex
Elliott et al. (2010) United Kingdom, 1999–2001	251	1004	Population-based study. Controls were children aged < 4 yr, individually matched to cases by sex and date of birth.	Location of birth residence relative to nearby macro-cell mobile-phone base stations; distance to nearest base station; total power output of all base-stations within 700 m; modelled power density at birth address	Brain and CNS (ICD-10 codes C71–C72)	Distance from nearest macro-cell mobile-phone base-station Lowest third Intermediate third Highest third For 15th to 85th centile increase (continuous measure) Total mobile-phone frequency power-output (kW) No base station within 700 m Lower half Upper half For 15th to 85th centile increase (continuous measure)	85 85 81 251	1.00 0.95 (0.67–1.34) 0.95 (0.65–1.38) 1.12 (0.91–1.39)	Covariates: percentage of population with education to degree level or higher, Carstairs score (a composite area-deprivation measure), population density, and population mixing (percentage immigration into the area over the previous year).

Table 2.7 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, Population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Comments
Elliott <i>et al.</i> (2010) (contd.)						<i>Modelled mobile-phone frequency power density (dBm)</i>			
						Lowest third	93	1.00	
						Intermediate third	80	0.97 (0.69–1.37)	
						Highest third	78	0.76 (0.51–1.12)	
						For 15th to 85th centile increase (continuous measure)	251	0.82 (0.55–1.22)	

AM, amplitude modulation (radio); CNS, central nervous system; DECT, Digital Enhanced Cordless Telecommunications; kW, kilowatt; NMT, Nordic Mobile Telephone (standard); RF, radiofrequency radiation; SES, socioeconomic status; Yr, year

study was limited by the lack of a clear population base, possible mismatch between the population sampled for cases and that sampled for controls, and the lack of a cumulative measure of exposure to RF radiation that took into account variation in an individual's place of residence between birth and diagnosis of cancer or respiratory disease.]

[[Oberfeld \(2008\)](#): the status of this study (printed version, German and English online versions) is controversial. It was therefore decided to remove the description of this study from text and tables.]

[Spinelli et al. \(2010\)](#) undertook a pilot case-control study of newly diagnosed, histopathologically confirmed malignant primary tumours of the brain (defined as previously untreated glioma, grades II–IV) in people aged ≥ 18 years treated in the two principal referral hospitals for cancer of the brain in the west of the Provence-Alpes-Côte d'Azur (PACA) region in France. Controls were other patients in the neurosurgery department who were hospitalized for reasons other than cancer (mainly herniated intervertebral disc, intracranial aneurysm, trauma, and epidural haematoma) who were individually matched to cases by age, sex and residence in the west of PACA. Participants completed a self-administered questionnaire and were interviewed by an occupational physician at the hospital they attended within 3 months after surgery; the physician also checked their questionnaire. [It was not stated whether the interviewer was blind to the case or control status of participants.] Family members also helped with self-administered questionnaires, more often for cases than controls. Proxy interviews were completed for 2% of cases. Occupational exposures were the principal focus of the questionnaire and interview, but participants were also asked about use of mobile phones and residence in proximity to a mobile-phone tower. Information was obtained from 75.3% of cases [the participation rate of controls was not stated]. Nineteen cases and thirty-three

controls reported a mobile-phone tower within 500 m of their residence (age- and sex-adjusted OR, 0.49; 95% CI, 0.26–0.92) ([Table 2.7](#)). [This study was limited by its small size and because it was hospital-based. The participation rate for controls was not stated and it is likely that people prone to serious injury were over-represented among the controls. The interviewer may not have been blind to the case or control status of participants. Specific questions regarding proximity of residence to mobile-phone towers were not described and may have been highly prone to recall error, and there were few participants with occupational exposure to RF radiation.]

[Elliott et al. \(2010\)](#) undertook a case-control study of early childhood cancer in the United Kingdom based on all cases of cancer in children aged 0–4 years registered in 1999–2001. Of 1926 registered cases, the geographical coordinates of addresses at birth, and exposure based on the birth address were available for 1397 children (73%). Of the latter, 251 had cancers of the brain and CNS (ICD-10 codes C71–C72). For each case, four controls from the national birth register, with complete birth addresses and individually matched to cases by sex and date of birth (5588 controls), were obtained from 6222 originally randomly selected (90%). The four national mobile-phone operators provided detailed data on all 76 890 macro-cell base stations operating in 1996–2001. Three exposure measures for the birth address of each case and control were obtained: the distance from the nearest macro-cell mobile-phone station; the total power output (kW) from summation across all base stations within 700 m; and computed modelled power density (dBm) at each birth address for base stations within 1400 m. Exposures beyond 1400 m were considered to be at background levels. Measurements from field campaigns in a rural and an urban area were used to set parameter values in the power-density model. The models were validated with data from two further surveys and power-density measurements from 620 locations

across the country. Spearman's correlation coefficients between measured power density and the exposure measures were: 0.66 with modelled power density, 0.72 with distance from nearest base station, and 0.66 with total power output. The exposure measures estimated at each birth address were averaged across monthly estimates for the assumed 9 months of the pregnancy in each case. Each exposure measure was divided into thirds of the distribution across all cases and controls except for total power output, which was zero for 58% (no base station within 700 m), with the remaining 42% in two halves of their distribution. Exposure measures were fitted to models as continuous variables as well as in the above categories. Neither unadjusted nor partly or fully adjusted odds ratios suggested that risk of childhood cancer of the brain increased with increasing exposure to RF radiation from nearby macro-cell mobile-phone base stations ([Table 2.7](#)). [This study was limited by the fact that estimation of exposure was confined to the gestational period; application of birth address to the whole of gestation was assumed; and ecologically measured possible confounding variables were used to apply to individual subjects.]

(c) Cohort studies

No data were available to the Working Group.

2.2.2 Leukaemia and lymphoma

(a) Ecological studies

See [Table 2.8](#)

[Hocking et al. \(1996\)](#) published a study comparing incidence of and mortality from leukaemia during 1972–90 in nine municipalities, three of which were located around television towers and six that were more distant. Increased rate ratios for incidence (IRR, 1.24; 95% CI, 1.09–1.40) and mortality (MRR, 1.17; 95% CI, 0.96–1.43) for leukaemia at all ages were obtained and generally higher rate ratios were seen for childhood leukaemia (IRR, 1.58; 95%

CI, 1.07–2.34; MRR, 2.32; 95% CI, 1.35–4.01) than for leukaemia at all ages, comparing the three “inner ring” municipalities with six “outer ring” municipalities. A more marked association was observed between proximity to television towers and mortality (MRR, 2.4; 95% CI, 1.4–3.7) than incidence (IRR, 1.8; 95% CI, 1.2–2.5) from leukaemia. [No individual measurements were undertaken and main analyses could only be adjusted for covariates by group-level (aggregated) data.]

In 1997, [Dolk et al.](#) published two studies on cancer incidence during 1974–86. The first was a study in a small area in response to an unconfirmed report of a cluster of leukaemias and lymphomas near the Sutton Coldfield television and radio-transmitter in the West Midlands, England ([Dolk et al., 1997a](#)). The second, to place in context the findings of the Sutton Coldfield study, was carried out near 20 high-power television and radio-transmitters in the United Kingdom ([Dolk et al., 1997b](#)). In the Sutton Coldfield study, an increased risk of leukaemia in adults was found when the observed and expected numbers of cases (derived from national incidence rates) were compared (observed/expected, 1.83; 95% CI, 1.22–2.74) within 2 km of the transmitter and there was a decline in risk with distance (Stone's P value = 0.001). The latter was tested by use of 10 bands of increasing distance from the transmitter within a circle with a radius of 10 km around it. The findings appeared to be consistent between 1974 and 1980, and 1981 and 1986. For NHL, a suggestion of a decrease in risk was seen within the 2 km area (observed/expected, 0.66; 95% CI, 0.28–1.30) while for the total study area of 0–10 km, risk appeared to be increased (observed/expected, 1.23; 95% CI, 1.11–1.36). In the second study, covering the United Kingdom ([Dolk et al., 1997b](#)), evidence of a decline in risk of leukaemia was found with increasing distance from the transmitter (Stone's P value = 0.05); however, the magnitude (at 0–10 km: observed/expected, 1.03; 95% CI, 1.00–1.07) and the pattern

Table 2.8 Ecological studies of leukaemia and lymphoma and environmental exposure to radiation from transmitters of radiofrequency signals

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Covariates	Comments
Hocking <i>et al.</i> (1996) Australia	585 000	1972–90	Residential proximity to TV towers	Leukaemia (204–208)	Overall rate ratios for incidence and mortality, respectively, inner and outer residential area compared. Inner area <i>vs</i> ref. population Outer area <i>vs</i> ref. population Inner area <i>vs</i> ref. population Outer area <i>vs</i> ref. population	1206/847	Incidence, 1.24 (1.09–1.40) Mortality, 1.17 (0.96–1.43)	Age, sex, calendar period	Reference population: whole of New South Wales
Dolk <i>et al.</i> (1997a) United Kingdom	Around 408 000	1974–86	Distance to Sutton Coldfield radio and TV transmitter	Haemato-poietic and lymphatic cancers (200–202; 203 + 238.6; 204–208)	Distance 0–2 km Distance 0–10 km Stone's <i>P</i> -value	45 935	1.21 (0.91–1.62) 1.04 (0.98–1.11) Unconditional <i>P</i> = 0.153	Region	Observed/expected ratios and Stone's <i>P</i> -value are given for persons aged ≥ 15 yr, stratified by age, sex, year, and SES. Declining risk with increasing distance was seen only for all leukaemias.
				Leukaemia (204–208)	Distance 0–2 km Distance 0–10 km Stone's <i>P</i> -value	23 304	1.83 (1.22–2.74) 1.01 (0.90–1.13) Unconditional <i>P</i> = 0.001 Conditional <i>P</i> = 0.001		
				NHL	Distance 0–2 km Distance 0–10 km Stone's <i>P</i> value	8 357	0.66 (0.28–1.30) 1.23 (1.11–1.36) Unconditional <i>P</i> = 0.005 Conditional <i>P</i> = 0.958		

Table 2.8 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Covariates	Comments
Dolk <i>et al.</i> (1997b) United Kingdom	Around 3 390 000	1974–86	Distance to radio and television transmitters in the United Kingdom (excluding Sutton Coldfield)	Leukaemia (204–208)	Distance 0–2 km Distance 0–10 km Stone's <i>P</i> value	79 3 305	0.97 (0.78–1.21) 1.03 (1.00–1.07) Unconditional <i>P</i> = 0.001 Conditional <i>P</i> = 0.052	Region	Observed/expected ratios and Stone's <i>P</i> value are given for persons aged ≥ 15 yr, stratified by age, sex, year, and SES.
Cooper <i>et al.</i> (2001) United Kingdom	NR	1987–94	Distance to Sutton Coldfield television transmitter	Leukaemia (204–208)	Distance from transmitter: 0–2 km, all ages, all persons 0–10 km, all ages, all persons Stone's <i>P</i> values, all ages, all persons 0–2 km, age 0–14 yr, all persons 0–10 km, age 0–14 yr, all persons Stone's <i>P</i> values, age 0–14 yr, all persons	20 333 1 26	1.32 (0.81–2.05) 1.16 (1.04–1.29) Unconditional <i>P</i> = 0.038 Conditional <i>P</i> = 0.409 1.13 (0.03–6.27) 1.08 (0.71–1.59) Unconditional <i>P</i> = 0.420	-	Observed/expected ratios and Stone's <i>P</i> values (unconditional and conditional) are given. Stratified by age, sex, and social deprivation. Results for other haematopoietic cancers are reported in the manuscript.

Table 2.8 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Covariates	Comments
Michelozzi et al. (2002) Italy	49 656	1987–99	Distance to Vatican radio station, Rome	Leukaemia (204–208)	Distance from radio station (km), (cumulative areas)			Deprivation index	
					Total (age > 14 yr)		SMR		
					0–2	2	1.8 (0.3–5.5)		
					0–4	11	1.5 (0.8–2.6)		
					0–6	23	1.2 (0.8–1.8)		
					0–8	34	1.2 (0.8–1.6)		
					0–10	40	1.1 (0.8–1.4)		
					P, Stone's conditional test		0.14		
					Children (age 0–14 yr)		SIR		
					0–2	1	6.1 (0.4–27.5)		
					0–4	3	2.9 (0.7–7.6)		
					0–6	8	2.2 (1.0–4.1)		
					0–8	8	1.5 (0.7–2.7)		
					0–10	8	1.2 (0.6–2.3)		
					P, Stone's conditional test		0.036		

Table 2.8 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Covariates	Comments
Ha <i>et al.</i> (2003) Republic of Korea	From 3 152 to 126 523 persons per area (total not given)	1993–96	Distance ≤ 2 km from AM transmitter	Leukaemia (204–208)	High-power (≥ 100 kW) vs low-power (50 kW) transmitter sites:		Rate ratio	Age	Rate ratios (RR) and observed/expected (O/E) ratios are given For all cancers combined: RR, 1.2 (95% CI, 1.1–1.4) for high- vs low-power transmitters
					Men	8.3/6.8 per 100 000 person-yr	1.2 (0.5–5.3)		
					Women	8.7/4.6 per 100 000 person-yr	1.9 (0.8–8.7)		
					Total	8.5/5.7 per 100 000 person-yr	1.5 (0.7–6.6)		
					Transmitter power of sites:		O/E		
					100 kW	9	1.20 (0.55–2.28)		
					250 kW	12	2.45 (1.27–4.29)		
					500 kW	10	0.65 (0.31–1.19)		
					1500 kW	4	4.26 (1.16–10.89)		

Table 2.8 (continued)

Reference, study location	Total No. of subjects	Follow- up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Ha et al. (2003) (contd.)				Malignant lymphoma (200–202)	<i>High-power</i> (≥ 100 kW) vs <i>low-power</i> (50 kW) transmitter sites:		<i>Rate ratio</i>		
					Men	10.5/7.1 per 100 000 person- year	1.5 (0.7–8.6)		
					Women	8.7/7.1 per 100 000 person- year	1.2 (0.6–5.6)		
					Total	9.6/7.1 per 100 000 person- year	1.4 (0.6–7.0)		
					<i>Transmitting power of sites:</i>		<i>O/E</i>		
					100 kW	9	1.10 (0.51–2.10)		
					250 kW	13	1.28 (0.68–2.19)		
					500 kW	16	0.98 (0.56–1.59)		
					1 500 kW	1	0.44 (0.01–2.48)		

Table 2.8 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Covariates	Comments
Park <i>et al.</i> (2004) Republic of Korea	8 115 906 (of whom 1 234 123 in exposed area)	1994–95	Regions including AM-radio broadcasting towers of > 100 kW	Leukaemia (ICD-10 codes C90–95), including multiple myeloma	Total exposed	55	1.70 (0.84–3.45)	Age	Direct standardized MRRs are given
					<i>vs</i> control (unexposed)				
					Males	33	1.89 (0.75–4.75)		
					Females	22	1.55 (0.52–4.68)		
					<i>Age (yr)</i>				
					0–14	11	2.29 (1.05–5.98)		
					15–29	11	2.44 (1.07–5.24)		
					30–44	9	2.16 (0.95–4.04)		
					45–59	5	0.73 (0.48–2.89)		
					60–74	10	0.87 (0.57–2.78)		
					≥ 75	6	3.08 (0.95–6.59)		
					Total exposed	31	1.60 (0.72–3.56)		
					<i>vs</i> control (unexposed)				
					Males	19	1.52 (0.56–4.14)		
					Females	12	1.80 (0.48–6.71)		
					<i>Age (yr)</i>				
					0–14	1	2.46 (0.07–82.66)		
					15–29	2	1.51 (0.15–15.18)		
					30–44	5	1.94 (0.37–10.20)		
					45–59	8	1.76 (0.43–7.15)		
					60–74	13	1.41 (0.47–4.14)		
					≥ 75	2	0.55 (0.05–5.67)		

AM, amplitude modulation (radio); kW, kilowatt; MRR, mortality rate ratio; NR, not reported; O/E, observed/expected; SIR, standardized incidence ratio; SMR, standardized mortality ratio; TV, television; *vs*, versus; yr, year

of risk seen in the Sutton Coldfield study could not be replicated. Most notably, in the second, nationwide study no increase in risk was seen nearest (within 2 km) the transmitters.

In a letter to the editor, [Cooper et al. \(2001\)](#) published updated results on adult and childhood leukaemia (1987–94) near the Sutton Coldfield transmitter. To investigate risk according to distance, the authors defined the study area as a series of 10 concentric circles around the Sutton mast and calculated the expected number of cases (by numbers, child/adult and sex) for each of the circles and for different cancer sites. Most results for childhood cancers gave no evidence of a decline in the ratios of observed-to-expected numbers of cases with distance from the transmitter. There was some support for a decline in risk of childhood leukaemia in males, as indicated by Stone's test. The risk also declined for acute myeloid leukaemia in adult females, for all leukaemias (females and all persons separately), and for haematopoietic and lymphatic cancers in females. The same four groups were at higher risks over the whole study area (0–10 km). An increased risk was found for acute lymphatic leukaemia within 2 km of the transmitter; however this was based on only two cases. Elevated risks were found for leukaemias and NHL (males and females combined and separately) over the whole study area. No increase or decrease in the ratios of observed-to-expected numbers of cases was seen for NHL.

[Michelozzi et al. \(2002\)](#) published a study on incidence and mortality for adult and childhood leukaemia in an area of 10 km around a high-power radio station in Rome. This station had numerous transmitters with different transmission powers (5–600 kW) operating at different frequencies (short–medium wave). An increased incidence of childhood leukaemia (SIR, 2.2; 95% CI, 1.0–4.1) was found up to 6 km from the radio station; there was a decline with increasing distance from the station for mortality in males and for incidence from childhood leukaemia.

[The small number of cases, possible unmeasured confounding and lack of individual or calculated exposure assessment were some limitations of the study.]

[Ha et al. \(2003\)](#) published a study on the incidence of cancer in the Republic of Korea in 1993–96 in areas proximate to 42 AM-radio-transmitters, characterized by transmission power. An increased rate ratio comparing sites exposed to high-power versus low-power transmitters was seen for all cancers combined (rate ratio, 1.2; 95% CI, 1.1–1.4), while confidence intervals by cancer type were wide, e.g. for leukaemia (rate ratio, 1.5; 95% CI, 0.7–6.6) and malignant lymphoma (rate ratio, 1.4; 95% CI, 0.6–7.0). However, at two of eleven high-power sites, more pronounced increases in the incidence of leukaemia were found. [Interpretation was hampered by limitations related to the ecological design, study size, exposure and outcome assessment, and lack of controls for confounding. There was partial overlap in the populations included in [Park et al. \(2004\)](#) and [Ha et al. \(2007\)](#).

[Park et al. \(2004\)](#) published a study that evaluated cancer mortality in the Republic of Korea in relation to exposure to AM-radio-transmitters. Mortality from leukaemia was higher in exposed areas than in control areas (standardized mortality rate ratio, MRR, 1.70; 95% CI, 0.84–3.45), particularly among young adults (MRR, 2.44; 95% CI, 1.07–5.24), but also in children (MMR, 2.29; 95% CI, 1.05–5.98). According to the authors, however, there was no increasing or decreasing trend with respect to broadcasting power. [In this study, exposure assessment was poor (no individual data) and it was also unclear to what extent the mortality records reflected the true address of the subject, which was used as a proxy for exposure. Other limitations were the lack of control for confounding by socioeconomic status, and possible non-differential disease misclassification.]

(b) *Case-control studies*

See [Table 2.9](#)

[Maskarinec et al. \(1994\)](#) published the results of a small case-control study that indicated an increased incidence in childhood leukaemia (SIR, 2.09; 95% CI, 1.08–3.65) near radio towers in Hawaii, USA. The SIR for acute lymphocytic leukaemia was 1.58 (95% CI, 0.63–3.26) and for acute non-lymphocytic leukaemia it was 3.75 (95% CI, 1.20–8.71). Seven cases of leukaemia had been reported during 1982–84, including all five cases of acute non-lymphocytic leukaemia (SIR, 5.34; 95% CI, 2.14–11.0) that were unusual with respect to sex, age, and type of leukaemia. Twelve cases in children aged < 15 years diagnosed with acute leukaemia in 1979–90 and residing in certain census tracts before diagnosis were included in the case-control study, along with 48 (80%) sex- and age-matched controls that lived in the same area at the time of diagnosis. Collection of data was by non-blinded telephone interviews with parents, which included questions on pregnancy, address, and residence history, the child's medical history and exposure of various kinds, including X-rays and smoking. In addition, the occupational history of both parents was recorded, together with potentially relevant exposures. The odds ratio for acute leukaemia among those having lived within 2.6 miles (4.2 km) of the radio towers before diagnosis was increased (OR, 2.0; 95% CI, 0.6–8.3). [The limitations of this study, besides poor assessment of exposure, were its low power to detect an effect (~50% for OR = 5) and the apparent lack of controls for confounding by socioeconomic status.]

[Ha et al. \(2007, 2008\)](#) published the results of a case-control study that was large enough to give moderate statistical power for detecting an effect of exposure to RF radiation on the risk of childhood leukaemia. Patients aged < 15 years with leukaemia and controls with respiratory illnesses were selected from 14 hospitals in the

Republic of Korea and matched on age, sex and year of diagnosis (1993–99). From a total of 1928 cases of leukaemia and matched controls, risks were estimated by means of conditional logistic regression analysis adjusted for residential area, socioeconomic status and community population density. An increased risk of all types of leukaemia was found among children who lived within 2 km of the nearest AM-radio-transmitter (OR, 2.15; 95% CI, 1.00–4.67). For total exposure to RF radiation, most odds ratios decreased with predicted exposure. The authors reported an odds ratio of 1.40 (95% CI, 1.04–1.88) for lymphocytic leukaemia and 0.63 (95% CI, 0.41–0.97) for myelocytic leukaemia in the quartile of highest peak exposure, although no linear trend was evident with regard to the different exposure categories for total or peak exposure to RF radiation. [The main limitations of the study were related to the exposure estimates calculated by the prediction programme, e.g. the existence of buildings or irregular geographical features was not considered, nor was individual cumulative-exposure history assessed. There was partial overlap in the populations included in [Ha et al. \(2003\)](#) and [Park et al. \(2004\)](#).]

A case-control study on RF radiation and childhood leukaemia was conducted in west Germany by [Merzenich et al. \(2008\)](#). Cases (age, 0–14 years) diagnosed during 1984–2003 and registered at the German Childhood Cancer Registry were included, along with three age-, sex- and transmitter-area-matched controls per case that were drawn randomly from population registries. The analysis included 1959 cases and 5848 controls for which individual exposure to RF radiation 1 year before diagnosis was estimated by means of a field-strength prediction program. The study area encompassed municipalities in the vicinity of Germany's strongest transmitters, including 16 AM and 8 FM transmitters with a power of at least 20 kW. Conditional logistic regression analysis for all types of childhood leukaemia yielded no increase in odds ratio (OR,

Table 2.9 Case-control studies of leukaemia and lymphoma and environmental exposure to radiation from transmitters of radiofrequency signals

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comment
Maskarinec et al. (1994) Hawaii, USA, 1984–2003	12	48	Hospital	Having lived within 2.6 miles of low-frequency radio towers. Distances estimated both manually and by use of a geographical software package	Acute leukaemia (7 ALL, 5 ANLL)	Last residence before diagnosis within 2.6 miles [4.2 km] of radio towers. Residence at birth within 2.6 miles of radio towers	8	2.0 (0.6–8.3)		Matched ORs are given; matching variables: age, sex
Ha et al. (2007) Republic of Korea, 1993–99	1928	3082	Hospital	Prediction program incorporating a geographic information system	All leukaemia (204–208)	Distance (km) > 20 ≤ 2 > 2–4 > 4–6 > 6–8 > 8–10 > 10–20 Unknown P for trend	772 36 73 120 218 276 428 5	1.00 2.15 (1.00–4.67) 0.66 (0.44–0.99) 1.07 (0.77–1.49) 1.26 (0.96–1.65) 1.10 (0.85–1.41) 0.80 (0.65–0.99) 0.48 (0.12–1.95) 0.10	Residential location, population density, SES	Conditional logistic regression; matching variables: age, sex, year of diagnosis. Cases aged < 15 yr. Corrected estimates for total RF exposure according to Ha et al. (2008)

Table 2.9 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comment
Ha et al. (2007) (contd.)						Total exposure to RF (mV/m), quartiles (Q)				In category Q4: OR for LL was 1.40 (95% CI, 1.04–1.88), and for ML, 0.63 (95% CI, 0.41–0.97)
						Q1	737	1.00		
						Q2	362	0.75 (0.58–0.97)		
						Q3	330	0.70 (0.55–0.90)		
						Q4	494	0.83 (0.63–1.08)		
						Unknown	5	0.39 (0.10–1.54)		
						P for trend		0.44		
Merzenich et al. (2008) Germany, 1984–2003	1959	5848	Population	Field-strength prediction programme	ICCC Ia, ICCc Ib, ICCc Ic, ICCc Id, ICCc Ie	Quantiles of median exposure (V/m) to RF-EMFs (AM and FM/TV transmitter) one yr before diagnosis of case				Conditional logistic regression; matching variables age, sex, year of diagnosis, study region. Cases were aged 0–14 yr.
						0 to < 90%	1772	1.00		
						90 to < 95%	101	1.02 (0.80–1.31)		
						95 to ≤ 100%	86	0.86 (0.67–1.11)		
						Distance (km), AM or FM/TV transmitter				
						10 to < 15	551	1.00		
						0 to < 2	25	1.04 (0.65–1.67)		
						2 to < 6	172	0.81 (0.66–0.99)		
						6 to < 10	314	0.79 (0.67–0.93)		
						≥ 15	866	1.00 (0.88–1.14)		

Table 2.9 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comment
Elliott et al. (2010) United Kingdom, 1999–2001	527	5588	Population	(a) Distance from nearest mobile phone base station; (b) Total power output from summation across all base stations within 700 m; (c) Modelled power density at each birth address for base stations within 1400 m	Leukaemia and NHL (C91–95, C82–85)	<i>Distance from nearest base station (m)</i> Lowest Intermediate Highest <i>P</i> for trend <i>Total power output (kW)</i> Lowest Intermediate Highest <i>P</i> for trend <i>Modelled power density (dBm)</i> Lowest Intermediate Highest <i>P</i> for trend	182 167 178 305 112 110	1.00 0.99 (0.78–1.27) 1.05 (0.81–1.35) 0.75 1.00 1.08 (0.84–1.38) 1.08 (0.80–1.42) 0.58	Percentage of population with education to degree level or higher, Carstairs deprivation score, population density, population mixing	Conditional logistic regression; matching variables: age, sex. Cases aged 0–4 yr

ALL, acute lymphocytic leukaemia; AM, amplitude modulation; ANLL, acute non-lymphocytic leukaemia; dBm, modelled power density; FM, frequency modulation; ICC, International Classification of Childhood Cancer; kW, kilowatt; LL, lymphocytic leukaemia; ML, myelocytic leukaemia; OR, odds ratio; NHL, non-Hodgkin lymphoma; RF, radiofrequency radiation; SES, socioeconomic status; TV, television

0.86; 95% CI, 0.67–1.11) when the upper and lower quantiles of RF-radiation distribution were compared. In addition, there was no evidence for an association indicating increased or decreased risk by transmitter type or leukaemia subtype. Nor was there any increased risk (OR, 1.04; 95% CI, 0.65–1.67) for children residing within 2 km of the nearest transmitter. [Lack of information on peak and indoor exposure to RF radiation as well as cumulative lifetime exposure to RF radiation from transmitters, and the low number of cases residing within 2 km of the nearest AM transmitters were the main limitations of this study.]

A case–control study by [Elliott *et al.* \(2010\)](#) (described in Section 2.2.1) examined risk of childhood cancers (e.g. leukaemia and NHL) in association with maternal exposure to RF radiation from mobile-phone base stations during pregnancy. No association or trend for different exposure categories was found for leukaemia or NHL with any of the exposure metrics used. Sociodemographic measures as well as mean distance of birth address from nearest FM, television, and very high frequency (VHF) broadcast antennae were similar for cases and controls. [Although this study had strengths in its size, national coverage and sophisticated exposure assessment compared with previous studies, it was carried out during years when mobile-phone use had become fairly common, yet such usage was not accounted for.]

(c) Cohort studies

No data were available to the Working Group.

2.2.3 Other cancers

There have been several small ecological studies, generally of low quality, that have assessed the correlation between all cancers and distance from mobile-phone base stations ([Eger *et al.*, 2004](#); [Wolf & Wolf, 2004](#); [Gavin & Catney, 2006](#); [Eger & Neppe, 2009](#)). However, the

Working Group considered these studies to be uninformative for the reasons listed below.

Three ecological studies considered risk of all cancers in relation to sources of exposure to RF. [Wolf & Wolf \(2004\)](#) studied the incidence of all cancers around one base station located south of Netanya, Israel, which began operating in July 1996. Among the population of 622 people living within 350 m from the antenna, eight cases were identified between July 1997 and June 1998, and the rate of all cancers among these people was compared to the national rates of cancer in Israel (ratio of rates, 4.15; no confidence intervals provided). [The Working Group considered this study to be uninformative for various reasons, including its small size, unclear method of case ascertainment, crude analyses including incidence rate computed without age standardization, and other methodological limitations.]

Prompted by a reported clustering of cancer cases around a communication mast in Cranlome, Northern Ireland, an ecological study of cancer risk was carried out during 2001–02 ([Gavin & Catney, 2006](#)). The mast was erected in 1989, and was taken down in 2002. The Northern Ireland Cancer Registry was the source of case ascertainment. The rates of incidence of groups of cancer in several concentric geographical areas (up to 5 km) were compared with national rates of cancer incidence. The SIR for all cancers was 0.94 (95% CI, 0.88–0.99) for men and 1.00 (95% CI, 0.94–1.06) for women, while the SIR was 101 (95% CI, 79–104) for brain and 99 (95% CI, 74–124) for lymphoma and leukaemia. [The Working Group considered this study to be uninformative due to its small size, the fact that the number of cases was not reported and the absence of evaluation of exposure to RF radiation.]

[Eger *et al.* \(2004\)](#) studied the incidence of all cancers between 1994 and 2003 in areas determined by circles of radius 400 m around two mobile-phone base stations located in Naila, Germany. The first base station became operational in 1993 and the second in 1997. Streets

within and without the area were randomly selected, and the patient databases of general practitioners were searched for cases living the entire period of 10 years at the same address. [The completeness of the ascertainment appeared to be 90%.] The proportion of new cases of cancer was significantly higher among those patients who had lived for the past 10 years at a distance of up to 400 m from the cellular transmitter site, compared with patients living further away. [The Working Group considered this study uninformative due to the small and ill-defined study base and crude statistical methodology.] The same authors investigated the incidence of cancer around a mobile-phone base station in Westphalia, Germany, between 2000 and 2007 ([Eger & Neppe, 2009](#)). Twenty-three cases were identified by door-to-door interviews. The authors compared the incidence of all cancers in the 5 years immediately after installation of the mast to that in later years, and found a statistically significant increase in incidence 5 years after the base station started transmission. [The Working Group considered this study to be uninformative due to its small size and crude statistical methodology.]

Five additional studies ([Dolk et al., 1997a, b](#); [Ha et al., 2003](#); [Park et al., 2004](#); [Meyer et al., 2006](#)) described information on additional cancer sites ([Table 2.10](#), and see Section 2.2.1). [The interpretation of these results was limited by the small numbers and crude exposure classification.]

2.3 Exposure from mobile phones

With continuing changes in technology, use of mobile phones has become widespread over the last two decades. As a result, the population exposed to RF radiation has greatly increased and is still expanding, with more and more children among its number. Over these two decades, there has been rising concern regarding the potential health risks associated with use of mobile phones, particularly the possibility of increased

risk of cancer of the brain. These concerns have stimulated a diverse programme of research, including epidemiological studies carried out to assess the association of mobile-phone use with risk of cancer of the brain and other diseases. The strength of epidemiological studies is obviously the capacity to directly assess the risks associated with use of mobile phones in the general population; however, the observations collected in these studies clearly only address the various exposure scenarios that existed up to the time of observation. Thus the studies carried out to date include few participants who have used mobile phones for > 10–15 years. Any risks that might be associated with lengthier exposure or with a longer interval since first exposure would not be captured by existing studies.

Three types of study design have been applied to address the question whether an increased risk of cancer is associated with RF emitted by mobile phones. These are ecological studies (in particular, observations of time trends in disease rates), case-control studies, and cohort studies. The strengths and limitations of each of these designs in general have been well described. Here, the Working Group focused on the characteristics of these designs as applied to the investigation of the potential risks of mobile-phone use.

Ecological studies provide only indirect evidence on the potential risks associated with mobile-phone use. The general approach involves comparison of time trends in mobile-phone use with time trends in disease indicators, assessing whether the trends are parallel, and allowing for a potential lag in relationships. Over the last few decades, several factors have affected trends in incidence and mortality for cancer of the brain, in particular, the increasing availability of sensitive imaging technology (computed tomography, CT, and magnetic resonance imaging, MRI) for detecting cancers of the brain, which is likely to have had a variable influence on changes in diagnostic practices, depending on country. Consequently, the interpretation of time trends is

Table 2.10 Ecological studies of other cancers and environmental exposure to radiation from transmitters of radiofrequency signals

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95%CI)	Covariates	Comments
Dolk <i>et al.</i> (1997a) United Kingdom	Around 408 000	1974–86	Distance to Sutton Coldfield radio and TV transmitter	All cancers	Distance 0–2 km	703	1.09 (1.01–1.17)	Region	
					km	17 409	1.03 (1.02–1.05)		
					0–10 km		Unconditional		
					Stone's <i>P</i> value		<i>P</i> = 0.001		
							Conditional		
							<i>P</i> = 0.462		
				Skin melanoma	0–2 km	13	1.43 (0.83–2.44)		
				Eye melanoma		0	0 (0–4.22)		
				Male breast		1	1.64 (0.04–9.13)		
				Female breast		107	1.08 (0.90–1.31)		
				Lung		113	1.01 (0.84–1.21)		
				Colorectal		112	1.13 (0.94–1.35)		
				Stomach		33	0.75 (0.54–1.06)		
				Prostate		37	1.13 (0.82–1.55)		
				Bladder		43	1.52 (1.13–2.04)		
				Skin melanoma	0–10 km	189	0.96 (0.83–1.11)	Region	
				Eye melanoma		20	1.16 (0.75–1.80)		
Dolk <i>et al.</i> (1997b) United Kingdom	Around 3 390 000	1974–86	Distance to radio and TV transmitters in United Kingdom (excluding Sutton Coldfield)	Male breast		15	0.99 (0.60–1.64)		
				Female breast		2412	1.05 (1.01–1.10)		
				Lung		3466	1.01 (0.98–1.05)		
				Colorectal		2529	1.03 (0.99–1.07)		
				Stomach		1326	1.06 (1.01–1.12)		
				Prostate		785	1.03 (0.96–1.11)		
				Bladder		788	1.08 (1.01–1.16)		
				Skin melanoma	0–2 km	51	1.11 (0.84–1.46)	Region	
				Bladder		209	1.08 (0.94–1.24)		
				Skin melanoma	0–10 km	1540	0.90 (0.85–0.94)		
				Bladder		8307	1.09 (1.06–1.11)		

Table 2.10 (continued)

Reference, study location	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95%CI)	Covariates	Comments
Ha et al. (2003) Republic of Korea	From 3 152 to 126 523 persons per area (total not given)	1993–96	kW	Breast cancer	High-power (≥ 100 kW) vs low-power (50 kW) transmitter sites	39.7/33.6 per 100 000 person-years	1.2 (0.8–1.7)	Age	
			Transmitter power (kW)	Breast cancer	Sites with transmitter power:				
					100 kW	29	1.29 (0.86–1.86)		
					250 kW	20	0.88 (0.54–1.36)		
					500 kW	41	0.90 (0.64–1.23)		
					1500 kW	3	2.19 (0.45–6.39)		
Park et al. (2004) Republic of Korea	8 115 906	1993–95	Regions including AM-radio broadcasting towers of > 100 kW	All cancer	Total exposed vs control (unexposed)	6191	1.29 (1.12–1.49)	Age	Direct standardized MRRs are given.
				Oral cavity and pharynx		14	1.21 (0.41–3.57)		
				Oesophagus		49	1.20 (0.71–2.03)		
				Stomach		403	1.18 (0.96–1.44)		
				Colorectum including anus		78	1.33 (0.83–2.11)		
				Liver, including intrahepatic duct		271	1.01 (0.80–1.27)		
				Pancreas		74	1.52 (0.97–2.39)		
				Lung, including trachea		232	1.08 (0.84–1.38)		
				Thyroid		7	1.35 (0.22–8.19)		
				Breast		22	1.38 (0.63–3.02)		
				Bone and connective tissue		8	1.05 (0.21–5.22)		
				Urinary bladder		16	1.13 (0.48–2.65)		
				Skin		8	1.72 (0.36–8.21)		

Table 2.10 (continued)

Reference, study location	Total No. of subjects	Follow- up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95%CI)	Covariates	Comments
Meyer <i>et al.</i> (2006) Germany	177 428 persons living in 48 municipalities in Bavaria		Presence of mobile- telephone relay stations, classified into three categories of relay-station coverage	Breast Brain and CNS Thyroid		NR	NR		Incidence of all cancers combined was not found to be elevated in municipalities with mobile- telephone relay stations. Specific cancers not heterogeneously distributed

AM, amplitude modulation; CNS, central nervous system; kW, kilowatt; MRR, mortality rate ratio; NR, not reported; TV, television

complicated. Nonetheless, the ecological studies provide evidence for consideration in the assessment of the coherence of a causal association of mobile-phone use with cancer of the brain.

The critical evidence comes primarily from case-control studies, as only few cohort studies have been carried out. The basic design of most case-control studies reviewed in this section has involved interviews with cases (most studies are of cancer of the brain) and with appropriate controls; the interviews characterize use of mobile phones, exposures to other sources of RF radiation (e.g. cordless phones) in some instances, potential confounding factors, and other information. The critical methodological concerns around interpretation of the findings of case-control studies of mobile-phone use involve the comparability of cases and controls, the potential for selection bias, and information bias, particularly in ascertainment of exposure to RF radiation from mobile-phone use. Confounding is a less serious concern because, apart from age, the only well-established causal factor for cancer of the brain is ionizing radiation, and also because in the general population the distribution of exposures, primarily from diagnostic irradiation, is unlikely to introduce substantial confounding.

Information bias related to exposure assessment has been a principal concern in interpreting the findings of case-control studies. The investigators have developed interview and questionnaire approaches for ascertaining mobile-phone use and exposure characteristics that attempt to capture the full exposure profile. Key exposure metrics have included the duration of use, call frequency, and cumulative use indicators, the types of device used, and various potential modifiers of exposure, such as use of a hands-free device and the laterality of use. With this approach, some degree of non-differential (random) misclassification of exposure to RF radiation is unavoidable. In studies of the association between protracted exposures and risk of cancer, a related concern is that the key exposure

metrics used may not capture the etiologically relevant period of a person's exposure profile (for example, if the effect of a hazard does not persist indefinitely, or appears only after an induction and latency period). Additionally, as in any case-control study, there is the possibility of differential recall according to case status regarding mobile-phone use and other items. Such bias may be in the direction of underreporting, if, for example, cases with tumours of the brain had diminished cognitive function. The bias may be in the direction of over-reporting if, for example, cases were more likely to recall events that might have led to their disease. A validation study carried out with the INTERPHONE Study demonstrated non-differential information bias, as well as the possibility of greater recall of temporally remote use by cases compared with controls ([Vrijheid et al., 2009a, b](#)). There is the additional possibility that the degree of measurement error varies from study to study, depending on the interview approach and other factors. While random misclassification generally reduces associations, differential misclassification may increase or decrease observed associations from the "true" underlying association.

Selection bias may also affect the results. Selection bias from two sources is of potential concern: specifically, differential participation by cases and controls that is determined by factors influencing likelihood of exposure. Additional selection bias can arise from the process used to select cases and controls, such that the association is distorted from that in the underlying population. This bias is of particular concern in case-control studies involving cases selected from hospitals or other medical institutions, as the factors that lead to hospitalization and diagnosis may also be associated with the exposure(s) under investigation. Selection bias may reduce or increase the observed association.

In interpreting the results of the case-control studies, consideration was given to the net consequences of selection bias and information

bias to answer the question as to whether the observed association(s) could reflect bias (at least in part), rather than causation. The judgment of the Working Group as to the potential consequences of bias was critical to the classification of the evidence from humans. The complexities in interpretation of the findings of case-control studies of mobile phones and cancer of the brain have been reviewed recently ([Ahlbom et al., 2009](#); [Saracci & Samet, 2010](#)).

2.3.1 Cancer of the brain

(a) Ecological studies

Multiple ecological studies have been published that compare time trends in use of mobile phones and incidence and mortality rates of various cancers, primarily brain ([Table 2.11](#)). [Because these studies provided only limited and indirect evidence on the risk of cancer potentially associated with mobile-phone use, the Working Group presented a brief synthesis only.] These included two time-trend studies ([Lönn et al., 2004](#); [Deltour et al., 2009](#)) in the combined Nordic countries, two in the United Kingdom ([Nelson et al., 2006](#); [de Vocht et al., 2011a](#)), three in parts of the USA ([Muscat et al., 2006](#); [Propp et al., 2006](#); [Inskip et al., 2010](#)), one each in Japan ([Nomura et al., 2011](#)), New Zealand ([Cook et al., 2003](#)), Switzerland ([Röösli et al., 2007](#)) and Israel ([Czerninski et al., 2011](#)), and one in a set of eleven countries ([Saika & Katanoda, 2011](#)). Most studies provided some data on the temporal pattern of increasing use of mobile phones, based mostly on annual numbers of private subscriptions and, in a few instances, on estimated prevalence of use. The information on use of mobile phones clearly demonstrated the rapid increase between 1985 and 2000; in some countries, the increase started in about 1990, while in others the increase began later in that decade. In some countries, the reported number of subscriptions had approached the total population of the country in 2000. The number of subscriptions is

a surrogate for population exposure to RF radiation, but the number does not reflect temporal changes in patterns of actual usage. Most of these ecological studies had used rates of cancer incidence calculated from data obtained from national or subnational cancer registries, while two studies used mortality rates. In most of these studies, the temporal association between trends in use of mobile phones and cancer incidence was assessed informally and descriptively. [The geographical correlation study carried out in several states of the USA ([Lehrer et al., 2011](#)) failed to adequately account for population size and composition.]

Studies that covered a long period between increasing use of mobile phones among the population under investigation and available data on cancer incidence from high-quality cancer registries were most informative for evaluating time trends. In Scandinavia, the rise in use of the mobile phone occurred relatively early. The reported prevalence of mobile-phone use among men aged 40–59 years was 7% in 1989 and reached 28% in 1993 ([Deltour et al., 2010](#)). No change in trends in cancer incidence was observed between 1993 and 2003 for this age group, which had the highest proportion of people who started using mobile phones at an early stage ([Deltour et al., 2009](#)). In the USA, the use of mobile phones started to increase somewhat later; about 100 million subscribers were registered in 2000, i.e. 36% of the population ([Inskip et al., 2010](#)). According to data collected by the Surveillance, Epidemiology, and End Results (SEER) Program, age- and sex-specific trends and overall temporal trends in rates of incidence of brain cancer in the USA were flat or downward between 1992 and 2006, with the exception of women aged 20–29 years ([Inskip et al., 2010](#)). In this age group, a statistically significant increasing trend was driven by the rising incidence in tumours of the frontal lobe. [It is the temporal lobe that is most heavily exposed to radiation when using a mobile phone at the ear ([Cardis et al., 2008](#)).]

Table 2.11 Time trends in use of mobile phones and cancer occurrence

Reference	Location	Exposure data	Trend in exposure	Organ site	Period of cancer occurrence	Cancer data	Cancer trend	Comments
Cook <i>et al.</i> (2003)	New Zealand	Proportion of mobile-phone subscribers in the New Zealand population	Sharp increase from 1987 (1%) to 1998 (> 30%), particularly since 1993 (5%)	All brain and salivary gland; temporal lobe; parietal lobe	1986–98	Incidence rates from New Zealand Cancer Registry	Flat trends from 1986 to 1998	No apparent impact of mobile-phone use on incidence of brain cancer. This study could only detect a risk if it occurred within 4 yr of first exposure
Hardell <i>et al.</i> (2003)	Sweden	None	Presumably sharp increases between 1980s and 2000	Vestibular schwannoma	1960–98	Incidence rates from Swedish Cancer Registry	Increase from 1960 to 1985, then rather flat	No effect of mobile-phone trends. Too early
Lönn <i>et al.</i> (2004)	Denmark, Finland, Norway, Sweden	Proportion of mobile-phone subscribers per year in each country	Sharp increase from 1987 (1–2%) to 1998 (30–50%) particularly after 1993	All brain and subtypes	1969–98	Incidence rates from Nordic National Cancer Registries	Gradual increase from 1968–1983; flat from 1983–96; slight upticks in 1997 and 1998	No apparent impact of mobile-phone use on incidence of brain cancer. Long-standing, high-quality registries. Increased incidence in late 1970s and early 1980s coincides with improvements in diagnosis. This study could only detect a mobile-phone-related risk if it occurred within about 5 yr of first exposure.
Muscat <i>et al.</i> (2006)	USA (SEER Program); 17 registries; about one quarter of the USA population	Unclear	From 0% to about 50% of the population; “exponential increase”	Neuronal tumours	1973–2002	Incidence rates from SEER	No change in incidence between two periods (1973–85 and 1986–2002)	No apparent impact of mobile-phone use on incidence of neuronal tumours. No data on year-by-year variability. Not clear when the number of users increased, probably in the early to mid-1990s. Neuronal tumours are extremely rare.

Table 2.11 (continued)

Reference	Location	Exposure data	Trend in exposure	Organ site	Period of cancer occurrence	Cancer data	Cancer trend	Comments
Nelson <i>et al.</i> (2006)	England and Wales, United Kingdom	Active mobile-phone subscriptions by year, 1987–2004	Very little before 1993; gradual increase to 1997 (10 million) then sharp annual increase to 2004 (60 million)	Acoustic neuroma	1979–2001	Incidence rates from National Cancer Registry for England and Wales	Gradual increase from 1980 to 1990; sharp increase to 1997; decline to 2000. Rise and decline of acoustic neuroma attributed to changes in diagnosis and registration	No apparent impact of mobile-phone use on incidence of acoustic neuroma. The reason for decline in rates after 1997 is uncertain, but its magnitude illustrates the difficulty of detecting a signal if there is one, against the background noise of statistical variability and methodological challenges. The number of subscriptions, approx. 60 million, is clearly in excess of the number of people with subscriptions in England and Wales.

Table 2.11 (continued)

Reference	Location	Exposure data	Trend in exposure	Organ site	Period of cancer occurrence	Cancer data	Cancer trend	Comments
Propp <i>et al.</i> (2006)	Several centres in the USA	None	NR	Acoustic neuroma (vestibular schwannoma)	Los Angeles 1975–98; other centres 1985–99	Incidence rates from the Central Brain Tumor Registry of the USA, and the Los Angeles County Cancer Surveillance Program	Modest, but discernable gradual increases over the period of observation	No apparent impact of mobile-phone use on incidence of acoustic neuroma. Modest increase in risk over the period of time studied (1970s to 1990s) could be due to improvement in diagnosis and registration or to some environmental factor. While the authors present no data on trends in mobile-phone use, it is likely that use increased in the early to mid-1990s. This study could only detect a mobile-phone-related risk if it occurred within about 5 yr of first exposure.
Rösli <i>et al.</i> (2007)	Switzerland	Prevalence of mobile phone use by year, with mortality rates	None before 1987; slow increase to 1996 (< 10%) and then sharp increase to 2000 (> 60%)	All brain (ICD-8 code 191)	1969–2002	Mortality rates from Swiss Federal Statistical Office	Gradual increase from 1969 to 2002, reaching a plateau after 1997. Smaller increase in rates after 1987 than before. For the whole period, there was a significant increase for men and women in older age groups, but not in younger ones. From 1987 onwards, rather stable rates in all age groups.	No apparent impact of mobile-phone use on incidence of cancer of the brain. High-quality mortality data. Authors quantify difficulty in detecting risk in such an ecological study. Improvements in survival may influence trends in mortality.

Table 2.11 (continued)

Reference	Location	Exposure data	Trend in exposure	Organ site	Period of cancer occurrence	Cancer data	Cancer trend	Comments
Deltour <i>et al.</i> (2009)	Denmark, Finland, Norway, Sweden	Unclear	Use increased from zero in the mid-1980s to 'widespread' in the early 1990s to 'sharply increased' in the mid-1990s.	Glioma and meningioma	1974–2003	Incidence rates from Nordic National Cancer Registries	Very slight increases in incidence from 1974 to 1997; no change after 1998	No apparent impact of mobile-phone use on incidence of cancer of the brain. High-quality registration. Up to 10 yr potential latency
Hardell & Carlberg (2009)	Sweden	None	Presumably sharp increases between 1980s and 2000	Brain, age > 19 yr Acoustic neuroma, age > 19 yr	1970–2007	Incidence rates from Swedish Cancer Registry	Changing annual incidence: 1970–79 (+0.15%) 1980–89 (+1.54%) 1990–99 (–0.25%) 2000–07 (+1.26%) 1970–79 (–1.66%) 1980–89 (+4.86%) 1990–99 (+0.66%) 2000–07 (–7.08%)	No evidence of an impact of mobile-phone use on the risk of acoustic neuroma. No or very weak evidence of an effect of phone use on risk of tumours of the brain. Slightly stronger evidence for increased risk of astrocytoma in the most recent period
Inskip <i>et al.</i> (2010)	USA (SEER Program); nine state or regional population-based cancer registries	Number of mobile-phone subscribers in USA by year	From very few in 1990 to 25 million in 1995; 100 million in 2000 and 200 million in 2005	All brain, excluding meningioma and lymphoma	1977–2006	Incidence rates from SEER	Gradual increase in risks from 1977 to 1985; since 1986 the pattern is flat or slightly decreasing. Some age/sex subgroups show increasing trends in some subtypes	No apparent impact of mobile-phone use on incidence of cancer of the brain. Very large numbers of cases. Up to 10 yr of potential latency

Table 2.11 (continued)

Reference	Location	Exposure data	Trend in exposure	Organ site	Period of cancer occurrence	Cancer data	Cancer trend	Comments
Czerninski et al. (2011)	Israel	None	Exposure trend not shown but presumably sharp increase between mid-1980s and 2006	Parotid gland	1970–2006	Incident numbers of cases from Israel National Cancer Registry	Approximate tripling of number of tumours of the parotid gland, with increase starting around 1977 and picking-up around 1990	Authors state that population growth explains part of the increase, but they do not acknowledge the role of ageing of the population. Rates would be more convincing than numbers. While numbers increased greatly after 1998, there were, nevertheless, important increases in numbers of cases before mobile phones could plausibly have caused large numbers of cases.
de Vocht et al. (2011a)	England	Mobile-phone subscriptions	Sharp increase from 0 in 1985 to 10 million in 1997 to > 50 million in 2003	All brain and each of 11 subsites	1998–2007	Incidence rates from United Kingdom Office of National Statistics	Linear regression for each of 24 sex/site categories. No significant trend for all cancers combined. Significant increase in incidence of tumours of temporal lobe and decreases in tumours of parietal lobe	No apparent impact of mobile-phone use on incidence of cancer of the brain, except for a small but unconvincing increase in incidence of tumours of the temporal lobe. Up to 10 yr of potential latency. The number of subscriptions, approx. 50 million in 2003, is clearly in excess of the number of people with subscriptions in England.

Table 2.11 (continued)

Reference	Location	Exposure data	Trend in exposure	Organ site	Period of cancer occurrence	Cancer data	Cancer trend	Comments
Nomura <i>et al.</i> (2011)	Osaka	None	Presumably sharp increases between 1980s and 2000	Intracranial	1975–2004	Incidence rates from Osaka Cancer Registry	Age 0–1 yr, flat; age 20–74 yr, flat until 1999 then slight decline; age 75 yr, sharp increase to 1983 then flat	No increase in incidence rates in recent years. Increasing rates in early years may have been due to diagnostic improvements.
Saika & Katanoda, (2011)	Study involved 11 countries: Japan, Hong Kong Special Administrative Region, Republic of Korea, USA, Australia, the Russian Federation, United Kingdom, Italy, Spain, France, Germany	None	Presumably sharp increases between 1980s and 2000	Brain and CNS	1990–2005	Mortality rates from WHO database	In most of the 22 country/sex data sets, there was a rather flat or declining rate; only in the Russian Federation and Spain was there an increase among females	No apparent increase in mortality from cancer of the brain. Mortality rates may reflect trends in diagnostic standards and in survival.

NR, not reported; SEER, Surveillance, Epidemiology and End Results; yr, year

In another study, trends in rates of newly diagnosed cases of cancer of the brain in England between 1998 and 2007 were examined ([de Vocht et al., 2011a](#)). Overall rates of incidence of cancer of the brain in males or females, or in any specific age group were not increased. However, the incidence of tumours of the temporal lobe increased between 1998 and 2007. In a subsequent letter, the same authors reported separate time trends for the periods 1979–99 and 2000–08. For men, a linear regression of age-adjusted rates showed an overall annual increase in 2000–08 of 3.3% (95% CI, 1.1–5.4), whereas it was 2.0% (95% CI, 1.4–2.6) for 1979–99 ([de Vocht et al., 2011b](#)). [The linear regression used for this analysis was not an appropriate method and therefore the 95% confidence intervals reported may not be reliable.] For women, corresponding annual increases were 2.8% (95% CI, 0.9–4.9) for 2000–08 and 1.4% (95% CI, 0.7–2.2) for 1979–99.

[The Working Group noted that time-trend analyses did not provide any indication that the rapid increase in use of mobile phones had been followed by a parallel increase in incidence rates of cancer of the brain. Increases in rates of brain tumours in the 1970s and 1980s had paralleled the introduction and distribution of new diagnostic tools, namely CT and MRI. The Working Group further noted that these descriptive analyses would be null if an excess in cancer risk from mobile-phone use became manifest only decades after phone use began, or if an increase affected only a small proportion of the cases by location.]

(b) Cohort studies

An early attempt to conduct a cohort study in the USA on cancer and mobile-phone use was halted by legal action; consequently, the study did not provide useful results ([Dreyer et al., 1999](#)). A retrospective cohort study was conducted in Denmark based on the subscriber lists from the two Danish mobile-phone operating companies, including 420 095 individual (i.e. virtually all non-institutional) subscribers from 1982 to

1995. Using unique identifiers, these subscribers were linked to the Danish Cancer Registry from 1982 onwards. The linkage allowed the identification of all cancers occurring in this cohort, and notably cancers of putative target organs. Expected numbers of cases were based on rates in the Danish population. Two papers appeared, one covering cancer outcomes from 1982 to 1996 ([Johansen et al., 2001](#)) and the second covering outcomes from 1982 to 2002 ([Schüz et al., 2006c](#)). In the latter, more recent, analysis, the expected rates were computed with cohort members excluded from the reference population by subtracting the number of cases of cancer and person-years observed in the cohort from the corresponding figures for the total Danish population. Approximately 85% of the cohort members were males.

There were various sources of misclassification, as acknowledged by the authors. Members of the reference population, apart from cohort members, may well have used mobile phones, either with subscriptions that were not in their names (e.g. corporate accounts), or with subscriptions taken out after 1995. Moreover, a member of the cohort may have been the official subscriber to an account, but not the true user. Using information from a separate case-control study, it was estimated that as many as 39% of cohort members may not have been mobile-phone users before 1996 and as many as 16% of the reference population may have been users. Using information from Statistics Denmark, it appeared that the cohort members represented a somewhat more affluent section of the Danish population. While the investigators had no data on individual patterns of use, they had information on the year of the individual's first subscription, and this was used to compute SIRs by time since first use. The median duration of subscription among subscribers was 8 years and the maximum was 21 years.

For the entire cohort there was a slight deficit of total cancers among males (SIR, 0.93; 95% CI,

0.92–0.95), and a slight excess among females (SIR, 1.03; 95% CI, 0.99–1.07). For the main cancer types of interest, the results were similarly close to the null value, with relatively narrow confidence intervals, as shown in [Table 2.12](#). For subtypes of cancer of the brain, most SIRs were close to the null value.

The SIR for glioma was 1.01 (95% CI, 0.89–1.14; 257 cases). The odds ratios for glioma in the two lobes closest to the ear showed conflicting results, with a SIR of 1.21 (95% CI, 0.91–1.58) for the temporal lobe and a SIR of 0.58 (95% CI, 0.36–0.89) for the parietal lobe. The SIR was lower for all other areas of the brain, although confidence intervals were overlapping. [[Cardis et al. \(2008\)](#) have reported that it is the temporal lobe of the brain that receives the highest percentage of RF radiation deposition (50%).]

The SIR for meningioma was 0.86 (95% CI, 0.67–1.09) and for acoustic neuroma (nerve sheath tumour) it was 0.73 (95% CI, 0.50–1.03). There was no trend in SIR according to years since first subscription, and the subgroup with > 10 years since first subscription had a low SIR for all tumours of the brain and nervous system (SIR, 0.66; 95% CI, 0.44–0.95). [There were few subscribers who began using a mobile phone $\geq$ 10 years before the end of follow-up, and there was no information on individual levels of mobile-phone use.]

The Danish subscriber cohort study was updated for occurrence of acoustic neuroma (vestibular schwannoma) until 2006 ([Schüz et al., 2011](#)). This update and analysis was restricted to a large subset of subscribers and of the Danish population (2.9 million subscribers and non-subscribers) for which independent information was available on each subject's highest level of education, annual disposable income and marital status. Further to the follow-up with data from the Danish cancer registry, a clinical registry of acoustic neuroma was used to achieve completeness of case ascertainment and obtain additional tumour characteristics, such as laterality, and

spread and size of the acoustic neuroma. In this cohort analysis, having a long-term mobile-phone subscription of $\geq$ 11 years was not related to an increased risk of vestibular schwannoma in men (RR, 0.87; 95% CI, 0.52–1.46; adjusted for sociodemographic factors); and no cases of acoustic neuroma occurred among long-term female subscribers versus 1.6 cases expected. Although 53% of Danes reported that they mainly used their phones on the right side, with 35% preferring the left side and 13% having no preferred side, based on data from the launch of a prospective cohort study described in [Schüz et al., 2011](#)), acoustic neuroma in the subscriber cohort occurred equally on both sides (48% of tumours were on the right side, with no change in this proportion over time). Acoustic neuromas in long-term male subscribers were not larger than those in non-subscribers and short-term subscribers (mean diameter, 14.6 versus 15.9 mm).

(c) Case-control studies

There have been many case-control studies of tumours of the brain in relation to use of mobile phones: a series from one group in Sweden (this study also included cordless phones), an IARC-coordinated series from 13 countries known as INTERPHONE (this study included use of cordless phones among the unexposed group), and several others, including three from the USA, and one each from Finland, France, Greece and Japan. Some studies considered all major types of tumours of the brain, while others considered glioma and meningioma, or glioma only, or acoustic neuroma only. The studies are presented below by major tumour type. Most studies were based on interviews with study subjects or proxies, and involved questions on history of mobile-phone use. Various exposure metrics were used in the different studies, including binary indicators of ever versus never use, metrics of duration of use, frequency of use, and time since start of use. In addition, some analyses

Table 2.12 Cohort study of cancer of the brain and use of mobile phones

Reference, study location and period	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Comments
Schüz <i>et al.</i> (2006c) Denmark, 1982–2002	420 095, 1982–2002 357 553 men, 62 542 women	1982–2002	Subscribers to mobile-phone service	All cancers	Ever subscribed Ever subscribed: men Ever subscribed: women	14 291 11 802 2 447	0.95 (0.93–0.97) 0.93 (0.92–0.95) 1.03 (0.99–1.07)	Update of Johansen <i>et al.</i> (2001) . Median time since first subscription, 8 yr. Expected numbers derived from Danish National Cancer Registry after excluding cohort members from the population. Questionable correspondence between mobile-phone subscriptions and use levels.
				Brain, CNS	Ever subscribed	580	0.97 (NR)	
				Brain, CNS	Ever subscribed: men	491	0.96 (0.87–1.05)	
				Brain, CNS	Ever subscribed: women	89	1.03 (0.82–1.26)	
				Brain, CNS	Latency, < 1 yr since start	51	0.90 (0.67–1.18)	
				Brain, CNS	Latency, 1–4 yr since start	266	1.03 (0.91–1.17)	
				Brain, CNS	Latency, 5–9 yr since start	235	0.96 (0.84–1.09)	
				Brain, CNS	Latency, ≥ 10 yr since start	28	0.66 (0.44–0.95)	
				Glioma (191–191.9)	Ever subscribed	257	1.01 (0.89–1.14)	
				Temporal lobe (191.2)	Ever subscribed	54	1.21 (0.91–1.58)	
				Parietal lobe (191.3)	Ever subscribed	21	0.58 (0.36–0.89)	
				Meningioma (192.1)	Ever subscribed	68	0.86 (0.67–1.09)	
				Nerve sheath tumours (192.0) ^a	Ever subscribed	32	0.73 (0.50–1.03)	

^a Includes other rare tumours of the nerve sheath
CI, confidence interval; CNS, central nervous system; NR, not reported; yr, year or years

considered modifiers of exposure, such as laterality of mobile-phone use. The latter was based on the premise that if there were a risk related to mobile-phone use, it should manifest itself in a greater proportion of tumours on the side of the head corresponding to the subject's preferred side of phone use. Some studies analysed exposure in relation to the lobe in which the tumour appeared, based on the premise that some lobes absorb more RF radiation than others.

(i) *Glioma*

See [Table 2.13](#)

A case-control study of cancer of the brain was conducted in five academic medical centres in the north-eastern USA during 1994–1998 ([Muscat et al., 2000](#)). Interviews were conducted with the cases ($n = 469$), mainly patients with glioma, and with controls ($n = 422$) selected from the same medical centres. Analysis of reported histories of mobile-phone use, adjusting for sociodemographic factors, study centre, proxy status, and date of interview, yielded a set of odds-ratio estimates that showed no effect, whether by various exposure metrics, anatomical location of the tumour, or histological subtypes. The only exception was an odds ratio of 2.1 (95% CI, 0.9–4.7) for neuroepitheliomatous tumours (14 exposed cases). [The Working Group noted that the highest prevalence of these tumours occurred in the temporal lobe.] The longest duration of use considered was ≥ 4 years. [The numbers of cases were small, exposure levels were low: of the 422 controls, 346 had never used a mobile phone and 22 had used a mobile phone for ≥ 4 years.]

[Inskip et al. \(2001\)](#) conducted a case-control study of tumours of the brain in three centres between 1994 and 1998. A total of 489 cases of glioma were interviewed, as were 799 controls. Compared with non-users, self-reported regular use of mobile phones was not associated with excess risk of glioma (OR, 0.8; 95% CI, 0.6–1.2). Based on very small numbers, there was no indication of excess risk among people with the

heaviest (cumulative use, > 500 hours) or longest (5 years or more) use of mobile phones, or any relationship between reported laterality of use and laterality of the tumours, or any relationship with neuroepitheliomatous tumours (OR, 0.5; 95% CI, 0.1–2.0; eight exposed cases). [Of the 799 controls, 625 had never or rarely used a hand-held mobile phone and only 50 had used a hand-held mobile phone before 1993.]

In a case-control study in Finland, the researchers enrolled cases of tumours of the brain and salivary gland occurring in 1996, as well as a 5 : 1 control series selected from the general population ([Auvinen et al., 2002](#)). There were 198 cases of glioma. Each subject was linked to a list of all subscribers to the two mobile-phone companies operating in Finland, to establish whether the subject had been a subscriber, for how long, and what type of phone he or she was using (analogue/digital). Linkage of records to the census allowed the investigators to ensure that the case and control series were similar in occupational, socioeconomic and urban/rural characteristics. The odds ratio for glioma was 1.5 (95% CI, 1.0–2.4) for those who had ever had a mobile-phone subscription (about 12% of all subjects), and 1.7 (95% CI, 0.9–3.5) for those who had had a subscription for > 2 years ($< 4\%$ of all subjects). When examined separately, the ever-users of analogue phones had an odds ratio for glioma of 2.1 (95% CI, 1.3–3.4) and ever-users of digital phones had an odds ratio of 1.0 (95% CI, 0.5–2.0). [A strength of this study was the linkage of cancer records, population-register records, and mobile-phone subscription records. It was limited by small numbers, inability to assess impact of use of mobile phones for > 2 years, and uncertainty about the correspondence between subscription to a mobile-phone service and individual use of mobile phones.]

Two hospital-based case-control studies ([Gousias et al., 2009](#); [Spinelli et al., 2010](#)), one in Greece and the other in France, examined associations between glioma and malignant tumours

of the brain, respectively, and mobile-phone use. The results are summarized in [Table 2.13](#). Neither study was informative due to small numbers and unclear methods of exposure assessment.

The INTERPHONE study, a multicentre case-control study on use of mobile phones and various types of tumour of the brain, is the largest study on this topic so far. The study was coordinated by IARC and conducted in 16 study centres in 13 countries with a common core protocol (Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden, and the United Kingdom). A detailed description of the study design, epidemiological methods and study population can be found in [Cardis *et al.* \(2007\)](#). In brief, the source population was generally restricted to major metropolitan areas where mobile phones were first introduced and where most of the population was considered to be unlikely to leave the region for diagnosis and treatment. Residents aged between 30 and 59 years were eligible for the study, but somewhat larger age ranges were applied in some of the centres. The study periods also varied somewhat across centres, ranging from 2 to 4 years between 2000 and 2004. Eligible cases were ascertained rapidly through neurological and neurosurgical facilities in the study regions, and completeness of ascertainment was checked with secondary sources ([Cardis *et al.*, 2007](#)). Cases had a histologically confirmed or unequivocal imaging-based diagnosis of a first primary glioma, meningioma or acoustic neuroma. Three centres also included malignant tumours of the parotid gland, and Japan additionally included pituitary tumours. Population controls were randomly selected from population registries (part of Canada, Denmark, Finland, Germany, Italy, Norway, Sweden), electoral lists (Australia, part of Canada, France, New Zealand), patient lists from general practice (United Kingdom) or by random-digit dialling (part of Canada, France, Japan). Controls were individually (part of Canada, France, Japan,

New Zealand, United Kingdom) or frequency-matched (remaining countries) to cases on year of birth (within categories of 5 years), sex and study region. One control was recruited for each patient with a tumour of the brain, two for each patient with acoustic neuroma, and three for each patient with a tumour of the parotid gland.

All consenting subjects were interviewed face-to-face by trained interviewers by use of a computer-assisted personal interview (CAPI) whenever possible. If participants had died or were too ill to be interviewed, a proxy was interviewed. The questionnaire covered demographic factors, potential confounders and risk factors for the diseases of interest, including detailed questions on use of mobile phones and other wireless-communication devices. A regular mobile-phone user was defined as having used a mobile phone for at least one call per week during 6 months or more.

Since the first publications of national results in 2004 ([Christensen *et al.*, 2004](#); [Lönn *et al.*, 2004](#)), numerous papers have presented results from single countries ([Christensen *et al.*, 2005](#); [Lönn *et al.*, 2005](#); [Schoemaker *et al.*, 2005](#); [Hepworth *et al.*, 2006](#); [Schüz *et al.*, 2006a, b](#); [Takebayashi *et al.*, 2006, 2008](#); [Hours *et al.*, 2007](#); [Klaeboe *et al.*, 2007](#); [Schlehofer *et al.*, 2007](#); [Sadetzki *et al.*, 2008](#); [Hartikka *et al.*, 2009](#)) or pooled results from a subset of the INTERPHONE countries, such as the five north European countries: Denmark, Finland, Norway, Sweden, and the United Kingdom ([Schoemaker *et al.*, 2005](#); [Lahkola *et al.*, 2007, 2008](#)). In addition, various papers have addressed methodological issues such as exposure misclassification and selection bias ([Samkange-Zeeb *et al.*, 2004](#); [Berg *et al.*, 2005](#); [Lahkola *et al.*, 2005](#); [Vrijheid *et al.*, 2006a, b, 2009a, b](#)). The results presented here focus on the pooled results from all countries.

The [INTERPHONE Study Group \(2010\)](#) published the pooled analysis of the INTERPHONE study on the risk of glioma and meningioma in relation to use of mobile phones,

Table 2.13 Case-control studies of glioma and use of mobile phones

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell <i>et al.</i> (1999) Sweden, 1994-96	136	Two controls per case	Population	Self-administered standardized questionnaire	48 glioblastoma, 46 astrocytoma, 19 oligodendroglioma, 3 ependymoma, 16 mixed glioma, and 4 other malignant tumours	Never use of mobile phone Ever use	53	1.0 1.0 (0.6-1.5)	Age, sex, SEI, and year of diagnosis	
Muscat <i>et al.</i> (2000) USA, 1994-98	469	422	In-patients from five USA academic medical centres. Controls from the same hospitals as cases, from daily admission rosters	In-person interviews, history of mobile-phone use	Brain cancer (191.0-191.9)	Ever use Cumulative use (h): 0 > 0 to ≤ 8.7 > 8.7 to ≤ 60 > 60 to ≤ 480 > 480	NR 17 12 19 14	0.7 (0.5-1.1) 1.0 1.0 (0.5-2.0) 0.6 (0.3-1.3) 0.9 (0.5-1.8) 0.7 (0.3-1.4)	Age, education, sex, race, study centre, proxy, year of interview	Analyses showed no associations by year of use. Few subjects with long-term heavy exposure. Response rates were 82% for cases and 90% for controls.
	108	422			Temporal lobe	Ever use	108	0.9 (0.5-1.7)		
	60	422			Parietal lobe	Ever use	60	0.8 (0.3-2.0)		
	354	422			Astrocytic	Ever use	41	0.8 (0.5-1.2)		
	35	422			Neuro-epitheliomatous	Ever use	14	2.1 (0.9-4.7)		

Table 2.13 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Inskip <i>et al.</i> (2001) USA, 1994–98	489	799	Patients admitted to the same hospitals for a variety of non-malignant conditions.	Computer-assisted, personal interview in the hospital	Glioma	Cumulative use (h): Never or rarely used < 13 13–100 > 100 > 500 Regular use Start of use before 1993	398 26 26 32 11 85 23	1.0 0.8 (0.4–1.4) 0.7 (0.4–1.3) 0.9 (0.5–1.6) 0.5 (0.2–1.3) 0.8 (0.6–1.2) 0.6 (0.3–1.4)	Hospital, age, sex, race or ethnic group, proximity of residence to the hospital	There are results for other exposure metrics: average daily use, duration of use, year in which use began. Also results for acoustic neuroma, and for laterality by tumour type.
Auvinen <i>et al.</i> (2002) Finland, 1996	398 (198 glioma)	1990	Population Registry Centre of Finland	Information on subscriptions obtained from the two mobile-network providers operating in Finland in 1996	Glioma (191)	<i>Analogue:</i> Ever < 1 yr 1–2 yr > 2 yr <i>Digital:</i> Ever < 1 yr 1–2 yr > 2 yr	26 4 11 11 10 3 7 0	2.1 (1.3–3.4) 1.6 (0.5–5.1) 2.4 (1.2–5.1) 2.0 (1.0–4.1) 1.0 (0.5–2.0) 0.8 (0.2–2.6) 1.4 (0.6–3.4) 0	Age, sex	Cases, age 20–69 yr

Table 2.13 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell <i>et al.</i> (2002b) Sweden, 1997–2000	588	581	Population	Self- administered standardized questionnaire	415 astrocytomas, 6 medullo- blastomas, 54 oligodendro- gliomas, 11 ependymomas, 65 other/mixed gliomas, and 37 other malignant tumours of the brain	Never use of mobile/ cordless phone Analogue, ever use Digital, ever use Digital, > 1–6 yr latency Digital, > 6 yr latency	79 112 100 12	1.0 (reference) 1.1 (0.8–1.6) 1.1 (0.8–1.5) 1.1 (0.8–1.4) 1.7 (0.7–4.3)	Age, sex, SEI, and year of diagnosis	Ipsilateral use of analogue phone was associated with risk of malignant tumour of the brain (OR, 1.8; 95% CI, 1.2–3.0). Ipsilateral use of digital phone was also associated with risk of malignant tumour of the brain (OR, 1.6; 95% CI, 1.1–2.4).

Table 2.13 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell et al. (2006a,c) Sweden, 2000–03	317	1990	Population	Self-administered standardized questionnaire	248 astrocytomas, and 69 other malignant tumours of the brain	Never use of mobile/cordless phone	63	1.0	Age, sex, SEI, and year of diagnosis	
						Ever use, analogue	68	2.6 (1.5–4.3)		Analogue phone: Ipsilateral use: 3.1 (95% CI, 1.6–6.2); contralateral use: 2.6 (95% CI, 1.3–5.4)
						Ever use, digital	198	1.9 (1.3–2.7)		Digital phone: Ipsilateral use: 2.6 (95% CI, 1.6–4.1); contralateral use: 1.3 (95% CI, 0.8–2.2)
						<i>Time since start of use, analogue (yr)</i>				
						> 1–5	0	–		
						> 5–10	20	1.8 (0.9–3.5)		
						> 10	48	3.5 (2.0–6.4)		
						<i>Time since start of use, digital (yr)</i>				
						> 1–5	100	1.6 (1.1–2.4)		
						> 5–10	79	2.2 (1.4–3.4)		
						> 10	19	3.6 (1.7–7.5)		

Table 2.13 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell <i>et al.</i> (2006b) Sweden, 1997–2003	905	2162	Population	Self-administered standardized questionnaire	539 high-grade astrocytomas, 124 low-grade astrocytomas, 93 oligodendrogliomas, 78 other/mixed gliomas and 71 other malignant tumours of the brain	Never use of mobile/cordless phone		1.0 (reference)	Sex, age, SEI, and year of diagnosis	Pooled analysis of case-control data for living cases ascertained from 1997–2000 and 2000–03. See also further results of analyses of these data in Hardell <i>et al.</i> (2009)
						Ever use, analogue	178	1.5 (1.1–1.9)		
						Ever use, digital	402	1.3 (1.1–1.6)		
						<i>Time since start of use, analogue (yr)</i>				
						> 1–5	39	1.2 (0.8–1.8)		
						> 5–10	57	1.1 (0.8–1.6)		
						> 10	82	2.4 (1.6–3.4)		
						<i>Time since start of use, digital (yr)</i>				
						> 1–5	265	1.2 (1.0–1.5)		
						> 5–10	118	1.7 (1.2–2.2)		
						> 10	19	2.8 (1.4–5.7)		
						<i>Cumulative call time, analogue (h)</i>				
						1–1000	147	1.3 (1.0–1.7)		
						1000–2000	10	3.0 (1.1–7.7)		
						> 2000	21	5.9 (2.5–14)		
						<i>Cumulative call time, digital (h)</i>				
						1–1000	355	1.3 (1.0–1.6)		
						1001–2000	26	1.8 (1.0–3.1)		
						> 2000	21	3.7 (1.7–7.7)		

Table 2.13 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell et al. (2006b) (cont.)	<i>Ipsilateral use, analogue:</i>									
					All malignant		95	2.1 (1.5–2.9)		
					High-grade astrocytoma		62	2.4 (1.6–3.6)		
					Low-grade astrocytoma		10	1.8 (0.8–4.1)		
	<i>Contralateral use, analogue:</i>									
					All malignant		54	1.1 (0.8–1.6)		
					High-grade astrocytoma		37	1.6 (1.0–2.5)		
					Low-grade astrocytoma		4	0.5 (0.2–1.6)		
	<i>Ipsilateral use, digital:</i>									
					All malignant		195	1.8 (1.4–2.4)		
					High-grade astrocytoma		127	2.3 (1.7–3.1)		
					Low-grade astrocytoma		27	1.9 (1.0–3.5)		
	<i>Contralateral use, digital:</i>									
					All malignant		119	1.0 (0.7–1.3)		
					High-grade astrocytoma		69	1.1 (0.8–1.5)		
					Low-grade astrocytoma		16	1.1 (0.5–2.1)		

Table 2.13 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Gousias <i>et al.</i> (2009) Greece, 2005–07	41	82	Neuro-surgery patients	In-person interviews, history of mobile phone use	Glioma	Minutes per year of mobile-phone use	NR	1.00 (0.99–1.01)	Age, sex, residence area, smoking, alcohol, head trauma	Not informative because of low power and too finely resolved exposure metric
Hardell <i>et al.</i> (2010) Sweden, 1997–2003	346	343 cancer controls, 276 other controls	Swedish Death Registry	Interviews with relative of decedent	314 gliomas and 32 other malignant tumours of the brain	Never use of mobile/cordless phone Ever use, analogue Ever use, digital <i>Cumulative call time, analogue (h)</i> 1–1000 1001–2000 > 2000 <i>Cumulative call time, digital (h)</i> 1–1000 1001–2000 > 2000	61 83	1.0 1.7 (1.1–2.7) 1.4 (1.0–2.1)	Sex, age, SEI, and year of diagnosis	Analysis of deceased cases (and controls) only
							41 5 15	1.5 (1.0–2.5) 1.1 (0.3–3.3) 5.1 (1.8–14)		
							58 8 17	1.2 (0.8–1.8) 2.6 (0.9–8.0) 3.4 (1.5–8.1)		

Table 2.13 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Spinelli et al. (2010) France, 2005	122	122	In-patients from neurosurgery departments of the same hospitals; unrelated to cancer	In-person interviews	Malignant primary tumours of the brain, 72 glioblastomas	Subscription hours/year 0 < 4 4–36 ≥ 36	37 8 58 13	1.0 0.9 (0.3–2.4) 1.4 (0.8–2.8) 1.1 (0.4–2.8)	Sex, age	Unclear criteria for recruitment; small numbers
INTERPHONE Study Group (2010) Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden, United Kingdom, 2000–04	2708	2972	Population (except United Kingdom: GP patients)	Interviewer-administered standardized questionnaire	Glioma (D33.0, D43.0–43.9, C71.0–71.9)	Never regular use of mobile phone Regular use Time since start of use (yr) 1–5 2–4 5–9 ≥ 10 Cumulative call time with no hands-free devices (h) < 5 5–12.9 13–30.9 31–60.9 61–114.9 115–199.9 200–359.9 360–734.9 735–1639.9 ≥ 1 640	1042 1666 156 644 614 252 141 145 189 144 171 160 158 189 159 210	1.0 (ref.) 0.81 (0.70–0.94) 0.62 (0.46–0.81) 0.84 (0.70–1.00) 0.81 (0.60–0.97) 0.98 (0.76–1.26) 0.70 (0.52–0.94) 0.71 (0.53–0.94) 1.05 (0.79–1.38) 0.74 (0.55–0.98) 0.81 (0.61–1.08) 0.73 (0.54–0.98) 0.76 (0.57–1.01) 0.82 (0.62–1.08) 0.71 (0.53–0.96) 1.40 (1.03–1.89)	Sex, age, study centre, ethnicity (in Israel) and education	OR highest in short-term users (start of mobile phone use, 1–4 yr before reference date) (OR, 3.77; 95% CI, 1.25–11.4, based on eight cases)

Table 2.13 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell <i>et al.</i> (2011a) Sweden, 1997–2003	1148	2438	Population	Self-administered standardized questionnaire	Glioma	Never use of mobile/cordless phone Ever use (mobile phone) <i>Time since start of use (yr)</i> > 1–5 > 5–10 > 10 <i>Cumulative call time, mobile phone (h)</i> 1–1000 1001–2000 > 2000	529	1.0 1.3 (1.1–1.6) 1.1 (0.9–1.4) 1.3 (1.0–1.6) 2.5 (1.8–3.3) 1.2 (1.03–1.5) 1.8 (1.2–2.8) 3.2 (2.0–5.1)	Sex, age, SEI, and year of diagnosis	Pooled analysis of case-control data for living cases ascertained from 1997–2000, and 2000–03, as well as case-control data for deceased cases 1997–2003.

Table 2.13 (continued)

Reference, study location and period	Total cases	Total controls (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Cardis et al. (2011) Australia, Canada, France, Israel, Italy, New Zealand, 2000–04	553	1762	Interviewer-administered standardized questionnaire	Glioma (D33.0, D43.0–43.9, C71.0–71.9)	RF TCSE (// kg) < 76.7 76.7– 284.1– 978.9– 3123.9+	67 68 60 57 103	0.76 (0.53–1.09) 0.94 (0.66–1.35) 0.80 (0.54–1.18) 0.89 (0.61–1.30) 1.35 (0.96–1.90)	Sex, age, study centre, ethnicity (in Israel) and education	Interpretation of OR is most meaningful when compared with the corresponding OR for comparable exposure surrogates of mobile-phone use. When stratified for different time windows of time before diagnosis, the OR tended to increase with increasing TSCE for use ≥ 7 yr in the past. For the highest exposure quintile: OR, 1.91 (95% CI, 1.05–3.47)
<i>Case-only analyses:</i>									
			Ever regular user			30	1.35 (0.64–2.87)		
			<i>Time since start of use (yr)</i>						
			1–4			12	1.37 (0.59–3.19)		
			5–9			7	0.72 (0.27–1.90)		
			≥ 10			11	2.80 (1.13–6.94)		
			<i>Cumulative call time without hands-free devices (h)</i>						
			< 39			6	1.19 (0.40–3.51)		
			39–220			4	0.93 (0.27–3.14)		
			220–520			5	1.38 (0.42–4.53)		
			520–1147			10	2.55 (0.94–6.91)		
			> 1147			5	0.99 (0.30–3.27)		

Table 2.13 (continued)

[illegible]

GP, general practitioner; h, hour; NR, not reported; OR, odds ratio; RF, radiofrequency radiation; SEI, socioeconomic index; SES, socioeconomic status; TCSE, total cumulative specific energy; yr, year

and included 2708 cases of glioma and 2972 controls. The study included 252 cases of glioma and 232 controls who had first used a mobile phone at least 10 years before the reference date. Participation rates were 64% among cases of glioma and 53% among controls. There was wide variation in participation rates for controls between study centres (42–74%).

For regular users, the odds ratio for glioma was 0.81 (95% CI, 0.70–0.94) (Table 2.13). In most study centres, odds ratios of < 1.0 were also seen for all categories of time since start of use and of cumulative number of calls. [The reason for these low odds ratios was not established. While it is plausible that this may in part reflect selection/participation biases, sensitivity analyses carried out by [Vrijheid et al. \(2009a\)](#) indicated that it was unlikely to fully explain these results.] In terms of cumulative call time, all odds ratios were < 1.0 for all deciles of exposure except the highest (10th) decile (> 1640 hours). For this exposure group, the odds ratio for glioma was 1.40 (95% CI, 1.03–1.89). There were 252 cases and 253 controls who reported start of use ≥ 10 years before the reference date. The odds ratio for the highest exposure decile of cumulative call time dropped from 1.40 to 1.27 when subjects (both controls and cases) who reported use > 5 hours per day were excluded from the analysis. When mobile-phone use was truncated at 5 hours, the odds ratio was 1.38 (95% CI, 1.02–1.87). [There was reasonable doubt about the credibility of such reports and it is possible that the excess of cases in those with unreasonably high values reflected a general tendency for cases to overestimate more than controls, which could contribute to the apparent excess risk in the highest decile. As noted earlier, there is evidence that cases tended to overestimate their past exposure more than controls ([Vrijheid et al., 2009a](#)).] For cases of glioma, the proportion of proxy respondents, the number of imputations for missing values, and the proportion of subjects judged by their interviewer to be non-responsive or having

poor memory were all higher than for controls ([INTERPHONE Study Group, 2010](#)). However, sensitivity analyses showed that these differences by themselves did not explain the results seen in the highest decile of cumulative call time. More information on the various methodological issues and corresponding sensitivity analyses were discussed by the [INTERPHONE Study Group \(2010\)](#)] There was no evidence of heterogeneity in effect across study centres.

More detailed analyses were conducted by the INTERPHONE study team to evaluate the possible association between mobile-phone use and risk of glioma. The odds ratio in the highest exposure decile of cumulative use was larger for tumours in the highly exposed temporal lobe (OR, 1.87; 95% CI, 1.09–3.22) than in the less exposed parietal or frontal lobes (OR, 1.25; 95% CI, 0.81–1.91) or for tumours in other locations (OR, 0.91; 95% CI, 0.33–2.51). This result was consistent with patterns of energy deposition in the brain ([Cardis et al., 2008](#)).

The ratio of the odds ratios for ipsilateral phone use to those for contralateral use increased steadily with increasing cumulative number of calls. [This would be expected if there were an exposure–response association.] However, notwithstanding similar trends in higher exposure categories, the highest ratios of these odds ratios for cumulative call time and for time since start of use were observed in the lowest exposure categories. [While these odds ratios were highly imprecise, this pattern may suggest bias in recall of side of phone use.]

In Appendix 2 of the [INTERPHONE Study Group \(2010\)](#) publication, an additional analysis was reported in which never-regular users were excluded from the analysis and the lowest exposure category was used as the reference category. This analysis was based on the assumption that participation bias was the principal explanation for the decreased odds ratios of the main analysis and that bias was related only to mobile-phone user status and not to extent of use. As a result,

most of the odds ratios for glioma increased above unity. Increased odds ratios were found for people who started to use their phone 2–4 years before diagnosis (OR, 1.7; 95% CI, 1.2–2.4), 5–9 years before diagnosis (OR, 1.5; 95% CI, 1.1–2.2) or > 10 years before diagnosis (OR, 2.2; 95% CI, 1.4–3.3). In terms of cumulative call time, the odds ratio for glioma did not show an upward trend for the first nine deciles of exposure, but the odds ratio for the highest category (> 1640 hours) was increased (OR, 1.8; 95% CI, 1.2–2.9).

Some publications of the results for glioma from national INTERPHONE centres were based on broader eligibility criteria, e.g. extending the age range to 20–70 years ([Christensen et al., 2005](#)). Inclusion of additional cases did not yield markedly different results in these national publications compared with the pooled analysis.

[The strengths of the INTERPHONE study included its large sample size, the common core protocol, comprehensive data collection and in-depth data analyses (including a wide variety of sensitivity and validation analyses), and its use of population-based controls. The exposure assessment was, however, a limitation. As in most other case–control studies, mobile-phone use was estimated from retrospectively collected interview data and thus recall error was an issue. According to a comparison of self-reported mobile-phone use with operator-recorded data in a comparatively small sample of INTERPHONE participants from Australia, Canada and Italy, little differential exposure misclassification between cases and controls was found on average. However, in the highest category of cumulative number of calls, overestimation was more pronounced in cases than in controls ([Vrijheid et al., 2009a](#)). Furthermore, the ratio of self-reported phone use to recorded phone use increased with increasing time before the interview to a greater degree in cases than in controls. Such a pattern could explain an increased risk in the most extreme exposure categories. However, the number of subjects with long-term data was

relatively small and recall could only be assessed for 4–6 years at most.

Another limitation of the INTERPHONE study was the relatively low participation rate, particularly for controls (53%), which was less than that for cases (patients with glioma, 64%; meningioma, 78%; acoustic neuroma, 82%). This offered the potential for differentially selective study participation; and there is evidence that people who had ever used mobile phones regularly were more likely to agree to participate than people who had never used mobile phones regularly ([Lahkola et al., 2005](#); [Vrijheid et al., 2009b](#)). This would produce downwardly biased estimates of relative risk. [The Working Group noted that a strength of this study was its use of population-based controls and the relatively high participation rate of cases.]

In summary, there was no increased risk of glioma associated with having ever been a regular user of mobile phones in the INTERPHONE study. There were suggestions of an increased risk of glioma in the group in the highest decile of exposure, for ipsilateral exposures, and for tumours of the temporal lobe [although chance, bias or confounding may explain this increased risk].

After publication of the pooled data on glioma, additional analyses were undertaken by the INTERPHONE researchers to evaluate the association between mobile-phone use and risk of glioma. They included refined dose estimation, case–case analyses, and case–specular analyses. Each of these analyses has its merits in complementing the overall picture and in evaluating the role of bias, as discussed below.

Refined dose estimation

In principle, a measure of absorbed RF radiation should be a more biologically relevant metric than “use” of mobile phones, if estimated accurately. In an attempt to derive a more biologically relevant metric, data from five INTERPHONE countries (Australia, Canada, France, Israel and

New Zealand) were used to examine the associations of tumours of the brain with RF fields from mobile phones by estimating the total cumulative specific-energy (TCSE) dose for each individual ([Cardis et al., 2011](#)). For each case, the location of the tumour was determined by neuroradiologists and the centre of the tumour was estimated by a computer algorithm (Israel) or by the neuroradiologist (most participants in the other countries). This analogous tumour location was allocated to the controls matched to each case. Matching was done *post hoc* by use of an algorithm that optimized matching on interview time and age within strata defined by sex, region and, in Israel, country of birth. The number of controls per case varied from 1 to 19 (median, 3).

For each study participant, the TCSE was calculated with an algorithm considering the frequency band and communication system of all phones the subject had used, multiplied by call duration. In addition, laterality, use of hands-free devices, network characteristics and urban or rural residence were taken into account (for details, see [Cardis et al., 2011](#)). A census of TCSE was carried out 1 year before the reference date.

For the glioma analysis, the 553 cases of glioma for which localization data and communication-systems information were available (42% of all eligible cases) and their 1762 controls (36% of ascertained controls) were included. Odds ratios for glioma were < 1.0 in the first four quintiles of TCSE. In the highest quintile, the odds ratio for glioma was 1.35 (95% CI, 0.96–1.90). Various sensitivity analyses did not markedly affect this odds ratio. Odds ratios in categories of TCSE were also examined in time windows since first use of a mobile phone. There was a fairly consistent dose–response pattern with an odds ratio of 1.91 (95% CI, 1.05–3.47) in the highest exposure quintile when considering TCSE exposure ≥ 7 years before the reference date. There was little evidence of an association for exposures in more recent time windows. [The Working Group noted that TCSE was highly

correlated with cumulative call time (weighted kappa, 0.68). As this exposure surrogate was mainly determined by self-reported data, recall and selection bias were of concern, as they were for the other INTERPHONE analyses. Results from TCSE analyses were similar to those for cumulative duration of mobile-phone use.]

Case–case analyses

This is a novel approach for studying the effect of radiofrequency fields emitted by mobile phones. As it is based on cases only, differential participation and recall error between cases and controls is not of concern. In both studies presented below, reported preferred side of use was not considered for determining exposed brain areas. While, this should reduce the possible impact of recall bias, it probably also introduces exposure misclassification, which is expected to be random and thus would bias any risk estimates towards unity.

The same database of five countries discussed above ([Cardis et al., 2011](#)) was used to conduct a case–case analysis by comparing the characteristics of mobile-phone use among people with tumours in highly exposed areas of the brain, defined as areas absorbing > 50% of the specific absorption rate (SAR) from use of mobile phones at both sides of the head (i.e. without taking into account laterality), with the corresponding characteristics of people with tumours in other parts of the brain. Comparisons were made with respect to time since first use of a mobile phone and cumulative call time. The odds ratio for presence of the tumour in the most exposed part of the brain for people who had started using a mobile-phone ≥ 10 years previously was 2.80 (95% CI, 1.13–6.94; based on 11 exposed cases), but it was not increased for people who had started using a mobile-phone more recently. There was, in addition, moderate but inconsistent evidence that the odds ratio for presence of a tumour in the most exposed area increased with increasing cumulative call time.

Data from seven INTERPHONE European countries (Denmark, Finland, Germany, Italy, Norway, Sweden, and south-eastern England) were also used to conduct a case–case analysis ([Larjavaara et al., 2011](#)). In total, 888 cases of glioma in people aged between 18 and 69 years were included. For each case, the tumour midpoint on a three-dimensional grid was defined, based on radiological images. The distance to the estimated axis of a mobile phone in use on the same side of the head as the glioma was calculated, irrespective of the patient's reported typical side of phone use. Regression models were then computed to compare distance between the midpoint of the glioma and the mobile-phone axis for various exposure groups of self-reported mobile-phone use. In addition, unconditional logistic regression models were applied for the number of tumours occurring at a distance of ≤ 5 cm from the phone axis.

These analyses did not suggest an association between mobile-phone use and distance of glioma from the mobile-phone axis. For instance, the mean distance between tumour midpoint and the phone axis was similar among never-regular mobile-phone users and regular users (6.19 versus 6.29 cm; $P = 0.39$). In the dichotomized analysis examining the occurrence of tumours at a distance of ≤ 5 cm from the phone axis, odds ratios were below unity for the most exposed groups relative to never-regular users. [A limitation of the study was that exposed areas were defined on the basis of distance from the phone axis only; there were no dosimetric calculations. The results of analyses of the spatial distribution of SAR from more than 100 mobile phones ([Cardis et al., 2008](#)) showed that, although there was some variability, most exposure occurs in areas of the brain closest to the ear. Exposure is not evenly distributed along the phone axis; thus the approach used could result in substantial misclassification of exposure.]

Case–specular analysis

In the case–specular analysis, a hypothetical control location is defined in the head of each patient with glioma. This was done for the data from the seven European countries described above ([Larjavaara et al., 2011](#)) by symmetrically reflecting the location of the actual tumour site across the midpoint of the axial and coronal planes to obtain the mirror-image location as the control location. This counterfactual control site and the location of the actual case site were compared with respect to their distances orthogonal to the mobile-phone axis. An association would be indicated if the odds ratio increased systematically with the amount of exposure; however, this pattern was not observed. The odds ratio was larger for never-regular users than regular users. There was no increasing odds ratio for increasing use of cumulative call time.

[The strength of case–specular analysis is that each subject is his/her own control. Nevertheless, the analysis relies on self-reported use of mobile phones when comparing odds ratio between various strata. Thus exposure misclassification affects the analysis. Never-regular users were, on average, older and more commonly female, and if these factors were to affect the tumour location, bias could be introduced. However, there was little indication for this. A limitation of the study was the small number of long-term users in the case-specular analysis, resulting in wide confidence intervals. As noted above, the absence of dosimetric calculations and use of distance to the phone axis rather than to the most exposed part of the brain was a limitation.]

[Hardell et al. \(1999, 2000, 2001, 2002a, b, 2003, 2006a, b, 2009, 2010, 2011a\)](#) have published a series of papers reporting findings regarding associations between use of mobile phones and tumours of the brain. All these epidemiological analyses have been of the case–control design, with cases identified from records of regional cancer registries in Sweden and controls

identified from the Swedish population register or the Swedish death registry (the latter was used when sampling controls for deceased cases). [While reported in a series of publications, the Working Group noted that this research had involved the ongoing collection of case-control data over an extended period of time using a fixed protocol. The Working Group noted that a strength of these analyses followed from the early, and widespread, use of mobile phones in Sweden, implying a population that has accrued exposures from mobile phones over a relatively long time period (analogue phones have been in use since the early 1980s). The fairly long-term exposure from mobile phones permits consideration of any effect that may appear after a more protracted period of exposure than in other locations. Consequently, *Hardell et al.* could address higher cumulative exposures (when measured in terms of total duration of phone use), and include people using devices designed with early mobile-phone technologies, which tended to have higher power output than those based on later mobile-phone technologies.]

In the latest paper available, [Hardell et al. \(2011a\)](#) reported the findings of a pooled analysis of associations between mobile- and cordless-phone use and glioma. Cases were ascertained from 1 January 1997 to 30 June 2000 from population-based cancer registries in Uppsala-Orebro, Stockholm, Linkoping, and Gothenburg, and from 1 July 2000 to 31 December 2003 in Uppsala-Orebro and Linkoping. Eligible cases were aged 20–80 years at diagnosis. Population controls were selected from the Swedish population registry, which includes all residents; controls were matched to cases based on calendar year of diagnosis as well as age (within 5-year categories), sex and study region. Deceased controls for deceased cases were selected from the death registry. Environmental and occupational exposures were assessed by a self-administered 20-page questionnaire sent out by post. The questionnaire solicited information regarding demographic

characteristics, occupational history, and other potential risk factors for cancer of the brain, and asked detailed questions on use of mobile phones and other wireless communication technologies, including year of first use, type of phone, average number of minutes of daily use, and side of head on which the phone had been used most frequently. A maximum of two reminders was sent if the questionnaire was not completed. A trained interviewer, using a structured protocol, carried out supplementary phone interviews to verify information provided in the questionnaire. Questionnaires were assigned an identification code such that the phone interviews and coding of data from questionnaires were blinded to case-control status. Study participants were asked again as to the side of head on which a phone had been used most frequently. [The Working Group noted that bias could be introduced by such an interview process; [Hardell et al. \(2002a\)](#) provided some information regarding classification of cases and controls with respect mobile-phone use based on the questionnaire, and the participants' classification after supplementary interview.] All study participants using mobile or cordless phones were sent an additional letter to re-solicit information on the side of the head on which the phone had been used most frequently. Details regarding the exposure assessment are reported in [Hardell et al. \(2006a, b\)](#). For deceased participants, an interview with a proxy (relative of the deceased) was conducted. Exposure was defined as reported use of a mobile phone and separately reported use of a cordless phone; exposure in the year immediately before case diagnosis or control selection was not included.

Cumulative lifetime use in hours was dichotomized by use of the median number of hours among controls as a cut-off point; and, lifetime use in hours was categorized into the following groups: 1–1000, 1001–2000, and ≥ 2000 hours. Three categories of time since exposure were considered > 1 –5 years, > 5 –10 years, and

> 10 years. Primary statistical analyses were conducted using unconditional and conditional logistic regression models with adjustment for sex, age, socioeconomic index, and year of diagnosis. Participation rates were 85% among cases and 84% among controls.

The analysis included 1148 cases with a histopathological diagnosis of glioma ([Hardell *et al.*, 2011a](#)). When mobile-phone users were compared with people who reported no use of mobile or cordless phones, or exposure > 1 year before the reference date, the odds ratio for glioma was reported to be 1.3 (95% CI, 1.1–1.6) ([Table 2.13](#)). For study participants who first used a mobile phone ≥ 10 years before the reference date, the odds ratio was 2.5 (95% CI, 1.8–3.3). This study included 123 cases of glioma and 106 controls among those who first used a mobile phone ≥ 10 years before the reference date. In terms of cumulative call time using a mobile phone, odds ratios for glioma increased with increasing categories of lifetime exposure. For the highest exposure group (> 2000 hours), the odds ratio was 3.2 (95% CI, 2.0–5.1). Use of cordless phones was also associated with glioma: the odds ratios for 1–1000 hours, 1001–2000 hours and > 2000 hours of use were 1.2 (95% CI, 0.95–1.4), 2.0 (95% CI, 1.4–3.1), and 2.2 (95% CI, 1.4–3.2), respectively. When considering age at first use, the odds ratio for mobile-phone use for all malignant tumours of the brain was 2.9 (95% CI, 1.3–6.0) for ages < 20 years, 1.3 (95% CI, 1.1–1.6) for ages 20–49 years, and 1.2 (95% CI, 1.0–1.5) for ages ≥ 50 years.

[The Working Group noted that information obtained from next of kin may be less reliable than that from living cases and controls. Analyses reported by Hardell *et al.* that are based solely on information obtained from living cases and controls are not affected by the same concerns about bias arising from information obtained from next of kin.] Excluding deceased cases (and affiliated controls) yielded odds ratios of 1.5 (95% CI, 1.1–1.9) for ever-use of analogue phones, 1.3

(95% CI, 1.1–1.6) for ever-use of digital phones, and 1.3 (95% CI, 1.1–1.6) for ever-use of cordless phones ([Hardell *et al.*, 2006a](#)).

Information on laterality of phone use was collected only from living cases and controls. Pooled case–control analyses were restricted to 905 living cases with malignant tumours of the brain and 2162 controls ([Hardell *et al.*, 2006b](#); [Hardell & Carlberg, 2009](#)). Of the cases, 663 were astrocytomas (grades I–IV), 93 were oligodendrogliomas, and the remainder were other malignant tumours of the brain. Participation rates were 90% among cases with malignant tumours and 89% among controls. For users of analogue and digital mobile phones, an increased odds ratio was seen for all malignant tumours of the brain and high-grade astrocytomas with ipsilateral use of mobile phones and with the tumour on the same side of the head, but no increased risk for contralateral use of mobile phones when compared with people who had not used mobile or cordless phones ([Table 2.13](#)). [The Working Group noted that a strength of this study was its use of population-based controls and the high participation rate of cases and of controls.]

An earlier report by Hardell *et al.* included a different set of cases of tumours of the brain ascertained during 1994–96 in Uppsala and 1995–96 in Stockholm ([Hardell *et al.*, 1999](#)). Participation rates were 90% among cases and 91% among controls. The analyses included 136 cases of malignant tumours of the brain (including 48 cases of glioblastoma, 46 cases of astrocytoma, and 19 cases of oligodendroglioma), with controls matched on sex, age, and region. Of the 425 controls, 161 reported ever having used a mobile phone and 85 reported having used a mobile phone for > 136 hours. Use of a mobile phone was not associated with an increased risk of malignant tumours of the brain (OR, 1.0; 95% CI, 0.7–1.4). [The Working Group noted that a strength of the study was the high participation rates of cases and controls.]

It is useful to consider variation in effect estimates by calendar period. Among cases ascertained during 1997–2000 there were 588 malignant tumours of the brain, including 415 cases of astrocytoma and 54 cases of oligodendroglioma. Ever-use of analogue phones yielded an odds ratio of 1.13 (95% CI, 0.82–1.57), with the odds ratio for ipsilateral use being 1.85 (95% CI, 1.16–2.96) and the odds ratio for contralateral use being 0.62 (95% CI, 0.35–1.11). Ever-use of digital phones yielded an odds ratio of 1.13 (95% CI, 0.86–1.48), with an odds ratio for ipsilateral use of 1.59 (95% CI, 1.05–2.41) and an odds ratio for contralateral use of 0.86 (95% CI, 0.53–1.39) ([Hardell et al., 2002b](#)).

Among cases ascertained in 2000–2003, there were 359 malignant tumours of the brain, including 248 cases of astrocytoma and 69 other malignant tumours. Ever-use of analogue phones yielded an odds ratio of 2.6 (95% CI, 1.5–4.3), with 3.1 (95% CI, 1.6–6.2) for ipsilateral use and 2.6 (95% CI, 1.3–5.4) for contralateral use; and, ever-use of digital phones yielded an odds ratio of 1.9 (95% CI, 1.3–2.7) with 2.6 (95% CI, 1.6–4.1) for ipsilateral use and 1.3 (95% CI, 0.8–2.2) for contralateral use. Estimates of an association tended to be larger for use beginning > 10 years before diagnosis ([Hardell et al., 2006c](#)).

(ii) Meningioma

See [Table 2.14](#)

In the case–control study of [Inskip et al. \(2001\)](#) mentioned above, interviews were conducted with a total of 197 cases of meningioma and 799 controls. Compared with non-users, self-reported regular users of mobile phones did not manifest excess risks of meningioma (OR, 0.8; 95% CI, 0.4–1.3).

The Finnish case–control study mentioned above ([Auvinen et al., 2002](#)) included 129 cases of meningioma. The odds ratio for ever-use was 1.1 (95% CI, 0.5–2.4), with a slightly higher odds ratio for use of analogue phones (OR, 1.5; 95% CI, 0.6–3.5). [This study was limited by the short

time since first use of a mobile phone for most people and by the uncertain mobile-phone use ascertainment from subscription information.]

In the pooled INTERPHONE analysis, 2409 cases of meningioma and 2662 controls were included ([INTERPHONE Study Group, 2010](#)). Participation rates were 78% for cases of meningioma and 53% for controls. For regular users, a reduced odds ratio was seen for cases of meningioma (OR, 0.79; 95% CI, 0.68–0.91) (see [Table 2.14](#)). Odds ratios of < 1.0 were also seen for all categories of time since start of use and for cumulative calls. Study participants who first used a mobile phone at least 10 years before interview did not show an increased risk of meningioma. Regarding cumulative number of calls, the group with highest exposure did not show an increased risk of glioma or meningioma. In terms of cumulative call time, all odds ratios were < 1.0 for all deciles of exposure except the highest (10th) decile of recalled cumulative call time (≥ 1640 hours). For this exposure group, the odds ratio for meningioma was 1.15 (95% CI, 0.81–1.62). Increased risk in the highest exposure decile of cumulative call time was more pronounced in short-term users, who started to use phones 1–4 years before the reference date, than in long-term users (≥ 10 years). Sensitivity analyses had little effect on estimated associations between mobile-phone use and risk of meningioma.

The analysis of TCSE and risk of meningioma in five INTERPHONE countries ([Cardis et al., 2011](#)) was based on 674 cases of meningioma and 1796 controls. In the highest quintile of TCSE, the odds ratio for meningioma was 0.90 (95% CI, 0.66–1.24). An odds ratio of 1.01 (95% CI, 0.75–1.36) was reported for the highest quintile of cumulative call time without hands-free devices. In terms of TCSE exposure ≥ 7 years before the reference date, there was no consistent dose–response pattern, but the odds ratio was elevated in the quintile of highest exposure (OR, 2.01; 95% CI, 1.03–3.93). In case-only analyses, the

Table 2.14 Case-control studies of meningioma and use of mobile phones

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell <i>et al.</i> (1999) Sweden, 1994–96	46	439	Population, matched on sex, age, region, and year of diagnosis	Self-administered standardized questionnaire	Meningioma	Never use of mobile phone Ever use	30 16	1.0 1.0 (0.5–2.3)		
Inskip <i>et al.</i> (2001) Phoenix, Boston, Pittsburgh, 1994–98.	197	799	Patients admitted to the same hospitals for a variety of non-malignant conditions.	Computer-assisted, personal interview in the hospital	Meningioma	Regular use Duration ≥ 5 yr Cumulative use (<i>h</i>) Never or rarely used < 13 13–100 > 100 > 500	32 6 165 8 13 11 6	0.8 (0.4–1.3) 0.9 (0.3–2.7) 1.0 0.7 (0.3–1.9) 1.1 (0.5–2.4) 0.7 (0.3–1.7) 0.7 (0.2–2.4)	Hospital, age, sex, race or ethnic group, proximity of residence to the hospital	There are results for other exposure metrics: average daily use, duration, year use began. Also results for laterality.
Auvainen <i>et al.</i> (2002) Finland, 1996	398 (129 meningiomas)	1990	Population Registry Centre of Finland	Information on subscriptions obtained from the two mobile-network providers operating in Finland in 1996	Meningioma (225.2)	Analogue Ever < 1 yr 1–2 yr > 2 yr Digital Ever	8 3 3 2 3	1.5 (0.6–3.5) 2.3 (0.6–9.2) 1.6 (0.4–6.1) 1.0 (0.2–4.4) 0.7 (0.2–2.6)	Age, sex	Cases aged 20–69 yr

Table 2.14 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell et al. (2006a) Sweden, 1997–2003	916	2162	Population.	Self-administered questionnaire	Meningioma	Never used mobile or cordless phone	455	1.0	Age, sex, SEI, year of diagnosis	Ipsilateral use of analogue and digital phones was associated with meningioma (analogue: OR, 1.3; 95% CI, 0.9–2.0; digital: OR, 1.4; 95% CI, 1.0–1.8), contralateral use was not (OR, 1.2; 95% CI, 0.7–1.8; and OR, 1.1; 95% CI, 0.8–1.5, respectively).
						<i>Cumulative use, analogue (h)</i>				
						1–500	99	1.3 (1.0–1.7)		
						501–1000	8	1.1 (0.5–2.6)		
						> 1000	6	1.4 (0.5–3.8)		
						<i>Cumulative use, digital (h)</i>				
						1–500	268	1.1 (0.9–1.3)		
						501–1000	18	1.0 (0.6–1.8)		
						> 1000	9	0.7 (0.3–1.4)		
						<i>Latency, analogue (yr)</i>				
						> 1–5	32	1.2 (0.8–1.8)		
						> 5–10	47	1.2 (0.8–1.8)		
						> 10	34	1.6 (1.0–2.5)		

Table 2.14 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
INTERPHONE Study Group (2010)	2409	2662	Population (except United Kingdom: GP patients)	Interviewer-administered standardized questionnaire	Meningioma (D32.0, D32.9, D42.0, D42.9, C70.0, C70.9)	Never regular use of mobile phone	1147	1.00	Sex, age, study centre, ethnicity (in Israel), and education	
Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden, United Kingdom, 2000–04						Ever use	1262	0.79 (0.68–0.91)		
						<i>Time since start of use (yr)</i>				
						1–1.9	178	0.90 (0.68–1.18)		
						2–4	557	0.77 (0.65–0.92)		
						5–9	417	0.76 (0.63–0.93)		
						≥ 10	110	0.83 (0.61–1.14)		
						<i>Cumulative call time with no hands-free devices (h)</i>				OR, 4.80 (95% CI, 1.49–15.4) in short-term users (start of mobile-phone use 1–4 yr before reference date) with cumulative call time ≥ 1640 h (based on 22 cases)
						< 5	160	0.90 (0.69–1.18)		
						5–12.9	142	0.82 (0.61–1.10)		
						13–30.9	144	0.69 (0.52–0.91)		
						31–60.9	122	0.69 (0.51–0.94)		
						61–114.9	129	0.75 (0.55–1.00)		
						115–199.9	96	0.69 (0.50–0.96)		
						200–359.9	108	0.71 (0.51–0.98)		
						360–734.9	123	0.90 (0.66–1.23)		
						735–1639.9	108	0.76 (0.54–1.08)		
						≥ 1 640	130	1.15 (0.81–1.62)		

Table 2.14 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Cardis <i>et al.</i> (2011) Australia, Canada, France, Israel, Italy, New Zealand, 2000–04	674	1796	Population	Interviewer-administered standardized questionnaire	Meningioma	RF TCSE (J/kg)			Sex, age, study centre, ethnicity (in Israel) and education	Interpretation of OR is most meaningful when compared with the corresponding OR for comparable exposure surrogates of mobile-phone use
						Never regular user	294	1.0		Subjects with tumour centre estimated
						< 76.7	103	0.90 (0.67–1.21)		by a neuro-radiologist or by means of a computer algorithm
						76.7–284.1–978.9–3123.9+	71 56 62 88	0.74 (0.53–1.04) 0.56 (0.39–0.80) 0.72 (0.51–1.02) 0.90 (0.66 to 1.24)		Exposure ≥ 7 yr before reference date: OR, 2.01 (95% CI, 1.03–3.93), for highest quintile

h, hour; OR, odds ratio; RF, radiofrequency radiation; SEI, socioeconomic index; TCSE, total cumulative specific energy; yr, year

odds ratio for having the centre of the tumour within the most exposed area was 1.34 (95% CI, 0.55–3.25) in those who reported starting to use a mobile phone ≥ 10 years previously.

[Hardell et al. \(2006a\)](#) reported the results of a pooled analysis of case-control studies of benign tumours of the brain and use of mobile and cordless phones that included 1254 cases of benign tumours, of which 916 were meningioma; deceased cases (and controls) were not included in this analysis. An odds ratio of 1.3 (95% CI, 0.99–1.7) was reported for meningioma when users of analogue mobile phones were compared with people who reported no use of mobile or cordless phones, or exposure ≤ 1 year before the reference date. The odds ratio was 1.1 (95% CI, 0.9–1.3) for users of digital mobile phones and 1.1 (95% CI, 0.9–1.4) for users of cordless phones. Study participants who first used an analogue, digital, or cordless phone at least 10 years previously showed increased risks of meningioma, although estimates were imprecise (OR, 1.6; 95% CI, 1.0–2.5; OR, 1.3; 95% CI, 0.5–3.2; OR, 1.6; 95% CI, 0.9–2.8, respectively).

(iii) Acoustic neuroma

See [Table 2.15](#)

[Inskip et al. \(2001\)](#) included a total of 96 cases with acoustic neuroma and 799 controls. Compared with non-users, self-reported regular users of mobile phones did not manifest excess risks of acoustic neuroma (OR, 1.0; 95% CI, 0.5–1.9).

A case-control study of 90 cases of acoustic neuroma and 86 controls selected from among other patients was conducted in a hospital in New York ([Muscat et al., 2002](#)). Subjects were interviewed regarding use of mobile phones and other factors. Analysis of reported histories of mobile-phone use, adjusting for sociodemographic factors and date of interview, yielded a set of odds-ratio estimates that were close to the null value for cumulative hours of use and years of use. [The Working Group noted that numbers

were small, exposure levels were low, and time since first use was short.]

[Schoemaker et al. \(2005\)](#) reported pooled results on acoustic neuroma from a subset of the INTERPHONE countries (the five north European countries: Denmark, Finland, Norway, Sweden, and the United Kingdom). There was no indication of an increased risk of acoustic neuroma associated with mobile-phone use ([Table 2.15](#)). Similar negative findings were reported by the INTERPHONE groups in France ([Hours et al., 2007](#)) and Germany ([Schlehofer et al., 2007](#)), and from a case-control study in Japan ([Takebayashi et al., 2006](#)).

In Japan, [Sato et al. \(2011\)](#) identified a series of cases of acoustic neuroma diagnosed between 2000 and 2006 in 22 participating hospitals with neurosurgery departments (32% of hospitals solicited). Of 1589 cases identified, 816 agreed to respond to a self-administered questionnaire, received by post, focusing on history of mobile-phone use and history of pre-diagnosis symptoms. Two case series were constituted consisting of: (a) 180 cases among mobile-phone users whose symptoms had not appeared 1 year before diagnosis; and (b) 150 cases among mobile-phone users whose symptoms had not yet appeared 5 years before diagnosis. In each series, the investigators then compared laterality of the tumour with laterality of mobile-phone use and, using a formula described by [Inskip et al. \(2001\)](#), they derived an estimate of relative risk of acoustic neuroma related to various metrics of mobile-phone use. Overall, there was no excess risk of acoustic neuroma among ever-users of mobile phones. However, among some subgroups, namely those with the highest duration of daily calls, there were estimates of high risk ratios in the range of 2.74 (95% CI, 1.18–7.85) to 3.08 (95% CI, 1.47–7.41). This excess appeared to be restricted to a small group of cases who were persistently among the highest users during the past 5 years. The authors considered various alternative explanations for this finding,

Table 2.15 Case-control studies of acoustic neuroma and use of mobile phones

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Inskip et al. (2001) USA, 1994-98	96	799	Patients admitted to the same hospitals for a variety of non-malignant conditions	Computer-assisted personal interview in the hospital	Acoustic neuroma	Regular use Duration ≥ 5 yr	22 5	1.0 (0.5-1.9) 1.9 (0.6-5.9)	Hospital, age, sex, race or ethnic group, proximity of residence to the hospital	Analyses by cumulative use showed no associations. Analyses of laterality of tumour by laterality of phone use showed no associations. Very few subjects with long-term exposure. Response rates were 92% for cases and 86% for controls. In groups with highest duration of daily calls: RR ranged from 2.74 (95% CI, 1.18-7.85) to 3.08 (95% CI, 1.47-7.41)
Muscat et al. (2002) New York City, 1997-99	90	86	In-patients with non-malignant conditions from the same hospitals	Interviews with structured questionnaire	Acoustic neuroma (225.1)	Cumulative use (h): 0 1-60 > 60 Years of use: 0 1-2 3-6	72 9 9 72 7 11	1.0 0.9 (0.3-3.1) 0.7 (0.2-2.6) 1.0 0.5 (0.2-1.3) 1.7 (0.5-5.1)	Age, education, sex, study centre, occupation categories, and date of interview	Also presented as h/mo, with similar results. In mobile-phone users tumour was most often on contralateral side.

Table 2.15 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Schoemaker et al. (2005) Denmark, Finland, Norway, Sweden, United Kingdom, 1999–2004	678	3553	Population (except United Kingdom: GP patients)	Interviewer-administered standardized questionnaire	Acoustic neuroma (D33.3)	Never regular use of mobile phone Regular use	316 360	1.0 0.9 (0.7–1.1)	Educational level and combinations of interview year and interview lag time	Matched for centre, region, 5-yr age group, sex
						<i>Time since start of use (yr)</i> 1.5–4 5–9 ≥ 10 <i>P</i> for trend	174 139 47	0.8 (0.7–1.0) 0.9 (0.7–1.2) 1.0 (0.7–1.5) 0.9		
						<i>Cumulative use (h)</i> < 116 116–534 > 534 <i>P</i> for trend	168 89 94	0.9 (0.7–1.1) 0.9 (0.7–1.2) 0.9 (0.7–1.2) 0.5		
Takebayashi et al. (2006) Japan, 2000–04	101	339	Population (random-digit dialling)	Interviewer-administered standardized questionnaire	Acoustic neuroma (D33.3)	Never regular use of mobile phone Regular use	46 51	1.0 0.73 (0.43–1.23)	Education, marital status	Matched for age, sex, residency
						<i>Time since start of use (yr)</i> < 4 4–7 ≥ 8 <i>P</i> for trend	26 21 4	0.70 (0.39–1.27) 0.76 (0.38–1.53) 0.79 (0.24–2.65) 0.70		
						<i>Cumulative use (h)</i> < 300 300–900 > 900 <i>P</i> for trend	35 9 7	0.67 (0.38–1.17) 1.37 (0.54–3.50) 0.67 (0.25–1.83) 0.69		

Table 2.15 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Ha et al. (2007) France, 2001–03	109	214	Population (electoral rolls)	Interviewer-administered standardized questionnaire	Acoustic neuroma (D33.3)	Never regular use of mobile phone Regular use	51 58	1.0 0.92 (0.53–1.59)	SES, tobacco consumption, noise exposure	Sex, age (± 5 yr), place of residence
						<i>Duration of use (mo)</i> < 16 16–27 27–46 > 46	19 17 8 14	1.21 (0.55–2.69) 1.33 (0.58–3.03) 0.63 (0.26–1.53) 0.66 (0.28–1.57)	OR per 1 year, 0.96 (0.84–1.10)	
						<i>Cumulative use (h)</i> < 20 20–80 80–260 > 260	14 15 13 16	1.06 (0.48–2.36) 0.87 (0.40–1.91) 0.85 (0.38–1.88) 0.92 (0.41–2.07)	OR per 80 h, 1.0 (0.96–1.03)	
Schlehofer et al. (2007) Germany, 1976–88	97	194	Population	Interviewer-administered standardized questionnaire	Acoustic neuroma (D33.3)	Never regular use of mobile phone Regular use	68 29	1.0 0.67 (0.38–1.19)	SES, urbanity	Matched for centre, age, sex
						<i>Time since start of use (yr)</i> 1–4 5–9 ≥ 10	20 8 0	0.78 (0.40–1.50) 0.53 (0.22–1.27) -		
						<i>Cumulative use (h)</i> < 44 44–195 > 195	16 7 5	1.04 (0.51–2.16) 0.58 (0.22–1.48) 0.35 (0.12–1.01)		

Table 2.15 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Sato <i>et al.</i> (2011) Japan, 2000–06	787	787 (case–case)	Note: the affected ear is the case side; the opposite ear is regarded as the control.	Mailed questionnaire about history of mobile-phone use	Acoustic neuroma	Overall, for regular mobile-phone use until one yr before diagnosis	180	1.08 (0.93–1.28)	Same patients	The authors interpret these significant results with caution, mentioning detection and recall bias as possibilities.
						Overall, for regular mobile-phone use until 5 yr before diagnosis	150	1.14 (0.96–1.40)		
						Weighted daily average call duration > 20 min, 1 yr before diagnosis	23	2.74 (1.18–7.85)		
						Weighted daily average call duration > 20 min, 5 yr before diagnosis	33	3.08 (1.47–7.41)		

Table 2.15 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
INTERPHONE Study Group (2011) Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden, United Kingdom, 2000–04	1105	2145	Population (except United Kingdom: GP patients)	Interviewer-administered standardized questionnaire	Schwannoma of the acoustic nerve (ICD-9 code 225.1 or ICD-10 code D33.3, and ICD-O topography code C72.4 and morphology code 9560/0)	Never regular use of mobile phone Regular use <i>Time since start of use (yr)</i> 5–9 ≥ 10 <i>Cumulative call time (h) with no hands-free devices</i> < 5 5–12.9 13–30.9 31–60.9 61–114.9 115–199.9 200–359.9 360–734.9 735–1639.9 ≥ 1640	801 304 236 68 42 30 40 36 21 22 49 26 22 32	1.00 0.95 (0.77–1.17) 0.99 (0.78–1.24) 0.83 (0.58–1.19) 1.07 (0.69–1.68) 1.06 (0.60–1.87) 1.32 (0.80–2.19) 0.86 (0.52–1.41) 0.63 (0.35–1.13) 0.71 (0.39–1.29) 0.83 (0.48–1.46) 0.74 (0.42–1.28) 0.60 (0.34–1.06) 2.79 (1.51–5.16)	Sex, age, study centre, ethnicity (in Israel), and education	Data are given only for exposure up to 5 yr before reference date (risk estimates were generally smaller when exposure up to 1 yr before reference date was considered) When stratifying for duration of use, OR was highest in long-term users (start of mobile-phone use ≥ 10 yr ago): OR, 1.93 (95% CI, 1.10–3.38). Ipsilateral use: OR, 3.74 (95% CI, 1.58–8.83); contralateral use: OR, 0.48 (95% CI, 0.12–1.94)

Table 2.15 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell <i>et al.</i> (2006a), Sweden, 2000–03	243		Population	Self-administered standardized questionnaire	Acoustic neuroma	Never use of mobile or cordless phone	88	1.0	Age, sex, SEI, and year of diagnosis	
						Ever use of analogue phone	68	2.9 (2.0–4.3)		
						Ever use of digital phone	105	1.5 (1.1–2.1)		
						Ever use of cordless phone	96	1.5 (1.0–2.0)		
						Cumulative call time, analogue (h)				
						1–500	55	2.8 (1.8–4.2)		
						501–1000	7	3.3 (1.3–8.0)		
						> 1000	6	5.1 (1.9–14)		
						Cumulative call time, digital (h)				
						1–500	83	1.4 (1.0–2.0)		Users of analogue phone (> 10 yr) showed OR, 3.1 (95% CI, 1.7–5.7)
						501–1000	10	1.8 (0.8–3.8)		
						> 1000	12	3.1 (1.5–6.4)		
						Cumulative call time, cordless (h)				
						1–500	60	1.3 (0.9–1.9)		
						501–1000	15	1.6 (0.9–3.0)		
						> 1000	21	2.1 (1.2–3.7)		

GP, general practitioner; h, hour; min, minute; mo, month; OR, odds ratio; SEI, socioeconomic index; SES, socioeconomic status; yr, year

including selection bias and recall bias, and they concluded that it was unclear whether the finding was a consequence of bias.

The pooled INTERPHONE analysis for acoustic neuroma ([INTERPHONE Study Group, 2011](#)) followed in general the same methodology as the analyses for glioma and meningioma described above ([INTERPHONE Study Group, 2010](#)). Patients diagnosed with a schwannoma of the acoustic nerve in the study regions during study periods of 2–4 years between 2000 and 2004 were included in the study. For each case, two age-, sex- and study-region-matched controls were recruited. Controls were either specifically sampled for the cases of acoustic neuroma, taken from the pool of INTERPHONE controls drawn for all tumours together, or obtained with a combination of both approaches. In total, 1105 cases (participation rate, 82%) were included in the analyses, together with 2145 controls (participation rate, 53%). The odds ratio for regular use was 0.85 (95% CI, 0.69–1.04) when recording exposure at 1 year before the reference date and 0.95 (95% CI, 0.77–1.17) when recording exposure at 5 years before the reference date. For cumulative call time, the highest odds ratios were observed in the highest category of use: the odds ratios for ≥ 1640 hours were 1.32 (95% CI, 0.88–1.97) when recording exposure at 1 year and 2.79 (95% CI, 1.51–5.16) when recording exposure at 5 years. There was, however, no consistent trend in the exposure–response relationship in the first nine deciles of exposure. Stratifying the analyses according to time since start of mobile-phone use resulted in an increased odds ratio for heavy users of mobile phones only in long-term users (OR, 1.93; 95% CI, 1.10–3.38, based on 37 cases). This risk estimate was more pronounced with respect to ipsilateral use (OR, 3.74; 95% CI, 1.58–8.83, based on 28 cases) and decreased with respect to contralateral use (OR, 0.48; 95% CI, 0.12–1.94, based on 4 cases). Exclusion of participants with an implausible amount of use (> 5 hours per day) resulted in a decrease in odds ratio for exposure

up to 1 year before the reference date, but had little impact on the results of the analyses of exposure up to 5 years before the reference date. The results for cumulative number of calls were broadly similar, but risk estimates were smaller.

Overall, these results were broadly similar to the results for glioma from the INTERPHONE study. [The same methodological limitations were of concern, mainly selection and recall bias. Diagnostic bias was also of concern: patients with acoustic neuroma who use mobile phones may be diagnosed earlier than non-users, since acoustic neuroma affects hearing capability. However, such an effect would be expected to be most relevant for recent users, but of little relevance for exposure 5 years before diagnosis. On the other hand, prodromal symptoms might discourage cases from becoming mobile-phone users. Again, such an effect would be most relevant in the analysis of most recent use of mobile phones, but not in the analysis of exposure at earlier dates. There is also uncertainty as to how early symptoms may affect the preferred side of use. Regarding confounding, socioeconomic status, ionizing radiation and loud noise were considered, with little effect on the results.]

[Hardell et al. \(2006a\)](#) reported the results of a pooled analysis of associations between use of mobile and cordless phones and risk of benign tumours of the brain that included 243 cases of acoustic neuroma. An increased odds ratio was reported for acoustic neuroma (OR, 2.9; 95% CI, 2.0–4.3) when users of analogue mobile phones were compared with people who reported no use of mobile or cordless phones, or exposure ≤ 1 year before the reference date. The odds ratio was 1.5 (95% CI, 1.1–2.1) for users of digital mobile phones and 1.5 (95% CI, 1.04–2.0) for users of cordless phones. Study participants who first used an analogue phone at least 10 years before the reference date showed increased risks (OR, 3.1; 95% CI, 1.7–5.7), but users of digital or cordless phones did not. For users of analogue mobile phones, an increased odds ratio was

seen for ipsilateral use (OR, 3.0; 95% CI, 1.9–5.0) and contralateral use (OR, 2.4; 95% CI, 1.4–4.2) when compared with people who had not used mobile or cordless phones. For users of digital mobile phones, an increased odds ratio was seen for acoustic neuroma with ipsilateral use (OR, 1.7; 95% CI, 1.1–2.6), but not for contralateral use (OR, 1.3; 95% CI, 0.8–2.0) when compared with people who had not used mobile or cordless phones. Similar associations were found for use of cordless phones (ipsilateral use: OR, 1.7; 95% CI, 1.1–2.6; and contralateral use: OR, 1.1; 95% CI, 0.7–1.7, respectively) ([Schüz et al., 2006c](#)).

(iv) *All cancers of the brain combined*

See [Table 2.16](#)

In several studies already referred to above, analyses were presented for all cancers of the brain combined ([Hardell et al., 2000, 2001, 2011a](#); [Inskip et al., 2001](#); [Auvinen et al., 2002](#)). Only in [Hardell et al. \(2011a\)](#) were risks of cancer significantly elevated with prolonged use of mobile phones. A study in France by [Spinelli et al. \(2010\)](#) found no significant excess risks.

(v) *Other cancers of the brain*

A pooled analysis by [Hardell et al. \(2011a\)](#) included 103 cases with a histopathological diagnosis of malignant tumour of the brain other than glioma. Odds ratios for malignant tumours other than glioma by category of duration of mobile-phone use were 1.0 (95% CI, 0.6–1.6) for 1–1000 hours, 1.4 (95% CI, 0.4–4.8) for 1001–2000 hours, and 1.2 (95% CI, 0.3–4.4) for > 2000 hours.

(vi) *Pituitary tumours*

See [Table 2.17](#)

In a Japanese study, 102 cases of pituitary adenoma were included, together with 161 individually matched controls ([Takebayashi et al., 2008](#)). Neither regular use of mobile phones (OR, 0.90; 95% CI, 0.50–1.61) nor cumulative duration of use in years and cumulative call time in hours was associated with an increased risk of pituitary tumours.

In a population-based case–control study from south-eastern England, 291 cases of pituitary tumour diagnosed between 2001 and 2005 were included, together with 630 controls that were frequency-matched for sex, age, and health-authority of residence ([Schoemaker & Swerdlow, 2009](#)). The participation rate was 63% for cases and 43% for controls. Data were collected with a face-to-face interview at the subject's home or another convenient place. Regular use was not associated with an increased risk (OR, 0.9; 95% CI, 0.7–1.3) nor was any other exposure surrogate. Stratified analyses for analogue or digital mobile-phone user did not indicate consistent exposure–response associations.

(d) *Some reviews, meta-analyses, and other studies*

Various meta-analyses and other comparisons of the accumulating data on mobile-phone use and tumours of the brain have been published ([Hardell et al., 2003, 2007a, 2008](#); [Lahkola et al., 2006](#); [Kan et al., 2008](#); [Ahlbom et al., 2009](#); [Hardell & Carlberg, 2009](#); [Khurana et al., 2009](#); [Myung et al., 2009](#)). Such analyses are potentially useful for characterizing the accumulating evidence and for exploring heterogeneity of findings among studies, along with determinants of any observed heterogeneity. [The Working Group based its conclusions on review of the primary studies.]

2.3.2 Leukaemia and lymphoma

(a) *Leukaemia*

There have been four epidemiological studies on leukaemia and use of mobile phones.

In an early cohort study of 285 561 users of analogue phones, identified based on records from two mobile-phone providers in the USA in 1993, mortality attributable to leukaemia was not elevated among users of hand-held phones relative to users of non-hand-held phones (mostly car phones) ([Dreyer et al., 1999](#); [Table 2.18](#)). [A

Table 2.16 Case-control studies of all cancers of the brain and use of mobile phones

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell <i>et al.</i> (2000, 2001) Uppsala-Orebro region and Stockholm region, Sweden, 1994-96	209 cases of brain tumours diagnosed among people aged 20-80 yr at diagnosis	425	Population register: 1:2 case:control ratio with matching on age and sex, and drawn from the same geographical areas as the cases	Self-administered structured, mailed questionnaire	All malignant tumours of the brain. Benign tumours of the brain included from Stockholm in 1996, as part of feasibility study.	No use of mobile or cordless phone, or exposure ≤ 1 yr before reference date	78	1 0.98 (0.69-1.41)	Sex, age (as a continuous variable). Radiotherapy, diagnostic X-ray, asbestos, solvents, smoking	Participation rate was 90% for cases and 91% for controls. Increased risk for tumour in the temporal or occipital lobe on same side as cell-phone use (OR, 2.62; 95% CI, 1.02-6.71). Contralateral use did not increase the risk (OR, 0.97; 95% CI, 0.36-2.59). Deceased cases were not included. This analysis encompassed the case-control data included in Hardell <i>et al.</i> (2000)
Inskip <i>et al.</i> (2001) USA, 1994-98	782	799	Patients admitted to the same hospitals for a variety of non-malignant conditions.	Computer-assisted in person interview in the hospital, history of mobile-phone use	All brain	No use Regular use Duration ≥ 5 yr	471 139 22	1.0 0.8 (0.6-1.1) 0.9 (0.5-1.6)	Hospital, age, sex, race or ethnic group, proximity of residence to the hospital	Analyses by cumulative use showed no associations. Very few subjects with long-term exposure. Response rates 92% for cases and 86% for controls.

Table 2.16 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Auvinen et al. (2002) Finland, 1996	398	1990	Population Registry Centre of Finland	Information on subscriptions obtained from the two mobile-network providers operating in Finland in 1996	All brain (191 and 225.2)	<i>Analogue</i> Ever < 1 yr 1–2 yr > 2 yr <i>Digital</i> Ever < 1 yr 1–2 yr > 2 yr	40 8 15 17 16 4 11 1	1.6 (1.1–2.3) 1.6 (0.7–3.6) 1.5 (0.9–2.8) 1.6 (0.9–2.8) 0.9 (0.5–1.5) 0.6 (0.2–1.6) 1.2 (0.6–2.3) 0.6 (0.1–4.5)	Age, sex	Cases aged 20–69 yr
Spinelli et al. (2010) France, 2005	122	122	In-patients from neurosurgery departments of the same hospitals; unrelated to cancer	Face-to-face interviews with standardized questionnaire; and self-administered questionnaire	Malignant primary tumours of the brain	<i>Global cellular-phone use (hours-year)</i> 0 ≤ 4 4–36 ≥ 36	37 8 58 13	1 0.86 (0.30–2.44) 1.45 (0.75–2.80) 1.07 (0.41–2.82)	Age, sex	

Table 2.16 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell <i>et al.</i> (2011a)	1251 cases of malignant brain tumours diagnosed during 1997–2003 among people aged 20–80 yr at diagnosis	2438 controls	Population register. 1:1 case:control ratio with matching on age and sex, and drawn from the same region as the cases. For deceased cases, controls drawn from death registry. 1:1 matching on year of death, sex, age, and medical region	Self-administered structured, mailed questionnaire. For deceased cases and controls, mailed questionnaire was completed by relative of decedent.	All malignant tumours of the brain	No use of mobile or cordless phone, or exposure ≤ 1 yr before reference date Mobile-phone use: Ever 1–1000 h 1001–2000 h > 2000 h	677 574 466 47 61	1.00 1.3 (1.1–1.5) 1.2 (1.0–1.4) 1.8 (1.1–2.7) 3.0 (1.9–4.8)	Sex, age (as a continuous variable), SEI code, year of diagnosis	Participation rates were 85% for cases and 84% for controls. This analysis encompassed the data presented in earlier papers on pooled case–control studies of malignant tumours of the brain among living cases diagnosed in 1997–2003
					Malignant tumours of the brain other than glioma (<i>n</i> = 103)	Mobile-phone use: 1–1000 h 1001–2000 h > 2000 h	39 3 3	1.0 (0.6–1.6) 1.4 (0.4–4.8) 1.2 (0.3–4.4)		

h, hour or hours; SEI, socioeconomic index; yr, year

Table 2.17 Case-control studies of cancers of the pituitary and use of mobile phones

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Takebayashi et al. (2008) Japan, 2000–04	101	161	Population (random-digit dialling)	Interviewer-administered standardized questionnaire	Pituitary adenoma (ICD code not reported)	Never regular use of mobile phone	39	1.0	Education, marital status	Matched for age (5 yr), sex, residency
						Regular use	62	0.90 (0.50–1.61)		
						<i>Time since start of use (yr)</i>				
						< 2.2	14	0.86 (0.39–1.88)		
						2.2–4.69	13	0.75 (0.31–1.81)		
						4.7–6.5	22	1.64 (0.74–3.66)		
						> 6.5	13	0.75 (0.31–1.82)		
						<i>P</i> for trend		0.89		
						<i>Cumulative use (h)</i>				
						< 39	15	1.00 (0.46–2.16)		
Schoemaker & Sverdlow (2009) United Kingdom, 2001–05	291	630	Population (from GP patient list)	Interviewer-administered standardized questionnaire	Pituitary tumour (C75.1, D35.2, D44.3)	Never regular use of mobile phone	116	1.0	Age, sex, category, geographic area, reference date, and Townsend deprivation score	
						Regular use	175	0.9 (0.7–1.3)		
						<i>Time since start of use (yr)</i>				
						1.5–4	89	1.0 (0.7–1.5)		
						5–9	62	0.8 (0.5–1.2)		
						10–17	24	1.0 (0.5–1.9)		
						<i>P</i> for trend		0.7		
						<i>Cumulative use (h)</i>				
						< 113	79	0.9 (0.6–1.3)		
						113–596	44	1.1 (0.7–1.8)		
> 596	51	1.1 (0.7–1.7)								
<i>P</i> for trend		0.9								

GP, general practitioner; h, hour or hours; yr, year

limitation of this study was that there were only four deaths due to leukaemia among users of hand-held phones, as the study was truncated – with no access to mortality data beyond 1 year – as a result of a legal proceeding.]

A study of cancer incidence in a cohort of 420 095 users of mobile phones in Denmark found no evidence of an elevated risk of leukaemia in males or females (SIR, 1.05; 95% CI, 0.96–1.15) (Schüz *et al.*, 2006c; Table 2.18). The incidence of leukaemia was not increased in any of the reported time intervals since first subscription. Details concerning the design of the study were discussed above (Section 2.3.1). [The results for leukaemia were not reported separately by subtype.]

A hospital-based case–control study of adult-onset leukaemia in Thailand conducted between 1997 and 2003 (180 cases, 756 hospital controls) reported an odds ratio for all leukaemias combined of 1.5 (95% CI, 1.0–2.4) (Kaufman *et al.*, 2009; Table 2.19). Overall, the duration of mobile-phone use was short (median, 24–26 months). The results were similar for acute myeloid leukaemia, chronic myeloid leukaemia and chronic lymphocytic leukaemia. There were no trends in associations of all leukaemias with duration of ownership, lifetime hours of use, or amount of use per year. The odds ratio was highest for persons reporting exclusive use of GSM (Global System for Mobile Communications) services. Using an categorization ad hoc into “high risk” and “low risk” groups of mobile-phone users based on phone characteristics, the authors reported an odds ratio of 1.8 for high-risk versus low-risk users (95% CI, 1.1–3.2). [It was unclear to the Working Group as to how the “high risk” and “low risk” groups were derived and whether it was done *a priori* or *a posteriori*.]

In a study conducted in the United Kingdom between 2003 and 2009, which included 806 cases and 585 controls who were non-blood relatives, regular use of a mobile phone (defined as at least one call per week for at least 6 months) was

not associated with the incidence of leukaemia (Cooke *et al.*, 2010; Table 2.19). Risk was not significantly associated with years since first use, lifetime years of use, cumulative number of calls, or cumulative hours of use. Among people who reported using a phone for ≥ 15 years since first use, the odds ratio was 1.87 (95% CI, 0.96–3.63; 50 exposed cases); however, there was no apparent trend with years since first use. There also was no apparent trend in risk with cumulative hours of use. Findings were similar for digital and analogue phones. There was no apparent variation in results by subtype of leukaemia and no trend in risk with years since first use, years of use, or cumulative hours of use for any subtype. [Only 50% of potential cases participated, with the usual reasons for non-participation being death or disability related to leukaemia.]

(b) Lymphoma

In a population-based case–control study conducted in Sweden between 1999 and 2002 (910 cases, 1016 controls), neither mobile-phone use nor cordless-phone use was significantly associated with risk of NHL overall, nor for the B-cell subtype in particular (90% of the cases) (Hardell *et al.*, 2005; Table 2.19). High odds ratios were reported for some categories of use of cordless phones for T-cell lymphomas, based on very small numbers. Cases in this study were diagnosed between the ages of 18 and 74 years. Males and females were included, but the main results concerning mobile-phone use were presented for both sexes combined.

A population-based case–control study of NHL conducted in the USA between 1998 and 2000 (551 cases, 462 controls) also reported predominantly null findings (Linnet *et al.*, 2006; Table 2.19). Several exposure metrics of mobile-phone use were presented (latency, duration, amount of exposure), but overall there was no consistent trend in risk. Risk of NHL was not associated with minutes per week of use of mobile telephones, duration of use, cumulative

Table 2.18 Cohort studies of leukaemia, lymphoma, and other cancers, and use of mobile phones

Reference, study location and period	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/deaths	Relative risk (95% CI)	Covariates	Comments
Dreyer et al. (1999) USA, 1993	285 561	1993	Records of mobile-phone service providers	Leukaemia (204–207)	Hand-held phones < 2 min/d ≥ 2 min/d	2 2	SMR 1.6 4.9	Age, sex, metropolitan area	Mortality study; effect estimate = SMR; SMR for non-hand-held phones (non-exposed), 7.0
Schüz et al. (2006c) Denmark, 1982–2002	420 095	1982–2002	Records of mobile-phone service providers	Leukaemia (204–207)	Latency (yr) < 1 1–4 5–9 ≥ 10	33 151 135 32	SIR 1.09 (0.75–1.52) 1.05 (0.90–1.24) 0.92 (0.77–1.08) 1.08 (0.74–1.52)	Age, sex, calendar period of observation	Incidence study; cannot be certain who the user was; phones used under business accounts not included; details of phone use not available
Schüz et al. (2006c) Denmark, 1982–2002	65 542	1982–2002	Records of cellular service providers	Female breast (174)	Subscriber	711	1.04 (0.97–1.12)	Age, calendar year of observation	Incidence study; cannot be certain who the user was; phones used under business accounts not included; details of phone use not available
Schüz et al. (2006c) Denmark, 1982–2002	420 095	1982–2002	Records of cellular service providers	Eye (190)	Subscriber	38 (males) 6 (females)	0.94 (0.66–1.29) 1.10 (0.40–2.39)	Age, calendar year of observation	Incidence study; cannot be certain who the user was; phones used under business accounts not included; details of phone use not available

Table 2.18 (continued)

Reference, study location and period	Total No. of subjects	Follow-up period	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Covariates	Comments
Schüz <i>et al.</i> (2006c) Denmark, 1982–2002	357 553	1982–2002	Records of cellular service providers	Testis (186)	Subscriber	522	1.05 (0.96–1.15)	Age, calendar year of observation	Incidence study; cannot be certain who the user was; phones used under business accounts not included; details of phone use not available
Schüz <i>et al.</i> (2006c) Denmark, 1982–2002	420 095	1982–2002	Records of cellular service providers	Salivary gland (142)	Subscriber	26 (males) 0 (females)	0.86 (0.56–1.26) 0.00 (0.00–1.02)	Age, calendar year of observation	Incidence study; cannot be certain who the user was; phones used under business accounts not included; details of phone use not available

d, day; h, hour; SIR, standardized incidence ratio; SMR, standardized mortality ratio; yr, year

lifetime use, nor year of first use. The incidence of NHL was elevated among men who had used cell phones for > 8 years (OR, 2.4; 95% CI, 0.8–7.0, based on 17 cases).

2.3.3 Uveal (ocular) melanoma

In a study of 118 cases and 475 controls, [Stang et al. \(2001\)](#) reported an association between assessed occupational use of mobile phones and risk of uveal melanoma ([Table 2.19](#)). Methods for this study are described in greater detail in Section 2.1.3. [There was no adjustment for exposure to ultraviolet radiation, which may be a relevant confounder. Exposure information was crude, and concerns were raised about possible bias in the self-reported data in this small study ([Johansen et al., 2002](#)).]

The same investigators carried out a much larger case–control study (455 cases; aged 20–74 years) between 2002 and 2004 using a more refined exposure-assessment instrument ([Stang et al., 2009; Table 2.19](#)). Three control series were enrolled. One included 827 population controls selected from census data from local districts and matched to case patients on age (5-year age groups), sex and region of residence. A second control series included 180 ophthalmology patients – recruited from practices of the same ophthalmologists who had referred the case patients with uveal melanoma – who had a newly diagnosed benign disease of the eye. The third control group consisted of 187 siblings of cases. Participation rates were 94% for the case patients, 57% for the population and sibling control subjects, and 52% for the ophthalmologists control subjects. The risk of uveal melanoma was not associated with regular use of mobile phones based on any of the three control series (with population controls: OR, 0.7; 95% CI, 0.5–1.0; with ophthalmologist controls: OR, 1.1; 95% CI, 0.6–2.3; and with sibling controls: OR, 1.2 95% CI, 0.5–2.6). There were no associations with cumulative measures of exposure (years of

use, number of calls) based on any of the control series. [The Working Group noted the higher participation rate for cases than for controls and the attendant possibility of selection bias.]

The incidence of cancer of the eye (histology not specified, but likely to include a high proportion of melanomas) was not increased in a large cohort of Danish mobile-phone subscribers relative to the general population in a study that reported follow-up until 2002 ([Schüz et al., 2006c; Table 2.18](#)).

The substantial increase in use of mobile telephones has not been accompanied by an increase in uveal (ocular) melanoma in the USA up to 2000 ([Inskip et al., 2003, 2004](#)), nor was an increase seen in Denmark up to 1996 ([Johansen et al., 2002](#)). The annual percentage change in the USA was –0.7% for males (95% CI, –2.3–0.9) and –1.2% for females (95% CI, –2.5–0.0) ([Inskip et al., 2003](#)). Narrowing the time window to the 1990s failed to reveal any sign of a recent increase in incidence.

2.3.4 Cancer of the testis

The potential exists for the testes to be exposed to RF radiation if a mobile phone is kept in a trouser pocket while in stand-by mode, or when using a hands-free device. The incidence of cancer of the testis was not increased among 357 533 Danish male mobile-phone subscribers relative to that in the general population, based on an average follow-up of 8 years (maximum, 21 years) (SIR, 1.05; 95% CI, 0.96–1.15) ([Schüz et al., 2006c; Table 2.18](#)).

A case–control study of cell-phone use and testicular cancer in Sweden (542 seminomas, 346 non-seminomas, and 870 controls) gave null results for both histopathological subtypes ([Hardell et al., 2007b; Table 2.18](#)). Cases were diagnosed between 1993 and 1997.

Table 2.19 Case-control studies of leukaemia, lymphoma and other cancers and use of mobile phones

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Kaufman et al. (2009) Thailand, 1997-2003	180	756	Hospital	Interviewer-administered standardized questionnaire	Leukaemia (bone marrow) (204-207)	Ever use Use of GSM services	35 NR	1.5 (1.0-2.4) 2.1 (1.1-4.0)	Matching factors age, sex, area of residence, income, exposure to benzene, solvents, pesticides, or power lines	No association with duration of ownership, lifetime hours of use, or h/yr; short duration of use (median, 24-26 months); also evaluated by subtype of leukaemia
Cooke et al. (2010) United Kingdom, 2003-09	806	585	Non-blood relatives	Interviewer-administered standardized questionnaire	Leukaemia (204-207) exclusive of CLL (204.1)	Never, or non-regular use Regular use Lifetime years of use: 0.5-4 5-9 10-14 ≥ 15 <i>P</i> for trend	132 674 201 309 110 42 0.30	1.00 1.06 (0.76-1.46) 0.97 (0.67-1.39) 1.10 (0.77-1.58) 1.04 (0.67-1.61) 1.63 (0.81-3.28)	Age, sex, SES, area of residence, ethnicity, smoking, interview lag-time and period	No significant associations with year since first use, lifetime years of use, cumulative number of calls, or cumulative hours of use; low participation rate (50%)
Hardell et al. (2005) Sweden, 1999-2002	910	1016	Population	Mail questionnaire + telephone	NHL	<i>Use of analogue and digital phones (yr)</i> > 1 > 5 > 10	130 123 70	1.02 (0.73-1.44) 1.04 (0.73-1.46) 0.91 (0.61-1.36)	Age, sex, year of diagnosis	Ages 18-74 yr; no differences by subtype of NHL

Table 2.19 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Linet <i>et al.</i> (2006) USA, 1998–2000	551	462	Population	Mail + home questionnaire	NHL	Ever use Cumulative use (h): ≤ 78 79–208 ≥ 209	234 35 23 35	1.0 (0.7–1.3) 0.8 (0.4–1.4) 0.8 (0.4–1.5) 1.1 (0.6–2.1)	Age, ethnicity, education, geographic site	Risk also not significantly associated with min/wk duration, or year when use started. Results were null for total NHL, large B-cell and follicular lymphoma
Stang <i>et al.</i> (2001) Germany, 1995–98	118	475	Population, hospital	Interview	Uveal melanoma (190)	<i>Probable/certain mobile-phone use</i> Ever ≥ 5 yr in past	6 3	4.2 (1.2–14.5) 4.9 (0.5–51.0)	Age, sex, geographic area	Crude exposure assessment; low prevalence of exposure; few long-term users
Stang <i>et al.</i> (2009) Germany 2002–04	459	1194	Population, ophthalmology, siblings	Questionnaire	Uveal melanoma (190)	Regular use Cumulative use (yr): ≤ 4 5–9 ≥ 10	30 17 11 2	<i>Relative risk</i> 0.7 (0.5–1.0) 0.8 (0.5–1.2) 0.6 (0.4–1.0) 0.6 (0.3–1.4)	Age, sex, residence	RR estimates based on population controls; low participation rate among controls (57%)

Table 2.19 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Hardell <i>et al.</i> (2007b) Sweden 1993–97	888 (542 seminoma; 346 non-seminoma)	870	Population	Questionnaire	Testicular cancer (178)	Cumulative use of mobile-phone (h) Analogue: 1–127 128–547 > 547 Digital: 1–127 128–547 > 547	102 46 27	1.3 (0.9–1.8) 0.7 (0.5–1.0) 0.8 (0.5–1.4)	Age, year of diagnosis, cryptorchidism	Similar null results for seminoma and non-seminoma, as well as by latency
Auvinen <i>et al.</i> (2002) Finland, 1996	34	170	Population	Mobile-phone subscriber lists	Salivary gland cancer (142)	Ever (analogue and digital) Duration (yr): < 1 1–2 > 2	4 0 3 1	1.3 (0.4–4.7) - 1.7 (0.4–7.5) 2.3 (0.2–25.3)	Age, sex	Small number of cases; limited information on exposure; results shown are for analogue and digital phones combined
Hardell <i>et al.</i> (2004) Sweden, 1994–2000	267	1053	Population	Questionnaire	Malignant and benign salivary-gland tumours (142, 210)	Ever use (analogue) Ever use (digital) Latency (yr): > 5 > 10	31 45 17 6	0.92 (0.58–1.44) 1.01 (0.68–1.50) 0.78 (0.44–1.38) 0.71 (0.29–1.74)	Age, sex	Only living cases included; latency results are for analogue phones. No cases among long-term users of digital phones

Table 2.19 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Lönn <i>et al.</i> (2006) Denmark, Sweden, 2000–02	60	681	Population	Interviewer-administered standardized questionnaire	Malignant parotid gland (ICD codes not reported)	Never regular use of mobile phone	35	1.0	Age, sex, geographic region, education	
						Regular use	25	0.7 (0.4–1.3)		
						<i>Time since start of use (yr)</i>				
						< 5	14	0.7 (0.3–1.3)		
						5–9	8	0.7 (0.3–1.7)		
						≥ 10	2	0.4 (0.1–2.6)		
Lönn <i>et al.</i> (2006) Sweden, 2000–02	112	321	Population	Interviewer-administered standardized questionnaire	Benign pleomorphic adenomas (ICD codes not reported)	<i>Cumulative use (h)</i>			Age, sex, geographic region, education	Risk for ipsilateral use: OR, 1.4 (95% CI, 0.2–2.2)
						< 30	7	0.7 (0.3–1.6)		
						30–449	11	0.7 (0.3–1.4)		
						≥ 450	5	0.6 (0.2–1.8)		
						Never regular use of mobile phone	35	1.0		
						Regular use	77	0.9 (0.5–1.5)		
						<i>Time since start of use (yr)</i>				
						< 5	47	1.0 (0.6–1.8)		
						5–9	23	0.8 (0.4–1.5)		
						≥ 10	7	1.4 (0.5–3.9)		
						<i>Cumulative use (h)</i>				
						< 30	20	1.1 (0.6–2.3)		
						30–449	34	0.9 (0.5–1.6)		
						≥ 450	22	1.0 (0.5–2.1)		

Table 2.19 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments
Sadetzki <i>et al.</i> (2008) Israel, 2001–03	460 (48 malignant; 402 benign)	1266	Population	Personal interview	Malignant and benign salivary-gland tumours (142, 210)	Not regular use of mobile phone < 1 yr	175	1.0	Unadjusted (cigarette smoking was considered but did not change OR)	Separate analyses for benign and malignant tumours, with similar results
						Regular use	285	0.87 (0.68–1.13)	Gender, interview date, age, continent of birth	Age at diagnosis, ≥ 18 yr
						<i>Duration of use (yr)</i>				
						1–4.9	138	0.84 (0.63–1.12)		
						5–9.9	134	0.92 (0.67–1.27)		
						≥ 10	13	1.0 (0.48–2.09)		
						<i>Time since start of use (yr)</i>				
						1–4.9	138	0.82 (0.61–1.10)		
						5–9.9	134	0.95 (0.70–1.30)		
						≥ 10	13	0.86 (0.42–1.77)		
						<i>Cumulative use (h)</i>				OR for ipsilateral use: 1.49 (95% CI, 1.05–2.13)
						≤ 266.3	121	0.82 (0.62–1.09)		
						266.4–1034.9	80	1.03 (0.72–1.47)		
						$\geq 1\ 035$	83	1.09 (0.75–1.60)		

Table 2.19 (continued)

Reference, study location and period	Total cases	Total controls	Control source (hospital, population)	Exposure assessment	Organ site (ICD code)	Exposure categories	Exposed cases	Odds ratio (95% CI)	Covariates	Comments					
Duan <i>et al.</i> (2011) China 1993–2010	136	2051	Hospital	Personal or telephone interviews	Salivary-gland cancer (142)	Regular use model	91	1.14 (0.72–1.81)	Age, sex, residential area, marital status, education, income, smoking status	Possible over-parameterization; difficult to reconcile overall RR with exposure category-specific RRs					
						<i>No. of calls since first use</i>									
						≤ 24 000	78	1.78 (1.12–2.84)	As above	Implausible RR and CI for highest exposure category (one exposed case)					
						24 001–42 000	12	1.76 (1.01–2.51)							
						> 42 000	1	15.36 (13.34–17.38)							
						<i>Duration of use (yr)</i>									
						0–6	67	1.69 (1.05–2.73)	As above	Preceding comments raise serious questions about analysis					
						7–8	7	3.69 (2.82–4.57)							
						9–10	2	7.70 (6.20–9.20)							
						> 10	15	4.14 (1.76–9.69)							

CLL, chronic lymphocytic leukaemia; GSM, Global System for Mobile Communications; min, minute; NHL, non-Hodgkin lymphoma; NR, not reported; RR, relative risk; SES, socioeconomic status; h, hour; yr, year

2.3.5 Cancers of the parotid gland

The salivary glands are potentially exposed to high doses of RF radiation from mobile phones, particularly the parotid gland on the side of the head on which the phone is used. Five case-control studies and one cohort study have addressed a possible relationship between cancer of the salivary gland and use of mobile phones.

An early case-control study by [Auvinen et al. \(2002\)](#) ([Table 2.19](#)) gave null results, but was quite small (34 cases), included only malignant tumours, and provided limited information about details of phone use. Cases were ascertained from the Finnish Cancer Registry and controls from the nationwide population registry. Personal identifiers were linked with subscription records for two cellular networks in 1996. [This register-based approach precludes selection bias to non-response as well as recall bias in the ascertainment of mobile phone use. Information on the frequency or duration of calls was not available, nor was mobile-phone use under a corporate account.]

A case-control study by [Hardell et al. \(2004\)](#) ([Table 2.19](#)) included 267 cases, considered both benign and malignant tumours of the parotid gland, and provided detailed exposure information. Again, the results were null. [The study included few people who had used mobile phones for > 10 years.]

A case-control study by [Lönn et al. \(2006\)](#) ([Table 2.19](#)), which was part of the INTERPHONE study, included 172 cases (benign and malignant parotid tumours combined), 681 controls (for the 60 malignant cases), and 321 controls (for the 112 benign cases). The study found no association with regular use of mobile phones for either malignant or benign parotid tumours. The surrogate exposure metrics considered included frequency of use, duration of regular use, time since first regular use, cumulative use and cumulative number of calls. For benign tumours, there was a slightly elevated risk associated

with ipsilateral use of mobile phones (OR, 1.4; 95% CI, 0.2–2.2, based on 51 cases) but not for contralateral tumours (OR, 0.7; 95% CI, 0.4–1.1, based on 35 cases). [There may have been bias in reporting of laterality of phone use.]

A case-control study of tumours of the parotid gland was conducted in Israel, where use of mobile phones was reported to be very high ([Sadetzki et al., 2008](#); [Table 2.19](#)). This was the largest study of this type (402 cases with benign tumours, 58 with malignant tumours, and 1266 controls), also conducted as part of the INTERPHONE study. Cases were diagnosed at age 18 years or more during 2001 and 2003. In the main analyses, no increased risk was observed for any of the exposure surrogates examined. Laterality analyses generally indicated increased risk for ipsilateral use and reduced risk for contralateral use, e.g. for > 266 hours of cumulative call time with no hands-free devices, the odds ratio for ipsilateral use was 1.49 (95% CI, 1.05–2.13, based on 115 cases), while the odds ratio for contralateral use was 0.84 (95% CI, 0.55–1.28, based on 48 cases). Stratified analyses according to type of residence produced a somewhat higher odds ratio for rural and mixed rural/urban areas than for poor urban areas. For rural and rural/urban users, exposure-response associations were significant for cumulative call time ($P = 0.04$) and borderline significant for number of calls ($P = 0.06$). When the analyses were restricted to regular users only, taking the lowest category of use as the reference, increased odds ratios were found if time since start of use was > 5 years before diagnosis (OR, 1.40; 95% CI, 1.03–1.90, based on 134 cases) and for the highest exposure category of cumulative number of calls (OR, 1.51; 95% CI, 1.05–2.17, based on 81 cases) and duration of calls (OR, 1.50; 95% CI, 1.04–2.16, based on 83 cases). [The fact that there were increased odds ratios for ipsilateral tumours and decreased odds ratios for contralateral tumours suggested the presence of bias in reporting side of use.]

In a hospital-based case-control study of epithelial cancers of the parotid gland conducted in China between 1993 and 2010 (136 cases, 2051 controls), no overall association of cancer risk with regular use of mobile phones was observed ([Duan et al., 2011](#); [Table 2.19](#)). The authors also evaluated several more detailed exposure metrics and commented that several showed evidence of a dose-response relationship. [This interpretation was made uncertain by aspects of variation in the odds ratios. In several instances, there was no indication of a gradient in risk, but a very large increase in the odds ratio for the highest exposure category. Perhaps more puzzling was the fact that, for many of the exposure variables, odds ratios for all categories of exposure were higher than the overall odds ratio of 1.14. One would expect the overall odds ratio for regular use to be a weighted average of category-specific odds ratios. For number of calls since first use, the authors reported an odds ratio of 15.36 (95% CI, 13.34–17.38) for the highest exposure category, based on one exposed case. This cannot be correct and raises doubt about other analyses. The odds ratio presented may be 1/OR, as 0.7% of cases and 12.6% of controls were in this category.]

The incidence of cancers of the salivary gland was not increased relative to that in the general population in a large cohort of mobile-phone subscribers in Denmark followed up for up to 21 years ([Schüz et al., 2006c](#); [Table 2.19](#)).

A recent descriptive study reported an increase in the occurrence of cancer of the parotid gland (not incidence rate) in Israel, which appeared to begin around 1990 and continue through 2006 ([Czerninski et al., 2011](#)). [Interpretation of these findings was difficult given the increase in population size in Israel, possible improvements over time in the ascertainment of cancers of the parotid gland, a substantial shift in diagnoses over time from the category “major salivary gland cancers, not otherwise specified” to more precisely defined types – the large majority of which were cancers of the parotid gland – and the lack of information about mobile-phone use.]

2.3.6 Other cancers

(a) Cancer of the breast

[There was little information concerning mobile-phone use and risk of breast cancer.] Breast cancer did not occur more often than expected based on incidence rates in the general population in a cohort of 65 542 Danish female mobile-phone subscribers followed from as early as 1982 until 1995 ([Schüz et al., 2006c](#); [Table 2.18](#)).

(b) Cancer of the skin

In a case-control study of cutaneous melanoma in the head and neck region (347 cases, 1184 controls), [Hardell et al. \(2011b\)](#) reported no overall association with use of mobile phones (OR, 1.0; 95% CI, 0.7–1.3, based on 223 cases) or cordless phones (OR, 0.9; 95% CI, 0.6–1.2, based on 138 cases), nor among those with heavier use. Use of cordless phones, but not mobile phones, was associated with an increased risk of melanoma in the temporal region, cheek, and ear for the group with 1–5 year latency among those with heavier use (OR, 2.1; 95% CI, 1.1–3.8 for > 365 cumulative hours, based on 21 cases). [The overall pattern in the data pointed more in the direction of no effect. The odds ratio mentioned in the Abstract for the latency period of 1–5 years did not match that in Table 2 of the published manuscript regarding mobile-phone use.]

[To date, there have been no studies of non-melanoma skin cancer in relation to mobile-phone use.]

(c) Other cancer sites

Subscribers to mobile-phone services in Denmark followed from as early as 1982 until 2002 did not show significantly elevated incidence rates of cancers of the lung, larynx, bladder, buccal cavity, oesophagus, liver, uterine cervix, stomach, kidney, pancreas, prostate or other sites, relative to the incidence rates in the Danish general population ([Schüz et al., 2006c](#)).

References

- Ahlbom A, Feychting M, Green A *et al.* ICNIRP (International Commission for Non-Ionizing Radiation Protection) Standing Committee on Epidemiology (2009). Epidemiologic evidence on mobile phones and tumor risk: a review. *Epidemiology*, 20: 639–652. doi:10.1097/EDE.0b013e3181b0927d PMID:19593153
- Armstrong B, Thériault G, Guénel P *et al.* (1994). Association between exposure to pulsed electromagnetic fields and cancer in electric utility workers in Quebec, Canada, and France. *Am J Epidemiol*, 140: 805–820. PMID:7977291
- Auvinen A, Hietanen M, Luukkonen R, Koskela RS (2002). Brain tumors and salivary gland cancers among cellular telephone users. *Epidemiology*, 13: 356–359. doi:10.1097/00001648-200205000-00018 PMID:11964939
- Baldi I, Coureau G, Jaffré A *et al.* (2011). Occupational and residential exposure to electromagnetic fields and risk of brain tumors in adults: a case-control study in Gironde, France. *Int J Cancer*, 129: 1477–1484. doi:10.1002/ijc.25765 PMID:21792884
- Baumgardt-Elms C, Ahrens W, Broman K *et al.* (2002). Testicular cancer and electromagnetic fields (EMF) in the workplace: results of a population-based case-control study in Germany. *Cancer Causes Control*, 13: 895–902. doi:10.1023/A:1021999000651 PMID:12588085
- Berg G, Schüz J, Samkange-Zeeb F, Blettner M (2005). Assessment of radiofrequency exposure from cellular telephone daily use in an epidemiological study: German Validation study of the international case-control study of cancers of the brain–INTERPHONE-Study. *J Expo Anal Environ Epidemiol*, 15: 217–224. doi:10.1038/sj.jea.7500390 PMID:15266354
- Berg G, Spallek J, Schüz J *et al.* INTERPHONE Study Group, Germany (2006). Occupational exposure to radio frequency/microwave radiation and the risk of brain tumors: INTERPHONE Study Group, Germany. *Am J Epidemiol*, 164: 538–548. doi:10.1093/aje/kwj247 PMID:16873421
- Cardis E, Armstrong BK, Bowman JD *et al.* (2011). Risk of brain tumours in relation to estimated RF dose from mobile phones: results from five Interphone countries. *Occup Environ Med*, 68: 631–640 doi:10.1136/oemed-2011-100155 PMID:21659469
- Cardis E, Deltour I, Mann S *et al.* (2008). Distribution of RF energy emitted by mobile phones in anatomical structures of the brain. *Phys Med Biol*, 53: 2771–2783. doi:10.1088/0031-9155/53/11/001 PMID:18451464
- Cardis E, Richardson L, Deltour I *et al.* (2007). The INTERPHONE study: design, epidemiological methods, and description of the study population. *Eur J Epidemiol*, 22: 647–664. doi:10.1007/s10654-007-9152-z PMID:17636416
- Christensen HC, Schüz J, Kosteljanetz M *et al.* (2004). Cellular telephone use and risk of acoustic neuroma. *Am J Epidemiol*, 159: 277–283. doi:10.1093/aje/kwh032 PMID:14742288
- Christensen HC, Schüz J, Kosteljanetz M *et al.* (2005). Cellular telephones and risk for brain tumors: a population-based, incident case-control study. *Neurology*, 64: 1189–1195. doi:10.1212/01.WNL.0000156351.72313.D3 PMID:15824345
- Cook A, Woodward A, Pearce N, Marshall C (2003). Cellular telephone use and time trends for brain, head and neck tumours. *NZ Med J*, 116: U457 PMID:12838353
- Cooke R, Laing S, Swerdlow AJ (2010). A case-control study of risk of leukaemia in relation to mobile phone use. *Br J Cancer*, 103: 1729–1735. doi:10.1038/sj.bjc.6605948 PMID:20940717
- Cooper D, Hemming K, Saunders P (2001). Re: “Cancer incidence near radio and television transmitters in Great Britain. I. Sutton Coldfield transmitter; II. All high power transmitters”. *Am J Epidemiol*, 153: 202–204. doi:10.1093/aje/153.2.202 PMID:11159167
- Czerninski R, Zini A, Sgan-Cohen HD (2011). Risk of parotid malignant tumors in Israel (1970–2006). *Epidemiology*, 22: 130–131. doi:10.1097/EDE.0b013e3181feb9f0 PMID:21150362
- Davis RL & Mostofi FK (1993). Cluster of testicular cancer in police officers exposed to hand-held radar. *Am J Ind Med*, 24: 231–233. doi:10.1002/ajim.4700240209 PMID:8213849
- de Vocht F, Burstyn I, Cherrie JW (2011a). Time trends (1998–2007) in brain cancer incidence rates in relation to mobile phone use in England. *Bioelectromagnetics*, 32: 334–339. doi:10.1002/bem.20648 PMID:21280060
- de Vocht F, Burstyn I, Cherrie JW (2011b). Authors’ Reply to Kundi’s Comments on de Vocht *et al.* “Time trends (1998–2007) in brain cancer incidence rates in relation to mobile phone use in England”. *Bioelectromagnetics*, doi:10.1002/bem.20678
- Degrave E, Meeusen B, Grivegnée AR *et al.* (2009). Causes of death among Belgian professional military radar operators: a 37-year retrospective cohort study. *Int J Cancer*, 124: 945–951. doi:10.1002/ijc.23988 PMID:19035449
- Deltour I, Johansen C, Auvinen A *et al.* (2009). Time trends in brain tumor incidence rates in Denmark, Finland, Norway, and Sweden, 1974–2003. *J Natl Cancer Inst*, 101: 1721–1724. doi:10.1093/jnci/djp415 PMID:19959779
- Deltour I, Johansen C, Auvinen A *et al.* (2010). Response: Re: Time Trends in Brain Tumor Incidence Rates in Denmark, Finland, Norway, and Sweden, 1974–2003. *J Natl Cancer Inst*, 102: 742–743. doi:10.1093/jnci/djq123
- Dolk H, Elliott P, Shaddick G *et al.* (1997b). Cancer incidence near radio and television transmitters in Great Britain. II. All high power transmitters. *Am J Epidemiol*, 145: 10–17. PMID:8982017

- Dolk H, Shaddick G, Walls P *et al.* (1997a). Cancer incidence near radio and television transmitters in Great Britain. I. Sutton Coldfield transmitter. *Am J Epidemiol*, 145: 1–9. PMID:8982016
- Dreyer NA, Loughlin JE, Rothman KJ (1999). Cause-specific mortality in cellular telephone users. *JAMA*, 282: 1814–1816. doi:10.1001/jama.282.19.1814-a PMID:10573269
- Duan Y, Zhang Z, Bu RF (2011). Correlation between cellular phone use and epithelial parotid gland malignancies. *Int J Oral Medicine*, 40: 9966–972..
- Eger H, Hagen KU, Lucas B *et al.* (2004). The influence of being physically near to a cell phone transmission mast on the incidence of cancer. *Umwelt-medizin Gesellschaft*, 17: 1–7.
- Eger H & Neppe F (2009). Krebsinzidenz von Anwohnern im Umkreis einer Mobilfunksendeanlage in Westfalen. *Umwelt-medizin Gesellschaft*, 22: 55–60.
- Elliott P, Toledano MB, Bennett J *et al.* (2010). Mobile phone base stations and early childhood cancers: case-control study. *BMJ*, 340: jun22 1c3077 doi:10.1136/bmj.c3077 PMID:20570865
- Frei P, Mohler E, Bürgi A *et al.*; QUALIFEX Team (2010). Classification of personal exposure to radio frequency electromagnetic fields (RF-EMF) for epidemiological research: Evaluation of different exposure assessment methods. *Environ Int*, 36: 714–720. doi:10.1016/j.envint.2010.05.005 PMID:20538340
- Gavin AT & Catney D (2006). Addressing a community's cancer cluster concerns. *The Ulster Medical Society*, 75: 195–199.
- Gousias K, Markou M, Voulgaris S *et al.* (2009). Descriptive epidemiology of cerebral gliomas in northwest Greece and study of potential predisposing factors, 2005–2007. *Neuroepidemiology*, 33: 89–95. doi:10.1159/000222090 PMID:19494549
- Grayson JK (1996). Radiation exposure, socioeconomic status, and brain tumor risk in the US Air Force: a nested case-control study. *Am J Epidemiol*, 143: 480–486. doi:10.1093/oxfordjournals.aje.a008768 PMID:8610663
- Groves FD, Page WF, Gridley G *et al.* (2002). Cancer in Korean war navy technicians: mortality survey after 40 years. *Am J Epidemiol*, 155: 810–818. doi:10.1093/aje/155.9.810 PMID:11978584
- Ha M, Im H, Kim BC *et al.* (2008). Five authors reply [Letter] *Am J Epidemiol*, 167: 884–885. doi:10.1093/aje/kwn013
- Ha M, Im H, Lee M *et al.* (2007). Radio-frequency radiation exposure from AM radio transmitters and childhood leukemia and brain cancer. *Am J Epidemiol*, 166: 270–279. doi:10.1093/aje/kwm083 PMID:17556764
- Ha M, Lim HJ, Cho SH *et al.* (2003). Incidence of cancer in the vicinity of Korean AM radio transmitters. *Arch Environ Health*, 58: 756–762. doi:10.3200/AEOH.58.12.756-762 PMID:15859510
- Hardell L, Hansson Mild K, Pålsson A, Hallquist A (2001). Ionizing radiation, cellular telephones and the risk for brain tumours. *Eur J Cancer Prev*, 10: 523–529. doi:10.1097/00008469-200112000-00007 PMID:11916351
- Hardell L, Hansson Mild K & Carlberg M (2002b). Case-control study on the use of cellular and cordless phones and the risk for malignant brain tumours. *Int J Radiat Biol*, 78: 931–936. doi:10.1080/09553000210158038 PMID:12465658
- Hardell L, Hansson Mild K & Carlberg M (2003). Further aspects on cellular and cordless telephones and brain tumours. *Int J Oncol*, 22: 399–407. PMID:12527940
- Hardell L & Carlberg M (2009). Mobile phones, cordless phones and the risk for brain tumours. *Int J Oncol*, 35: 5–17. doi:10.3892/ijo_00000307 PMID:19513546
- Hardell L, Carlberg M, Hansson Mild K (2006a). Pooled analysis of two case-control studies on the use of cellular and cordless telephones and the risk of benign brain tumours diagnosed during 1997–2003. *Int J Oncol*, 28: 509–518. PMID:16391807
- Hardell L, Carlberg M, Hansson Mild K (2006b). Pooled analysis of two case-control studies on use of cellular and cordless telephones and the risk for malignant brain tumours diagnosed in 1997–2003. *Int Arch Occup Environ Health*, 79: 630–639. doi:10.1007/s00420-006-0088-5 PMID:16541280
- Hardell L, Carlberg M, Hansson Mild K (2009). Epidemiological evidence for an association between use of wireless phones and tumor diseases. *Pathophysiology*, 16: 113–122. doi:10.1016/j.pathophys.2009.01.003 PMID:19268551
- Hardell L, Carlberg M, Hansson Mild K (2010). Mobile phone use and the risk for malignant brain tumors: a case-control study on deceased cases and controls. *Neuroepidemiology*, 35: 109–114. doi:10.1159/000311044 PMID:20551697
- Hardell L, Carlberg M, Hansson Mild K (2011a). Pooled analysis of case-control studies on malignant brain tumours and the use of mobile and cordless phones including living and deceased subjects. *Int J Oncol*, 38: 1465–1474. doi:10.3892/ijo.2011.947 PMID:21331446
- Hardell L, Carlberg M, Hansson Mild K, Eriksson M (2011b). Case-control study on the use of mobile and cordless phones and the risk for malignant melanoma in the head and neck region. *Pathophysiology*, 18: 325–333. doi:10.1016/j.pathophys.2011.06.001 PMID:21764571
- Hardell L, Carlberg M, Hansson Mild K (2006c). Case-control study of the association between the use of cellular and cordless telephones and malignant brain tumors diagnosed during 2000–2003. *Environ Res*, 100: 232–241. doi:10.1016/j.envres.2005.04.006 PMID:16023098
- Hardell L, Carlberg M, Ohlson CG *et al.* (2007b). Use of cellular and cordless telephones and risk of testicular

- cancer. *Int J Androl*, 30: 115–122. doi:10.1111/j.1365-2605.2006.00721.x PMID:17209885
- Hardell L, Carlberg M, Söderqvist F *et al.* (2007a). Long-term use of cellular phones and brain tumours: increased risk associated with use for > or =10 years. *Occup Environ Med*, 64: 626–632. doi:10.1136/oem.2006.029751 PMID:17409179
- Hardell L, Carlberg M, Söderqvist F, Hansson Mild K (2008). Meta-analysis of long-term mobile phone use and the association with brain tumours. *Int J Oncol*, 32: 1097–1103. PMID:18425337
- Hardell L, Eriksson M, Carlberg M *et al.* (2005). Use of cellular or cordless telephones and the risk for non-Hodgkin's lymphoma. *Int Arch Occup Environ Health*, 78: 625–632. doi:10.1007/s00420-005-0003-5 PMID:16001209
- Hardell L & Hallquist A, Hansson Mild K *et al.* (2002a). Cellular and cordless telephones and the risk for brain tumours. *Eur J Cancer Prev*, 11: 377–386. doi:10.1097/00008469-200208000-00010 PMID:12195165
- Hardell L, Hallquist A, Hansson Mild K *et al.* (2004). No association between the use of cellular or cordless telephones and salivary gland tumours. *Occup Environ Med*, 61: 675–679. doi:10.1136/oem.2003.011262 PMID:15258273
- Hardell L, Näsman A, Pahlson A *et al.* (1999). Use of cellular telephones and the risk for brain tumours: A case-control study. *Int J Oncol*, 15: 113–116. PMID:10375602
- Hardell L, Nasman A, Pahlson A, Hallquist A (2000). Case-control study on radiology work, medical x-ray investigations, and use of cellular telephones as risk factors for brain tumors. *MedGenMed*, 2: E2 PMID:11104448
- Hartikka H, Heinävaara S, Mäntylä R *et al.* (2009). Mobile phone use and location of glioma: a case-case analysis. *Bioelectromagnetics*, 30: 176–182. doi:10.1002/bem.20471 PMID:19142876
- Hayes RB, Brown LM, Potters LM *et al.* (1990). Occupation and risk for testicular cancer: a case-control study. *Int J Epidemiol*, 19: 825–831. doi:10.1093/ije/19.4.825 PMID:1964675
- Hepworth SJ, Schoemaker MJ, Muir KR *et al.* (2006). Mobile phone use and risk of glioma in adults: case-control study. *BMJ*, 332: 883–887. doi:10.1136/bmj.38720.687975.55 PMID:16428250
- Hocking B, Gordon IR, Grain HL, Hatfield GE (1996). Cancer incidence and mortality and proximity to TV towers. *Med J Aust*, 165: 601–605. PMID:8985435
- Hours M, Bernard M, Montestrucq L *et al.* (2007). [Cell Phones and Risk of brain and acoustic nerve tumours: the French INTERPHONE case-control study] *Rev Epidemiol Sante Publique*, 55: 321–332. PMID:17851009
- IARC (2002). Non-ionizing radiation, Part 1: static and extremely low-frequency (ELF) electric and magnetic fields. *IARC Monogr Eval Carcinog Risks Hum*, 80: 1–395. PMID:12071196
- Inskip PD, Devesa SS, Fraumeni JF Jr (2003). Trends in the incidence of ocular melanoma in the United States, 1974–1998. *Cancer Causes Control*, 14: 251–257. doi:10.1023/A:1023684502638 PMID:12814204
- Inskip PD, Devesa SS, Fraumeni JF Jr (2004). The Authors Reply. *Cancer Causes Control*, 15: 101–102. doi:10.1023/B:CACO.0000016571.38245.83
- Inskip PD, Hoover RN, Devesa SS (2010). Brain cancer incidence trends in relation to cellular telephone use in the United States. *Neuro-oncol*, 12: 1147–1151. doi:10.1093/neuonc/noq077 PMID:20639214
- Inskip PD, Tarone RE, Hatch EE *et al.* (2001). Cellular-telephone use and brain tumors. *N Engl J Med*, 344: 79–86. doi:10.1056/NEJM200101113440201 PMID:11150357
- INTERPHONE Study Group (2010). Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Int J Epidemiol*, 39: 675–694. doi:10.1093/ije/dyq079 PMID:20483835
- INTERPHONE Study Group (2011). Acoustic neuroma risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. *Cancer Epidemiol*, 35: 453–464. doi:10.1016/j.canep.2011.05.012 PMID:21862434
- Johansen C, Boice J Jr, McLaughlin J, Olsen JH (2001). Cellular telephones and cancer—a nationwide cohort study in Denmark. *J Natl Cancer Inst*, 93: 203–207. doi:10.1093/jnci/93.3.203 PMID:11158188
- Johansen C, Boice JD Jr, McLaughlin JK *et al.* (2002). Mobile phones and malignant melanoma of the eye. *Br J Cancer*, 86: 348–349. doi:10.1038/sj.bjc.6600068 PMID:11875697
- Kan P, Simonsen SE, Lyon JL, Kestle JR (2008). Cellular phone use and brain tumor: a meta-analysis. *J Neurooncol*, 86: 71–78. doi:10.1007/s11060-007-9432-1 PMID:17619826
- Karipidis KK, Benke G, Sim MR *et al.* (2007). Occupational exposure to ionizing and non-ionizing radiation and risk of glioma. *Occup Med (Lond)*, 57: 518–524. doi:10.1093/occmed/kqm078 PMID:17728306
- Kaufman DW, Anderson TE, Issaragrisil S (2009). Risk factors for leukemia in Thailand. *Ann Hematol*, 88: 1079–1088. doi:10.1007/s00277-009-0731-9 PMID:19294385
- Khurana VG, Teo C, Kundi M *et al.* (2009). Cell phones and brain tumors: a review including the long-term epidemiologic data. *Surg Neurol*, 72: 205–215. doi:10.1016/j.surneu.2009.01.019 PMID:19328536
- Klaeboe L, Blaasaas KG, Tynes T (2007). Use of mobile phones in Norway and risk of intracranial tumours. *Eur J Cancer Prev*, 16: 158–164. doi:10.1097/01.cej.0000203616.77183.4c PMID:17297392
- Lagorio S, Rossi S, Vecchia P *et al.* (1997). Mortality of plastic-ware workers exposed to radiofrequencies. *Bioelectromagnetics*, 18: 418–421.

- doi:10.1002/(SICI)1521-186X(1997)18:6<418::AID-BEM3>3.0.CO;2-5 PMID:9261538
- Lahkola A, Auvinen A, Raitanen J *et al.* (2007). Mobile phone use and risk of glioma in 5 North European countries. *Int J Cancer*, 120: 1769–1775. doi:10.1002/ijc.22503 PMID:17230523
- Lahkola A, Salminen T, Auvinen A (2005). Selection bias due to differential participation in a case-control study of mobile phone use and brain tumors. *Ann Epidemiol*, 15: 321–325. doi:10.1016/j.annepidem.2004.12.009 PMID:15840544
- Lahkola A, Salminen T, Raitanen J *et al.* (2008). Meningioma and mobile phone use—a collaborative case-control study in five North European countries. *Int J Epidemiol*, 37: 1304–1313. doi:10.1093/ije/dyn155 PMID:18676984
- Lahkola A, Tokola K, Auvinen A (2006). Meta-analysis of mobile phone use and intracranial tumors. *Scand J Work Environ Health*, 32: 171–177. PMID:16804618
- Larjavaara S, Schüz J, Swerdlow A *et al.* (2011). Location of gliomas in relation to mobile telephone use: a case-case and case-specular analysis. *Am J Epidemiol*, 174: 2–11. doi:10.1093/aje/kwr071 PMID:21610117
- Lehrer S, Green S, Stock RG (2011). Association between number of cell phone contracts and brain tumor incidence in nineteen U.S. States. *J Neurooncol*, 101: 505–507. doi:10.1007/s11060-010-0280-z PMID:20589524
- Lilienfeld AM, Tonascia J, Libauer C *et al.* (1978). *Foreign Service Study: Evaluation of Foreign Service and Other Employees from Selected Eastern European Posts*. NTIS Document No. PB-28B 163/9GA, pp. 436
- Linnet MS, Taggart T, Severson RK *et al.* (2006). Cellular telephones and non-Hodgkin lymphoma. *Int J Cancer*, 119: 2382–2388. doi:10.1002/ijc.22151 PMID:16894556
- Lönn S, Ahlbom A, Christensen HC *et al.* (2006). Mobile phone use and risk of parotid gland tumor. *Am J Epidemiol*, 164: 637–643. doi:10.1093/aje/kwj242 PMID:16818464
- Lönn S, Ahlbom A, Hall P, Feychting M Swedish INTERPHONE Study Group (2005). Long-term mobile phone use and brain tumor risk. *Am J Epidemiol*, 161: 526–535. doi:10.1093/aje/kwi091 PMID:15746469
- Lönn S, Klaeboe L, Hall P *et al.* (2004). Incidence trends of adult primary intracerebral tumors in four Nordic countries. *Int J Cancer*, 108: 450–455. doi:10.1002/ijc.11578 PMID:14648713
- Maskarinec G, Cooper J, Swygert L (1994). Investigation of increased incidence in childhood leukemia near radio towers in Hawaii: preliminary observations. *J Environ Pathol Toxicol Oncol*, 13: 33–37. PMID:7823291
- Merzenich H, Schmiedel S, Bennack S *et al.* (2008). Childhood leukemia in relation to radio frequency electromagnetic fields in the vicinity of TV and radio broadcast transmitters. *Am J Epidemiol*, 168: 1169–1178. doi:10.1093/aje/kwn230 PMID:18835863
- Meyer M, Gärtig-Daug A, Radespiel-Tröger M (2006). Mobilfunkbasisstationen und Krebshäufigkeit in Bayern [Mobile phone base stations and cancer incidence in Bavaria] [German] *Umweltmed Forsch Prax*, 11: 89–97.
- Michelozzi P, Capon A, Kirchmayer U *et al.* (2002). Adult and childhood leukemia near a high-power radio station in Rome, Italy. *Am J Epidemiol*, 155: 1096–1103. doi:10.1093/aje/155.12.1096 PMID:12048223
- Milham S Jr (1988a). Increased mortality in amateur radio operators due to lymphatic and hematopoietic malignancies. *Am J Epidemiol*, 127: 50–54. PMID:3422125
- Milham S Jr (1988b). Mortality by license class in amateur radio operators. *Am J Epidemiol*, 128: 1175–1176. PMID:3189292
- Morgan RW, Kelsh MA, Zhao K *et al.* (2000). Radiofrequency exposure and mortality from cancer of the brain and lymphatic/hematopoietic systems. *Epidemiology*, 11: 118–127. doi:10.1097/00001648-200003000-00007 PMID:11021607
- Muscat JE, Hinsvark M, Malkin M (2006). Mobile telephones and rates of brain cancer. *Neuroepidemiology*, 27: 55–56. doi:10.1159/000094381 PMID:16825795
- Muscat JE, Malkin MG, Shore RE *et al.* (2002). Handheld cellular telephones and risk of acoustic neuroma. *Neurology*, 58: 1304–1306. PMID:11971109
- Muscat JE, Malkin MG, Thompson S *et al.* (2000). Handheld cellular telephone use and risk of brain cancer. *JAMA*, 284: 3001–3007. doi:10.1001/jama.284.23.3001 PMID:11122586
- Myung SK, Ju W, McDonnell DD *et al.* (2009). Mobile phone use and risk of tumors: a meta-analysis. *J Clin Oncol*, 27: 5565–5572. doi:10.1200/JCO.2008.21.6366 PMID:19826127
- Nelson PD, Toledano MB, McConville J *et al.* (2006). Trends in acoustic neuroma and cellular phones: is there a link? *Neurology*, 66: 284–285. doi:10.1212/01.wnl.0000194218.79519.ea PMID:16434678
- Nomura E, Ioka A, Tsukuma H (2011). Trends in the incidence of primary intracranial tumors in Osaka, Japan. *Jpn J Clin Oncol*, 41: 291–294. doi:10.1093/jjco/hyq204 PMID:21273377
- Oberfeld G (2008). [Environmental Epidemiological Study of Cancer Incidence in the Municipalities of Hausmannstätten & Vasoldsberg (Austria).] Amt der Steiermärkischen Landesregierung, Fachabteilung für das Gesundheitswesen (Landessanitätsdirektion), Printcenter University of Salzburg, Graz, Austria. Available at <http://www.verwaltung.steiermark.at/cms/ziel/21212/DE/> (disabled link) (in German).
- Park SK, Ha M, Im HJ (2004). Ecological study on residences in the vicinity of AM radio broadcasting towers and cancer death: preliminary observations in Korea. *Int Arch Occup Environ Health*, 77: 387–394. doi:10.1007/s00420-004-0512-7 PMID:15338224

- Propp JM, McCarthy BJ, Davis FG, Preston-Martin S (2006). Descriptive epidemiology of vestibular schwannomas. *Neuro-oncol*, 8: 1–11. doi:10.1215/S1522851704001097 PMID:16443943
- Richter E, Berman T, Ben-Michael E *et al.* (2000). Cancer in radar technicians exposed to radiofrequency/microwave radiation: sentinel episodes. *Int J Occup Environ Health*, 6: 187–193. PMID:10926722
- Robinette CD, Silverman C, Jablon S (1980). Effects upon health of occupational exposure to microwave radiation (radar). *Am J Epidemiol*, 112: 39–53. PMID:7395854
- Rösli M, Michel G, Kuehni CE, Spoerri A (2007). Cellular telephone use and time trends in brain tumour mortality in Switzerland from 1969 to 2002. *Eur J Cancer Prev*, 16: 77–82. doi:10.1097/01.cej.0000203618.61936.cd PMID:17220708
- Sadetzki S, Chetrit A, Jarus-Hakak A *et al.* (2008). Cellular phone use and risk of benign and malignant parotid gland tumors—a nationwide case-control study. *Am J Epidemiol*, 167: 457–467. doi:10.1093/aje/kwm325 PMID:18063591
- Saika K & Katanoda K (2011). Comparison of time trends in brain and central nervous system cancer mortality (1990–2006) between countries based on the WHO mortality database. *Jpn J Clin Oncol*, 41: 304–305. doi:10.1093/jjco/hyr004 PMID:21273379
- Samkange-Zeeb F, Berg G, Blettner M (2004). Validation of self-reported cellular phone use. *J Expo Anal Environ Epidemiol*, 14: 245–248. doi:10.1038/sj.jea.7500321 PMID:15141153
- Saracci R & Samet J (2010). Commentary: Call me on my mobile phone...or better not?—a look at the INTERPHONE study results. *Int J Epidemiol*, 39: 695–698. doi:10.1093/ije/dyq082 PMID:20483832
- Sato Y, Akiba S, Kubo O, Yamaguchi N (2011). A case-case study of mobile phone use and acoustic neuroma risk in Japan. *Bioelectromagnetics*, 32: 85–93. doi:10.1002/bem.20616 PMID:21225885
- Schlehofer B, Schlaefer K, Blettner M *et al.*; INTERPHONE Study Group (2007). Environmental risk factors for sporadic acoustic neuroma (Interphone Study Group, Germany). *Eur J Cancer*, 43: 1741–1747. doi:10.1016/j.ejca.2007.05.008 PMID:17600696
- Schmiedel S, Brüggemeyer H, Philipp J *et al.* (2009). An evaluation of exposure metrics in an epidemiologic study on radio and television broadcast transmitters and the risk of childhood leukemia. *Bioelectromagnetics*, 30: 81–91. doi:10.1002/bem.20460 PMID:19025781
- Schoemaker MJ & Swerdlow AJ (2009). Risk of pituitary tumors in cellular phone users: a case-control study. *Epidemiology*, 20: 348–354. doi:10.1097/EDE.0b013e31819c7ba8 PMID:19279493
- Schoemaker MJ, Swerdlow AJ, Ahlbom A *et al.* (2005). Mobile phone use and risk of acoustic neuroma: results of the Interphone case-control study in five North European countries. *Br J Cancer*, 93: 842–848. doi:10.1038/sj.bjc.6602764 PMID:16136046
- Schüz J, Böhler E, Berg G *et al.* (2006a). Cellular phones, cordless phones, and the risks of glioma and meningioma (Interphone Study Group, Germany). *Am J Epidemiol*, 163: 512–520. doi:10.1093/aje/kwj068 PMID:16443797
- Schüz J, Böhler E, Schlehofer B *et al.* INTERPHONE Study Group, Germany (2006b). Radiofrequency electromagnetic fields emitted from base stations of DECT cordless phones and the risk of glioma and meningioma (INTERPHONE Study Group, Germany). *Radiat Res*, 166: 116–119. doi:10.1667/RR3581.1 PMID:16808597
- Schüz J, Elliott P, Auvinen A *et al.* (2011). An international prospective cohort study of mobile phone users and health (Cosmos): design considerations and enrolment. *Cancer Epidemiol*, 35: 37–43. doi:10.1016/j.canep.2010.08.001 PMID:20810339
- Schüz J, Jacobsen R, Olsen JH *et al.* (2006c). Cellular telephone use and cancer risk: update of a nationwide Danish cohort. *J Natl Cancer Inst*, 98: 1707–1713. doi:10.1093/jnci/djj464 PMID:17148772
- Selvin S, Schulman J, Merrill DW (1992). Distance and risk measures for the analysis of spatial data: a study of childhood cancers. *Soc Sci Med*, 34: 769–777. doi:10.1016/0277-9536(92)90364-V PMID:1604371
- Spinelli V, Chinot O, Cabaniols C *et al.* (2010). Occupational and environmental risk factors for brain cancer: a pilot case-control study in France. *Presse Med*, 39: e35–e44. doi:10.1016/j.lpm.2009.06.020 PMID:19962851
- Stang A, Anastassiou G, Ahrens W *et al.* (2001). The possible role of radiofrequency radiation in the development of uveal melanoma. *Epidemiology*, 12: 7–12. doi:10.1097/00001648-200101000-00003 PMID:11138823
- Stang A, Schmidt-Pokrzywniak A, Lash TL *et al.* (2009). Mobile phone use and risk of uveal melanoma: results of the risk factors for uveal melanoma case-control study. *J Natl Cancer Inst*, 101: 120–123. doi:10.1093/jnci/djn441 PMID:19141780
- Szmigielski S (1996). Cancer morbidity in subjects occupationally exposed to high frequency (radiofrequency and microwave) electromagnetic radiation. *Sci Total Environ*, 180: 9–17. doi:10.1016/0048-9697(95)04915-0 PMID:8717316
- Szmigielski S, Sobiczewska E, Kubacki R (2001). Carcinogenic potency of microwave radiation: overview of the problem and results of epidemiological studies on Polish military personnel. *European Journal of Oncology*, 6: 193–199.
- Takebayashi T, Akiba S, Kikuchi Y *et al.* (2006). Mobile phone use and acoustic neuroma risk in Japan. *Occup Environ Med*, 63: 802–807. doi:10.1136/oem.2006.028308 PMID:16912083
- Takebayashi T, Varsier N, Kikuchi Y *et al.* (2008). Mobile phone use, exposure to radiofrequency electromagnetic

- field, and brain tumour: a case-control study. *Br J Cancer*, 98: 652–659. doi:10.1038/sj.bjc.6604214 PMID:18256587
- Thomas TL, Stolley PD, Stemhagen A *et al.* (1987). Brain tumor mortality risk among men with electrical and electronics jobs: a case-control study. *J Natl Cancer Inst*, 79: 233–238. PMID:3474455
- Tynes T, Hannevik M, Andersen A *et al.* (1996). Incidence of breast cancer in Norwegian female radio and telegraph operators. *Cancer Causes Control*, 7: 197–204. doi:10.1007/BF00051295 PMID:8740732
- Viel JF, Clerc S, Barrera C *et al.* (2009). Residential exposure to radiofrequency fields from mobile phone base stations, and broadcast transmitters: a population-based survey with personal meter. *Occup Environ Med*, 66: 550–556. doi:10.1136/oem.2008.044180 PMID:19336431
- Vrijheid M, Armstrong BK, Bédard D *et al.* (2009a). Recall bias in the assessment of exposure to mobile phones. *J Expo Sci Environ Epidemiol*, 19: 369–381. doi:10.1038/jes.2008.27 PMID:18493271
- Vrijheid M, Cardis E, Armstrong BK *et al.*; INTERPHONE Study Group (2006b). Validation of short term recall of mobile phone use for the Interphone study. *Occup Environ Med*, 63: 237–243. doi:10.1136/oem.2004.019281 PMID:16556742
- Vrijheid M, Deltour I, Krewski D *et al.* (2006a). The effects of recall errors and of selection bias in epidemiologic studies of mobile phone use and cancer risk. *J Expo Sci Environ Epidemiol*, 16: 371–384. doi:10.1038/sj.jes.7500509 PMID:16773122
- Vrijheid M, Richardson L, Armstrong BK *et al.* (2009b). Quantifying the impact of selection bias caused by nonparticipation in a case-control study of mobile phone use. *Ann Epidemiol*, 19: 33–41. doi:10.1016/j.annepidem.2008.10.006 PMID:19064187
- Wolf R & Wolf D (2004). Increased incidence of cancer near a cell-phone transmitter station. *International Journal of Cancer Prevention*, 1: 123–128.

3. CANCER IN EXPERIMENTAL ANIMALS

3.1 Studies of carcinogenicity

See [Table 3.1](#)

3.1.1 Mouse

Groups of 50 male and 50 female B6C3F₁ mice (age, 8–9 weeks) were sham-exposed or received whole-body exposure to GSM (Global System for Mobile communications)-modulated radiofrequency (RF) radiation at 902 MHz, or to DCS (Digital Cellular System)-modulated RF radiation at 1747 MHz, in a Ferris wheel/tube-restrained design for 2 hours per day, 5 days per week, for 24 months. Exposures were performed with a three-phase signal imitating “basic,” “talk” and “environment” GSM signals. Cage controls were run in parallel. The average specific absorption rate (SAR) for each signal phase (0, 0.4, 1.3, and 4.0 mW/g), organ-averaged SARs, and corresponding standard variations were calculated. No increases in tumour incidence at any site were observed in exposed mice compared with sham-exposed mice. Decreases in the incidence of liver adenoma were seen in males exposed to GSM at 4.0 mW/g and in males exposed to DCS at 4.0 mW/g ([Tillmann et al., 2007](#)).

3.1.2 Rat

Groups of 100 male Sprague-Dawley rats (age, 8 weeks) were sham-exposed or exposed to RF radiation as pulsed microwaves at 2450 MHz, at 800 pulses per second (pps) with a pulse

width of 10 μ s (range of SAR values: young rats, 0.4 mW/g; older rats, 0.15 mW/g) for 21.5 hours per day, 7 days per week, for 25 months. The exposure to microwaves had no statistically significant effect on survival (median survival time: sham-exposed rats, 663 days; exposed rats, 688 days) or body weight. No statistically significant increases in the incidence of any benign or malignant tumours were identified at any site in exposed rats compared with sham-exposed controls. An increased incidence of total malignant tumours (all sites) was observed in rats exposed to RF radiation compared with sham-exposed controls ([Chou et al., 1992](#)). [The Working Group considered this finding to be of limited biological significance, since it resulted from pooling of non-significant changes in tumour incidence in several sites.]

Groups of female Sprague-Dawley rats (age, 52–70 days) were sham-exposed or exposed to RF radiation as GSM at 900 MHz, with a pulse of 217 Hz, for more than 23 hours per day, 7 days per week, for up to 37 months. In the four experiments that were carried out, the number of rats per group was 12 in experiments 1 and 2, and 30 in experiments 3 and 4. Rats were group-housed with up to 12 rats per cage. Whole-body averaged SARs (wbSARs) during the studies ranged from 32.5–130 mW/kg in rats weighing 170–200 g, to 15–60 mW/kg in rats weighing ~400 g. In experiment 1, surviving rats were killed and necropsied at 770 days [26.7 months] (mortality, 33%), while in experiment 2, surviving rats were killed and

Table 3.1 Studies of carcinogenicity in experimental animals exposed to radiofrequency radiation

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, C3H/ HeA (F) 10.5 mo Szmigielski et al. (1982)	2 450 MHz MW far field: sham, 5 mW/cm ² (SAR, 2–3 mW/g), 15 mW/cm ² (SAR, 6–8 mW/g), confinement stress group, cage control 2 h/d, 6 d/wk 40/group	Power density (mW/cm ²) at 8 mo at 10 mo 0 (sham) 3/40 14/40 322 d 5 18/40* 32/40* 261 d 15 26/40* 37/40* 219 d Confined 16/40* 31/40* 255 d	*P < 0.01	Mammary-gland tumours detected only by palpation
Mouse, <i>Eμ-Pim1</i> (F) 18 mo Repacholi et al. (1997)	900 MHz (217 Hz [pulse repetition, similar to GSM]; pulse width, 0.6 ms), sham SAR: 0.008–4.2 mW/g, 0.13–1.4 mW/g (average) 2 × 30 min/d, 7 d/wk 100/sham-exposed group, 101/RF radiation-exposed group	Lymphoma (sham, RF-EMF): 3/100, 6/101 (lymphoblastic) 19/100, 37/101 (non-lymphoblastic) 22/100, 43/101 (all)	P = 0.0002 (non-lymphoblastic lymphoma) P = 0.0006 (all lymphomas)	No standardized assessment criteria were defined for deciding which mice would be selected for necropsy. Mice surviving the 18 mo of exposure or sham-exposure were discarded without necropsy.
Mouse, C3H/ HeJ (F) 21 mo Toler et al. (1997)	435 MHz (420–450 MHz) RF radiation with pulse-wave (pulse width, 1.0 μs; pulse rate, 1.0 kHz), sham Incident power density of 1.0 mW/cm ² ; SAR, 0.32 mW/g 22 h/d, 7 d/wk 200/group	Mammary-gland adenocarcinoma: 77/193 (exposed), 74/190 (sham)	NS	Complete histopathology
Mouse, C3H/ HeJ (F) 18 mo Frei et al. (1998a)	2 450 MHz MW (SAR, 0.3 mW/g), sham 20 h/d, 7 d/wk 100/group	Mammary-gland carcinoma: 44% (RF radiation), 52% (sham)	NS	Complete histopathology
Mouse, C3H/ HeJ (F) 78 wk Frei et al. (1998b)	2 450-MHz MW (SAR: 1.0 mW/g), sham 20 h/d, 7 d/wk 100/group	Mammary-gland carcinoma: 38% (RF radiation), 30% (sham)	NS	Complete histopathology

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, C3H/HeJ (F) 76 wk lauchem et al. (2001)	UWB (rise time, 176 ps; fall time, 3.5 ns; pulse width, 1.9 ns; peak energy field, 40 kV/m; repetition rate, 1 kHz; SAR, 0.0098 mW/g), sham 2 min/wk, 12 wk 100/group	Mammary-gland carcinoma: 48/100 (UWB), 52/100 (sham)	NS	Complete histopathology
Mouse, <i>Eμ-Pim1</i> and wild-type (C57BL/6N ^{Tac}) (F) 104 wk Uttridge et al. (2002)	GSM-modulated 898.4 MHz (pulse width, 0.6 ms); SAR, 0.25, 1.0, 2.0, 4.0 mW/g; sham, cage control 1 h/d, 5 d/wk 120/group (wild-type and <i>Eμ-Pim1</i>)	Number of tumour-bearing animals: <i>Lymphoblastic lymphoma</i> Sham-exposed control (wild-type, transgenic): 3, 15; SAR = 0.25: 0, 8*; SAR = 1: 2, 8; SAR = 2: 2, 9; SAR = 4: 0, 15; total: 7, 55 <i>Non-lymphoblastic lymphoma</i> Sham-exposed control (wild-type, transgenic): 35, 74; SAR = 0.25: 40, 80; SAR = 1: 35, 78; SAR = 2: 43, 84; SAR = 4: 36, 84; total: 189, 400 <i>Neurological tumours</i> Sham-exposed control (wild-type, transgenic): 11, 1; SAR = 0.25: 17, 4; SAR = 1: 15, 0; SAR = 2: 10, 2; SAR = 4: 9, 2; total: 62, 9	* <i>P</i> = 0.02 (decrease)	Restrained exposure (Ferris wheel) also for sham, but cage-control group unrestrained. Necropsy was performed on all mice.
Mouse, AKR/J (F) 40 wk Sommer et al. (2004)	GSM 900 MHz (overall max. SAR, 5.9 mW/g; average SAR, 0.4 mW/g [whole body]), sham 24 h/d, 7 d/wk 160/group	No increase in tumour incidence	NS	Histopathology was performed on spleen, thymus, lymph nodes, liver, kidney, lung and brain.
Mouse, <i>Eμ-Pim1</i> (M, F) 18 mo Oberto et al. (2007)	GSM-modulated 900 MHz (pulse width, 0.577 ms); SAR, 0.5, 1.4, 4.0 mW/g (whole body); sham, cage control 2 × 30 min/d, 7 d/wk 50 M and 50 F/group	Number of tumour-bearing animals: <i>Lymphoma</i> (all): (M) – 8 (cage), 9 (sham), 10 (0.5, 1.4 mW/g), 3 (4 mW/g); (F) – 26 (cage), 22 (sham), 18 (0.5 mW/g), 30 (1.4 mW/g), 20 (4.0 mW/g) <i>Harderian gland adenoma</i> : (M) – 0 (sham), 0 (0.5 mW/g), 2 (1.4 mW/g), 4 (4.0 mW/g)	Harderian-gland adenoma: <i>P</i> = 0.0028 (one-tailed test, trend) (M)	Restrained exposure (Ferris wheel). Mortality was higher (<i>P</i> < 0.05) in all three groups of exposed males and in the females exposed at 0.5 mW/g. GLP

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F ₁ (M, F) 24 mo Tillmann et al. (2007)	GSM 902 MHz, DCS 1 747 MHz, sham, cage control; wSAR: 0.4, 1.3, 4 mW/g for each signal. 2 h/d, 5 d/wk 50 M and 50 F/group	<i>All tumours (%)</i> GSM (M/F):sham (68/78), low dose (62/78), medium dose (66/74), high dose (64/78); DCS (M/F): sham (74/74), low dose (60/62), medium dose (50/70), high dose (48/66) DCS: No. of males with tumours: 37 (sham), 30 (low dose), 25 (medium dose)* and 24 (high dose)*; No. of males with benign tumours: 27 (sham), 21 (low dose), 17 (medium dose), 12 (high dose)* <i>Liver adenoma in males (%)</i> DCS: 22 (sham), 4 (high dose)*; GSM: 30 (sham); 12 (high dose)*	*P < 0.05 (decrease)	Restrained exposure (Ferris wheel) Complete histopathology GLP
Mouse, <i>Ptcl</i> ^{+/+} , <i>Ptcl</i> ^{+/+} (wild-type) (M, F) Lifetime Saran et al. (2007)	GSM-modulated 900 MHz (wbSAR, 0.4 mW/g), sham, cage control 2 × 30 min/d, 5 d, starting on PND 2 23–26 heterozygous and 22–29 wild-type mice/sex/group	No increase in tumour incidence	NS	Histopathology was performed on brain, a 5 cm ² piece of skin, and any visible neoplasm.
Mouse, AKR/J (F) 43 wk Sommer et al. (2007)	UMTS (FDD, 1 966 MHz; SAR, 0.4 mW/g), sham, cage control 24 h/d, 7 d/wk 160/sham- or RF radiation-exposed group and 30/cage-control group	<i>Lymphoma</i> RF radiation: 141 (88.1%); sham: 149/150 (93.1%); cage control, 29/30 (96.7%)	NS	Histopathology was performed on spleen, thymus, lymph nodes, liver, kidney, lung and brain.
Mouse, AKR/J (M, F) 42 wk Lee et al. (2011)	CDMA 849 MHz and WCDMA 1950 MHz (combined) with SAR of 2 mW/g for CDMA and WCDMA [variation estimated: 1.59–2.52 mW/g], sham 45 min/d, 5 d/wk 40 M and 40 F/group	<i>Thymic lymphoma</i> Sham: M: 30/40 (75%); F: 32/40 (80%) Combined RF radiation: M: 31/40 (78%); F: 31/40 (78%)	NS	Exposure was performed in a reverberation chamber. Histopathology was performed on spleen, thymus, lymph nodes, liver, kidney, lung and brain.
Rat, Sprague-Dawley (M) 25 mo Chou et al. (1992)	2 450 MHz (800 pps; pulse width, 10 µs; pulse modulation, 8 Hz), sham; SAR: 0.15 (800 g bw) and 0.4 mW/g (200 g bw) 21.5 h/d, 7 d/wk 100/group	<i>Malignant neoplasms (all sites)</i> Sham, 5/100; exposed, 18/100 <i>Adrenal gland, pheochromocytoma</i> Sham, 1/100; exposed, 7/100 <i>Adrenal gland, cortical carcinoma</i> Sham, 0/100; exposed, 3/100	P = 0.005, χ ² NS	Complete histopathology No increase in tumour incidence at any site.

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M, F) 24 mo La Regina et al. (2003)	FDMA 835.6 MHz, CDMA 847.7 MHz, sham; SAR (brain): 0.85 ± 0.34 mW/g (time-averaged) SAR, 1.3 $\pm$ 0.5 mW/g (nominal time-averaged brain SAR) 4 h/d, 5 d/wk 80 M and 80 F/group	<i>Total No. of tumours</i> (Sham/FDMA/CDMA): 76/79/78 (F), 163/162/148 (M) Mixed glioma (%): 0/1/0 (F) Astrocytoma (%): 0/0/1 (F), 0/1/0 (M) Granular cell tumour (%): 1/0/0 (F), 0/1/0 (M)	NS	Restrained exposure (Ferris wheel). Over the 2-yr time-course study, the brain SAR varied from 0.5 to 2.5 mW/g. Complete histopathology, 20–30 brain sections were examined per rat.
Rat, F344 (M, F) 24 mo Anderson et al. (2004)	1 620 MHz Dams and pups: far-field exposure from GD 19 until weaning (pups aged 23 days). Pups (age, 36 days): near-field exposure of ~2 yr. Brain SAR: 0.16 mW/g (fetuses, far field), 0.16 or 1.6 mW/g (offspring, near-field), sham, cage control. 2 h/d, 7 d/wk (far-field), 2 h/d, 5 d/wk (near field) 80–90 M and 80–90 F pups/group: near-field (2 groups), sham (1 group), cage control (1 group)	No increase in tumour incidence	NS	Restrained exposure (Ferris wheel) for near-field exposure Complete histopathology The incidence of brain neoplasms was within the range for historical controls
Rat, Wistar (M, F) 24 mo Smith et al. (2007)	902 MHz (GSM), 1 747 MHz (DCS), sham, cage control; time-averaged wbSAR: 0.44, 1.33, 4.0 mW/g for each signal. 2 h/d, 5 d/wk 50 M and 50 F/group	No increase in tumour incidence	NS	Restrained exposure (Ferris wheel) Due to increase in bw, the wbSAR of the group at the highest dose (4.0 mW/g targeted) was reduced to 3.0 mW/g after about 2 years; on average, a wbSAR of 3.7 mW/g was obtained; detailed SAR values and uncertainty were estimated for many organs. Complete histopathology GLP

bw, body weight; B[a]P, benzo[a]pyrene; CDMA, code-division multiple access; CDT₅₀, cancer-development time 50 (i.e. time in which 50% of the mice developed skin carcinoma); d, day; DCS, digital personal communications system; FDD, frequency-division duplexing; FDMA, frequency-division multiple access; GD, day of gestation; GLP, good laboratory practice; GSM, Global System for Mobile Communication; min, minute; mo, month; MW, microwave; NS, not significant; PND, postnatal day; RF-EMF, radiofrequency electromagnetic field; SAR, specific absorption rate; UWB, ultra-wide band; WCDMA, wide-band code division multiple access; wk, week; Yr, year

necropsied at 580 days [19.3 months] (mortality, 50%). In experiment 1, histopathological evaluations were performed on the main organs, while only gross pathology was performed in experiment 2. In experiments 3 and 4, the rats were followed until natural death and histopathology was done on macroscopically detected changes only. In experiments 1 and 2, fewer pituitary tumours were detected in rats exposed to RF radiation (42% and 33% in experiments 1 and 2, respectively) than in sham-exposed controls (75% and 50% in experiments 1 and 2, respectively). Decreased incidences of mammary tumours (possibly associated with significantly shortened median survival times) were seen in experiments 3 and 4. No evidence of increased incidence of cancer in any tissue was reported in exposed rats compared with sham-exposed controls in any of the four experiments performed ([Bartsch et al., 2010](#)). [The Working Group considered that the value of these experiments was limited by the lack of reproducibility in survival times in experiments 1 and 2 (performed with identical protocols), by the small group sizes in all experiments, and by the poor reporting of tumour data from all experiments. Because complete pathology results were not reported, this study cannot be regarded as a comprehensive carcinogenicity bioassay, and it was not considered in the evaluation.]

Groups of 80 female and 80 male F344 rats (age, 6 weeks) were sham-exposed or exposed to RF radiation in the FDMA mode (frequency-division multiple access) 835.6 MHz, or in the CDMA mode (code-division multiple access) at 847.7 MHz, for 4 hours per day, 5 days per week, for 24 months. Rats were tube-restrained during exposure; time-averaged SAR in the brain was 1.3 mW/g for both signals. There were no significant differences in survival, body weight or tumour incidence at any site in exposed males or females when compared with sex-matched sham-exposed controls ([La Regina et al., 2003](#)).

Groups of pregnant Fischer 344 rats were exposed to far-field RF radiation at 1620 MHz

for 2 hours per day, 7 days per week, from day 19 of gestation until weaning. At age 36 days, groups of 90 male and 90 female offspring were sham-exposed or exposed in tubes to near-field RF radiation at 1620 MHz (head mostly) for 2 hours per day, 5 days per week, for 24 months. Sham-exposure and near-field exposure were performed using a Ferris wheel/tube-restrained design at two targeted levels (brain SAR, 0.16 and 1.6 mW/g). No statistically significant differences between exposed and control groups were observed in number of live pups per litter, survival index, or weaning weights. There were no statistically significant effects of exposure on mean body weight of surviving rats. The percentage of rats surviving at study termination did not differ among groups. Incidences of tumours were similar in all groups ([Anderson et al., 2004](#)).

Groups of 50 male and 50 female Wistar rats (age, approximately 6 weeks) were sham-exposed or received whole-body exposure to GSM-modulated RF radiation at 902 MHz, or to DCS-modulated RF radiation at 1747 MHz, in a Ferris wheel/tube-restrained design for 2 hours per day, 5 days per week, for 24 months. Exposures were performed with a three-phase signal imitating “basic,” “talk” and “environment.” Cage controls were run in parallel. Time-averaged *wbSARs* in the three exposure groups were 0.44, 1.33, and 4.0 mW/g for each signal phase. Body weight and survival were not statistically different between exposed and sham-exposed groups. No significant differences in the incidences of benign or malignant neoplasms at any site were observed between the exposed and sham-exposed groups ([Smith et al., 2007](#)).

3.1.3 Transgenic and tumour-prone models

(a) *Eμ-pim1* transgenic mouse

The *Eμ-Pim1* transgenic mouse strain has been reported to spontaneously develop lymphoma and to show an increased incidence of lymphoma

in response to exposure to chemical carcinogens ([Breuer et al., 1989](#); [van Kreijl et al., 1998](#)).

Groups of 100–101 female heterozygous *Eμ-Pim1* mice (age, 6–8 weeks) were sham-exposed or exposed to RF radiation as “GSM basic” at 900 MHz for up to 18 months. Mean SAR values in exposed mice were 0.13–1.4 mW/g. At study termination, mice that were clinically healthy were counted as survivors and discarded without further investigation. Exposure to RF radiation had no statistically significant effect on body weight [survival data were not reported]. The authors reported a twofold increase in the incidence of lymphoma in *Eμ-Pim1* mice exposed to GSM RF radiation ($P = 0.006$ versus the sham-exposed group) ([Repacholi et al., 1997](#)). [The Working Group considered the complete lack of pathology data to be a major limitation in the design of this study.]

Groups of 120 female heterozygous *Eμ-Pim1* mice and 120 female wild-type mice (C57BL/6NTac) (age, 7.5–9.5 weeks) were sham-exposed or exposed to GSM-modulated RF radiation at 898.4 MHz in a Ferris-wheel/restrained design at four different exposure levels (SAR: 0.25, 1.0, 2.0 or 4.0 mW/g) for 1 hour per day, 5 days per week, for 104 weeks. An unrestrained cage-control group was also included in the study. No significant differences in survival or body weight were observed between exposed and sham-exposed mice of either strain. Survival of the transgenic mice was significantly lower than that of wild-type mice ($P < 0.001$). No significant increases in the incidence of lymphoblastic or non-lymphoblastic lymphoma were seen in exposed mice compared with sham-exposed mice at any exposure level ([Utteridge et al., 2002](#)).

Groups of 50 male and 50 female *Eμ-Pim1* mice (age, 9 weeks) were sham-exposed or exposed to RF radiation as “GSM basic” phase signal at 900 MHz, with a pulse of 217 Hz, and pulse width of 0.5 ms, at wbSARs of 0, 0.5, 1.4, or 4.0 mW/g. Exposures were for 1 hour per day, split into two sessions of 30 minutes (morning and afternoon),

7 days per week, for up to 18 months. Cage controls were run in parallel. As in the study by [Utteridge et al. \(2002\)](#), the mice were restrained in tubes during exposure or sham exposure. Compared with sham-exposed mice, survival until termination of the study was shorter in male mice in all groups exposed to RF radiation and in female mice exposed at 0.5 mW/g. Compared with sham-exposed groups, there was no significant difference in the mean body weight of either females or males. No statistically significant differences were seen in the incidences of malignant lymphoma (lymphoblastic and non-lymphoblastic) in sham-exposed or exposed males or females. The incidences of tumours of the Harderian gland were significantly higher in male mice exposed to RF radiation than in controls, with a dose-dependent trend ($P = 0.0028$, one-tailed test); this resulted in a significant positive trend in the overall incidence of benign tumours ($P < 0.01$). For females, no dose-related trends related to exposure to RF radiation were seen in the overall incidence of benign or malignant tumours, or of tumours regardless of type ([Oberto et al., 2007](#)). [The Working Group noted that in the study of [Repacholi et al. \(1997\)](#), 22% of the sham-exposed female mice had lymphomas, whereas in this study, 44% of the sham-exposed and 52% of the cage-control female mice developed lymphomas. The incidence of lymphoma in the exposed group was 43% in the study of [Repacholi et al. \(1997\)](#), a value similar to that for the control groups in this study.]

(b) *Patched1*^{+/-} mouse

[Saran et al. \(2007\)](#) used newborn *Patched1* heterozygous knockout mice (*Ptc1*^{+/-}), a mouse model characterized by predisposition to tumours of the brain and other tissues, and by hypersensitivity to ionizing radiation. Groups of 23–36 male and 23–36 female *Ptc1*^{+/-} mice, and groups of 22–29 male and 22–29 female wild-type mice were exposed to RF radiation at 900 MHz (wbSAR, 4 mW/g) from postnatal days 2 to

6 (30 minutes, twice per day), the time window of extreme susceptibility to induction of medulloblastoma by ionizing radiation in this strain. Mice were monitored throughout their lifespan for the onset of brain tumours or any other visible neoplasm. No significant differences between exposed and sham-exposed groups were observed in the incidence or size of medulloblastoma, or in the incidence of any other neoplasms in either *Ptc1*^{+/-} mice or wild-type mice. [The Working Group noted that tumour data were not reported by sex. The very short duration of exposure, its timing during the immediate post-parturition period, and the lack of exposure of older juvenile or adult animals may limit the value of this study for hazard identification.]

(c) *AKR mouse*

The AKR mouse strain is known to develop lymphomas and other haematopoietic malignancies within the first year of life.

Groups of 160 unrestrained female AKR/J mice were sham-exposed or exposed to GSM-like RF radiation at 900 MHz for 24 hours per day, 7 days per week, for 40 weeks, at an average wbSAR of 0.4 mW/g. Exposure had a significant effect on body weight gain, with higher values in exposed than in sham-exposed mice. Survival and incidence of lymphoma did not differ between exposed and sham-exposed mice ([Sommer et al., 2004](#)). [The Working Group noted that in the absence of any difference in survival, the ability of the study design to detect any effect on tumour incidence between groups was small.]

Groups of 160 female AKR/J mice (age, 8 weeks) were sham-exposed or exposed to RF radiation as Universal Mobile Telecommunications System (UMTS) at 1966 MHz (SAR, 0.4 mW/g) for 24 hours per day, for 248 days (43 weeks). The 30 mice in the cage-control group gained significantly less weight than did the exposed and sham-exposed animals. No statistically significant differences in total body weight, survival, or incidence of neoplasms were observed between

exposed and sham-exposed mice. The incidence of lymphoma in all three groups was above 88% (RF-radiation exposed, 88.1%; sham-exposed, 93.1%; and cage controls, 96.7%) ([Sommer et al., 2007](#)). [The Working Group noted that in the absence of any difference in survival, the ability of the study design to detect any effect on tumour incidence between groups was small.]

Groups of 40 female and 40 male AKR/J mice (age, 5 weeks) were exposed simultaneously to RF radiation at 849 MHz (SAR, 2 mW/g) and 1950 MHz (SAR, 2 mW/g), for 45 minutes per day, 5 days per week, for 42 weeks. Sham exposures were performed in parallel. No differences in body weight, survival or tumour incidence were observed. The incidence of lymphomas in all groups was greater than 75% ([Lee et al., 2011](#)). [The Working Group noted the short daily exposure period. Furthermore, in the absence of any difference in survival, the ability of the study design to detect any effect on tumour incidence between groups was small.]

(d) *C3H mouse*

The C3H tumour-prone mouse carries a milk-borne virus that induces tumours of the mammary gland.

Groups of 40 female C3H/HeA mice were exposed to RF radiation at 2450 MHz as continuous microwaves from ages 6 weeks to 12 months. Five experimental groups (SAR, 0 [sham-exposed control], 2–3 mW/g, or 6–8 mW/g, confinement-stress group, cage-control group) were used. Mammary-gland tumours were detected by palpation. A more rapid appearance of mammary-gland tumours and a statistically significant increase in the incidence of mammary-gland tumours in both groups of mice exposed to microwave radiation was reported, compared with controls ([Szmigielski et al., 1982](#)). [The Working Group noted that no histopathology was performed.]

Groups of 200 female C3H/HeJ mice were sham-exposed or received whole-body exposure

to a horizontally polarized pulse wave at 435 MHz (pulse width, 1.0 ps; pulse rate, 1.0 kHz; wbSAR, 0.32 mW/g) for 22 hours per day, 7 days per week, for 21 months. No statistically significant differences in survival or body weight, or in the incidence, latency or growth rate of mammary-gland tumours were seen between exposed and sham-exposed groups ([Toler et al., 1997](#)).

Groups of 100 female C3H/HeJ mice (age, 3–4 weeks) were sham-exposed or exposed to continuous microwave radiation at 2450 MHz for 20 hours per day, 7 days per week, for 18 months. The average wbSAR was 0.3 mW/g. No significant differences in survival or body weight, or in the incidence, latency or growth rate of mammary-gland tumours were seen ([Frei et al., 1998a](#)).

A study with a similar design was performed at a higher SAR (1.0 mW/g). Groups of 100 female C3H/HeJ mice (age, 3–4 weeks) were sham-exposed or exposed to continuous microwave radiation at 2450 MHz, for 20 hours per day, 7 days per week, for 78 weeks. No differences in survival or body weight or in the incidence, latency or growth rate of mammary-gland tumours were observed ([Frei et al., 1998b](#)).

Groups of 100 female C3H/HeJ mice (age, 3–4 weeks) were exposed to pulses composed of an ultra-wide band (UWB) of frequencies with a rise time of 176 ps and a peak-energy field of 40 kV/m (SAR, 0.0098 mW/g). The mice were exposed for 2 minutes per week for 12 weeks, followed by a post-exposure period of 64 weeks. No significant differences between groups with respect to body weight, incidence of palpated mammary-gland tumours, latency to onset of mammary-gland tumour development, rate of mammary-gland tumour growth, or survival were found. Histopathological evaluations revealed no significant differences in tumour incidences between the two groups for all tissues studied ([Jauchem et al., 2001](#)). [The Working Group considered that the exposure was very limited.]

(e) *OF1 mouse*

The Ico:OF1 mouse strain is known to develop spontaneous tumours of the lymphoid tissue. Groups of 20 female mice were sham-exposed or exposed to RF radiation at 800 MHz for 1 hour per week, for 4 months, and followed for up to 18 months ([Anghileri et al., 2005](#)). Compared with controls, the exposure caused an earlier onset of general lymphocyte infiltration, formation of lymphoblastic ascites, and development of extranodal tumours of different histological types. [The Working Group considered that the inadequate description of the exposure level and dosimetry, the lack of histopathology, and the small group size did not permit a proper evaluation of this study.]

3.2 Initiation–promotion studies

See [Table 3.2](#)

The effect of exposure to RF radiation on tumours initiated by a chemical or physical carcinogen has been tested in various rodent models.

3.2.1 *Skin-tumour model*

Four groups of female ICR mice (age, 10 weeks) were given a single application of 100 µg of 7,12-dimethylbenz[*a*]anthracene (DMBA) on pre-shaved dorsal skin. Exposure to RF radiation started 1 week later and was continued for 19 weeks. Group 1 (48 mice) was exposed to a TDMA (time-division multiple access) signal at 1.49 GHz (50 pps, near-field), for 90 minutes per day, 5 days per week, at a skin local peak SAR of 2.0 mW/g. Group 2 (48 mice) was sham-exposed. Group 3 (30 mice) was exposed weekly and topically to 4.0 µg of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) per mouse. Group 4 (30 mice) received no further treatment. The incidences of skin papilloma or carcinoma (combined) were 0 out of 48, 0 out of 48, 29 out of 30, and 1 out of 30, respectively ([Imaida et al., 2001](#)).

In a comparable experiment, groups of 20 male ICR mice (age, 7 weeks) received the same single skin application (100 µg of DMBA per mouse). Exposure to RF radiation started 1 week later and was continued for 19 weeks. Group 1 was exposed topically to 4 µg of TPA per mouse, twice per week. Group 2 was sham-exposed. Group 3 was exposed to RF radiation at 849 MHz (45 minutes, twice per day, with an interval of 15 minutes between exposures, for 5 days per week). Group 4 was exposed to RF radiation at 1763 MHz (with a schedule similar to that for group 3). A CDMA signal was used with a wbSAR of 0.4 mW/g. Skin tumours [not further specified] were detected only in the DMBA/TPA-treated positive control group ([Huang et al., 2005](#)). [The Working Group noted the short duration of daily exposures and the use of only one exposure level per experiment.]

Groups of 10 male Swiss albino mice (age, 8 weeks) received a single skin application of 100 µg of DMBA (initiated groups) or were left untreated. Exposure to RF radiation or to croton oil (the positive control) started 2 weeks later. Group 1 was not initiated and was sham-exposed. Group 2 was exposed to DMBA only (cage control). Group 3 was exposed to DMBA plus amplitude-modulated (AM) RF radiation at 112 MHz, with a SAR of 0.75 mW/g, for 2 hours per day, 3 days per week, for 16 weeks. Group 4 was exposed to DMBA plus RF radiation at 2450 MHz with a SAR of 0.1 mW/g for 2 hours per day, 3 days per week, for 16 weeks. Group 5 was exposed to AM RF radiation at 112 MHz only. Group 6 was exposed to RF radiation at 2450 MHz only. Group 7 was exposed to DMBA plus a topical application of croton oil at 1% in 100 µL of acetone per mouse, twice per week, for 16 weeks. At study termination, skin tumours were detected only in the positive-control group (DMBA plus croton oil) ([Paulraj & Behari, 2011](#)). [The Working Group noted that the study was limited by the small group size and the relatively short duration of exposure.]

The promoting activity of RF radiation at 94 GHz was tested in groups of 27–55 female SENCAR mice previously initiated by dorsal application of DMBA at 10 nmol (2.56 µg). In a first experiment, 2 weeks after initiation, restrained mice were dorsally exposed once for 10 seconds to RF-EMF as follows: group 1 was exposed to millimetre wavelength (MMW) continuous wave far-field RF radiation (94 GHz, 1.0 W/cm²) and group 2 was exposed to infrared radiation at 1.5 W/cm². Both exposures led to similar skin heating (13–15 °C). Mice in group 3 were sham-exposed. In the positive-control group, initiated mice received the promoter TPA. After 23 weeks, the incidence and multiplicity of skin tumours was found to be similar in mice exposed to RF radiation, infrared radiation or sham-irradiated. TPA significantly increased both incidence and multiplicity of skin tumours compared with the other groups. [The Working Group noted that the importance of these findings was diminished by the very limited exposure to RF radiation.] In a second experiment, the effects of repeated exposure to RF radiation (333 mW/cm²) or infrared radiation (600 mW/cm²) for 10 seconds, twice per week, for 12 weeks, on skin-cancer promotion or co-promotion together with TPA were investigated. Groups of 50 female SENCAR mice were initiated with DMBA as above, and promotion treatment was started 2 weeks later. Group 1 was exposed to DMBA and sham-exposed; group 2 was exposed to DMBA + TPA and sham-exposed; group 3 was not initiated, exposed to TPA, and sham-exposed; group 4 was exposed to DMBA plus RF radiation at 333 mW/cm²; group 5 was exposed to DMBA plus RF radiation at 333 mW/cm² plus TPA; group 6 was exposed to DMBA plus infrared radiation at 600 mW/cm²; group 7 was exposed to DMBA plus infrared radiation at 600 mW/cm² plus TPA; and group 8 was sham-exposed only. The study was terminated 25 weeks after initiation. TPA promotion increased the incidence and multiplicity of skin tumours. Exposure to RF or infrared radiation did not

Table 3.2 Initiation–promotion studies in experimental animals exposed to radiofrequency radiation

Species, strain (sex) Tumour initiator Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, CBA/S (F) X-ray ionizing radiation, 4–6 MV (4 Gy as three 1.33 Gy fractions at 1-wk intervals) on wk 1 78 wk Heikkinen et al. (2001)	902.5 MHz (continuous NMT900), SAR, 1.5 mW/g; 902.4 MHz (pulsed GSM, 217 Hz), SAR, 0.35 mW/g; sham; and cage controls Time averaged input power: 6.1 ± 0.8 W for continuous RF group and 1.3 ± 0.1 W for pulsed RF group 1.5 h/d, 5 d/wk, 78 wk 50/group	Lymphoma (cage, sham, NMT and GSM): 0/50, 12/50, 12/50, 10/50	NS	Restrained exposure Full histopathology
Mouse, ICR (F) DMBA (dermal): 100 µg/100 µL acetone/mouse on wk 1 20 wk Imaida et al. (2001)	1.49 GHz TDMA signal (50 pulses/s), near-field 90 min/d, 5 d/wk, 19 wk (on wk 2) SAR (skin): 2.0 mW/g, SAR (wb, av): 0.084 mW/g Group 1: DMBA + RF-EMF ($n = 48$) Group 2: DMBA + sham ($n = 48$) Group 3: DMBA + TPA ($n = 30$) Group 4: DMBA + cage control ($n = 30$)	Skin squamous cell papilloma or carcinoma (combined), tumour multiplicity 0/48, 0 0/48, 0 29/30*, 18.8 $\pm$ 13.4* 1/30, 0.1 $\pm$ 0.5	NS NS * $P < 0.001$ -	
Mouse, SENCAR (F) DMBA (dermal): 10 nmol/200 µL acetone on wk 1 Exp. 1 and Exp. 2: 25 wk Mason et al. (2001)	Exp. 1: 94 GHz MMW CW far-field or IR heating, single skin exposure of 10 s (on wk 3); TPA, 2 $\times$ /wk for 23 wk Group 1: DMBA + 1.0 W/cm ² MMW ($n = 55$) Group 2: DMBA + 1.5 W/cm ² IR for 10 s ($n = 55$) Group 3: DMBA + sham ($n = 55$) Group 4: DMBA + TPA ($n = 27$) Exp. 2: MMW or IR, skin exposure of 10 s, 2 $\times$ /wk, 12 wk; TPA, 2 $\times$ /wk for 23 wk Group 1: DMBA + sham Group 2: DMBA + sham + TPA Group 3: sham + TPA Group 4: DMBA + 333 mW/cm ² MMW Group 5: DMBA + MMW + TPA Group 6: DMBA + 600 mW/cm ² IR Group 7: DMBA + IR + TPA Group 8: sham 50/group	Exp. 1: Comparable skin tumour incidence and multiplicity in sham-, MMW- or IR-exposed groups. TPA increased incidence and multiplicity of skin tumours. Exp. 2: TPA promotion led to increased incidence and multiplicity of DMBA-induced skin tumours; exposure to MMW or IR did not further increase the incidence or multiplicity of DMBA + sham or DMBA + TPA + sham-induced skin tumours.	No SAR given	

Table 3.2 (continued)

Species, strain (sex) Tumour initiator Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, ICR (M) DMBA (dermal): 100 µg/100 µL acetone/mouse on wk 1 20 wk Huang et al. (2005)	849 MHz CMDA signal or 1 763 MHz CMDA signal 2 × 45 min/d (15-minute interval between exposures), 5 d/wk, 19 wk (on wk 2) SAR (wb, av): 0.4 mW/g Group 1: DMBA + TPA Group 2: DMBA + sham Group 3: DMBA + 849 MHz Group 4: DMBA + 1 763 MHz 20/group	No skin tumours in RF-EMF-exposed groups. Skin tumours (95%) in DMBA + TPA group only.	NS	Free-moving mice were exposed in a reverberation chamber. The short duration of daily RF- EMF-exposure is questionable.
Mouse, Swiss (M) DMBA (dermal): 100 µg on wk 1 18 wk Paulraj & Behari (2011)	112 MHz, AM at 16 Hz (1.0 mW/cm ² ; SAR, 0.75 mW/g) or 2 450 MHz (0.34 mW/cm ² ; SAR, 0.1 mW/g) 2 h/d, 3 d/wk, 16 wk (on wk 3) Group 1: control Group 2: DMBA Group 3: DMBA + 112 MHz Group 4: DMBA + 2 450 MHz Group 5: 112 MHz Group 6: 2 450 MHz Group 7: DMBA + croton oil 18/group	No skin tumours in any group, except in group 7		Small group size and short duration of exposure
Rat, F344 (M, F) ENU <i>in utero</i> , 4 mg/kg bw iv on GD 18 24 mo Adey et al. (1999)	836.55 MHz, NADC-modulated Far-field: GD 19–PND 21 (weaning) 2 h/d, 7 d/wk Near-field: starting on PND 33/35 2 h/d (8 × 7.5 min field on/off), 4 d/wk, 22 months SAR (brain): 1.1–1.6 mW/g SAR (wb, av): 1.8–2.3 mW/g	CNS tumours Total [%] Group 1: sham/sham, n = 30 M + 30 F Group 2: sham/RF, n = 30 M + 30 F Group 3: ENU/sham, n = 30 M + 30 F Group 4: ENU/RF, n = 30 M + 26 F	Brain [%] 8.3 3.3 15.0 3.6 - NS - NS	Ferris wheel/restrained exposure 25 (M) or 20 (F) sections per brain

Table 3.2 (continued)

Species, strain (sex) Tumour initiator Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments	
Rat, Sprague-Dawley (F) B[a]P, 2 mg s.c. 160 d Chagnaud et al. (1999)	900 MHz, GSM-modulated, far-field (55 or 200 μW/cm ²)	Small palpable tumours (sarcomas) detectable from d 90–100 onwards.		Poor and confusing description of experiment and results. The authors stated that tumour onset was “slightly different” (<i>P</i> = 0.05) in the sham-exposed group and one of the exposed groups (55 μW/cm ² , 40 days).	
	SAR (wb, av): 75 or 270 mW/kg Exposure started on d 20, 40 or 75 after B[a]P initiation	Tumour incidence not reported. No consistent pattern of differences in time to tumour or survival.	NS		
	2 h/d, 5 d/wk, 2 wk				
	Group	RF (μW/cm ²)	No. of rats		No. of days after B[a]P initiation
	1, 2	55	17/17		20
	3, 4	55	18/18		40
	5, 6	55	14/17		75
	7, 8	200	8/9		40
	9	cage control	6		-
	Rat, F344 (M, F) ENU <i>in utero</i> , 4 mg/kg bw i.v. on GD 18 24 mo Adex et al. (2000)	836.55 MHz, NADC-modulated Far-field: GD 19–PND 21 (weaning) 2.6 ± 0.50 mW/cm ² Near-field: PND 31–731/734 2 h/d (8 × 7.5 min field on/off), 4 d/wk SAR (brain): 1.1–1.6 mW/g SAR (wb, av): 1.8–2.3 mW/g	Primary CNS tumours		
		Total [%]	Brain [%]		
Group 1: sham/sham, <i>n</i> = 45 M + 45 F		1.1	1.1	-	
Group 2: sham/RF, <i>n</i> = 45 M + 45 F		4.4	3.3	NS	
Group 3: ENU/sham, <i>n</i> = 45 M + 45 F		22.2	18.9	-	
Group 4: ENU/RF, <i>n</i> = 38 M + 52 F		17.8	15.6	NS	
Group 5: ENU/cage control, <i>n</i> = 45 M + 45 F		14.4	14.4		
Group 6: cage control, <i>n</i> = 45 M + 45 F		4.4	3.3		

Table 3.2 (continued)

Species, strain (sex) Tumour initiator	Dosing regimen Animals/group at start	Incidence of tumours		Significance	Comments
Duration					
Reference					
Rat, Sprague-Dawley (M,F)	860 MHz, PW or CW, near-field	No evidence that PW or CW increased the incidence of tumours in any studied tissues or promoted cranial or spinal or spinal nerve-root tumours initiated by ENU.	NS (overall)	Restraint exposure of the head in tube (Ferris wheel)	Tissues studied histologically included brain (18–26 step sections [1 mm]/brain), spinal cord, trigeminal nerves, lungs, liver, heart, kidneys, spleen, adrenal, pituitary and thyroid glands, and any gross lesions, including all neoplasms.
ENU <i>in utero</i> , on GD 15,	PND 57)				
0.2.5 or 10 mg/kg bw i.v.	SAR (brain, av): 1.0 ± 0.2 mW/g				
	SAR (wb, av): 0.27–0.42 mW/g				
	15 groups, 30 M + 30 F/group	No. of rats with brain tumours (M + F combined)	Oligodendroglioma	Mixed glioma	
Zoek & Simmens (2001)	Group ENU RF	All Multiple	Astrocytoma		
	1 0 PW	5 0 5	0	0	NS
	2 0 Sham	3 0 3	0	0	-
	9 0 CW	3 0 2	1	0	NS
	10 0 Sham	5 0 5	0	0	-
	13 0 Cage control	6 0 5	1	0	
	5 2.5 PW	7 2 4	2	4	NS
	6 2.5 Sham	9 1 3	2	5	-
	7 2.5 CW	9 0 2	6	1	NS
	8 2.5 Sham	10 1 5	5	1	-
	11 2.5 CW	3 0 0	0	3	NS
	12 2.5 Sham	6 0 3	1	3	-
	14 2.5 Cage control	5 0 0	4	0	
	3 10.0 PW	36 15 0	26	32	NS
	4 10.0 Sham	35 12 3	19	26	-
	15 10.0 Cage control	41 9 2	24	25	
Rat, Sprague-Dawley (F)	900 MHz GSM signal (217 Hz pulsed; pulse width, 577 µs)	Mammary-gland tumours	Cumulative incidence of tumours [%]		
DMBA, 50 mg/kg bw by gavage	Far-field, 100 µW/cm ² ± 3 dB; SAR (wb, av), 17.5–70 mW/kg		Last day of observation	Malignant Benign	Malignant tumours were adenocarcinomas
Bartsch et al.(2002)	259–334 d	Median tumour latency (d)			
	Two groups each in three similar experiments performed over 3 years, 60/ group				
	Exp. 1: Sham	Maligant Benign			
	Exp. I: Exposed	145 316	334	90	
	Exp. 2: Sham	278 310	334	91	
	Exp. 2: Exposed	95 > 265	259	38	
	Exp. 3: Sham	95 221	259	60	
	Exp. 3: Exposed	216 293	343	89	
		195 321	343	92	

Table 3.2 (continued)

Species, strain (sex) Tumour initiator Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M, F) ENU <i>in utero</i> , 4 mg/kg bw i.v. on GD 18 24 mo Shirai et al. (2005)	1 439 MHz TDMA signal (near-field) 90 min/d, 5 d/wk, wk 5–109 (offspring) SAR (brain): 0.67, 2.0 mW/g SAR (wb, av): < 0.4 mW/g	Pituitary tumours lower in ENU/high group	$P < 0.01$	Tube exposure/restrained Full histopathology ~10 sections/brain
		CNS tumours [%]		
		Brain		
		M/F		Spinal cord
		0/0		M/F
	Group 1: cage control	18/18		0/0
	Group 2: ENU control	24/30		2/6
	Group 3: ENU/sham	30/18	-	2/4
	Group 4: ENU/low (0.67 mW/g)	22/16	NS	0/6
	Group 5: ENU/high (2.0 mW/g)		NS	4/4
Rat, Sprague-Dawley (F) DMBA, 35 mg/kg bw by gavage on d 1 26 wk Yu et al. (2006)	900 MHz GSM; SAR (wb, av): 0.44, 1.33, 4.0 mW/g 4 h/d, 5 d/wk, 26 wk (starting on d 2)	No significant differences in incidence, latency, multiplicity or size of mammary-gland tumours between sham- and RF-exposed groups		
		Mammary-gland tumours (all) (%)		
		Mammary-gland adenocarcinoma (%)		
		Mammary-gland tumours (%)		
		Benign mammary-gland tumours (%)		
		Mammary-gland hyperplasia (%)		
	Group 1: cage control	60*		14
	Group 2: sham	45		29
	Group 3: 0.44 mW/g	38		24
	Group 4: 1.33 mW/g	41		15
Rat, F344 (M, F) ENU <i>in utero</i> , 4 mg/kg bw i.v. on GD 18 24 mo Shirai et al. (2007)	1.95 GHz WCDMA signals for IMT-2000 cellular system (near-field) 90 min/d, 5 d/wk, wk 5–109 (offspring) SAR (brain): 0.67, 2.0 mW/g SAR (wb, av): ≤ 0.464 mW/g	Skin fibroma and large granular lymphocytic leukaemia incidences lower in ENU/high group	$P < 0.05$	Tube exposure/restrained Full histopathology ~10 sections/brain
		CNS tumours [%]		
		Brain		
		M/F		Spinal cord
		2/2		M/F
	Group 1: cage control	16/14		0/0
	Group 2: ENU/cage control	8/10		2/0
	Group 3: ENU/sham	16/10	-	2/0
	Group 4: ENU/low (0.67 mW/g)	16/22	NS	0/0
	Group 5: ENU/high (2.0 mW/g)		NS	2/0

Table 3.2 (continued)

Species, strain (sex) Tumour initiator Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments		
Rat, Sprague-Dawley (F) DMBA, 17 mg/kg bw by gavage on d 1 6 mo Hruby et al. (2008)	902 MHz GSM (crest factor of 8; pulse width, 0.57 ms); SAR (wb, av), 0.4, 1.3, 4.0 mW/g 4 h/d, 5 d/wk, 6 mo (starting on d 2) 100/group	Mammary-gland tumour multiplicity or volume	NS (RF-exposed vs sham-exposed)	Restrained exposure in tube (Ferris wheel) GLP Malignant tumours were mainly adenocarcinomas.		
		Mammary-gland lesions (%)				
		Malignant or benign			Malignant	Benign
		73			45	28
		60			30	30
		57			40	17*
		50			35	15*
		65			47**	18*
		Group 1: cage control				
		Group 2: sham				
Group 3: 0.4 mW/g						
Group 4: 1.3 mW/g						
Group 5: 4.0 mW/g						

B[a]P, benzo[a]pyrene; CDMA, code-division multiple access; CNS, central nervous system; CWRF, continuous-wave radiofrequency; d, day or days; DCS, Digital Personal Communication System; DEN, diethylnitrosamine; DMH, dimethylhydrazine; DMBA, 7,12-dimethylbenz[a]anthracene; EMF, electromagnetic field; ENU, *N*-ethyl-*N*-nitrosourea; FDMA, frequency-division multiple access; GD, gestational day; GSM, Global System for Mobile communication; h, hour; i.v., intravenously; IR, infrared radiation; min, minute; MMW, millimetre wavelength; mo, month; NADC, North American Digital Cellular; NS, not significant; ODC, ornithine decarboxylase; PH, partial hepatectomy; PND, postnatal day; p.o., oral administration; PW, pulse-modulated radiofrequency; RF, radiofrequency radiation; s, second; SAR (wb, av), (time-averaged whole-body) specific absorption rate; s.c., subcutaneously; TDMA, time-division multiple access; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; UMTS, Universal Mobile Telecommunication System; UWB, ultra-wide band; WCDMA, wide-band code-division multiple access; wk, week

increase tumour incidence or multiplicity when compared with DMBA-treated sham-exposed controls. Exposure to TPA and RF radiation or TPA and infrared radiation did not increase the incidence of tumours or tumour multiplicity when compared with TPA controls. The authors concluded that MMW did not promote or co-promote skin tumorigenesis ([Mason et al., 2001](#)).

Starting at 20, 40, or 75 days after treatment with a single subcutaneous dose of 2 mg of benzo[a]pyrene, groups of 8–18 female Sprague-Dawley rats were exposed to GSM RF radiation at a wbSAR of 75 mW/kg for 2 hours per day, 5 days per week, for 2 weeks. An additional group was exposed to the GSM signal at a wbSAR of 270 mW/kg starting 40 days after the treatment with benzo[a]pyrene. For each GSM-exposed group, a sham-exposure group was included, resulting in a total of eight groups. The study was terminated at approximately 160 days after the treatment with benzo[a]pyrene. Small palpable tumours (sarcomas) were detectable from days 90 to 100. No consistent pattern of differences in time to tumour development or survival was observed between groups ([Chagnaud et al., 1999](#)). [The Working Group noted that the value of this study was diminished by the very limited exposure, the small group sizes, and the absence of histopathology.]

3.2.2 Lymphoma model

CBA/S mice are prone to develop lymphomas after exposure to ionizing radiation. In this study, groups of 50 female CBA/S mice (age, 3–5 weeks) (except the cage-control group) received whole-body exposure to ionizing radiation (X-rays, 4–6 MV, 4 Gy, delivered as three equal fractions of 1.33 Gy at intervals of 1 week) at the beginning of the study, followed by exposure to RF radiation for 1.5 hours per day, 5 days per week, for 78 weeks. A first “X-ray plus RF” group was exposed to continuous NMT900 (Nordic Mobile Telephony

900)-type frequency-modulated RF radiation at a frequency of 902.5 MHz and a nominal average SAR of 1.5 mW/g. A second “X-ray plus RF” group was exposed to pulsed GSM-type RF radiation (carrier-wave frequency, 902.4 MHz; pulse frequency, 217 Hz) at a nominal average SAR of 0.35 mW/g. An X-ray-exposed control group received sham exposure to RF radiation. Exposure to RF radiation did not significantly increase the incidence of tumours compared with the sham-exposed group ([Heikkinen et al., 2001](#)).

3.2.3 Mammary-gland tumour model

Groups of 60 female Sprague-Dawley rats (Hsd:SD) (age, 51 days) were given DMBA as a single intragastric dose of 50 mg/kg bw. On the same day, the rats were sham-exposed or exposed to RF radiation as a GSM signal at 900 MHz (pulse, 217 Hz) for 23 hours per day, 7 days per week, for 259–334 days. Over 3 years, three identical experiments with group-housed rats were performed. At the beginning of each experiment, wbSARs ranged from 32.5 to 130 mW/kg; wbSARs at 11 months ranged from 15 to 60 mW/kg; on average, wbSARs ranged from 17.5 to 70 mW/kg. Rats were killed when mammary-gland tumours reached 1–2 cm in diameter, and tumours were evaluated histopathologically. The incidence of benign or malignant mammary-gland tumours did not differ between sham-exposed and exposed groups. A statistically significant delay in the appearance of mammary-gland adenocarcinoma was seen in RF-exposed rats in the first experiment; this effect was not confirmed in the second or third experiment ([Bartsch et al., 2002](#)). [The Working Group noted the lack of reproducibility in tumour response between the three experiments.]

Two experiments were performed with the same GSM signal at 900 MHz as mentioned above, but with different intensities. In both experiments, groups of 16 female Sprague-Dawley rats were

sham-exposed or exposed to GSM RF radiation for 9 weeks, starting 10 days after administration by gastric intubation of 10 mg of DMBA at the age of 55 days, and were observed for an additional 3 weeks. In the first experiment, groups were exposed at wbSAR 0 (sham), 1.4, 2.2, or 3.5 mW/g and the authors reported that mammary-gland tumours developed more rapidly in rats exposed to signals at wbSAR 1.4 and 2.2 mW/g compared with controls. In the second experiment, groups were exposed at wbSAR 0 (sham), 0.1, 0.7, or 1.4 mW/g, and a decreased incidence of malignant mammary-gland tumours was seen in the group exposed to the signal at a wbSAR of 1.4 mW/g. Overall, no differences in the latency, multiplicity, or volume of mammary-gland tumours were observed ([Anane et al., 2003](#)). [The Working Group noted that the value of this study was reduced by the lack of reproducibility between exposure to RF radiation and mammary-gland tumour responses.]

Groups of 99–100 female Sprague-Dawley rats (age, 48 days) were given DMBA as a single oral dose of 35 mg/kg bw, followed by sham-exposure or exposure to RF radiation as a GSM signal at 900 MHz, for 4 hours per day, 5 days per week, for 26 weeks, in a Ferris wheel/tube-restrained system. Values for wbSAR were 0 (sham), 0.44, 1.33, and 4.0 mW/g. A cage-control group was also included. No differences in body weight, or in the incidence, latency to onset, multiplicity, or size of mammary-gland tumours were seen in this study ([Yu et al., 2006](#)).

In an experiment with a design very similar to that of [Yu et al. \(2006\)](#), groups of 100 female Sprague-Dawley rats (age, 46–48 days) were given DMBA as a single oral dose of 17 mg/kg bw, followed 1–2 days later by sham-exposure or exposure to RF radiation as a GSM signal at 900 MHz (pulse, 217 Hz), for 4 hours per day, 5 days per week, for 6 months, in a Ferris wheel/tube-restrained system. Values for wbSAR were 0 (sham), 0.4, 1.3, and 4.0 mW/g. A cage-control group was also included. Exposure to RF radiation

had no effect on survival or body weight. When compared with the sham-exposed control group, the group at 4.0 mW/g demonstrated a statistically significant increase in the number of rats with malignant mammary-gland tumours (mainly adenocarcinomas) and a significant decrease in the number of rats with benign mammary-gland tumours ([Hruby et al., 2008](#)). [The Working Group noted that incidences of mammary-gland cancer were similar in the group at 4.0 mW/g and in the cage-control group.]

3.2.4 Brain-tumour model

Groups of pregnant F344 rats received *N*-ethyl-*N*-nitrosourea (ENU) as a single intravenous dose at 4 mg/kg bw on day 18 of gestation. From day 19 of gestation to postnatal day 21, the pregnant dams and offspring were exposed to far-field RF radiation as an NDAC (North American Digital Cellular)-modulated signal at 836.55 MHz for 2 hours per day, 7 days per week. On postnatal day 33/35, the offspring were sham-exposed or exposed to intermittent near-field RF radiation, 2 hours (8 × 7.5 minutes field on/off) per day, 4 days per week. The total duration of the near-field plus far-field exposure was 24 months. The head region of each rat was exposed to near-field RF radiation in a Ferris wheel/tube-restrained system. Calculated SAR values in the brain ranged from 1.1–1.6 mW/g. The study included four groups: group 1 was sham-exposed (30 males, 30 females); group 2 was exposed to RF radiation (30 males, 30 females); group 3 was ENU/sham-exposed (30 males, 30 females); and group 4 was ENU/RF-exposed (30 males, 26 females). No statistically significant differences in the incidence of tumours of the brain or spinal cord were observed in the sham-exposed and RF-exposed groups ([Adey et al., 1999](#)).

The same laboratory performed a second study with a similar design in pregnant F344 rats exposed to ENU, the offspring of which then became treatment cohorts in six groups. Group

1 was sham-exposed (45 males and 45 females per group); group 2 was RF-exposed (45 males and 45 females per group); group 3 was ENU/sham-exposed (45 males and 45 females per group); group 4 was ENU/RF-exposed (38 males, 52 females); group 5 was exposed to ENU and served as cage control (45 males and 45 females per group); and group 6 served as cage control (45 males and 45 females per group). Treatment with ENU on day 18 of gestation and exposure to far-field RF radiation ($2.6 \pm 0.50 \text{ W/cm}^2$) from day 19 of gestation to postnatal day 21 was identical to that described in [Adey et al. \(1999\)](#). Sham exposure or exposure to near-field RF radiation (836.55 MHz, “balanced speech” modulation; brain SAR, 1.1–1.6 mW/g) for 2 hours per day, 4 days per week, began on postnatal day 31. The total duration of the near-field plus far-field exposure was 24 months. No statistically significant differences were identified in the incidence or histological type of tumours of the brain and spinal cord in the RF-exposed and sham-exposed groups ([Adey et al., 2000](#)).

Pregnant F344 rats received ENU as a single intravenous dose at 4 mg/kg bw on day 18 of gestation. Offspring were randomized into groups of 50 males and 50 females as follows: group 1 was a cage-control group; group 2 was exposed to ENU only; group 3 was exposed to ENU and sham-exposed to RF radiation; group 4 was exposed to ENU and exposed to RF radiation at a low level (brain averaged SAR, 0.67 mW/g); and group 5 was exposed to ENU and exposed to RF radiation at a high level (brain averaged SAR, 2.0 mW/g). Offspring received “head-only” exposure to near-field RF radiation (1439 MHz, TDMA signal), 90 minutes per day, 5 days per week, until age 104 weeks. Exposure to TDMA-modulated RF radiation had no effect on the survival or body weight of rats treated with ENU. Comparisons of the incidences of tumours of the brain and spinal cord in rats treated with ENU did not reveal any statistically significant effects

of exposure to TDMA RF radiation ([Shirai et al., 2005](#)).

A second study was performed by the same laboratory, with a design that was essentially identical to that described in [Shirai et al. \(2005\)](#). Pregnant F344 rats received ENU as a single intravenous dose at 4 mg/kg bw on day 18 of gestation. Offspring were randomized into groups of 50 males and 50 females as follows: group 1 was a cage-control group; group 2 was exposed to ENU only; group 3 was exposed to ENU and sham-exposed; group 4 was exposed to ENU and exposed to RF radiation at a low level (brain averaged SAR, 0.67 mW/g); and group 5 was exposed to ENU and exposed to RF radiation at a high level (brain averaged SAR, 2.0 mW/g). Offspring received “head-only” exposure to near-field RF radiation as a WCDMA (wide-band code-division multiple access) signal at 1.95 GHz from cell phones for IMT-2000 (International Mobile Telecommunication) cellular systems, for 90 minutes per day, 5 days per week, until age 104 weeks. Exposure to RF radiation had no effect on the survival or body weight of rats treated with ENU. Comparisons of the incidences of tumours of the brain and spinal cord in rats treated with ENU did not reveal any statistically significant effects of exposure to WCDMA RF radiation ([Shirai et al., 2007](#)).

Pregnant Sprague-Dawley rats received ENU by intravenous injection at a dose of 0, 2.5 or 10 mg/kg bw on day 15 of gestation. Beginning on postnatal day 57, groups of offspring were sham-exposed or exposed to RF radiation in a Ferris wheel/tube-restrained system for 6 hours per day, 4 days per week for 22 months. RF metrics tested included a pulsed-wave signal (PW) at 860 MHz and a continuous-wave signal (CW) at 860 MHz. Average brain SAR was 1.0 mW/g for both. Including cage controls, the entire experiment consisted of 15 groups of 30 males and 30 females. Key groups included ENU plus sham-exposure; ENU plus PW exposure; and ENU plus CW exposure. Detailed data regarding

treatment and tumour incidences are tabulated in [Table 3.2](#). The results of this study provided no statistically significant evidence that exposure to PW or to CW increased the incidence of tumours in any of the tissues studied, or that it promoted the induction of cranial or spinal-cord tumours initiated by ENU ([Zook & Simmens, 2001](#)).

In a follow-up study by the same authors, pregnant female Sprague-Dawley rats received ENU as a single intravenous dose at 6.25 or 10.0 mg/kg bw on day 15 of gestation. Offspring were randomized by ENU-dose into groups of 90 males and 90 females and then, as in the previous study, exposed to RF radiation from postnatal day 52 ± 3 as a PW signal at 860 MHz, in a Ferris wheel/tube-restrained system, 6 hours per day, 5 days per week, at an average brain SAR of 1.0 mW/g. The study was terminated when the offspring were aged 24 months. Each group included three cohorts and the study was conducted in three phases, each containing six groups. Groups 1, 2, and 3 received ENU at 6.25 mg/kg bw plus: (i) sham exposure to RF radiation (group 1); or (ii) exposure to RF radiation (group 2); or (iii) no treatment (cage control; group 3); while groups 4, 5 and 6 received ENU at 10.0 mg/kg bw plus: (i) sham exposure to RF radiation (group 4); or (ii) exposure to RF radiation (group 5); or (iii) no treatment (cage control; group 6). Necropsies were performed monthly on selected rats from each group, beginning at age 171 days. Exposure to RF radiation had no statistically significant effects on the survival or body weight of rats treated with ENU. Histopathological evaluation of tissues from the nervous system provided no evidence that exposure to the RF signal affected the incidence, multiplicity or latency of any type of neurogenic tumour ([Zook & Simmens, 2006](#)).

3.3 Co-carcinogenesis

See [Table 3.3](#)

To evaluate the possible effects of RF-radiation exposure on colon carcinogenesis, three groups

of 26–32 male and 26–32 female BALB/c mice (age, 4–5 weeks) were given dimethylhydrazine (DMH) as a subcutaneous injection at a dose of 15 mg/kg bw every week for 14 weeks, and subsequently at a dose of 20 mg/kg bw for 8 weeks. Starting 3 weeks after the first injection of DMH, the mice were either sham-exposed, exposed to RF radiation at 2450 MHz (SAR, 10–12 mW/g) for 3 hours per day, 6 days per week, for 5 months, or given weekly intraperitoneal injections of TPA at 2 µg per mouse for 10 weeks. Mice in the control group were given a subcutaneous injection of saline solution only. The incidences of tumours of the colon were similar in all groups treated with DMH ([Wu et al., 1994](#)).

The possible effects of exposure to RF radiation on tumorigenesis were investigated in the offspring of pregnant female B6C3F₁ mice treated with ENU. Exposure of pregnant mice to RF radiation as a UMTS signal at 1966 MHz was initiated on day 6 of gestation, and was continued throughout pregnancy and for 2 years post-parturition. Pregnant mice were also intraperitoneally injected with ENU at a dose of 40 mg/kg bw on day 14 of gestation. Groups of 54–60 offspring were exposed to UMTS RF radiation at an intensity of 0, 4.8, or 48 W/m² for 20 hours per day, 7 days per week. Group 1 served as a cage control; group 2 was exposed to ENU only; group 3 was sham-exposed only; group 4 was exposed to ENU plus UMTS RF radiation at 4.8 W/m²; and group 5 was exposed to UMTS RF radiation at 48 W/m². Comparable incidences of tumours were seen in the groups that were not exposed to ENU. In groups exposed to ENU, UMTS RF radiation increased the incidence of bronchiolo-alveolar carcinoma and hepatocellular adenoma ([Tillmann et al., 2010](#)). [The Working Group noted that this experimental model had not been used previously in other studies of hazard identification, and its concordance with the human carcinogenic response is unknown.]

Three groups of 45–49 transgenic female K2 mice overexpressing the human ornithine

decarboxylase (ODC) gene and their wild-type littermates were exposed to a combination of ultraviolet (UV) radiation and pulsed RF radiation. The UV dose was 240 J/m² delivered three times per week for 52 weeks. The mice were sham-exposed or exposed to RF radiation for 1.5 hours per day, 5 days per week, for 52 weeks. One group of mice was exposed to D-AMPS (digital advanced mobile phone system)-modulated RF radiation at 849 MHz; a second group was exposed to GSM RF radiation at 902.4 MHz; and a third group was sham-exposed. Nominal average SAR for both exposed groups was 0.5 mW/g. A cage-control group of 20 mice was included. There were no differences in the cumulative survival or body weight in groups exposed to UV, regardless of exposure to RF radiation. UV exposure induced macroscopic tumours of the skin in 12% of the non-transgenic mice and in 37% of the transgenic mice. Exposure to RF radiation had no effect on the induction of squamous cell carcinoma of the skin in either transgenic or wild-type mice ([Heikkinen et al., 2003](#)).

A study evaluated the possible effects of exposure to RF radiation on tumorigenesis induced by the mutagen 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX), a by-product of water disinfection. Groups of 72 female Wistar rats (age, 7 weeks) were given drinking-water containing MX at a daily average dose of 0 (cage-control) or 1.7 mg/kg bw for 104 weeks, and were then sham-exposed or exposed to pulsed RF radiation at 900 MHz (wbSARs of 0 [sham control], 0.3 or 0.9 mW/g) in restrainers for 2 hours per day, 5 days per week, for 104 weeks. Exposure to RF radiation had no statistically significant effects on mortality or body weight of rats treated with MX. Compared with the MX-treated sham-exposed control group [but not the cage control group], a statistically significant increase in the incidence of combined vascular tumours (haemangiomas, haemangiosarcomas and lymphangiomas combined) was

observed in the mesenteric lymph nodes of the group treated with MX and RF radiation at a high intensity (wbSAR, 0.9 mW/g). Exposure to RF radiation had no significant effect on the incidence of tumours in any other tissue ([Heikkinen et al., 2006](#)). [The Working Group noted that this experimental model had not been used previously in other hazard-identification studies, and its concordance with human carcinogenic response is unknown.]

Groups of 40 male BALB/c mice received 10 µL of a 5% solution of benzo[a]pyrene by skin painting on alternate days for 5 months, and were exposed to RF radiation as microwaves at 2450 MHz for 2 hours per day, 6 days per week, in an anechoic chamber, according to two different protocols. In the pre-exposure protocol, the mice were exposed to microwave radiation at SARs of 0 mW/g (sham) or 2–3 mW/g for 1 or 3 months before application of benzo[a]pyrene. In the simultaneous-exposure protocol, groups of mice were exposed to RF radiation at SARs of 0 mW/g, 2–3 mW/g, or 6–8 mW/g concurrently with administration of benzo[a]pyrene. Pre-exposure or simultaneous exposure to microwave radiation at either SAR value accelerated the development of benzo[a]pyrene-induced skin cancer. A comparable acceleration of skin tumorigenesis was reported in benzo[a]pyrene-treated mice undergoing confinement stress for 1 or 3 months ([Szmigielski et al., 1982](#)). [The Working Group noted that the study design and experimental data from this paper were poorly presented and difficult to interpret.]

In a second study performed by the same group, six groups of 100 adult male BALB/c mice were painted with 10 µL of 1% benzo[a]pyrene on the interscapular region of the skin on alternate days for 6 months. Two different schedules of exposure to microwave radiation at 2450 MHz were used. In the first experiment, three groups were exposed to microwave radiation (mean wbSAR, 4 mW/g) for 2 hours per day, 6 days per week, for 1, 2 or 3 months before the start of

Table 3.3 Co-carcinogenicity studies in experimental animals exposed to radiofrequency radiation

Species, strain (sex) Carcinogen Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, K2 (ODC-transgenic and wild-type) (F) UV radiation: 240 J/m ² , 3 × /wk, 52 wk 52 wk Heikkinen et al. (2003)	DAMPS-type (849 MHz) or GSM-type (902.4 MHz) RF, SAR: 0.5 mW/g 1.5 h/d, 5 d/wk, 52 wk Sham (ODC-transgenic + wild-type): 19 + 26; D-AMPS: 20 + 26; GSM: 22 + 27; and cage control: 12 + 8	Squamous-cell carcinoma of the skin: ODC-transgenic (sham): 6/19 ODC-transgenic (GSM): 5/21 ODC-transgenic (DAMPS): 8/20 Wild-type (sham): 2/26 Wild-type (GSM): 4/27 Wild-type (DAMPS): 4/26	NS	Restrained exposure Histopathological evaluation of all skin lesions
Rat, Wistar (F) 3-Chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone [MX], 1.7 mg/kg bw, drinking-water, 104 wk 104 wk Heikkinen et al. (2006)	GSM (900 MHz) PW (whole body) with wBSARs of 0.3 mW/g (low RF) or 0.9 mW/g (high RF), sham, cage control 2 h/d, 5 d/wk, 104 wk 72/group	Combined vascular tumours (haemangioma, haemangiosarcoma and lymphangioma) in the mesenteric lymph nodes (cage control, sham, low RF, high RF): 10/72 (14%), 3/72 (4%), 1/72 (1%), 11/72 (15%)	$P < 0.05$ (Fisher test), high RF vs sham	Complete histopathology No significant difference between high RF-radiation-exposed group and cage-control group
Mouse, BALB/c (M, F) DMH, 15 mg/kg bw per wk for 14 wk followed by 20 mg/kg bw per wk for 8 wk, i.p. 25 wk Wu et al. (1994)	2 450 MHz MW, 3 h/d, 6 d/wk, 5 mo, 10 mW/cm ² (SAR, 10–12 mW/g); sham exposure; or TPA promotion (i.p., 2 µg/wk, 10 wk) 3 wk after 1 st DMH injection A control group was i.p. injected with saline only 26–32/group	Colon tumours: DMH + sham: 13/28 (46%) DMH + MW: 13/26 (50%) DMH + TPA: 17/32 (53%) Control (saline only): 0/29 Protuberant or invasive colon tumours: DMH + sham: 13.9% DMH + MW: 16.3% DMH + TPA: 44.1%	- NS NS - NS $P < 0.05$	Single housing in small plexiglass cages during MW exposure Tumour bearing mice with total tumour areas > 5 mm ² : 71% in DMH + TPA-treated group ($P < 0.05$) vs 31% in DMH- and 31% in DMH + MW-treated groups.
Mouse, B6C3F ₁ (F) ENU, 40 mg/kg bw i.p., on GD 14 106 wk Tillmann et al. (2010)	1966 MHz, UMTS signal 20 h/d, 7 d/wk, 106 wk (starting on GD 6) 0 (sham), 4.8, 48 W/m ² SAR: variable Group 1: cage control Group 2: ENU Group 3: sham exposure Group 4: ENU + UMTS (4.8 W/m ²) Group 5: UMTS (48 W/m ²) 54–60/group	Bronchiolo-alveolar adenoma: group 4 (36/58, 62%) vs group 2 (27/60, 45%) Bronchiolo-alveolar carcinoma: group 4 (45/58, 78%) vs group 2 (33/60, 55%) Hepatocellular adenoma: group 4 (49/58, 85%) vs group 2 (30/60, 50%) Hepatocellular carcinoma: group 4 (30/58, 52%) vs group 2 (31/60, 52%) Comparable incidences of tumours in group 1, 3 and 5	NS $P < 0.05$ $P < 0.001$ NS	Tissues that were histopathologically evaluated included brain, lungs, liver, spleen, kidneys, mesenteric lymph nodes, and any gross lesions detected.

80

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benzo[a]pyrene application. In the second experiment, three groups were exposed to RF radiation (wbSAR, 0 mW/g [sham-exposed control], 2 mW/g, or 6 mW/g), 2 hours per day, 6 days per week, for 6 months, concurrently with exposure to benzo[a]pyrene. Irradiation by either schedule resulted in an acceleration in the development of benzo[a]pyrene-induced skin carcinoma and decreased the lifespan of the animals ([Szudziński et al., 1982](#)). [The Working Group noted that the study design and experimental data were poorly presented and difficult to interpret. Survival and tumour data from groups receiving pre-exposure to microwave radiation may be invalid due to the lack of concurrent sham-exposed controls.]

References

- Adey WR, Byus CV, Cain CD *et al.* (1999). Spontaneous and nitrosourea-induced primary tumors of the central nervous system in Fischer 344 rats chronically exposed to 836 MHz modulated microwaves. *Radiat Res*, 152: 293–302. doi:10.2307/3580329 PMID:10453090
- Adey WR, Byus CV, Cain CD *et al.* (2000). Spontaneous and nitrosourea-induced primary tumors of the central nervous system in Fischer 344 rats exposed to frequency-modulated microwave fields. *Cancer Res*, 60: 1857–1863. PMID:10766172
- Anane R, Dulou PE, Taxile M *et al.* (2003). Effects of GSM-900 microwaves on DMBA-induced mammary gland tumors in female Sprague-Dawley rats. *Radiat Res*, 160: 492–497. doi:10.1667/RR3052 PMID:12968925
- Anderson LE, Sheen DM, Wilson BW *et al.* (2004). Two-year chronic bioassay study of rats exposed to a 1.6 GHz radiofrequency signal. *Radiat Res*, 162: 201–210. doi:10.1667/RR3208 PMID:15387148
- Anghileri LJ, Mayayo E, Domingo JL, Thouvenot P (2005). Radiofrequency-induced carcinogenesis: cellular calcium homeostasis changes as a triggering factor. *Int J Radiat Biol*, 81: 205–209. doi:10.1080/09553000500076957 PMID:16019929
- Bartsch H, Bartsch C, Seebald E *et al.* (2002). Chronic exposure to a GSM-like signal (mobile phone) does not stimulate the development of DMBA-induced mammary tumors in rats: results of three consecutive studies. *Radiat Res*, 157: 183–190. doi:10.1667/0033-7587(2002)157[0183:CETAGL]2.0.CO;2 PMID:11835682
- Bartsch H, Küpper H, Scheurlen U *et al.* (2010). Effect of chronic exposure to a GSM-like signal (mobile phone) on survival of female Sprague-Dawley rats: modulatory effects by month of birth and possibly stage of the solar cycle. *Neuro Endocrinol Lett*, 31: 457–473. PMID:20802457
- Breuer M, Slebos R, Verbeek S *et al.* (1989). Very high frequency of lymphoma induction by a chemical carcinogen in pim-1 transgenic mice. *Nature*, 340: 61–63. doi:10.1038/340061a0 PMID:2786994
- Chagnaud JL, Moreau JM, Veyret B (1999). No effect of short-term exposure to GSM-modulated low-power microwaves on benzo(a)pyrene-induced tumours in rat. *Int J Radiat Biol*, 75: 1251–1256. doi:10.1080/095530099139403 PMID:10549601
- Chou CK, Guy AW, Kunz LL *et al.* (1992). Long-term, low-level microwave irradiation of rats. *Bioelectromagnetics*, 13: 469–496. doi:10.1002/bem.2250130605 PMID:1482413
- Frei MR, Berger RE, Dusch SJ *et al.* (1998a). Chronic exposure of cancer-prone mice to low-level 2450 MHz radiofrequency radiation. *Bioelectromagnetics*, 19: 20–31. doi:10.1002/(SICI)1521-186X(1998)19:1<20::AID-BEM2>3.0.CO;2-6 PMID:9453703
- Frei MR, Jauchem JR, Dusch SJ *et al.* (1998b). Chronic, low-level (1.0 W/kg) exposure of mice prone to mammary cancer to 2450 MHz microwaves. *Radiat Res*, 150: 568–576. doi:10.2307/3579874 PMID:9806599
- Heikkinen P, Ernst H, Huuskonen H *et al.* (2006). No effects of radiofrequency radiation on 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone-induced tumorigenesis in female Wistar rats. *Radiat Res*, 166: 397–408. doi:10.1667/RR3588.1 PMID:16881741
- Heikkinen P, Kosma VM, Alhonen L *et al.* (2003). Effects of mobile phone radiation on UV-induced skin tumorigenesis in ornithine decarboxylase transgenic and non-transgenic mice. *Int J Radiat Biol*, 79: 221–233. doi:10.1080/0955300031000096298 PMID:12775446
- Heikkinen P, Kosma VM, Hongisto T *et al.* (2001). Effects of mobile phone radiation on X-ray-induced tumorigenesis in mice. *Radiat Res*, 156: 775–785. doi:10.1667/0033-7587(2001)156[0775:EOMPRO]2.0.CO;2 PMID:11741502
- Hruby R, Neubauer G, Kuster N, Frauscher M (2008). Study on potential effects of “902-MHz GSM-type Wireless Communication Signals” on DMBA-induced mammary tumours in Sprague-Dawley rats. *Mutat Res*, 649: 34–44. PMID:17981079
- Huang TQ, Lee JS, Kim TH *et al.* (2005). Effect of radiofrequency radiation exposure on mouse skin tumorigenesis initiated by 7,12-dimethylbenz[alpha]anthracene. *Int J Radiat Biol*, 81: 861–867. doi:10.1080/09553000600568093 PMID:16524842
- Imaida K, Kuzutani K, Wang J *et al.* (2001). Lack of promotion of 7,12-dimethylbenz[a]anthracene-initiated mouse skin carcinogenesis by 1.5 GHz electromagnetic

- near fields. *Carcinogenesis*, 22: 1837–1841. doi:10.1093/carcin/22.11.1837 PMID:11698347
- Jauchem JR, Ryan KL, Frei MR *et al.* (2001). Repeated exposure of C3H/HeJ mice to ultra-wideband electromagnetic pulses: lack of effects on mammary tumors. *Radiat Res*, 155: 369–377. doi:10.1667/0033-7587(2001)155[0369:REOCHM]2.0.CO;2 PMID:11175673
- La Regina M, Moros EG, Pickard WF *et al.* (2003). The effect of chronic exposure to 835.62 MHz FDMA or 847.74 MHz CDMA radiofrequency radiation on the incidence of spontaneous tumors in rats. *Radiat Res*, 160: 143–151. doi:10.1667/RR3028 PMID:12859224
- Lee HJ, Jin YB, Lee JS *et al.* (2011). Lymphoma development of simultaneously combined exposure to two radiofrequency signals in AKR/J mice. *Bioelectromagnetics*, n/a doi:10.1002/bem.20655 PMID:21437920
- Mason PA, Walters TJ, DiGiovanni J *et al.* (2001). Lack of effect of 94 GHz radio frequency radiation exposure in an animal model of skin carcinogenesis. *Carcinogenesis*, 22: 1701–1708. doi:10.1093/carcin/22.10.1701 PMID:11577012
- Oberto G, Rolfo K, Yu P *et al.* (2007). Carcinogenicity study of 217 Hz pulsed 900 MHz electromagnetic fields in Pim1 transgenic mice. *Radiat Res*, 168: 316–326. doi:10.1667/rr0425.1 PMID:17705642
- Paulraj R & Behari J (2011). Effects of low level microwave radiation on carcinogenesis in Swiss Albino mice. *Mol Cell Biochem*, 348: 191–197. doi:10.1007/s11010-010-0654-8 PMID:21086023
- Repacholi MH, Basten A, Gebiski V *et al.* (1997). Lymphomas in E mu-Pim1 transgenic mice exposed to pulsed 900 MHz electromagnetic fields. *Radiat Res*, 147: 631–640. doi:10.2307/3579630 PMID:9146709
- Saran A, Pazzaglia S, Mancuso M *et al.* (2007). Effects of exposure of newborn patched1 heterozygous mice to GSM, 900 MHz. *Radiat Res*, 168: 733–740. doi:10.1667/RR1065R1.1 PMID:18088186
- Shirai T, Ichihara T, Wake K *et al.* (2007). Lack of promoting effects of chronic exposure to 1.95-GHz W-CDMA signals for IMT-2000 cellular system on development of N-ethylnitrosourea-induced central nervous system tumors in F344 rats. *Bioelectromagnetics*, 28: 562–572. doi:10.1002/bem.20324 PMID:17516507
- Shirai T, Kawabe M, Ichihara T *et al.* (2005). Chronic exposure to a 1.439 GHz electromagnetic field used for cellular phones does not promote N-ethylnitrosourea induced central nervous system tumors in F344 rats. *Bioelectromagnetics*, 26: 59–68. doi:10.1002/bem.20079 PMID:15605402
- Smith P, Kuster N, Ebert S, Chevalier HJ (2007). GSM and DCS wireless communication signals: combined chronic toxicity/carcinogenicity study in the Wistar rat. *Radiat Res*, 168: 480–492. doi:10.1667/RR0680.1 PMID:17903030
- Sommer AM, Bitz AK, Streckert J *et al.* (2007). Lymphoma development in mice chronically exposed to UMTS-modulated radiofrequency electromagnetic fields. *Radiat Res*, 168: 72–80. doi:10.1667/RR0857.1 PMID:17723000
- Sommer AM, Streckert J, Bitz AK *et al.* (2004). No effects of GSM-modulated 900 MHz electromagnetic fields on survival rate and spontaneous development of lymphoma in female AKR/J mice. *BMC Cancer*, 4: 77 doi:10.1186/1471-2407-4-77 PMID:15538947
- Szmigielski S, Szudzinski A, Pietraszek A *et al.* (1982). Accelerated development of spontaneous and benzo-pyrene-induced skin cancer in mice exposed to 2450-MHz microwave radiation. *Bioelectromagnetics*, 3: 179–191. doi:10.1002/bem.2250030202 PMID:7126270
- Szudziński A, Pietraszek A, Janiak M *et al.* (1982). Acceleration of the development of benzopyrene-induced skin cancer in mice by microwave radiation. *Arch Dermatol Res*, 274: 303–312. doi:10.1007/BF00403734 PMID:6299207
- Tillmann T, Ernst H, Ebert S *et al.* (2007). Carcinogenicity study of GSM and DCS wireless communication signals in B6C3F₁ mice. *Bioelectromagnetics*, 28: 173–187. doi:10.1002/bem.20283 PMID:17019729
- Tillmann T, Ernst H, Streckert J *et al.* (2010). Indication of cocarcinogenic potential of chronic UMTS-modulated radiofrequency exposure in an ethylnitrosourea mouse model. *Int J Radiat Biol*, 86: 529–541. doi:10.3109/09553001003734501 PMID:20545575
- Toler JC, Shelton WW, Frei MR *et al.* (1997). Long-term, low-level exposure of mice prone to mammary tumors to 435 MHz radiofrequency radiation. *Radiat Res*, 148: 227–234. doi:10.2307/3579606 PMID:9291353
- Utteridge TD, Gebiski V, Finnie JW *et al.* (2002). Long-term exposure of E-mu-Pim1 transgenic mice to 898.4 MHz microwaves does not increase lymphoma incidence. *Radiat Res*, 158: 357–364. doi:10.1667/0033-7587(2002)158[0357:LTEOEP]2.0.CO;2 PMID:12175314
- van Kreijl CF, van der Houven van Oordt CW, Kroese ED *et al.* (1998). Evaluation of the Emu-pim-1 transgenic mouse model for short-term carcinogenicity testing. *Toxicol Pathol*, 26: 750–756. doi:10.1177/019262339802600606 PMID:9864091
- Wu RY, Chiang H, Shao BJ *et al.* (1994). Effects of 2.45-GHz microwave radiation and phorbol ester 12-O-tetradecanoylphorbol-13-acetate on dimethylhydrazine-induced colon cancer in mice. *Bioelectromagnetics*, 15: 531–538. doi:10.1002/bem.2250150606 PMID:7880166
- Yu D, Shen Y, Kuster N *et al.* (2006). Effects of 900 MHz GSM wireless communication signals on DMBA-induced mammary tumors in rats. *Radiat Res*, 165: 174–180. doi:10.1667/RR3497.1 PMID:16435916
- Zook BC & Simmens SJ (2001). The effects of 860 MHz radiofrequency radiation on the induction or promotion of brain tumors and other neoplasms in rats. *Radiat Res*, 155:

572–583. doi:10.1667/0033-7587(2001)155[0572:TEOM
RR]2.0.CO;2 PMID:11260659

Zook BC & Simmens SJ (2002). Effects of a cell phone radi-
ofrequency (860 MHz) on the latency of brain tumors
in rats. *Int Congr Ser*, 1236: 137–139. doi:10.1016/
S0531-5131(01)00779-8

Zook BC & Simmens SJ (2006). The effects of pulsed 860
MHz radiofrequency radiation on the promotion of
neurogenic tumors in rats. *Radiat Res*, 165: 608–615.
doi:10.1667/RR3551.1 PMID:16669743

4. OTHER RELEVANT DATA

Data on specific absorption rate (SAR) and distribution of radiofrequency (RF) radiation inside tissues and organs and at the subcellular level are presented elsewhere in this Volume (Section 1.3, Dosimetry).

4.1 Genetic and related effects

4.1.1 Humans

During the past decades, extensive research efforts have focused on determining the extent of DNA damage in eukaryotic and prokaryotic cells exposed to RF radiation. Several published reviews concluded that: (i) the existing data are not sufficiently strong to suggest that RF radiation is directly genotoxic; (ii) exposure to RF radiation probably does not enhance the damage induced by known genotoxic agents; and (iii) some of the reported “adverse effects” may be attributed to hyperthermia induced by RF radiation ([Brusick et al., 1998](#); [Verschaeve & Maes, 1998](#); [Moulder et al., 1999, 2005](#); [Heynick et al., 2003](#); [Meltz, 2003](#); [Vijayalaxmi & Obe, 2004](#); [Verschaeve, 2005](#); [Krewski et al., 2007](#); [Lai, 2007](#); [Vijayalaxmi & Prihoda, 2008](#); [Phillips et al., 2009](#); [Rüdiger, 2009a](#); [Verschaeve, 2009](#); [Verschaeve et al., 2010](#)). International organizations and expert scientific advisory groups in several countries, including Canada, France, the Netherlands, Sweden, the United Kingdom and the USA, have reached similar conclusions ([ICNIRP, 2009](#)).

This Section of the *Monograph* deals with studies on primary DNA damage in humans exposed occupationally or as mobile-phone users;

in these studies DNA damage was measured in peripheral blood lymphocytes and buccal cells by means of the alkaline or neutral single-cell gel electrophoresis assay (comet assay), which reveals alkali-labile lesions and single- and double-strand breaks in DNA, or by use of cytogenetic tests for chromosomal aberrations, micronucleus formation and sister-chromatid exchange (SCE). The studies reviewed below are summarized in [Table 4.1](#) and [Table 4.2](#) (with details of the exposure conditions).

(a) Peripheral blood lymphocytes

(i) Occupational exposure

[Garaj-Vrhovac et al. \(1990a\)](#) were the first to report an increased frequency of chromosomal aberrations in the form of chromatid and chromosome breaks, acentric fragments, dicentrics, rings and polycentric chromosomes, as well as micronuclei in 10 individuals employed in a radar service-station facility. The frequency of cells with chromosomal aberrations and micronuclei ranged from 1.6% to 31.5% and from 1.6% to 27.9%, respectively, in exposed subjects, while the corresponding values in controls were 1.8% and 1.5% [no range given].

In a study in Australia, [Garson et al. \(1991\)](#) collected lymphocytes from 38 radio linesmen,

Table 4.1 Genetic and related effects of radiofrequency radiation in peripheral blood lymphocytes of occupationally exposed individuals

End-point	No. of subjects	Occupation	Frequency	SAR or power density	Duration	Results	Reference
Aneuploidy	18	Air-traffic controllers; engineers	100 kHz to 300 GHz	-	10–27 yr	+	Othman et al. (2001)
CA	10	Radar maintenance workers	0.2 MHz to 26 GHz	0.010–50 mW/cm ²	8–25 yr	+	Garaj-Vrhovac et al. (1990a)
CA	38	Radio linesmen	400 kHz to 20 GHz	614 V/m	5 yr	-	Garson et al. (1991)
CA	6	Air-traffic radar-repairmen	1250–1350 MHz	0.01–20 mW/cm ²	16 yr	+ [after a 30-wk follow-up, total aberrations had decreased]	Garaj-Vrhovac et al. (1993)
CA	6	Transmission-antenna maintenance workers	450–900 MHz	NR	1 yr	-	Maes et al. (1995)
CA	20	Workers in telecommunication and radio-relay stations	8 GHz	1 mW/cm ²	6 yr (12 h/d)	+	Lalić et al. (2001)
CA	50	Air-traffic controllers, engineers	100 kHz to 300 GHz	NR	8–27 yr	+	Aly et al. (2002)
CA	49	Radio engineers	450–900 MHz	NR	2.3 yr (> 1 h/d)	-	Maes et al. (2006)
CA	10	Radar maintenance workers	1250–1350 MHz	0.010–20 mW/cm ²	7–29 yr	+	Garaj-Vrhovac & Orescanin (2009)
MN	10	Radar maintenance workers	0.2 MHz to 26 GHz	0.010–50 mW/cm ²	8–25 yr	+	Garaj-Vrhovac et al. (1990a)
MN	NR	Multiple occupations	1250–1350 MHz	0.01–20 mW/cm ²	15 yr	+	Fucić et al. (1992)
MN	12	Radar maintenance workers	1250–1350 MHz	0.01–20 mW/cm ²	13 yr	+	Garaj-Vrhovac (1999)
SB	40	Flight crew	NR	NR	5–18 yr	-	Cavallo et al. (2002)
SB	49	Radio engineers	450–900 MHz	NR	2.3 yr (> 1 h/d)	-	Maes et al. (2006)
SB	10	Radar maintenance workers	1250–1350 MHz	0.010–20 mW/cm ²	7–29 yr	+	Garaj-Vrhovac & Orescanin (2009)
SCE	50	Air-traffic controllers	100 kHz to 300 GHz	NR	8–27 yr	-	Aly et al. (2002)
SCE	49	Radio engineers	450–900 MHz	NR	2.3 yr (> 1 h/d)	-	Maes et al. (2006)

+ increase; -, no effect; CA, chromosomal aberration; d, day; h, hour; MN, micronucleus formation; NR, not reported; SAR, specific absorption rate; SB, DNA single- and double-strand breaks; SCE, sister-chromatid exchange; wk, week; yr, year

Table 4.2 Genetic and related effects of radiofrequency radiation in peripheral blood lymphocytes and buccal cells of mobile-phone users

End-point	No. of subjects	Frequency	SAR	Duration	Results	Reference
<i>Peripheral blood lymphocytes</i>						
CA	24	890–960 MHz	NR	2 yr	+	Gadhia et al. (2003)
CA	25	NR	0.1–1.9 W/kg	3–5 yr	+	Gandhi & Singh (2005)
MN	24	800–2000 MHz	0.6–1.6 W/kg	1–5 yr	+	Gandhi & Anita (2005)
SB	24	800–2000 MHz	0.6–1.6 W/kg	1–5 yr	+	Gandhi & Anita (2005)
SCE	24	890–960 MHz	NR	2 yr	+	Gadhia et al. (2003)
<i>Buccal cells</i>						
MN	25	NR	0.1–1.9 W/kg	3–5 yr	+	Gandhi & Singh (2005)
MN	85	NR	0.3–1.0 W/kg	2.3 yr (1 h/d)	+	Yadav & Sharma (2008)
MN	112	NR	NR	5–10 yr (3 h/wk)	–	Hintzsche & Stopper (2010)

+, increase; –, no effect; CA, chromosomal aberration; d, day; h, hour; MN, micronucleus formation; NR, not reported; SAR, specific absorption rate; SB, DNA single- and double-strand breaks; SCE, sister-chromatid exchange; wk, week; yr, year

who erected and maintained broadcasting, telecommunication and satellite RF-transmission towers, and found no increase in the frequency of chromosomal aberrations compared with the frequency in 38 controls working as clerical staff. In this study, exposure to RF radiation was at or below occupational limits for Australia.

[Fucić et al. \(1992\)](#) measured the surface area of micronuclei in lymphocytes of workers in multiple occupations exposed to pulsed microwaves, X-rays (< 25 mSv during the previous 2 years) and vinyl-chloride monomer (VCM; average concentration, 50 ppm). The sample size in each category was not mentioned in the paper. There were increased numbers of smaller micronuclei in individuals exposed to X-rays and VCM, indicating a clastogenic effect. Increased numbers of smaller as well as larger micronuclei were found in individuals exposed to microwaves, suggesting a dual role of this type of radiation, as clastogen and aneugen.

In a regular 30-week follow-up investigation of six individuals who were acutely exposed to pulsed-wave RF radiation of high power density at an air-traffic radar-repair station,

[Garaj-Vrhovac et al. \(1993\)](#) observed a decline in the total number of chromosomal aberrations.

A preliminary study conducted by [Maes et al. \(1995\)](#) involved six workers in charge of maintaining transmission antennae linked to a mobile-phone network, and six matched controls. No increase in the frequency of chromosomal aberrations was observed in the maintenance workers. The authors mentioned the limited size of the study and the fact that exposure to RF radiation was intermittent. They then extended the study to 49 professionally employed radio engineers working in the field, and 11 administrative staff. Some of these had participated in the earlier study. No differences between exposed and controls were observed with the alkaline comet assay, the assay for chromosomal aberration, or the test for SCE ([Maes et al., 2006](#)).

[Garaj-Vrhovac \(1999\)](#) examined 12 subjects employed in repair services for radar equipment and antennae, and reported frequencies of 8–23 micronuclei per 500 cells in exposed workers compared with 2–7 per 500 cells in control subjects; this difference was statistically significant.

[Lalić et al. \(2001\)](#) investigated 20 workers in telecommunication and radio-relay stations who were exposed to non-ionizing electromagnetic fields, and 25 subjects employed as X-ray technicians, nurses and engineers in radiology, exposed to ionizing radiation. The analysis indicated an increased frequency of chromosomal aberration in both groups. The incidence of dicentric chromosomes was higher in the group exposed to non-ionizing radiation than in the group exposed to ionizing radiation.

[Othman et al. \(2001\)](#) studied professional air-traffic controllers and engineers exposed to RF radiation emitted by different pieces of equipment at the workplace. In a first study, blood lymphocytes were collected from 18 workers and 5 unexposed controls (all males), and cultured for 72 hours. Fluorescence *in situ* hybridization (FISH) with repetitive α -satellite probes for chromosomes 7, 12, 17, and the heterochromatic region of the Y-chromosome, was used to determine the number of aneuploid cells. The results showed increased frequencies of monosomic cells containing a single copy of chromosome 7 (6.6%) or 17 (6.1%), and of cells lacking the Y-chromosome (8.4%); the corresponding values for the controls were 3.2%, 3.7% and 4.5%, respectively.

In a further study by the same group, [Aly et al. \(2002\)](#) examined lymphocytes from 26 air-traffic controllers, 24 engineers and 10 controls. Conventional cytogenetic techniques revealed an increase in the frequency of structural aberrations (2.7–5.3%) and numerical aberrations (8.9–9.3%) in exposed individuals relative to controls (0.8% and 3.2%, respectively). In subjects exposed to RF radiation, 90% of the cells were hypodiploid, i.e. showed loss of chromosomes. The frequency of SCE was also increased, but this increase did not reach statistical significance. [The Working Group noted that conventional cytogenetic techniques may be less reliable than the FISH technique for counting numerical aberrations.]

[Cavallo et al. \(2002\)](#) studied 40 airline pilots and flight technicians exposed to cosmic rays, electromagnetic fields from radar equipment, pollutants from jet-propulsion fluid etc. and 40 non-exposed individuals working on the ground. In the comet assay, visual examination of the results revealed a small increase in the frequency of DNA strand breaks in exposed individuals compared with ground staff, but this increase was not statistically significant.

[Garaj-Vrhovac & Orescanin \(2009\)](#) used the comet assay to measure DNA strand breaks and the test for sensitivity to bleomycin described by [Michalska et al. \(1998\)](#) to investigate genomic instability in 10 individuals working in radar-equipment and antenna-system services, and in 10 control subjects. In the latter method, the cells were treated with bleomycin (a drug used in clinical treatment of cancer) during the last 5 hours before harvesting after a culture period of 72 hours, to assess the incidence of chromosomal aberrations in the form of chromatid breaks. The results of the comet assay revealed increased DNA damage (tail length, 17.1 μm , and tail moment, 14.4, in the exposed individuals compared with 14.2 μm and 11.7, respectively, in the controls). The test for sensitivity to bleomycin showed a higher number of chromatid breaks (1.7 per cell in the exposed, compared with 0.5 per cell in the controls). All these differences were statistically significant.

[The Working Group noted the following limitations in the above-mentioned studies. Exposure assessment was poor or was not mentioned in many reports. The sample size in terms of number of individuals or number of cells analysed was not sufficient to allow robust statistical analysis. Except in one study, “blind” evaluation of microscope slides, and inclusion of positive controls (subjects or cells) while culturing the lymphocytes *in vitro*, was either not performed or not reported. Several investigations were conducted with blood samples collected from workers in one radar-service

facility in Croatia; it was unclear whether the same individuals had been included in more than one of these studies.]

[Although the reports from Australia ([Garson et al., 1991](#)) and Belgium ([Maes et al., 1995](#)) indicated no effect on the frequency of chromosomal aberrations from exposure to RF radiation, the Working Group noted that situations and exposure conditions in those countries may not have been comparable to those in other countries. Chromosomal changes are highly variable during carcinogenesis and are generally grouped into two categories: (i) reciprocal and balanced structural rearrangements resulting in translocations; and (ii) unbalanced and nonreciprocal structural or numerical changes in which genetic material may be lost or added: the latter can range from a single base pair to the entire chromosome. In the studies reviewed above, reciprocal and balanced structural rearrangements were either not observed or not reported in individuals exposed to RF radiation.]

(ii) *Personal exposure from mobile phones*

[Gadhia et al. \(2003\)](#) collected samples of peripheral blood from 24 users of digital mobile phones and 24 matched controls. Both groups comprised 12 nonsmokers/nondrinkers and 12 smokers/alcoholics [smokers consumed 10–15 cigarettes per day; data on alcohol consumption were not given]. Cytogenetic analysis of lymphocytes cultured for 72 hours indicated a significantly increased incidence ($P < 0.05$) of chromatid gaps and dicentric chromosomes among mobile-phone users who smoked and drank alcohol, but not in nonsmokers/nondrinkers. A significantly increased frequency ($P < 0.05$) of SCE was seen in mobile-phone users of both categories.

[Gandhi & Singh \(2005\)](#) studied G-banded chromosomes in lymphocytes (cultured for 72 hours) from 25 users of mobile phones and 25 non-users. There was a statistically significant increase in the frequency of aberrant metaphases,

including triploid chromosomes, acrocentric associations and centromere separation in lymphocytes of mobile-phone users (31.3%) compared with non-users (10.7%). In a subsequent study, [Gandhi & Anita \(2005\)](#) investigated DNA strand breaks by use of the comet assay in lymphocytes from 24 mobile-phone users and 10 controls. Unstimulated lymphocytes were also examined to record the frequency of micronuclei in 20 of those users and 8 non-users. In mobile-phone users, the frequency of damaged cells was 40%, with an average comet-tail length of 27 μm (determined by visual examination with a micrometer), while these values were lower in non-users, at 10% and 8 μm , respectively; both differences were highly significant. The total number of micronuclei was 100 in 40 000 cells in users, and 8 in 16 000 cells in non-users, *i.e.* 2.5% in the former and 0.5% in the latter ($P < 0.05$). [The Working Group noted that the observations reported by [Gandhi & Singh \(2005\)](#) and [Gandhi & Anita \(2005\)](#) were questioned by others ([Vijayalaxmi et al., 2007](#)), pointing out several inconsistencies and weaknesses in laboratory methods, data collection, exposure assessment, etc. in both publications.]

(b) *Buccal cells: personal exposure from mobile phones*

The oral cavity is within the range of RF emissions from mobile phones used at the ear. Hence, examination of the cells in this region is relevant to evaluation of genotoxicity. The oral mucosa has a rich blood supply and is relatively permeable. It has an outer layer of stratified squamous epithelium that is approximately 40–50 cell-layers thick. These exfoliating cells can easily be obtained by non-invasive procedures (oral swabs) from adults, adolescents and children. The turnover of these cells is estimated at 1–3 weeks ([Harris & Robinson, 1992](#)).

The frequency of micronuclei in exfoliated buccal cells has been investigated in mobile-phone users. [Gandhi & Singh \(2005\)](#) collected

buccal cells from 25 mobile-phone users and 25 non-users. The average frequencies of micronuclei (in %) were 0.82 ± 0.09 in users and 0.06 ± 0.003 in non-users ($P < 0.05$). [The Working Group noted the same limitations for this study as those mentioned above.]

[Yadav & Sharma \(2008\)](#) collected buccal cells from 85 mobile-phone users and 24 controls. In a total of 1000 cells from each donor, the frequency of micronuclei was determined, along with other indications of degeneration, i.e. karyolysis, karyorrhexis, “broken egg” effect, and binucleate cells. The mean frequency in users (10.7 per 1000 cells) was significantly higher than that in non-users (4.0 per 1000 cells). The changes in incidence of other end-points were not statistically significant. There was also a positive, albeit non-significant, correlation of the total number of micronuclei with increased duration of mobile-phone use.

[Hintzsche & Stopper \(2010\)](#) determined the frequency of micronuclei in buccal cells from 112 mobile-phone users and 13 non-users. Four patients receiving radiotherapy were included as positive controls, along with four healthy controls. The average frequency of micronucleus formation in users was not different from that in non-users. Also, there was no difference when the users were subdivided according to the number of hours of use per week and duration of use of up to 10 years. In contrast, the frequency of micronucleated cells in patients receiving radiotherapy was 131 ± 29.1 per 1000 cells. The authors mentioned that the larger number of individuals studied, the use of DNA-specific staining, and the genotypic variation in the study populations may have contributed to the discrepancy between their results and those of [Yadav & Sharma \(2008\)](#).

[The Working Group noted that counting of 2000 differentiated cells and 200 basal cells is recommended for studies using buccal cells, ([Thomas & Fenech, 2011](#)); this was not accomplished in the studies discussed above. Known confounding factors such as tobacco smoking

and alcohol consumption were mentioned in some of the studies, but in view of the limited sample size the influence of such factors on the observed abnormalities is difficult to determine.]

[The Working Group further noted that studies of genotoxicity in humans exposed to RF radiation have been carried out by a limited number of research groups; that methodological weaknesses were found in many studies; and that confounding factors were generally not addressed. Overall, although there were studies with positive results for genotoxicity associated with occupational exposure to RF radiation or with the use of mobile phones, the Working Group concluded that the available evidence was not strong enough to draw firm conclusions.]

4.1.2 Experimental systems: in vivo

The studies on experimental animals exposed to RF radiation were not uniformly clear in describing the rationale for choosing a specific dose.

(a) *Drosophila melanogaster*

Adult male fruit flies (*Drosophila melanogaster*) were exposed to RF radiation at either 146.34 MHz produced by a transmitter of 20 W, or 29.00 MHz produced by a transmitter of 300 W, for 12 hours ([Mittler, 1976](#)). Loss of the X or Y chromosomes, nondisjunction, and the induction of sex-linked recessive lethal mutations were investigated. There was no significant difference between exposed and non-exposed flies for any of these end-points.

In a subsequent study ([Mittler, 1977](#)), *D. melanogaster* were exposed to RF radiation at 98.5 MHz (field strength, 0.3 V/m) for 32 weeks. No significant difference in the incidence of sex-linked recessive lethal mutations was observed in the exposed group compared with the controls.

[Hamnerius et al. \(1979\)](#) examined the effect of exposure to RF radiation on somatic mutation of genes involved in eye pigmentation in

D. melanogaster. When embryos were exposed to continuous-wave RF radiation at 2450 MHz (average SAR, 100 W/kg) for 6 hours, no evidence of mutagenicity was found. The same investigators used the same test system to examine mutation frequency in *D. melanogaster* under different conditions of exposure for 6 hours: continuous-wave radiation at 2.45 GHz, pulsed-wave radiation at 3.1 GHz, and continuous-wave magnetic or electric fields at 27.12 MHz. Under none of these conditions was a change in mutation frequency observed ([Hamnerius et al., 1985](#)).

[Marec et al. \(1985\)](#) investigated the effect of repeated exposures to RF radiation on sex-linked recessive lethal mutations in *D. melanogaster* exposed to continuous-wave RF radiation at 2375 MHz (SAR values: 15 W/cm² for 60 minutes per day; or 20 W/cm² for 10 minutes per day; or 25 W/cm² for 5 minutes per day) for five consecutive days. The mutation frequency in the groups exposed to RF radiation was not significantly different from that in the control group.

In a series of studies from Greece, adverse effects were reported on the reproduction of *D. melanogaster* after exposure to RF radiation at non-thermal mobile-phone frequencies (900 or 1800 MHz). In these experiments commercially available mobile phones were used as exposure devices. The exposures were conducted with the mobile-phone antenna outside the glass vials containing the flies, either in contact with or at a certain distance from the glass wall. The daily duration of exposure varied from 1 to 20 minutes, depending on the experiment. Exposure always started on the day of eclosion and lasted for a total of 5 or 6 days. The temperature within the vials during exposure was monitored with a mercury thermometer with an accuracy of 0.05 °C. The authors explained the decreased reproductive ability as the result of RF radiation-induced DNA fragmentation in the gonads ([Panagopoulos, 2011](#); [Panagopoulos & Margaritis, 2008, 2010a, b](#); [Panagopoulos et al., 2004, 2007, 2010](#)).

[In reviewing these studies with *Drosophila*, the Working Group noted several shortcomings related to the methods of exposure assessment and temperature control, which could have influenced the results.]

(b) *Mouse*

See [Table 4.3](#)

(i) 900 MHz

[Sykes et al. \(2001\)](#) studied somatic intra-chromosomal recombination in the spleen of transgenic pKZ1 mice exposed to pulsed-wave RF radiation at 900 MHz (SAR, 4 W/kg) for 30 minutes per day, for 1, 5, or 25 days. There was a significant reduction in inversions below the spontaneous frequency in the group exposed for 25 days, whereas no effect was found in mice exposed for 1 or 5 days. The authors indicated that the number of mice in each treatment group in this study was small, and that repetition of this study with a larger number of mice was therefore required to confirm these observations.

[Aitken et al. \(2005\)](#) found a significant genotoxic effect on the epididymal spermatozoa of CD1 Swiss mice exposed to low-level RF radiation at 900 MHz (SAR, 0.09 W/kg) for 12 hours per day, for 7 days. No impact on male germ-cell development was observed. [The Working Group noted that insufficient information on dosimetry was provided in this study, which prevented a complete evaluation.]

Two cytogenetic studies were conducted with mice exposed to RF radiation from a mobile phone, with or without coexposure to X-rays or ultraviolet (UV) light. In the first study, female CBA/S mice were exposed for 78 weeks (1.5 hours per day, 5 days per week) either to continuous-wave RF radiation at 902.5 MHz (whole-body SAR, 1.5 W/kg) similar to that emitted by analogue NMT (Nordic Mobile Telephony) phones, or to a pulsed-wave signal at 902.4 MHz (SAR, 0.35 W/kg) similar to that emitted by digital GSM phones. All mice, except

the cage controls, were also exposed to X-rays (3×1.33 Gy; interval, 1 week) for the first 3 weeks of this experiment. In the second study, female transgenic mice (line K2) and their non-transgenic littermates were exposed to one of two digital mobile-phone signals at a frequency of 849 MHz GSM or 902 MHz DAMPS (Digital Advanced Mobile Phone System), with a SAR of 0.5 W/kg, for 1.5 hours per day, 5 days per week, for 52 weeks. All mice in the second study, except the cage controls, were also exposed to UV radiation mimicking the solar spectrum at 1.2 times the human minimal erythema dose (MED, 200 J/m²), three times per week. The results did not show any effects of RF fields on frequency of micronuclei in polychromatic erythrocytes or normochromatic erythrocytes, either alone or in combination with X-rays or UV radiation. The results were consistent in the two mouse strains (and in a transgenic variant of the second strain), after 52 or 78 weeks of exposure, at three SAR levels relevant to human exposure from mobile phones, and for three different mobile signals ([Juutilainen et al., 2007](#)).

(ii) 900 and 1800 MHz

In a study in B6C3F₁ mice exposed to RF radiation at 900 MHz or 1800 MHz (2 hours per day, for 1 week or 6 weeks) at different intensities (with SARs up to 33.2 W/kg in the 1-week experiment, and 24.9 W/kg in the 6-week experiment), the frequency of micronuclei was not increased in erythrocytes of peripheral blood or bone marrow, in keratinocytes or in spleen lymphocytes of the exposed animals compared with controls ([Görlitz et al., 2005](#)).

In a long-term study, micronucleus formation was measured in erythrocytes of B6C3F₁/CrIBR mice exposed to RF radiation at 902 MHz GSM or 1747 MHz (DCS, Digital Cellular System), at SARs of 0.4, 1.3 or 4.0 W/kg, for 2 hours per day, 5 days per week, for 2 years. No differences were found in the frequencies of micronuclei in exposed, sham-exposed or cage-control mice ([Ziemann et al., 2009](#)).

(iii) 1500 MHz

Male Big Blue mice, which are transgenic for the *lacI* marker gene, were locally exposed (in the head region) to near-field RF radiation at 1500 MHz with SARs of 0.67 or 2.0 W/kg, for 90 minutes per day, 5 days per week, for 4 weeks. There was no significant difference between exposed and control mice in the frequency of mutation in the *lacI* transgene in the brain ([Takahashi et al., 2002](#)).

(iv) 450 MHz

[Sarkar et al. \(1994\)](#) found significant alterations in the length of a DNA microsatellite sequence in the brain and testes of Swiss albino mice exposed to RF radiation at 2450 MHz (power level, 1 mW/cm²; SAR, 1.18 W/kg) for 2 hours per day, for 120, 150 or 200 days. The authors hypothesized that a DNA fragment (7.7 kb) – generated by the restriction enzyme *HinfI* – that was found after exposure could represent a hypermutable locus and that exposure to these microwaves may have led to amplification of tandem sequences, generating more copies of 5'-GACA-3' sequences in this particular region. The authors also indicated that the radiation dose applied in the study was close to the prescribed safe limit for population exposure, according to Guidelines of the International Radiation Protection Association at the time ([IRPA, 1988](#)).

C3H/HeJ mice were exposed continuous-wave RF radiation at 2450 MHz in circularly polarized wave-guides (average whole-body SAR, 1.0 W/kg) for 20 hours per day, 7 days per week, for 18 months. Peripheral-blood and bone-marrow smears were examined for the presence of micronuclei in polychromatic erythrocytes. The initial publication reported no difference in micronucleus formation between exposed and sham-exposed mice, but a subsequent correction indicated that there was a slight but significant increase in the incidence of micronucleated cells in peripheral-blood and bone-marrow smears

of mice receiving long-term exposure to this RF radiation ([Vijayalaxmi et al., 1997a, 1998](#)).

Pregnant *lacZ*-transgenic mice (MutaTMMouse) were exposed (16 hours per day) to intermittent (10 seconds on, 50 seconds off) RF radiation at 2450 MHz with an average whole-body SAR of 0.71 W/kg (4.3 W/kg during the exposure periods of 10 seconds), daily between day 0 and day 15 of gestation. Offspring were examined at age 10 weeks. Mutation frequencies at the *LacZ* gene in the spleen, liver, brain, and testis were similar to those observed in offspring of sham-exposed mice ([Ono et al., 2004](#)).

(v) 42 GHz (millimetre waves)

Adult male BALB/c mice were exposed (30 minutes per day) in the nasal region to RF radiation at 42 GHz (incident power density, 31.5 mW/cm²; peak SAR, 622 W/kg), on three consecutive days. The frequency of micronuclei in peripheral blood and in bone marrow was not increased in exposed mice compared with sham-exposed controls. One group of mice received a single injection of cyclophosphamide (15 mg/kg bw) immediately after the exposure to RF radiation on day 2. The micronucleus frequency in this group was not different from that in mice treated with cyclophosphamide only ([Vijayalaxmi et al., 2004](#)).

(vi) Ultra-wide band EMF

Male CF1 mice were exposed for 15 minutes to ultra-wide band (UWB) electromagnetic fields (600 pulses per second) at an estimated whole-body average SAR of 37 mW/kg. The mice were killed at 18 hours or 24 hours after exposure, and peripheral blood and bone marrow were collected and examined for the presence of micronuclei in polychromatic erythrocytes. Under the experimental conditions of this study, there was no evidence of cytogenetic effects in blood or bone marrow of the exposed mice ([Vijayalaxmi et al., 1999](#)).

(c) Rat

See [Table 4.3](#)

(i) 834 MHz

Micronucleus formation was investigated in the offspring of rats exposed to RF radiation. Wistar rats were placed in experimental cages on the first day of pregnancy and exposed (8.5 hours per day) to RF radiation at 834 MHz (26.8–40 V/m; vertical polarization; peak power, 600 mW; calculated SAR, 0.55–1.23 W/kg) from an analogue mobile telephone that was placed close to the plexiglass cage. Exposure was continued throughout gestation. Newborn pups (age, 2 days) showed a statistically significant increase ($P < 0.003$) in micronucleus frequency in erythrocytes (1.23 ± 0.17 per 1000 cells) compared with controls (0.5 ± 0.1 per 1000 cells). Oxidative parameters measured in blood plasma or liver were not different between exposed and control rats ([Ferreira et al., 2006](#)).

(ii) 900–915 MHz

Wistar rats were exposed to RF radiation at 910 MHz (maximum SAR, 0.42 W/kg) for 2 hours per day on 30 consecutive days. Compared with non-exposed control rats, an almost threefold increase in the frequency of micronuclei was found in polychromatic erythrocytes of males and females ($P < 0.001$ and $P < 0.01$, respectively); the induction was significantly lower in females than in males ($P < 0.001$). An increase in micronucleus frequency was also observed in polymorphonuclear cells ([Demsia et al., 2004](#)).

Genotoxic effects of coexposure to RF radiation at 900 MHz with 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX, a by-product of water chlorination; 19 µg/ml in drinking-water) were investigated in female Wistar rats ([Verschaeve et al., 2006](#)). The rats were exposed to RF radiation for 2 hours per day, 5 days per week, for 2 years, at an average SAR of 0.3 or 0.9 W/kg; exposure to MX was continuous. Blood samples were collected at 3, 6 and 24

Table 4.3 Genetic and related effects of radiofrequency radiation, alone or in combination with chemical/physical mutagens: studies in experimental animals *in vivo*

End-point	Frequency	SAR	Duration	Chemical/physical mutagen	Results	Comments	References
<i>Mouse</i>							
MN formation in peripheral blood and bone-marrow cells in tumour-prone C3H/HeJ mice	2450 MHz, CW	1.0 W/kg	20 h/d, 7 d/wk, for 1.5 yr	None	+	Corrected statistical analysis in 1998 paper	Vijayalaxmi <i>et al.</i> (1997a, 1998)
MN formation in PCEs from peripheral blood and bone marrow of CF1 mice	Ultra-wide band radiation	0.037 W/kg	15 min	None	-		Vijayalaxmi <i>et al.</i> (1999)
MN formation in peripheral-blood and bone-marrow cells of male BALB/c mice	42 200 MHz	622 ± 100 W/kg	30 min/d for 3 consecutive days	Coexposure with cyclophosphamide	-	No effect of RF radiation alone; no effect on MN induced by cyclophosphamide	Vijayalaxmi <i>et al.</i> (2004)
MN formation in erythrocytes of blood or bone marrow, in keratinocytes and in spleen lymphocytes of B6C3F ₁ mice	900 MHz (GSM) and 1800 MHz (DCS); AM	3.7, 11 and 33.2 W/kg (1-wk study); and 2.8, 8.3 and 24.9 W/kg (6-wk study)	2 h/d during 1 or 6 wk	None	-		Görlitz <i>et al.</i> (2005)
MN formation in erythrocytes of female inbred CBA/S mice (taken from study by Heikkinen <i>et al.</i> , 2001)	902.5 MHz (NMT), CW or 902.5 MHz (GSM), PW	1.5 W/kg or 0.35 W/kg	1.5 h/d, 5 d/wk, for 78 wk	Also exposed to X-rays (3 × 1.33 Gy, during first 3 wk)	-	No effect of RF radiation alone; no effect on MN induced by X-rays	Juutilainen <i>et al.</i> (2007)
MN formation in erythrocytes of female K2 transgenic and non-transgenic mice (taken from Heikkinen <i>et al.</i> , 2003)	Digital mobile-phone signals, GSM at 849 MHz and DAMPS at 902 MHz	0.5 W/kg	1.5 h/d, 5 d/wk, for 52 wk	Also exposed to UV radiation (1.2 MED), 3×/wk	-	No effect of RF radiation alone; no effect on MN induced by UV	Juutilainen <i>et al.</i> (2007)
MN formation in erythrocytes of B6C3F ₁ /CrIBR male and female mice	GSM (902 MHz) or DCS (1747 MHz)	0.4, 1.3 or 4.0 W/kg	2 h/d, 5 d/wk, for 2 yr	None	-	No difference in MN frequency in exposed, sham-exposed or cage-control mice	Ziemann <i>et al.</i> (2009)
Mutation assay (<i>lacI</i> transgene) in brain tissue of Big Blue mice	1500 MHz	0, 0.67, or 2 W/kg	90 min/d, 5 d/wk, for 4 wk	None	-		Takahashi <i>et al.</i> (2002)

Table 4.3 (continued)

End-point	Frequency	SAR	Duration	Chemical/physical mutagen	Results	Comments	References
Mutation frequency of the <i>lacZ</i> gene in cells from the spleen, liver, brain and testes of the offspring of <i>lacZ</i> -transgenic mice	2450 MHz (intermittent, 10 s on, 50 s off)	0.71 W/kg (average); 4.3 W/kg (for 10 s exposures)	Exposure <i>in utero</i> for 16 h/d on days 0–15 of gestation	None	–	Offspring was analysed at age 10 wk	Ono et al. (2004)
DNA microsatellite analysis with synthetic oligonucleotide probes in cells of brain and testis of Swiss albino mice	2450 MHz, CW	1.2 W/kg	2 h/d, for 120, 150, 200 d	None	+	Change in length of a microsatellite sequence	Sarkar et al. (1994)
DNA damage assessed by quantitative PCR (Q-PCR), alkaline- and pulsed-field electrophoresis in caudal epididymal spermatozoa of CD1 Swiss mice	900 MHz	0.09 W/kg	12 h/d, for 7 d	None	+	No effect on male germ-cell development; Q-PCR showed damage in mitochondrial genome and in nuclear β -globin locus	Aitken et al. (2005)
Somatic intrachromosomal recombination in spleen cells of pKZ1 transgenic mice	900 MHz, PW	4 W/kg	30 min/d for 1, 5, 25 d	None	–	Reduction in inversions below the spontaneous frequency in the group exposed for 25 d	Sykes et al. (2001)
Rat							
MN formation in peripheral-blood and bone-marrow cells of male Sprague-Dawley rats	2450 MHz, CW	12 W/kg	24 h	None	–		Vijayalaxmi et al. (2001a)
MN formation in peripheral blood cells of male Wistar rats	2450 MHz, CW	1 and 2 W/kg	2 h/d for up to 30 d	None	+	Only after 8 (not 2, 15, or 30) exposures of 2 h each	Trosic et al. (2002)
MN formation in PCEs in bone marrow and peripheral blood of Wistar rats	2450 MHz	Whole-body SAR, 1.25 W/kg	2 h/d, 7 d/wk, 30 d	None	+	Increased MN frequency in PCEs in bone marrow on day 15, and in the peripheral blood on day 8	Trosic & Busljeta (2006)
MN formation in bone-marrow cells of male and female Wistar rats	910 MHz	Peak SAR, 0.42 W/kg	2 h/d for 30 consecutive days	None	+		Demsia et al. (2004)

Table 4.3 (continued)

End-point	Frequency	SAR	Duration	Chemical/physical mutagen	Results	Comments	References
MN formation in bone-marrow cells of male Wistar rats	2450 MHz, CW	1.25 W/kg	2 h/d for up to 30 days (total exposure 4, 16, 30 or 60 h)	None	+	Increase in PCE in bone marrow on day 15 (exposure, 30 h). Transient effect on proliferation and maturation of erythropoietic cells	Trosic et al. (2004) ; Busijeta et al. (2004)
MN formation in blood from adult pregnant Wistar rats	834 MHz, mobile-phone antenna, 26.8–40 V/m	0.55–1.23 W/kg	From day 1 of gestation, for 8.5 h/d, until birth of offspring	None	+	Significant increase of MN frequency in erythrocytes of newborn pups exposed <i>in utero</i>	Ferreira et al. (2006)
MN formation in blood of female Wistar rats	900 MHz, AM	0.3 and 0.9 W/kg	2 h/d, 5 d/wk, for 2 yr	Coexposure with MX in drinking-water	–	No increase in MN after coexposure to MX and RF radiation compared with MX [no group exposed to RF only]	Verschaeve et al. (2006)
MN formation in blood cells of Wistar rats	10 000 MHz 50 000 MHz	0.04 W/kg 0.0008 W/kg	2 h/d for 45 d	None	+	Also significant increase of ROS in serum	Kumar et al. (2010)
DNA breaks (SSB, DSB) measured with comet assay in brain cells of male Sprague-Dawley rats	2450 MHz, PW or CW	0.6 and 1.2 W/kg	2 h	None	+	Significant and SAR-dependent increase in SB immediately and at 4 h after exposure to CW; only at 4 h after exposure to PW	Lai & Singh (1995)
DNA breaks (SSB, DSB) measured with comet assay in brain cells of male Sprague-Dawley rats	2450 MHz, PW or CW	1.2 W/kg	2 h	None	+	Significant increase in SB at 4 h after exposure to either PW or CW	Lai & Singh (1996)
DNA breaks (SSB, DSB) measured with comet assay in brain cells of male Sprague-Dawley rats	2450 MHz, PW	1.2 W/kg	2 h	Melatonin or N-tert-butyl- α -phenylnitron (free-radical scavengers)	+	Significant increase in SB at 4 h after exposure. Treatment with radical scavengers before and after exposure to RF prevented/reversed induction of SB	Lai & Singh (1997)

Table 4.3 (continued)

End-point	Frequency	SAR	Duration	Chemical/physical mutagen	Results	Comments	References
DNA breaks (SSB) measured with comet assay in brain cells of male Sprague-Dawley rats	2450 MHz, CW	1.2 W/kg	2 h	None	-		Malyapa et al. (1998)
DNA breaks (SSB) measured with alkaline comet assay (with or without proteinase K) in brain cells of male Sprague-Dawley rats	2450 MHz, PW	1.2 W/kg	2 h	None	-		Lagroye et al. (2004a)
DNA breaks (SSB, DSB) measured with comet assay in brain cells of male Sprague-Dawley rats	2450 MHz, CW, circular polarization	0.6 W/kg	2 h	None	+	Significant increase in SB at 4 h after exposure	Lai & Singh (2005)
DNA breaks (DSB) measured with pulsed-field electrophoresis. Changes in chromatin conformation detected with AVTD assay in brain cells from Wistar rats	915 MHz (GSM)	0.4 W/kg	2 h	None	-	Changes in gene expression were detected	Belyaev et al. (2006)
DNA breaks (SSB) measured with alkaline comet assay in brain cells of male and female Wistar rats	2450 MHz or 16 500 MHz	1.0 W/kg or 2.01 W/kg	2 h/d, for 35 d	None	+	DNA breakage was observed at both frequencies	Paulraj & Behari (2006)
DNA breaks (SSB) measured with alkaline comet assay in blood, liver and brain of female Wistar rats	900 MHz, AM	0.3 or 0.9 W/kg	2 h/d, 5 d/wk for 2 yr	Co-exposure with MX in drinking-water	-	No increase in SB after co-exposure to MX and RF radiation compared with MX [no group exposed to RF only]	Verschaeve et al. (2006)
DNA breaks (DSB) measured with neutral comet assay in brain of male Wistar rats	2450 MHz, from MW oven	0.11 W/kg (whole-body)	2 h/d, 35 d	None	+	Highly significant decrease in anti-oxidant enzymes and increase in catalase were also seen ($P < 0.006$)	Kesari et al. (2010)

Table 4.3 (continued)

End-point	Frequency	SAR	Duration	Chemical/physical mutagen	Results	Comments	References
<i>Rabbit</i>							
Oxidative DNA damage (8-OHdG) in liver of pregnant and non-pregnant New Zealand White rabbits	1800 MHz (GSM-like)	NR	15 min/d for 1 wk (for pregnant rabbits; days 15–22 of gestation)	None	–	No difference in 8-OHdG/10 ⁶ dG between exposed and sham-exposed non-pregnant or pregnant rabbits, or between newborns exposed <i>in utero</i> and sham-exposed newborns	Tomruk et al. (2010)
<i>Cow</i>							
MN formation in erythrocytes of Latvian Brown cows living in the Skrunda radio-station area	154–162 MHz, PW	NR	Cows had been living in the area for at least 2 yr	None	+	Significant increase in MN compared with cows in a control area. Frequencies of MN were low in all cases	Balode (1996)

+, increase; –, no effect; AVTD, anomalous viscosity time-dependence; CW, continuous wave; d, day; DAMPS, Digital Advanced Mobile Phone System, DCS, Digital Cellular System; DSB, DNA double-strand breaks; GSM, Global System for Mobile Communications; h, hour; MED, minimal erythema dose; min, minute; MN, micronuclei; MW, microwave; MX, 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone; NMT, Nordic Mobile Telephone; NR, not reported; PCE, polychromatic erythrocytes; PW, pulsed wave; s, second; SAR, specific absorption rate; SB, DNA strand breaks, SSB, DNA single-strand breaks; wk, week; yr, year

months and brain and liver samples were taken at the end of the study (24 months). The extent of DNA strand breaks in blood, liver and brain cells was determined by means of the alkaline comet assay; the frequency of micronuclei was measured in erythrocytes. Coexposure to MX and RF radiation did not significantly change the effects in blood, liver and brain cells compared with those seen with MX only [the Working Group noted that this study did not include a treatment group exposed to RF radiation only].

Induction of DNA double-strand breaks was measured by means of pulsed-field gel electrophoresis, and changes in chromatin conformation were assessed by use of the anomalous viscosity time-dependence (AVTD) assay in brain tissue of Fisher rats exposed to RF radiation at 915 MHz (GSM; SAR, 0.4 W/kg) for 2 hours. No effects of exposure to RF radiation were found. Analysis of gene-expression profiles in the cerebellum of exposed rats revealed changes in genes associated with neurotransmitter regulation, melatonin production and regulation of the blood-brain barrier ([Belyaev et al., 2006](#)).

(iii) 1600 MHz

Timed-pregnant Fischer 344 rats were exposed from day 19 of gestation, and their nursing offspring until weaning at 3 weeks of age, to far-field RF radiation at 1600 MHz (iridium wireless-communication signal) for 2 hours per day, 7 days per week. The whole-body average SAR was 0.036–0.077 W/kg (0.10–0.22 W/kg in the brain). This first exposure was followed by long-term, head-only exposures of male and female offspring (starting at age 35 days) to a near-field 1600 MHz signal, with a SAR of 0.16 or 1.6 W/kg in the brain, for 2 hours per day, 5 days per week, for 2 years. The micronucleus frequency in polychromatic erythrocytes of the bone marrow was not significantly different between exposed, sham-exposed and cage-control rats ([Vijayalaxmi et al., 2003](#)).

(iv) 2450 MHz

In several publications from the same laboratory it was reported that brain cells of male Sprague-Dawley rats exposed for 2 hours to low-intensity pulsed-wave or continuous-wave RF radiation at 2450 MHz (SAR, 0.6 or 1.2 W/kg) showed an increased number of DNA single- and double-strand breaks – measured by the neutral and alkaline comet assays – at 4 hours after exposure. The authors suggested that this could be due either to a direct effect on DNA or to an effect on DNA repair ([Lai & Singh, 1995, 1996](#)). In subsequent experiments, treatment of the rats with free-radical scavengers appeared to block this effect of RF exposure, suggesting that free radicals may be involved in RF-radiation-induced DNA damage in the rat brain ([Lai & Singh, 1997](#)).

Male Sprague-Dawley rats were exposed to continuous-wave RF radiation at 2450 MHz (SAR of 1.2 W/kg) for 2 hours, which did not cause a rise in the core body-temperature of the rats. One group of rats was killed by carbon dioxide (CO₂) asphyxia, another by decapitation. DNA breakage was assessed by means of the alkaline comet assay. No significant differences were observed in the comet length or the normalized comet moment of cells isolated from either the cerebral cortex or the hippocampus of irradiated rats and those from sham-exposed rats. This was independent of the method by which the rats were killed. However, there was more intrinsic DNA damage and more experiment-to-experiment variation in cells from the asphyxiated rats than from rats killed by decapitation. Therefore, the latter method appeared to be the most appropriate in this type of study ([Malyapa et al., 1998](#)). [The Working Group noted that this study was not a valid replication of the [Lai & Singh \(1995\)](#) study, contrary to the authors' intention, but it provided independent evidence contrary to those results. The Working Group also noted that the increased number of DNA strand breaks after

exposure to RF radiation *in vivo* was particularly protocol-dependent, specifically with respect to the method of killing the animals and the treatment of tissue samples between exposure of the animals and analysis of the tissues.]

[Vijayalaxmi et al. \(2001a\)](#) found no evidence for the induction of micronuclei in peripheral-blood and bone-marrow cells of Wistar rats exposed continuously to continuous-wave RF radiation at 2450 MHz, with an average whole-body SAR of 12 W/kg, for 24 hours.

[Lagroye et al. \(2004a\)](#) investigated the induction of DNA damage in brain cells of Sprague-Dawley rats exposed to pulsed-wave RF radiation at 2450 MHz, with a SAR of 1.2 W/kg, for 2 hours. The rats were decapitated 4 hours after exposure. No DNA damage was detected in separate samples of the same brain-cell preparation from exposed rats, assessed by two variants of the alkaline comet assay.

Wistar rats were exposed to non-thermal RF radiation at 2450 MHz for 2 hours per day on 7 days per week, for up to 30 days. The power-density range was 5–10 mW/cm², which corresponded to an approximate SAR of 1–2 W/kg. Erythrocyte counts, haemoglobin concentrations and haematocrit values were significantly increased in peripheral blood on days 8 and 15, and anuclear cells and erythropoietic precursor cells in bone marrow were significantly decreased. The frequency of micronucleated cells in the bone marrow was significantly increased on day 15, not on days 2, 8, and 30 ([Busljeta et al., 2004](#)).

Adult male Wistar rats were exposed to continuous-wave RF radiation at 2450 MHz for 2 hours per day, 7 days per week, for up to 30 days. The power-density range was 5–10 mW/cm², which corresponded to an approximate SAR of 1–2 W/kg. The frequency of micronuclei in polychromatic erythrocytes was significantly increased in the group that had received 8 irradiation treatments of 2 hours each, but not in the groups that received 2, 15 or 30 treatments, in comparison with the sham-exposed group.

These results would be in line with an adaptive or recovery mechanism that was triggered in this experimental model during treatment ([Trosic et al., 2002, 2004](#)). Similar results were presented in a later publication ([Trosic & Busljeta, 2006](#)).

[Paulraj & Behari \(2006\)](#) reported a significantly increased ($P < 0.001$) level of DNA breakage – measured by means of the alkaline comet assay – in brain cells of rats exposed to RF radiation at 2450 MHz or 16.5 GHz (SAR, 1.0 or 2.01 W/kg) for 2 hours per day, for 35 days.

Wistar rats were exposed to RF radiation at 2450 MHz (power density, 0.34 mW/cm²) for 2 hours per day, for 35 days. The whole-body SAR was estimated to be 0.11 W/kg. After exposure, rats were killed and whole-brain tissue was dissected and used for analysis of DNA double-strand breaks by means of the neutral comet assay. A significant increase was observed in various comet parameters in exposed brain cells compared with controls. Statistically significant changes were also observed in the levels of different antioxidant enzymes, *i.e.* a decrease in glutathione peroxidase, superoxide dismutase and histone kinase, and an increase in catalase ([Kesari et al., 2010](#)).

(v) 10–50 GHz

Wistar rats were exposed continuously to RF radiation at 10 GHz or 50 GHz (SAR, 0.014 W/kg and 0.0008 W/kg, respectively) for 2 hours per day, for 45 days. In both cases, significant increases ($P < 0.05$) in the frequency of micronuclei – deduced from a reduced polychromatic/normochromatic erythrocyte ratio – and in concentrations of reactive oxygen species (ROS) were found in blood cells and serum, respectively ([Kumar et al., 2010](#)).

(d) Rabbit

A study was performed with non-pregnant and pregnant New Zealand White rabbits. The rabbits were exposed (whole-body) to 1800 MHz RF radiation (GSM) for 15 minutes per day,

for 1 week. For the pregnant rats, this exposure period was between day 15 and day 22 of gestation. Control groups of non-pregnant and pregnant rabbits were sham-exposed. No difference was found in the level of 8-hydroxy-2'-deoxyguanosine (an indicator of oxidative DNA damage; expressed as 8-OHdG/ 10^6 dG) in DNA from liver tissue of exposed and sham-exposed rabbits (pregnant or non-pregnant). Changes in malondialdehyde concentration and ferrous oxidation in xylenol orange in the liver of exposed non-pregnant and pregnant rabbits indicated an effect on lipid peroxidation. In pups exposed *in utero*, a reduction in ferrous oxidation in xylenol orange was seen in the liver, but no change was observed in malondialdehyde concentration. These results supported the notion that 1800 MHz GSM-like RF radiation may induce oxidative stress in exposed tissues ([Tomruk et al., 2010](#)).

(e) Cow

Blood samples were obtained from 67 female Latvian Brown cows living on a farm in the vicinity of the Skrunda radio-location station (Latvia), and from 100 cows in a control area, which was selected on the basis of the similarity to the exposed area with regards to many factors except exposure. Frequencies of micronuclei were scored in the erythrocytes and found to be low but statistically significantly increased in the exposed cows compared with those in the controls (0.6/1000 cells compared with 0.1/1000 cells; $P < 0.01$) ([Balode, 1996](#)).

4.1.3 Experimental systems: in vitro

(a) Humans: peripheral blood lymphocytes

The most widely used cell type for investigations *in vitro* is the peripheral blood lymphocyte. Some details on the exposure conditions to RF radiation and a short conclusion of the publications discussed below are presented in [Table 4.4](#).

(i) Studies with a single end-point

DNA-damage induction and repair

The effects of exposure to RF radiation at frequencies ranging from approximately 800 to 8000 MHz were examined by several investigators, who reported no significant effect on induction of DNA strand breaks ([Baohong et al., 2005, 2007](#); [Chemeris et al., 2006](#); [Sannino et al., 2006](#)).

[Vijayalaxmi et al. \(2000\)](#) assessed DNA strand breaks in human lymphocytes and also the capacity of these cells to repair such damage after exposure to RF radiation at 2450 MHz, and observed no effect on either parameter. [Zhijian et al. \(2009\)](#) also reported no effect of exposure to RF radiation at 1800 MHz, not only on induction of DNA strand breaks but also on the repair kinetics of X-irradiation-induced DNA strand breaks. [Tiwari et al. \(2008\)](#) exposed human lymphocytes to RF radiation at 835 MHz (SAR, 1.17 W/kg) and subsequently incubated the cells in the presence of aphidicolin (APC; an inhibitor of DNA repair) at a dose of 0.02 or 2 $\mu\text{g/ml}$. There was no effect on DNA strand breakage from exposure to RF radiation alone. APC (2 $\mu\text{g/ml}$) and combinations of RF radiation with APC (0.02 and 2 $\mu\text{g/ml}$) enhanced the number of DNA strand breaks; this damage is repairable (see Section 4.1.3c).

Chromosomal aberrations

[Maes et al. \(1995\)](#) found an increase in the frequency of chromosomal aberrations in the form of dicentrics and acentric fragments in human lymphocytes exposed to pulsed-wave RF radiation at 954 MHz, while using a cooled box to maintain the temperature at $17 \pm 1^\circ\text{C}$. [Manti et al. \(2008\)](#) carried out FISH analysis with molecular probes specific for whole chromosomes 1 and 2 in lymphocytes from four donors. The cells were exposed to RF radiation at 1950 MHz (UMTS, Universal Mobile Telecommunications System) at SAR 0.5 or 2.0 W/kg, for 24 hours. There was no effect on the fraction of aberrant cells at a

Table 4.4 Genetic and related effects in human peripheral blood lymphocytes exposed to radiofrequency radiation *in vitro*

End-point	Frequency	SAR or power density	Duration	Results	Comments	Reference
Aneuploidy	830 MHz, CW	2.0–8.2 W/kg	72 h	+ (chromosome 17)	Temperature kept at 33.5–37.5 °C. In control without RF, no aneuploidy was seen up to 38.5 °C	Mashevich et al. (2003)
Aneuploidy	100 GHz, CW	0.31 mW/cm ²	1–24 h	+ (chromosomes 11, 17) – (chromosomes 1, 10)	Direct effect questionable. High values in control cells.	Korenstein-Ilan et al. (2008)
Aneuploidy	800 MHz, CW	2.9, 4.1 W/kg	24 h	+ (chromosomes 11, 17) at SAR of 2.9 W/kg + (chromosomes 1, 10) at SAR of 4 W/kg	High values in control cells. In control without RF, no aneuploidy was seen up to 40 °C	Mazor et al. (2008)
Chromosomal aberration	7700 MHz, CW	0.5, 10, 30 mW/cm ²	10, 30, 60 min	+	Aberrations increased at 10 and 30 mW/cm ² at all time-points	Garaj-Vrhovac et al. (1992)
Chromosomal aberration	2450 MHz, PW	75 W/kg	30 min, 2 h	+	MW output was adjusted with a thermistor to keep cells at 36.1 °C	Maes et al. (1993)
Chromosomal aberration	954 MHz, PW; GSM	1.5 W/kg	2 h	±	Questionable dosimetry (pylon from GSM base-station connected to indoor antenna); no statistics provided	Maes et al. (1995)
Chromosomal aberration	440, 900, 1800 MHz, PW; GSM	1.5 W/kg	30–72 h	–		Eberle et al. (1996)
Chromosomal aberration	935.2 MHz, PW; GSM	0.3–0.4 W/kg	2 h	–		Maes et al. (1997)
Chromosomal aberration	2450 MHz, CW	12.5 W/kg	90 min or 3 × 30 min	–		Vijayalaxmi et al. (1997b)
Chromosomal aberration	455.7 MHz, PW	6.5 W/kg	2 h	–	Cells were placed 5 cm from a car phone	Maes et al. (2000)
Chromosomal aberration	900 MHz, PW; CDMA	0.4–10 W/kg	2 h	–		Maes et al. (2001)
Chromosomal aberration	835.62 MHz, CW; FDMA	4.4, 5.0 W/kg	24 h	–		Vijayalaxmi et al. (2001a)
Chromosomal aberration	847.74 MHz, CW; CDMA	4.9, 5.5 W/kg	24 h	–		Vijayalaxmi et al. (2001b)
Chromosomal aberration	2500 MHz 10 500 MHz	627 W/kg 0.25 W/kg	40 s 5 min	– –	MW oven at 3 W	Figueiredo et al. (2004)

Table 4.4 (continued)

End-point	Frequency	SAR or power density	Duration	Results	Comments	Reference
Chromosomal aberration	900 MHz, PW; GSM	0.3, 1 W/kg	2 h	-		Zeni et al. (2005)
Chromosomal aberration	935 MHz, PW; GSM	1, 2 W/kg	24 h	-		Stronati et al. (2006)
Chromosomal aberration	2450, 8200 MHz, PW	2.1, 21 W/kg	2 h	-		Vijayalaxmi et al. (2006)
Chromosomal aberration	1950 MHz, PW; UMTS	0.5, 2 W/kg	24 h	- at SAR of 0.5 W/kg + at SAR of 2 W/kg	Frequency of aberrations/cell was increased at higher SAR; FISH technique was used	Manti et al. (2008)
Chromosomal aberration	18 000 MHz, CW 16 500 MHz, PW	1 mW/cm ² 10 mW/cm ²	53 h	-		Hansteen et al. (2009a)
Chromosomal aberration	2300 MHz, CW, PW	1 mW/cm ²	53 h	-		Hansteen et al. (2009b)
Micronucleus formation	7700 MHz, CW	0.5, 10, 30 mW/cm ²	10, 30, 60 min	+	MN frequency increased at 30 mW/cm ² , after 30 and 60 min of exposure	Garaj-Vrhovac et al. (1992)
Micronucleus formation	2450 MHz, PW	75 W/kg	30 min, 2 h	+	MW output was adjusted with a thermistor to keep cells at 36.1 °C	Maes et al. (1993)
Micronucleus formation	9000 MHz, CW, PW	90 W/kg	10 min	+ with PW - with CW	Temperature during exposure was 30–35 °C. Control cultures were kept at 37 °C	d'Ambrosio et al. (1995)
Micronucleus formation	440, 900, 1800 MHz, PW; GSM	1.5 W/kg	30–72 h	-		Eberle et al. (1996)
Micronucleus formation	2450 MHz, CW	12.5 W/kg	3 × 30 min	-		Vijayalaxmi et al. (1997b)
Micronucleus formation	2450, 7700 MHz, CW	10, 20, 30 mW/cm ²	15, 30, 60 min	+	Experiment carried out at 20–22 °C. Temperature-control measurements were made in water	Zotti-Martelli et al. (2000)
Micronucleus formation	835.62 MHz, CW; FDMA	4.4, 5.0 W/kg	24 h	-		Vijayalaxmi et al. (2001a)
Micronucleus formation	847.74 MHz, CW; CDMA	4.9, 5.5 W/kg	24 h	-		Vijayalaxmi et al. (2001b)
Micronucleus formation	1748 MHz, CW, PW; GSM	5 W/kg	15 min	+ with PW - with CW	Temperature during exposure was 30–35 °C. Control cultures were kept at 37 °C	d'Ambrosio et al. (2002)
Micronucleus formation	1900 MHz, CW, PW	0.1–10 W/kg	2 h	-		McNamee et al. (2002a)

Table 4.4 (continued)

End-point	Frequency	SAR or power density	Duration	Results	Comments	Reference
Micronucleus formation	2450 MHz, PW	5 mW/cm ²	2 h	-		Zhang et al. (2002)
Micronucleus formation	837, 1909 MHz, CW, PW; CDMA, TDMA	1.0, 2.5, 5.0, 10.0 W/kg	3 h, 24 h	+ after 24 h, at SARs of 5 or 10 W/kg	Some exposures were from mobile telephones. Temperature variations were $\pm 0.3^{\circ}\text{C}$ and $\pm 0.5^{\circ}\text{C}$ at 3 h and 24 h, respectively. EMS was included as a positive control	Tice et al. (2002)
Micronucleus formation	1900 MHz, CW, PW	0.1–10 W/kg	24 h	-		McNamee et al. (2003)
Micronucleus formation	120, 130 GHz PW	1 and 0.6 mW average power	20 min	-		Scarfi et al. (2003)
Micronucleus formation	900/925 MHz, CW, PW(i); GSM	1.6 W/kg 0.2 W/kg	14 $\times$ (6 min on, 3 h off) at 1.6 W/kg; 1 h/d for 3 d at 0.2 W/kg	-		Zeni et al. (2003)
Micronucleus formation	1800 MHz, CW	5, 10, 20 mW/cm ²	1, 2, 3 h	+	Large variation between individuals and repeat experiments	Zotti-Martelli et al. (2005)
Micronucleus formation	900 MHz, PW; GSM	0.1–10 W/kg	24 h	-	Concordant results between two research groups in interlaboratory study	Scarfi et al. (2006)
Micronucleus formation	935 MHz, PW; GSM	1, 2 W/kg	24 h	-		Stronati et al. (2006)
Micronucleus formation	2450, 8200 MHz, PW	2.1, 21 W/kg	2 h	-		Vijayalaxmi et al. (2006)
Micronucleus formation	1950 MHz, PW (c, i); UMTS	0.05–2 W/kg	4–48 h	-	Controversial data	Schwarz et al. (2008)
Micronucleus formation	1950 MHz, PW (c, i); UMTS	2.2 W/kg	24–68 h	-		Zeni et al. (2008)
Micronucleus formation	900 MHz, PW; GSM	1.25 W/kg	20 h	-	No effect of RF radiation alone. Reduction of MMC-induced micronucleus frequency. Data indicative of an adaptive response	Sannino et al. (2009a)
Sister-chromatid exchange	2450 MHz, PW	75 W/kg	30 min, 2 h	-	MW output was adjusted with a thermistor to keep cells at 36.1 $^{\circ}\text{C}$	Maes et al. (1993)
Sister-chromatid exchange	954 MHz, PW; GSM	1.5 W/kg	2 h	-		Maes et al. (1996)

Table 4.4 (continued)

End-point	Frequency	SAR or power density	Duration	Results	Comments	Reference
Sister-chromatid exchange	380, 900, 1800 MHz, PW; TETRA, DCS, GSM	0.08–1.7 W/kg	72 h	-		Antonopoulos et al. (1997)
Sister-chromatid exchange	440, 900, 1800 MHz, PW; GSM	1.5 W/kg	30–72 h	-		Eberle et al. (1996)
Sister-chromatid exchange	935.2 MHz, PW; GSM	0.3–0.4 W/kg	2 h	-		Maes et al. (1997)
Sister-chromatid exchange	455.7 MHz, PW; car phone	6.5 W/kg	2 h	-		Maes et al. (2000)
Sister-chromatid exchange	900 MHz, PW; GSM	0.4–10 W/kg	2 h	-		Maes et al. (2001)
Sister-chromatid exchange	900 MHz, PW; GSM	0.3, 1 W/kg	2 h	-		Zeni et al. (2005)
Sister-chromatid exchange	400–900 MHz, PW	-	-	-		Maes et al. (2006)
Sister-chromatid exchange	935 MHz, PW; GSM	1, 2 W/kg	24 h	-		Stronati et al. (2006)
DNA single- and double-strand breaks	935.2 MHz, PW; GSM	0.3–0.4 W/kg	2 h	-		Maes et al. (1997)
DNA single- and double-strand breaks	2450 MHz, PW	2.1 W/kg	2 h	-	No effect, immediately or 4 h after exposure	Vijayalaxmi et al. (2000)
DNA single- and double-strand breaks	1900 MHz, CW, PW	0.1–10 W/kg	2 h	-		McNamee et al. (2002a)
DNA single- and double-strand breaks	2450 MHz, PW	5 mW/cm ²	2 h	-		Zhang et al. (2002)
DNA single- and double-strand breaks	837, 1909 MHz, CW, PW; CDM, TDM	1.0, 2.5, 5.0, 10.0 W/kg	3 h, 24 h	-	Some exposures were from mobile telephones. Temperature variations were ± 0.3 °C and ± 0.5 °C at 3 h and 24 h, respectively. EMS was included as a positive control.	Tice et al. (2002)
DNA single- and double-strand breaks	1900 MHz, CW, PW	0.1–10 W/kg	24 h	-		McNamee et al. (2003)

Table 4.4 (continued)

End-point	Frequency	SAR or power density	Duration	Results	Comments	Reference
DNA single- and double-strand breaks	1800 MHz, PW; GSM	3 W/kg	2 h	-		Baohong et al. (2005)
DNA single- and double-strand breaks	900 MHz, PW; GSM	0.3, 1 W/kg	2 h	-		Zeni et al. (2005)
DNA single- and double-strand breaks	8800 MHz, PW	1.6 kW/kg	40 min	-		Chemeris et al. (2006)
DNA single- and double-strand breaks	1950 MHz, PW; UMTS	0.5, 2 W/kg	24 h	-		Sannino et al. (2006)
DNA single- and double-strand breaks	935 MHz, PW; GSM	1, 2 W/kg	24 h	-		Stronati et al. (2006)
DNA single- and double-strand breaks	1800 MHz, PW; GSM	3 W/kg	1.5, 4 h	-		Baohong et al. (2007)
DNA single- and double-strand breaks	120 000, 130 000 MHz, PW; THz	0.2–2 W/kg	20 min	-		Zeni et al. (2007a)
DNA single- and double-strand breaks	1950 MHz, PW(c, i); UMTS	0.05–2 W/kg	4–48 h	-	Controversial data	Schwarz et al. (2008)
DNA single- and double-strand breaks	835 MHz, PW; CDMA	1.17 W/kg	1 h	-	RF radiation induced repairable DNA damage in the presence of aphidicolin	Tiwari et al. (2008)
DNA single- and double-strand breaks	1950 MHz, PW(c, i); UMTS	2 W/kg	24–68 h	-		Zeni et al. (2008)
DNA single- and double-strand breaks	1800 MHz, PW(i); GSM	2 W/kg	24 h	-	No effect of RF-radiation on repair of X-ray-induced DNA damage	Zhijian et al. (2009)
Mutation at <i>HPRT</i> locus	440, 900, 1800 MHz, PW; GSM	1.5 W/kg	30–72 h	-		Eberle et al. (1996)

Table 4.4 (continued)

End-point	Frequency	SAR or power density	Duration	Results	Comments	Reference
Foci	915 MHz, PW; GSM	37 mW/kg	2 h	+	Decrease in 53BP1-foci (measured by immuno-staining); enhanced chromatin condensation (measured by AVTD)	Belyaev et al. (2005)
Foci	905, 915 MHz, PW; GSM	37 mW/kg	1 h	+ at 915 MHz - at 905 MHz	Decrease in 53BP1- and γ -H2AX-foci (measured by immunostaining) and enhanced chromatin condensation (measured by AVTD)	Marková et al. (2005)
Foci	905, 915, 1947 MHz, PW; GSM, UMTS	0.015–0.145 W/kg	1 h	+ at 915 MHz - at 905 MHz + t 1947 MHz	Decrease in 53BP1- and γ -H2AX-foci (measured by immunostaining) and enhanced chromatin condensation (measured by AVTD). Strongest effect at 1947 MHz	Belyaev et al. (2009)

+, increase; ±, equivocal; -, no effect; APC, aphidicholin (inhibitor of DNA repair); AVTD, anomalous viscosity time-dependence; (c, i); continuous or intermittent exposure; CA, chromosomal aberration; CDMA, code-division multiple access; CW, continuous wave; d, day; DCS, Digital Communication System; EMS, ethylmethane sulfonate; FDMA, frequency-division multiple access; FISH, fluorescence *in situ* hybridization; GSM, Global System for Mobile Communication; h, hour; HPRT, hypoxanthine(guanine)phosphoribosyl transferase; min, minute; MMC, mitomycin C; MW, microwave; PW, pulsed wave; s, second; TDMA, time-division multiple access; TETRA, Trans European Trunked Radio; THz; teraHertz; UMTS, Universal Mobile Telecommunication System

SAR of 0.5 W/kg, while there was a small but statistically significant increase in the frequency of aberrations per cell at 2 W/kg. [Figueiredo et al. \(2004\)](#) and [Hansteen et al. \(2009a, b\)](#) carried out conventional analyses of chromosomal aberrations on Giemsa-stained slides prepared with lymphocytes exposed to RF radiation at 1800–10 500 MHz, and observed no effect.

Micronucleus formation

[Zotti-Martelli et al. \(2000\)](#) exposed whole blood from two volunteers to continuous-wave RF radiation at 2450 MHz or 7700 MHz, with power densities of 10, 20 and 30 mW/cm² for 15, 30, and 60 minutes, and reported an increased micronucleus frequency in exposed cells at 30 mW/cm². In a subsequent study, [Zotti-Martelli et al. \(2005\)](#) observed an increase in the frequency of micronuclei in lymphocytes from nine different donors after exposure to RF radiation at 1800 MHz. This experiment was repeated after 3 months; there was significant variation between experiments. [The Working Group noted that temperature variation in the first study was not measured in blood samples during exposure, and the increased frequency of micronucleus formation may have been related to heating of the blood samples. Also, there were discrepancies between the data on micronuclei given in the text, figures, and tables]. [d'Ambrosio et al. \(1995, 2002\)](#) reported an increase in the formation of micronuclei in lymphocytes exposed to pulsed-wave RF radiation at 1748 MHz or 9000 MHz for 15 and 10 minutes, respectively, while no such increase was observed in cells exposed to continuous-wave RF at the same frequencies. [Zeni et al. \(2003\)](#) observed no significant effect on micronucleus formation in lymphocytes exposed to continuous or pulsed-wave RF radiation at 900 MHz (GSM). [Scarfi et al. \(2003\)](#) reported no micronucleus induction in lymphocytes exposed to continuous-wave RF radiation at 120–130 GHz. [Sannino et al. \(2009a\)](#) reported that a 20-hour pre-exposure of peripheral blood lymphocytes in the S-phase of the cell

cycle to pulsed-wave RF radiation at 900 MHz decreased the micronucleus frequency induced by mitomycin C (MMC), suggesting the existence of an adaptive response (see [Table 4.4](#) for details).

Sister-chromatid exchange (SCE)

[Maes et al. \(1996\)](#) did not find an effect on SCE in lymphocytes exposed to pulsed-wave RF radiation at 954 MHz, with a SAR of 1.5 W/kg, for 2 hours. Likewise, [Antonopoulos et al. \(1997\)](#) did not find an effect on SCE in lymphocytes exposed to RF radiation at 380–1800 MHz, with a SAR of 0.08–1.7 W/kg, for 72 hours.

Phosphorylation of histone protein H2AX and TP53-binding protein 53BP1

Over the past decade, several studies have demonstrated that two cellular check-point proteins, H2AX and TP53-binding protein 53BP1 are rapidly phosphorylated after induction of DNA damage in the form of double-strand breaks. These proteins then conglomerate to provide a scaffold structure to the repair sites ([Paull et al., 2000](#); [Schultz et al., 2000](#); [DiTullio et al., 2002](#); [Fernandez-Capetillo et al., 2002, 2004](#); [Sedelnikova et al., 2002](#); [Ismail et al., 2007](#)). By use of specific antibodies with fluorescent tags, γ -H2AX – the phosphorylated form of H2AX – and 53BP1 can be visualized as discrete foci, which can be counted directly with a fluorescence microscope.

The AVTD assay is used to detect stress-induced changes in chromatin conformation. [Shckorbatov et al. \(1998, 2009\)](#) and [Sarimov et al. \(2004\)](#) have reported changes in chromatin condensation in human lymphocytes exposed to RF radiation at 42.2 GHz, 35 GHz or 895–915 MHz, respectively, which prevented access of proteins involved in repair of DNA double-strand breaks. [Belyaev et al. \(2005\)](#) exposed human lymphocytes for 2 hours to pulsed-wave RF radiation at 915 MHz (GSM), with a SAR of 37 mW/kg, and reported significant

effects on chromatin condensation and a distinct reduction in the number of 53BP1-foci in samples from all individuals; these results were similar to those found after heat-shock treatment. The overall data suggested a reduced accessibility of 53BP1 to repair DNA double-strand breaks due to chromatin condensation. [Markovà et al. \(2005\)](#) exposed human lymphocytes to pulsed-wave RF radiation at 905 MHz or 915 MHz (GSM), with a SAR of 37 mW/kg, for 1 hour. Chromatin condensation and decreased numbers of 53BP1- and γ -H2AX-foci were observed in cells after exposure at 915 MHz, but not at 905 MHz. The response was similar in healthy subjects and in subjects hypersensitive to RF radiation. [Belyaev et al. \(2009\)](#) exposed lymphocytes to pulsed-wave RF radiation at 905 MHz or 915 MHz (GSM), or 1947 MHz (UMTS), with a SAR of 15–145 mW/kg, for 1 hour. Chromatin condensation and reduction in numbers of 53BP1- and γ -H2AX-foci were much more pronounced in cells after exposure at 1947 MHz than at 915 MHz; there were no such effects after exposure at 905 MHz. The decrease in number of foci persisted for up to 72 hours after exposure, suggesting that not only the formation of double-strand breaks was affected, but also their repair. [Markovà et al. \(2010\)](#) used VH10 primary fibroblasts established from human foreskin and mesenchymal stem cells isolated from adipose tissue of two healthy persons. These cells were exposed to pulsed-wave RF radiation at 905 MHz or 915 MHz (GSM; SAR, 37 mW/kg), or at 1947 MHz (UMTS; SAR, 39 mW/kg), as a single exposure for 1, 2 or 3 hours, or as repeated exposures for 1 hour per day, 5 days per week, for 2 weeks. The decrease in the number of 53BP1-foci was more pronounced in stem cells than in foreskin fibroblasts, and the stem cells did not adapt to long-term exposure to RF radiation.

Aneuploidy

Peripheral blood lymphocytes from five individuals were stimulated with phytohaemagglutinin (PHA) and exposed for 72 hours

to continuous-wave RF radiation at 830 MHz (SAR, 1.6–8.8 W/kg), in an incubator set at temperatures between 33.5 °C (at the highest SAR value) and 37.5 °C. The incidence of aneuploidy of chromosome 17 was determined by use of a probe for α -satellite DNA repeat-sequences present in its centromeric region. The data indicated a linear and SAR-dependent increase in aneuploidy in cells exposed to RF radiation at SAR 2.0–8.2 W/kg (6–9%) compared with control cells (4–5%). Control experiments without RF radiation were conducted at 34.5–41 °C, showing no change in aneuploidy at temperatures up to 38.5 °C. This indicates that the effect of RF radiation was produced via a non-thermal pathway ([Mashevich et al., 2003](#)).

Peripheral blood lymphocytes from nine donors were stimulated with PHA for 1–6 hours, then exposed to continuous-wave RF radiation at 100 GHz (power density, 0.031 mW/cm²) for 1, 2 or 24 hours in an incubator in which CO₂ levels were not controlled. After exposure, the cells were incubated for a total culture period of 69–72 hours, with CO₂ levels at 5%. The cells were harvested and changes in chromosomes 1, 10, 11 and 17 were analysed by means of the FISH technique. For chromosomes 11 and 17, a 30% increase in aneuploidy was found after exposure for 2 or 24 hours, while chromosomes 1 and 10 were not affected. Asynchronous replication of centromeres 1, 11, and 17 was increased by 40% after 2 hours of exposure, while that of all four centromeres had increased by 50% after 24 hours of exposure. During the experiments, fibre-optic sensors were used to measure differences in temperature between exposed and sham-exposed samples; the difference never exceeded 0.3 °C ([Korenstein-Ilan et al., 2008](#)).

[Mazor et al. \(2008\)](#) exposed PHA-stimulated lymphocytes from 10 individuals to continuous-wave RF radiation at 800 MHz (SAR, 2.9 or 4.1 W/kg) for 72 hours, with the incubator set at 33.5 °C to maintain the sample temperature at 36–37 °C, in particular at the high SAR value.

Aneuploidy was scored for chromosomes 1, 10, 11, and 17 by use of the FISH technique. An increased frequency of cells aneuploid for chromosomes 11 and 17 was observed at the lower SAR of 2.9 W/kg, and for chromosomes 1 and 10 at the higher SAR of 4.1 W/kg. Multisomy (chromosomal gain) was the primary contributor to the increase in aneuploidy. Control experiments – without exposure to RF radiation – were conducted in the temperature range 33.5–41 °C; there was no change in aneuploidy.

Spindle disturbance (experiments with human-hamster hybrid cells)

The well established human–hamster hybrid (A_L) cell line, containing a single copy of human chromosome 11, was exposed to pulsed-wave RF radiation at 835 MHz, with increasing electric field strengths from 5 to 90 V/m, for 30 minutes ([Schmid & Schrader, 2007](#)). The results indicated a field strength-dependent increase in the frequency of spindle disturbances during anaphase/telophase of cell division. [The Working Group noted the absence of negative and positive controls.] [Schrader et al. \(2008\)](#) reported similar increases in spindle disturbances in A_L cells exposed for 30 minutes or 2 hours to RF radiation at 835 MHz (90 V/m) compared with non-exposed controls. [Schrader et al. \(2011\)](#) exposed A_L cells to RF radiation at 900 MHz (amplitude-modulated and unmodulated), at electric field strengths of 45 or 90 V/m, and with a SAR of 11.5 W/kg, for 30 minutes. The experiments were conducted with separate electric (E field) and magnetic (H field) components of RF radiation, at 20–22 °C. A significant increase in the frequency of spindle disturbances was observed in cells exposed to the E component, while no effect was seen in cells exposed to the H component (compared with non-exposed control cells). [Hintzsche et al. \(2011\)](#) also reported an increase in spindle disturbance during the anaphase/telophase of cell division in the same A_L cell line exposed to continuous-wave RF radiation at

106 GHz (power densities, 0.043–4.3 mW/cm²) for 30 minutes.

(ii) *Studies with two or more end-points*

[Tice et al. \(2002\)](#) reported a significant and reproducible increase in micronucleus formation in human lymphocytes exposed for 24 hours to RF radiation at 837 or 1909.8 MHz, with an average SAR of 5.0 or 10.0 W/kg. There was no increase in the number of DNA strand breaks in leukocytes, as measured with the alkaline comet assay. [McNamee et al. \(2002a, 2003\)](#) reported no effects on DNA strand-break induction or micronucleus formation in cells exposed to continuous- or pulsed-wave RF radiation at 1900 MHz, with SARs of up to 10 W/kg, for 2 or 24 hours. [Zhang et al. \(2002\)](#) observed no induction of DNA strand breaks or formation of micronuclei in human lymphocytes exposed to pulsed-wave RF radiation at 2450 MHz compared with controls. [Zeni et al. \(2008\)](#) reported no increase in DNA strand breaks or micronucleus formation in human lymphocytes exposed to intermittent (6 minutes on, 2 hours off) RF radiation at 1900 MHz (SAR, 2.2 W/kg) for 24–68 hours. Likewise, [Schwarz et al. \(2008\)](#), reported no increase in DNA strand-break induction or micronucleus formation in PHA-stimulated or non-stimulated human lymphocytes exposed for 16 hours to intermittent (5 minutes on, 10 minutes off) RF radiation at 1950 MHz (SAR, 0.1 W/kg).

[Garaj-Vrhovac et al. \(1992\)](#) reported significantly increased frequencies of chromosomal aberrations and micronuclei in human peripheral blood lymphocytes exposed for up to 60 minutes to continuous-wave RF radiation at 7700 MHz, with power densities up to 30 mW/cm².

In a series of studies from one laboratory, no increase in the frequency of chromosomal aberrations or micronuclei was reported in human lymphocytes exposed to RF radiation at 2450 MHz for 90 minutes, to continuous-wave RF radiation at 835 or 847 MHz for 24 hours, or

to RF radiation at 2450 or 8200 MHz for 2 hours ([Vijayalaxmi et al., 1997b, 2001b, c, 2006](#)).

[Maes et al. \(1993\)](#) found a time-dependent increase in the frequencies of chromosomal aberrations and micronuclei in peripheral blood lymphocytes exposed to pulsed-wave RF radiation at 2450 MHz (SAR, 75 W/kg) for 30 or 120 minutes. Both effects were statistically significant for the exposure of 120 minutes. No induction of SCE was found. In this study, the microwave output was adjusted by use of a thermistor thermometer to maintain the temperature of the cells at 36.1 °C. In subsequent experiments, [Maes et al. \(2000, 2001\)](#) examined human lymphocytes exposed to pulsed-wave RF radiation at 455.7 MHz (SAR, 6.5 W/kg) or 900 MHz (SAR, 0.4–10 W/kg) for 2 hours; no increase in chromosomal aberrations or SCE was observed.

[Stronati et al. \(2006\)](#) did not report significant changes in DNA strand-break induction, chromosomal aberrations, micronucleus formation or SCE in blood cells exposed to pulsed-wave RF radiation at 935 MHz (SAR, 1 or 2 W/kg). [Eberle et al. \(1996\)](#) measured chromosomal aberrations, micronucleus formation, SCE, and mutations at the *HPRT* locus in human lymphocytes exposed to RF radiation at 440, 900, or 1800 MHz (SAR, 1.5 W/kg). Exposure times varied (39, 50, 70 hours), depending on the experiment. No significant effects were observed for any of these end-points in RF-exposed cells compared with controls.

(b) Humans: other primary and continuously growing cultured cells

Some details on the exposure conditions to RF radiation and a short conclusion for each publication are presented in [Table 4.5](#).

(i) Amniotic cells

Human amniotic cells were exposed to RF radiation at 900 MHz (GSM; SAR, 0.25 W/kg) for 24 hours. Chromosomes were stained by use of the R-banding method and examined to determine

the incidence of structural and numerical aberrations. Exposure to RF radiation had no effect ([Bourthoumieu et al., 2010](#)). [The Working Group noted that R-banding is not recommended for analysis of chromosomal aberrations.] In a subsequent study by the same authors, amniotic cells were collected during amniocentesis from three separate donors. The cells were cultured for 15 days before being exposed to RF radiation at 900 MHz (GSM, pulsed-wave; pulse duration, 0.577 ms; pulse-repetition rate, 217 Hz; SAR, 0.25, 1, 2 or 4 W/kg) for 24 hours in a wire-patch cell at exposure temperatures of 36.3 ± 0.4 °C, 37.0 ± 0.2 °C, 37.5 ± 0.4 °C and 39.7 ± 0.8 °C, respectively, for the four SAR levels. The cells were processed for analysis by two-colour FISH with centromeric α -satellite repetitive probes for chromosomes 11 and 17 in interphase cells. No significant differences were observed between exposed and sham-exposed cells in the percentages of monosomic, trisomic cells or the total number of cells aneuploid for chromosomes 11 or 17 ([Bourthoumieu et al., 2011](#)).

(ii) Glioblastoma and neuroblastoma cells

No effects on DNA strand-break induction were observed in human U87MG glioblastoma cells exposed for up to 24 hours to continuous-wave or pulsed-wave RF radiation at 835, 847, or 2450 MHz (SAR, 0.6 W/kg at 835/847 MHz, and 0.7 or 1.9 W/kg at 2450 MHz) ([Malyapa et al. \(1997a, b\)](#)).

[Miyakoshi et al. \(2002\)](#) did not find an effect on DNA strand-break induction in human MO54 glial cells – derived from a patient with a brain tumour – exposed to RF radiation at 2450 MHz (average SAR, 50 or 100 W/kg) for 2 hours. Likewise, [Sakuma et al. \(2006\)](#) reported no effect on DNA strand-break induction in human A172 glioblastoma cells exposed to pulsed-wave RF radiation at 2142.5 MHz (SAR, up to 800 mW/kg) for 2 or 24 hours, and [Luukkonen et al. \(2009, 2010\)](#) found no effects on DNA strand-break induction in cultured human SH-SY5Y

Table 4.5 Genetic and related effects in human cells (other than lymphocytes) exposed to radiofrequency radiation *in vitro*

End-point	Cells	Frequency	SAR or power density	Duration	Results	Comments	Reference
Aneuploidy	HAC	900 MHz, PW; GSM	0.25, 1, 2, 4 W/kg	24 h	-	Chromosomes 11 and 17 were included in this study	Bourthoumieu et al. (2011)
Chromosomal aberration	HAC	900 MHz, PW; GSM	0.25 W/kg	24 h	-		Bourthoumieu et al. (2010)
Micronucleus formation	BUC	PW; mobile phone	NR	1 h/d for 2.3 yr	+		Yadav & Sharma (2008)
Micronucleus formation	BUC	PW; mobile phone	NR	3 h/wk for 5–10 yr	-		Hintzsche & Stopper (2010)
Micronucleus formation	HSF	1800 MHz, CW, PW(i); GSM	2 W/kg	1, 4, 24 h	-	Replication study. Previous results not confirmed.	Speit et al. (2007)
Micronucleus formation	SHF	1950 MHz, PW(c-i); UMTS	0.05–2 W/kg	4–48 h	+ after 12 h exposure	Controversial data	Schwarz et al. (2008)
Micronucleus formation	SHF	900 MHz, PW; GSM	1 W/kg	24 h	-		Sannino et al. (2009b)
DNA single- and double-strand breaks	GLB	2450 MHz, CW	0.7 W/kg	2–24 h	-		Malyapa et al. (1997a)
DNA single- and double-strand breaks	GLB	835, 847 MHz, CW, PW; FMCW, CDMA	0.6 W/kg	2–24 h	-		Malyapa et al. (1997b)
DNA single- and double-strand breaks	GLB	2450 MHz	13–100 W/kg	2 h	-		Miyakoshi et al. (2002)
DNA single- and double-strand breaks	GLB	2000 MHz, PW; CW, IMT	0.08, 0.25, 0.80 W/kg	2 h, 24 h	-		Sakuma et al. (2006)
DNA single- and double-strand breaks	HSF	1800 MHz, CW, PW(i); GSM	2 W/kg	1, 4, 24 h	-	Replication study. Previous results not confirmed.	Speit et al. (2007)
DNA single- and double-strand breaks	HTR	1817 MHz, PW; GSM	2 W/kg	1 h	-		Valbonesi et al. (2008)

Table 4.5 (continued)

End-point	Cells	Frequency	SAR or power density	Duration	Results	Comments	Reference
DNA single- and double-strand breaks	HTR	1800 MHz, CW, PW(i); GSM	2 W/kg	4–24 h	– with CW – with PW at 4 h + with PW at 16 h and 24 h	Differential response between CW and PW and exposure duration	Franzelli et al. (2010)
DNA single- and double-strand breaks	LEP	1800 MHz, PW; GSM	1, 2, 3 W/kg	2 h	– at 1 and 2 W/kg + at 3 W/kg		Lixia et al. (2006)
DNA single- and double-strand breaks	LEP	1800 MHz, PW(i); GSM	1, 2, 3, 4 W/kg	2 h	– at 1 and 2 W/kg + at 3 and 4 W/kg		Yao et al. (2008)
DNA single- and double-strand breaks	LUF	2000 MHz, PW, CW; IMT	0.08 W/kg	2, 24 h	–		Sakuma et al. (2006)
DNA single- and double-strand breaks	LYB	813, 836 MHz, PW; iDEN, TDMA	2.4–26 mW/kg	2–21 h	±	Inconsistent results	Phillips et al. (1998)
DNA single- and double-strand breaks	LYB	813, 836, 835, 847 MHz, CW, PW; iDEN, TDMA, FDMA, CDMA	0.0024–0.026 W/kg, 3.2 W/kg	2–21 h	–		Hook et al. (2004a)
DNA single- and double-strand breaks	LYB	1800 MHz, PW; GSM	2 W/kg	6–24 h	–		Zhijian et al. (2010)
DNA single- and double-strand breaks	NUB	872 MHz, CW, PW; GSM	5 W/kg	1 h	–	Temperature-controlled conditions	Luukkonen et al. (2009)
DNA single- and double-strand breaks	NUB	872 MHz, CW, PW; GSM	5 W/kg	3 h	–	Temperature-controlled conditions	Luukkonen et al. (2010)
DNA single- and double-strand breaks	SHF	1800 MHz, PW (c, i)	2 W/kg	4–24 h	+	Controversial data	Diem et al. (2005)
DNA single- and double-strand breaks	SHF	1950 MHz, PW(c-i); UMTS	0.05–2 W/kg	4–48 h	+	Controversial data	Schwarz et al. (2008)

Table 4.5 (continued)

End-point	Cells	Frequency	SAR or power density	Duration	Results	Comments	Reference
DNA single- and double-strand breaks	SHF	900 MHz, PW; GSM	1 W/kg	24 h	-		Sannino et al. (2009b)
Foci	HFB, MST	905, 915, 1947 MHz, PW; GSM, UMTS	0.037, 0.039 W/kg	1–3 h	+ at 915 MHz - at 905 MHz + at 1947 MHz	Decrease in 53BP1-foci, measured by immunostaining	Marková et al. (2010)
Spindle disturbance	HHH	835 MHz, PW; GSM	5–90 V/m	30 min	+	Mitotic cell fraction was scored on slides stained with 2% acetic orcein.	Schmid & Schrader (2007)
Spindle disturbance	HHH	835 MHz, PW	62.5 mW/kg	10 min to 2 h	+	Mitotic cell fraction was scored on slides stained with 2% acetic orcein.	Schrader et al. (2008)
Spindle disturbance	HHH	1060 MHz, CW	0.043–4.3 mW/cm ²	30 min	+	Mitotic cell fraction was scored on slides stained with 2% acetic orcein.	Hintzsche et al. (2011)
Spindle disturbance	HHH	900 MHz, CW, PW	0.0115 W/kg	30 min	+	Mitotic cell fraction was scored on slides stained with 2% acetic orcein.	Schrader et al. (2011)
8-OHdG, oxidative damage in DNA	SPR	1800 MHz	0.4–27.5 W/kg	16 h	+	Temperature controlled at 21 °C; maximum increase 0.4 °C during exposure.	De Iuliis et al. (2009)

+, increase; ±, equivocal; -, no effect; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; BUC, human buccal cells; (c, i), continuous and intermittent exposure; d, day; FDMA, frequency-division multiple access; FMCW, frequency-modulated continuous wave; GLB, glioblastoma cells; h, hour; HAC, human amniotic cells; HFB, human foreskin fibroblasts; HHH, hamster-human hybrid cells; HTR, trophoblast cells; iDEN, Integrated Digital Enhanced Network; IMT, International Mobile Telecommunication; LEP, lens epithelial cells; LUF, human fibroblasts from fetal lung; LYB, lymphoblastoid cells; min, minute; MST, mesenchymal stem cells; NUB, neuroblastoma cells; NR, not reported; SHF, skin human fibroblasts; SPR, sperm cells; TDAM, time-division multiple access; yr, year

neuroblastoma cells exposed to continuous- or pulsed-wave RF radiation at 872 MHz, with a SAR of 5 W/kg. In the studies mentioned above the alkaline comet assay was used to measure strand breakage in DNA.

(iii) *Lens epithelial cells*

Immortalized SRA01/04 human lens epithelial cells were exposed to pulsed-wave RF radiation at 1800 MHz (SAR, 1, 2 or 3 W/kg) for 2 hours to investigate induction of DNA breakage, which was measured by means of the alkaline comet assay. DNA-damage repair was evaluated by further incubation of the exposed cells for 30, 60, 120 or 240 minutes. There was a significant increase ($P < 0.05$) in DNA strand-breaks at a SAR of 3 W/kg immediately after exposure, which had decreased at 30 minutes, and had diminished to control levels at later time-points. At SARs of 1 and 2 W/kg, there were no significant differences between exposed cells and sham-exposed controls ([Lixia et al., 2006](#)).

In a similar study, DNA strand breaks were measured in SRA01/04 human lens epithelial cells exposed to intermittent (5 minutes on, 10 minutes off) pulsed-wave RF radiation at 1800 MHz (SAR, 1, 2, 3, or 4 W/kg) for 2 hours. There was no effect on DNA single-strand breaks – measured with the alkaline comet assay – at SARs of 1 or 2 W/kg, but a significant increase at SARs of 3 or 4 W/kg ($P < 0.001$). At these two higher SAR values, there was no difference in the induction of DNA double-strand breaks, measured with the γ H2AX-focus formation assay ([Yao et al., 2008](#)).

(iv) *Lung fibroblasts*

[Sakuma et al. \(2006\)](#) exposed human IMR-90 fetal lung fibroblasts to pulsed-wave RF radiation at 2000 MHz (SAR, 80 mW/kg) for 24 hours, and observed no effect on induction of DNA strand breaks.

(v) *Lymphoblastoid cells*

[Phillips et al. \(1998\)](#) studied DNA strand-break induction in human Molt-4 lymphoblastoid cells exposed for 2, 3 or 21 hours to RF radiation at 813 or 835 MHz as iDEN (Integrated Digital Enhanced Network) and TDMA (time-division multiple access) signals, with very low SARs of 2.4, 24, 2.6 and 26 mW/kg. There was a general decrease in the number of strand breaks at lower SARs at 2 and 21 hours (but not at 3 hours), and inconsistent results at higher SARs, depending on the type of RF signal, power intensity and duration of exposure. [Hook et al. \(2004a\)](#) examined DNA strand-break induction in Molt-4 cells exposed to the same and additional signals (813.56–847.74 MHz) at the same and higher SARs (2.4 mW/kg–3.4 W/kg) than in the study by [Phillips et al. \(1998\)](#). No effect on DNA strand-break induction was noted. [Zhijian et al. \(2010\)](#) did not find any effect on DNA strand-break induction when human HMy2.CIR lymphoblastoid B-cells were exposed to pulsed-wave RF radiation at 1800 MHz (SAR, 2 W/kg), for 6–24 hours.

(vi) *Skin fibroblasts*

[Diem et al. \(2005\)](#) exposed human ES-1 skin fibroblasts to continuous or intermittent (5 minutes on, 10 minutes off) RF radiation at 1800 MHz (SAR, 1.2 or 2 W/kg) for 4–24 hours. The cells were examined visually and subjectively to evaluate DNA single- and double-strand breaks by use of the alkaline and neutral comet assays. A “tail factor” was devised to express the results. The authors concluded that: there was a significant increase in tail factor after a 16-hour exposure, with no further increase after 24 hours; and that intermittent exposure produced a stronger effect than continuous exposure.

In a study from the same group, [Schwarz et al. \(2008\)](#) used ES-1 cells exposed for 4–48 hours to continuous and intermittent RF radiation at 1950 MHz (UMTS), with a range of SAR values (0.05–2 W/kg). The results from the analyses of

DNA strand breaks by means of the comet assay indicated a significant increase in tail factor ($P < 0.02$) at SAR 0.05 W/kg. In addition, there was a significant increase ($P < 0.02$, at SAR 0.05 W/kg) in the frequency of micronuclei, which turned out be centromere-negative (suggesting a clastogenic effect). In a similar experiment in peripheral blood lymphocytes, there was no effect on the comet tail factor or micronucleus formation (see above). Several discussions about the mode of data acquisition in these two studies subsequently appeared in scientific journals ([Rüdiger et al., 2006](#); [Vijayalaxmi et al., 2006](#); [Tuffs, 2008](#); [Vogel, 2008](#); [Wolf, 2008](#); [Balzano, 2008](#); [Kuster, 2008](#); [Drexler & Schaller, 2009](#); [Rüdiger, 2009b, c](#); [Lerchl & Wilhelm, 2010](#); [Baan, 2009](#)).

[Speit et al. \(2007\)](#) performed independent experiments to replicate and confirm the results of the two studies mentioned above, by use of the same ES-1 skin fibroblasts, the same exposure system supplied by the same company, and the same laboratory protocols. The comet tail factor as well as computerized image-analysis were used to quantify the DNA strand breaks. The experiments were also performed in Chinese hamster V79 cells. The results showed no effect on DNA breakage either by the alkaline comet assay or by the micronucleus test, in either fibroblasts or V79 cells.

Skin fibroblasts established from healthy individuals or from subjects with Turner syndrome were exposed to 900 MHz pulsed-wave RF radiation (SAR, 1 W/kg). It was suggested that cells from patients with Turner syndrome were sensitive to the effects of weakly genotoxic agents ([Scarfi et al., 1997a, b](#)). No effects on DNA strand-break induction or micronucleus formation were observed in either cell line ([Sannino et al., 2009b](#)).

[Marková et al. \(2010\)](#) observed no effect on 53BP1 foci in skin fibroblasts exposed to RF radiation at 905 MHz (SAR, 37 mW/kg). In contrast, a decrease was seen when the same cells were exposed at 915 or 1947 MHz at similar SAR

levels [the Working Group noted that this technique assesses repair foci of DNA double-strand breaks; it is different from the comet assay used for analysis of DNA strand breaks in the other studies with skin cells discussed above].

(vii) *Mesenchymal stem cells*

[Marková et al. \(2010\)](#) observed a decrease in the number of 53BP1 foci in mesenchymal stem cells exposed to RF radiation at 915 or 1947 MHz (GSM; SAR 37 and 39 mW/kg, respectively) for 1, 2, or 3 hours; no effect was noted after exposure at 905 MHz (SAR, 37 mW/kg).

(viii) *Sperm cells*

[De Iuliis et al. \(2009\)](#) studied purified human spermatozoa exposed to RF radiation at 1800 MHz (SAR, 0.4–27.5 W/kg) for 16 hours at 21 °C. With increasing SAR values, motility and vitality of the sperm cells were significantly reduced, while mitochondrial production of reactive oxygen species was significantly increased ($P < 0.001$). There was also a significant increase ($P < 0.05$) in formation of 8-OHdG adducts (measured immunochemically) and DNA fragmentation (measured with the TUNEL – terminal deoxynucleotidyl transferase dUTP nick end labelling – assay) at SARs of 2.8 W/kg and higher. The temperature during these experiments was kept at 21 °C; the highest observed exposure-induced temperature increase was +0.4 °C, at a SAR of 27.5 W/kg.

(ix) *Trophoblast cells*

[Valbonesi et al. \(2008\)](#) observed no effects on DNA strand-break induction in human HTR-8/SVneo trophoblast cells exposed to pulse-modulated RF radiation at 1817 MHz (SAR, 2 W/kg) for 1 hour.

[Franzellitti et al. \(2010\)](#) observed no effects on DNA strand-break induction in HTR-8/SVneo trophoblast cells exposed to continuous-wave RF radiation at 1800 MHz (SAR, 2 W/kg) for 4, 16 or 24 hours. Exposure to this radiation as pulsed-wave amplitude-modulated signals (GSM-217 Hz

and GSM-Talk), caused a significant increase in DNA strand breakage after all three treatment periods when the results of the comet assay were expressed as “% DNA in tail.” The number of DNA strand breaks decreased rapidly during the 2 hours after exposure.

(c) *Humans: interaction of RF radiation with known genotoxic agents*

Some details on the exposure conditions to RF radiation and a short conclusion for each publication are presented in [Table 4.6](#). Unless otherwise mentioned, the results discussed below refer to those observed in human peripheral blood lymphocytes exposed to RF radiation before, during or after exposure to a genotoxic agent.

(i) *Chemotherapeutic drugs*

[Gadhia et al. \(2003\)](#) reported a synergistic increase in chromosomal aberrations (rings, dicentrics) and SCE in lymphocytes collected from mobile-phone users and treated with mitomycin C (MMC) *in vitro*, compared with cells from controls (non-phone users) treated with MMC. This effect was stronger in mobile-phone users who smoked and consumed alcohol.

[Maes et al. \(2006\)](#) found no effect of treatment with MMC on induction of DNA strand breaks, chromosomal aberrations or SCE in lymphocytes obtained from workers at a mobile-phone company. In a series of experiments *in vitro*, the same authors reported a highly reproducible synergistic effect ([Maes et al., 1996](#)), a weak synergistic effect ([Maes et al., 1997](#)), an inconsistent synergistic effect ([Maes et al., 2000](#)), or no synergistic effect ([Maes et al., 2001](#)) of exposure to RF radiation on MMC-induced SCE. [The Working Group noted that the authors made several suggestions regarding possible mechanistic explanations for their findings, which were not pursued in detail. The authors also mentioned the possibility of a thermal effect, and indicated

the incomplete characterization of the exposure conditions in their studies.]

[Zhang et al. \(2002\)](#) investigated a possible synergistic effect in human lymphocytes exposed to RF radiation at 2450 MHz (5 mW/cm²; 2 hours) followed by treatment with MMC (0.0125–0.1 µg/ml; 24 hours). While RF radiation had no effect by itself, it significantly increased the effect of the higher doses of MMC on DNA strand-break induction and micronucleus formation. Since the temperature increase during the 2-hour exposure was less than 0.5 °C, the synergy was not likely to be due to thermal effects.

[Baohong et al. \(2005\)](#) exposed human lymphocytes to pulsed-wave RF radiation at 1800 MHz (SAR, 3 W/kg) for 2 hours, before, together with, or after incubation for 3 hours with four different chemicals. After these treatments, the cells were washed and processed for measurement of DNA strand-break induction at once or after further incubation for 21 hours. Exposure to RF radiation alone had no effect. All combinations of MMC or 4-nitroquinoline-1-oxide (4NQO) with RF radiation showed a significant increase in DNA breakage, compared with the results after incubation with the chemical alone. No such effect was observed when exposure to RF radiation was combined with treatment with bleomycin or methylmethane sulfonate (MMS), suggesting that interaction between RF radiation and different chemical mutagens could vary.

[Hansteen et al. \(2009a\)](#) found no effect on MMC-induced chromosomal aberrations after exposure of human lymphocytes to pulsed-wave RF radiation at 16.5 GHz (power density, 10 W/m²) or 18 GHz continuous-wave RF radiation (power density 1 W/m²) for 53 hours, with MMC added after 30 hours. Similar results were reported by the same authors for exposures to continuous-wave or pulsed-wave RF radiation at 2.3 GHz (power density, 10 W/m²) in combination with MMC ([Hansteen et al., 2009b](#)).

[Sannino et al. \(2009a\)](#) reported that pre-exposure of human lymphocytes to pulsed-wave RF

Table 4.6 Interaction between radiofrequency radiation and known genotoxic agents in human cells *in vitro*

End-point	Cells	Genotoxic agent	Frequency (MHz)	SAR or power density	Duration	Results	Comments	Reference
Chromosomal aberration	PBL	MMC or X-rays	900 MHz, PW; GSM	0.4–10 W/kg	RF radiation for 2 h, followed by X-rays for 1 min (1 Gy) or MMC for 72 h	-	No effect of RF radiation; no synergistic effects of RF radiation and MMC or X-rays	Maes et al. (2001)
Chromosomal aberration	PBL from phone users	MMC	890–960 MHz, PW; GSM	NR	Phone use for 1–3 h/d for 2 yr, MMC for 48 h	+	Increased gaps/dicentric after RF radiation; synergistic effect of RF radiation with MMC	Gadhia et al. (2003)
Chromosomal aberration	PBL	Gamma-rays	2500 MHz 10 500 MHz, PW	627 W/kg 0.25 W/kg	40 s 5 min	-	MW oven used as 2.5 GHz source. No effect of RF radiation; no synergistic effect with gamma-rays	Figueiredo et al. (2004)
Chromosomal aberration	PBL	MMC	400–900 MHz, PW	NR	2.3 yr (> 1h/d) MMC for 72 h	-	Lymphocytes from exposed workers. No synergistic effect with MMC	Maes et al. (2006)
Chromosomal aberration	PBL	X-rays	935 MHz, PW; GSM	1 or 2 W/kg	1 min (1 Gy) X-rays, 24 h RF radiation	-	No effect of RF radiation; no synergistic effect with X-rays	Stronati et al. (2006)
Chromosomal aberration	PBL	X-rays	1950 MHz, PW, UMTS	0.5, 2 W/kg	X-rays 5 min, RF radiation for 24 h	+ at 2 W/kg - at 0.5 W/kg	No effect of RF radiation; synergistic effect of RF radiation with X-rays (4 Gy) at the higher SAR	Manti et al. (2008)
Chromosomal aberration	PBL	MMC	1800, 1650 MHz, CW, PW	0.1, 1 mW/cm ²	53 h; MMC added at 30 h	-	No effect of RF radiation; no synergistic effect with MMC	Hansteen et al. (2009a)
Chromosomal aberration	PBL	MMC	2300 MHz, CW, PW	1 mW/cm ²	53 h; MMC added at 30 h	-	No effect of RF radiation; no synergistic effect with MMC	Hansteen et al. (2009b)
Micronucleus formation	PBL	MMC	2450 MHz, PW	5 mW/cm ²	2 h, then MMC for 24 h	+	No effect of RF radiation; synergistic effect with MMC	Zhang et al. (2002)
Micronucleus formation	PBL	X-rays	935 MHz, PW; GSM	1 or 2 W/kg	1 min (1 Gy) X-rays, 24 h RF	-	No effect of RF radiation; no synergistic effect with X-rays	Stronati et al. (2006)
Micronucleus formation	PBL	MMC	900 MHz, PW; GSM	1.25 W/kg	20 h; MMC for 24 h	+	Reduction of MMC-induced MN frequency (adaptive response?) in lymphocytes from 4 out of 5 donors	Sannino et al. (2009a)

Table 4.6 (continued)

End-point	Cells	Genotoxic agent	Frequency (MHz)	SAR or power density	Duration	Results	Comments	Reference
DNA single- and double-strand breaks	PBL	MMC	2450 MHz, PW	5 mW/cm ²	2 h, then MMC for 24 h	+	No effect of RF radiation; synergistic effect with MMC	Zhang et al. (2002)
DNA single- and double-strand breaks	PBL	MMC, 4NQO	1800 MHz, PW; GSM	3 W/kg	2 h RF irradiation, 3 h with the chemical	+	No effect of RF radiation. Exposure to chemicals before, during or after RF irradiation showed a synergistic effect with MMC and 4NQO	Baohong et al. (2005)
DNA single- and double-strand breaks	PBL	BLM, MMS	1800 MHz, PW, GSM	3 W/kg	2 h RF radiation 3 h with the chemical	-	No effect of RF radiation. Exposure to chemicals before, during or after RF irradiation showed no synergistic effect with BLM and MMS	Baohong et al. (2005)
DNA single- and double-strand breaks	PBL	MMC	400–900 MHz, PW	NR	2.3 yr (> 1 h/d) MMC for 72 h	-	Lymphocytes from exposed workers. No synergistic effect with MMC	Maes et al. (2006)
DNA single- and double-strand breaks	PBL	X-rays	935 MHz, PW; GSM	1 or 2 W/kg	1 min (1 Gy) X-rays, 24 h RF	-	No effect of RF radiation; no synergistic effect with X-rays	Stronati et al. (2006)
DNA single- and double-strand breaks	PBL	UV	1800 MHz, PW; GSM	3 W/kg	1.5 or 4 h; just after UVC at 0.25–2.0 J/m ²	+ at 4 h + at 1.5 h	Effect with UV depended on exposure duration: decrease at 1.5 h, increase at 4 h	Baohong et al. (2007)
DNA single- and double-strand breaks	PBL	APC	835 MHz, PW; CDMA	1.2 W/kg	1 h RF irradiation and APC at 0.2 or 2 µg/ml	+	No effect of RF radiation; synergistic RF effect on aphidicolin-induced repairable DNA damage.	Tiwari et al. (2008)
DNA single- and double-strand breaks	NUB	Menadione	872 MHz, CW, PW; GSM	5 W/kg	1 h RF and 50 µM menadione	+ with CW - with PW	Differential effect of CW and PW with menadione	Luukkonen et al. (2009)
DNA single- and double-strand breaks	HSF	MX	900 MHz, PW; GSM	1 W/kg	24 h RF, 1 h MX at 25 µM	-	No synergistic effect on MX-induced SB	Sannino et al. (2009b)
DNA single- and double-strand breaks	PBL	X-rays	1800 MHz, PW(i); GSM	2 W/kg	24 h (on/off for 5/10 min) then 0.25–2 Gy of X-rays	-	No effect of RF radiation; no synergistic effect with X-rays on SB induction or repair	Zhijian et al. (2009)

Table 4.6 (continued)

End-point	Cells	Genotoxic agent	Frequency (MHz)	SAR or power density	Duration	Results	Comments	Reference
DNA single- and double-strand breaks	NUB	FeCl ₂ + DEM	872 MHz, CW; PW; GSM	5 W/kg	1 h or 3 h RF; 1 h FeCl ₂ ± DEM	-	No effect of RF radiation; no synergistic effect with free radical-inducing chemicals	Luukkainen et al. (2010)
DNA single- and double-strand breaks	LYB	DOX	1800 MHz, PW; GSM	2 W/kg	6–24 h RF; 2 h DOX	-	No effect of RF radiation; no synergistic effect with doxorubicin on induction of single- or double-strand breaks; effect on repair (?)	Zhijian et al. (2010)
Sister-chromatid exchange	PBL	MMC	954 MHz, PW; GSM	1.5 W/kg	2 h RF radiation; 72 h MMC	+	No effect of RF radiation; highly reproducible synergistic effect with MMC	Maes et al. (1996)
Sister-chromatid exchange	PBL	MMC	935.2 MHz, PW; GSM	0.3–0.4 W/kg	2 h RF radiation; 72 h MMC	+	No effect of RF radiation; weak synergistic effect with MMC	Maes et al. (1997)
Sister-chromatid exchange	PBL	MMC	455.7 MHz, PW; car phone	6.5 W/kg	2 h (72 h MMC)	±	No effect of RF radiation; inconsistent synergistic effect with MMC	Maes et al. (2000)
Sister-chromatid exchange	PBL	MMC, X-rays	900 MHz, PW; GSM	0.4–10 W/kg	2 h (72 h MMC)	-	No effect of RF radiation; synergistic effect with MMC or with X-rays	Maes et al. (2001)
Sister-chromatid exchange	PBL from phone users	MMC	890–960 MHz, PW; GSM	NR	1–3 h/d for 2 yr; 48 h MMC	+	Increased SCE after RF radiation; synergistic effect with MMC	Gadhia et al. (2003)
Sister-chromatid exchange	PBL	MMC	400–900 MHz, PW	NR	72 h	-	No effect of RF radiation; synergistic effect with MMC	Maes et al. (2006)
Sister-chromatid exchange	PBL	X-rays	935 MHz, PW; GSM	1, 2 W/kg	24 h	-	No effect of RF radiation; synergistic effect with X-rays	Stronati et al. (2006)

+, increase; ±, equivocal; -, no effect; 4NQO, 4-nitroquinoline-1-oxide; APC, aphidicolin; BLM, bleomycin; CW, continuous wave; d, day; DEM, diethyl maleate; FeCl₂, ferrous chloride; h, hour; HSF, human skin fibroblasts; (i), intermittent exposure; LYB, lymphoblastoid cells; min, minute; MMC, mitomycin C; MMS, methylmethane sulfonate; MX, 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone; NUB, neuroblastoma cells; NR, not reported; PBL, peripheral blood lymphocytes; PW, pulsed wave

radiation at 900 MHz (peak SAR, 10 W/kg) for 20 hours reduced the incidence of MMC-induced micronucleus formation, suggesting that non-ionizing radiation is capable of inducing an “adaptive response” similar to that observed in several studies of ionizing radiation.

[Zhijian et al. \(2010\)](#) treated cultured human lymphoblastoid cells with doxorubicin (DOX) for 2 hours before, during and after exposure to pulsed-wave RF radiation at 1800 MHz (SAR, 2 W/kg). No significant effects on DOX-induced DNA strand-break formation were found.

(ii) Genotoxic chemicals

[Tiwari et al. \(2008\)](#) exposed human peripheral blood lymphocytes to RF radiation at 835 MHz (SAR, 1.17 W/kg) for 1 hour, with and without treatment with aphidicolin (APC; 0.2 or 2 µg/ml), an inhibitor of DNA repair. There was no effect on DNA strand-break induction of RF radiation by itself, or of the low dose of APC alone. There was a significant increase in DNA breakage after combined exposure of the cells to RF radiation with the low ($P = 0.025$) and the high dose ($P = 0.002$) of APC. [Sannino et al. \(2009b\)](#) found no effect on the number of DNA strand breaks induced by 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX) in skin fibroblasts from healthy individuals or from subjects with Turner syndrome exposed to pulsed-wave RF radiation at 900 MHz (SAR, 1 W/kg) for 24 hours, followed by treatment with MX for 1 hour.

[Luukkonen et al. \(2009\)](#) found a significant increase ($P < 0.01$) in the number of menadione-induced DNA strand breaks in cultured human SH-SY5Y neuroblastoma cells exposed to continuous-wave RF radiation at 872 MHz (SAR, 5 W/kg) and menadione (25 µM) for 1 hour, but not in cells exposed to pulsed-wave RF radiation (GSM) and menadione. In a subsequent study with the same cell type, the same authors did not observe an increase in the number of DNA strand breaks after exposure to continuous- or pulsed-wave RF radiation at the same frequency

and SAR (872 MHz; 5 W/kg), with or without ferrous chloride and diethyl maleate (the latter compound was added to enhance the free-radical production induced by the former) ([Luukkonen et al., 2010](#)).

(iii) Ionizing radiation

[Figueiredo et al. \(2004\)](#) reported no effects of RF radiation on the induction of chromosomal aberration by gamma radiation in human lymphocytes exposed to pulsed-wave RF radiation at 2.5 or 10.5 GHz (SAR, 627 and 0.25 W/kg, respectively) for 40 seconds or 5 minutes, respectively, followed 2 hours later by exposure to 1.5 Gy gamma radiation from a cobalt-60 source. No effect was observed after exposure to RF radiation alone. [Stronati et al. \(2006\)](#) found no effect of RF radiation on X-ray-induced DNA strand breaks, chromosomal aberrations, micronucleus formation or SCE in human peripheral blood lymphocytes exposed to pulsed-wave RF radiation at 935 MHz (SAR 1 or 2 W/kg) for 24 hours, combined with 1.0 Gy of 250 kVp X-rays, given for 1 minute immediately before or after exposure to RF radiation. In the FISH assay used by [Manti et al. \(2008\)](#), there was no effect of RF radiation on X-ray-induced chromosomal aberrations in human lymphocytes exposed to 4 Gy of X-rays immediately before exposure to pulsed-wave RF radiation at 1950 MHz (SAR, 0.5 W/kg), while a small but statistically significant increase ($P = 0.036$) was observed at a SAR of 2 W/kg. [Zhijian et al. \(2009\)](#) did not find an effect of RF radiation on DNA strand breaks induced by X-rays, or their repair, in lymphocytes exposed to intermittent (5 minutes on, 10 minutes off) pulsed-wave RF radiation at 1800 MHz (SAR, 2 W/kg) for 24 hours, followed by exposure to X-rays (0.25–2.0 Gy).

(iv) Ultraviolet radiation

[Baohong et al. \(2007\)](#) exposed peripheral blood lymphocytes to 254 nm ultraviolet radiation (UVC) at 0.25–2.0 J/m², followed by RF

radiation at 1800 MHz (SAR, 3 W/kg), for 1.5 or 4 hours. The number of UV-induced DNA strand breaks decreased after exposure to RF radiation for 1.5 hours, and increased after exposure for 4 hours.

(d) *Mammalian cells (non-human)*

See [Table 4.7](#)

(i) *800–1800 MHz*

Mouse C3H 10T½ fibroblast cells (both exponentially growing and in plateau phase) were exposed to RF radiation at 835.62 MHz as a frequency-modulated continuous-wave (FMCW) signal, or to RF radiation as a code-division multiple access (CDMA) signal at 847.74 MHz (SAR, 0.6 W/kg), for up to 24 hours. The alkaline comet assay was used to measure induction of DNA strand breaks. No significant differences were observed between the results obtained with FMCW or CDMA radiation and the sham-exposed negative controls ([Malyapa et al., 1997b](#)). The same authors did not find any effects in a similar experiment with continuous-wave RF radiation at 2450 MHz (SAR, 0.7 or 1.9 W/kg) ([Malyapa et al., 1997a](#)).

C3H 10T½ fibroblast cultures (exponentially growing or in the plateau phase) were exposed to RF radiation at 847.74 MHz as a CDMA signal, or to RF radiation at 835.62 MHz as a FDMA signal (SAR, 3.2–5.1 W/kg) for 2, 4, or 24 hours. The alkaline comet assay was used to measure induction of DNA strand breaks. No statistically significant change was found in tail moment or tail length for cells that had been exposed to RF radiation (CDMA or FDMA), compared with sham-exposed controls. Furthermore, in cells exposed for 2 hours to RF radiation, a post-incubation of 4 hours did not result in significant changes in tail moment or tail length ([Li et al., 2001](#)).

Exponentially growing or plateau-phase C3H 10T½ cells – derived from mouse-embryo fibroblasts – were exposed to RF radiation at

835.62 MHz, as CDMA (SAR, 3.2 or 4.8 W/kg) signal, or at 847.74 MHz as frequency-division multiple access (FDMA) signal (SAR, 3.2 or 5.1 W/kg), for 3, 8, 16 or 24 hours. No significant exposure-related differences in micronucleus formation were found for either plateau-phase cells or exponentially growing cells ([Bisht et al., 2002](#)).

[Diem et al. \(2005\)](#) reported the results of an alkaline comet assay with SV40-transformed rat granulosa cells exposed to continuous or intermittent (5 minutes on, 10 minutes off) RF radiation at 1800 MHz (SAR, 1.2 or 2 W/kg) for 4–24 hours. Both continuous and intermittent exposures induced DNA single- and double-strand breaks, with the greatest effect found with intermittent exposure. [Speit et al. \(2007\)](#) independently repeated some of the experiments with V79 Chinese hamster cells, using the same equipment and exposure conditions (1800 MHz; 2 W/kg SAR; continuous wave with intermittent exposure). No effects of exposure to RF radiation were found in assays for DNA strand-break induction and micronucleus formation.

Chinese hamster lung cells exposed to intermittent (5 minutes on, 10 minutes off) RF radiation at 1800 MHz (SAR, 3 W/kg) for 24 hours contained an increased number of γ -H2AX foci – a measure of DNA double-strand breaks – compared with sham-exposed cells. There was no effect after a 1-hour exposure to RF radiation ([Zhang et al., 2006](#)).

Because auditory cells could be exposed to RF radiation at frequencies at which mobile phones operate, [Huang et al. \(2008\)](#) used HEI-OC1 immortalized mouse auditory hair cells to characterize their response to exposure to RF radiation at 1763 MHz (SAR, 20 W/kg), in a CDMA exposure chamber for 24 or 48 hours. No changes were found in the phase-distribution of the cell cycle, DNA strand-break induction, stress response, or gene-expression profiles in the exposed cells, compared with sham-exposed controls.

Table 4.7 Genetic and related effects of exposure to radiofrequency radiation in experimental systems in vitro

Test system, end-point	Exposure conditions	Genotoxic agent	Results and comments	Reference
pBluescript SK(+) plasmid, DNA strand breaks (DNA degradation <i>in vitro</i>)	835 MHz, CW; SAR, 4 W/kg; 48 h	-	Exposure to RF radiation did not change the rate of degradation of plasmid pBluescript SK(+) exposed to H ₂ O ₂ (Fenton-type reaction) as an indicator.	Chang et al. (2005)
<i>Escherichia coli</i> WP2 <i>uvrA</i> , reverse mutation	835 MHz, CW; SAR, 4 W/kg; 48 h	4-NQO, for 48 h during exposure to RF radiation	RF radiation increased 4-NQO-induced mutation rate in <i>Escherichia coli</i> WP2.	Chang et al. (2005)
<i>Escherichia coli</i> WP2 <i>uvrA</i> , reverse mutation	2450 MHz; SAR, 5–200 W/kg; 30 min	-	No effect on mutagenicity	Koyama et al. (2007)
<i>Salmonella typhimurium</i> TA98, TA100, TA102 and TA1535, reverse mutation	835 MHz, CW; SAR, 4 W/kg; 48 h	4-NQO, cumene hydroperoxide (CHP) sodium azide (SA) for 48 h during exposure to RF radiation	RF radiation increased CHP-induced mutation rate in TA102, had no effect on SA-induced revertants in TA100, and reduced SA-induced mutation rate in TA1535	Chang et al. (2005)
<i>Salmonella typhimurium</i> TA98, TA100, TA1535 and TA1537; reverse mutation	2450 MHz; SAR, 5–200 W/kg; 30 min	-	No effect on mutagenicity	Koyama et al. (2007)
<i>Saccharomyces cerevisiae</i> , gene-specific forward mutation at <i>CAN1</i>	900 MHz, GSM pulsed-wave; SAR, 0.13; 1.3 W/kg	MMS	No significant effect on mutation rates at <i>CAN1</i> ± MMS	Gos et al. (2000)
<i>Saccharomyces cerevisiae</i> , induction of respiration-deficient (<i>petite</i>) clones (loss of mitochondrial function)	900 MHz, GSM pulsed-wave; SAR, 0.13; 1.3 W/kg	MMS	No significant effect on the frequency of <i>petite</i> colony formation ±MMS	Gos et al. (2000)
<i>Saccharomyces cerevisiae</i> , intrachromosomal deletion-formation assay	900 MHz, GSM pulsed-wave; SAR, 0.13; 1.3 W/kg	MMS	No significant effect on formation of intrachromosomal deletions ±MMS	Gos et al. (2000)
<i>Saccharomyces cerevisiae</i> , intra-genic recombination assay in the <i>ADE2</i> gene	900 MHz, GSM pulsed-wave; SAR, 0.13; 1.3 W/kg	MMS	No significant effect on rates of intragenic recombination ± MMS	Gos et al. (2000)
<i>Xenopus laevis</i> ; DNA SSB measured in erythrocytes sampled immediately after exposure	8800 MHz pulsed-wave; peak power, 65 kW; SAR, 1.6 W/kg; 40 min	-	No indication of non-thermal effects. Observed DNA damage probably due to temperature rise	Chemieris et al. (2004)
C3H10T½ mouse; DNA SSB measured in fibroblasts, sampled immediately and up to 4 h after exposure	2450 MHz CW; SAR, 0.7 and 1.9 W/kg; 2, 4 and 24 h	-	No effect	Malayapa et al. (1997a)

Table 4.7 (continued)

Test system, end-point	Exposure conditions	Genotoxic agent	Results and comments	Reference
C3H10T½ mouse; DNA SSB measured in fibroblasts, sampled immediately after exposure	835.62 MHz FMCW and 847.7 MHz, CDMA CW; SAR, 0.6 W/kg; 2, 4, 24 h	-	No effect	Malyapa et al. (1997b)
C3H10T½ mouse; DNA SSB measured in fibroblasts, sampled immediately and 4 h after exposure	835.6 MHz FDMA and 847.7 MHz FDMA; SAR, 3.2 and 5.1 W/kg; 2, 4 and 24 h exposure	-	No effect	Li et al. (2001)
C3H10T½ mouse; DNA SB, DNA-DNA and DNA-protein cross-links measured in fibroblasts	2450 MHz CW; SAR, 1.9 W/kg; 2 h exposure followed by 4 Gy gamma-rays	Gamma radiation	No effect of RF radiation on SB. No reduction by RF radiation of DNA migration induced by gamma-rays. No induction of DNA-protein crosslinks or changes in amount of DNA-associated protein by RF radiation	Lagroye et al. (2004b)
HEL-OC1 (immortalized mouse auditory hair) cells; DNA damage, stress response and gene expression	1763 MHz; SAR, 20 W/kg; CDMA; continuous exposure for 24 or 48 h		No effect on cellular responses, including cell-cycle distribution, DNA damage, stress response or gene expression	Huang et al. (2008)
L5178Y <i>Tk</i> ^{-/-} mouse lymphoma cells (DNA damage) and Chinese hamster lung fibroblasts (chromosomal aberrations, CA)	835 MHz; SAR, 4 W/kg; exposure for 48 h, alone or combined with chemicals	CPA, 4-NQO	No effect on DNA damage or CA. No effect on EMS-induced CA. Significant increase in CPA- and 4NQO-induced DNA damage.	Kim et al. (2008a)
Chinese hamster V79 cells; DNA damage (SSB, DSB)	1800 MHz; CW or pulsed-wave; continuous or intermittent (5 min on, 10 min off); SAR, 2 W/kg; exposure 1–24 h	-	No induction of DNA damage found in independent repeat experiments.	Speit et al. (2007)
Rat granulosa cells; DNA damage (SSB, DSB), sampled immediately after exposure	1800 MHz; CW or pulsed-wave; continuous and intermittent (5 min on, 10 min off); SAR, 2 W/kg; exposure 1–24 h	-	Induction of DNA SSB and DSB after 16 h intermittent exposure, at different mobile-phone modulations. Objections were raised to the analysis of the data	Diem et al. (2005)
Chinese hamster V79 cells; DNA synthesis, incorporation of [³ H] thymidine	7700 MHz; 300 mW/cm ² ; 15, 30, 60 min	-	Cells are blocked in entering S-phase	Garaj-Vrhovac et al. (1990b)

Table 4.7 (continued)

Test system, end-point	Exposure conditions	Genotoxic agent	Results and comments	Reference
Chinese hamster lung cells; DNA damage, gamma-H2AX focus formation	1800 MHz; intermittent (5 min on, 10 min off); SAR, 3.0 W/kg; for 1 or 24 h	-	RF radiation (24 h exposure, not 1 h) caused gamma-H2AX focus formation. A cell was classified positive when it contained more than five foci.	Zhang et al. (2006)
L5178Y <i>Tk</i> ^{+/+} mouse lymphoma cells; gene mutation	2450 MHz, pulsed-wave; power density, 488 W/m ² ; SAR, 30 or 40 W/kg; 4 h, together with MMC (at lower SAR) of proflavin (at higher SAR).	-	No effect of RF radiation alone. No influence by RF radiation on cell-growth inhibition or on MMC- or proflavin-induced mutagenesis	Meltz et al. (1989, 1990)
Chinese hamster ovary CHO K1 cells; gene mutation <i>Hprt</i> locus	2450 MHz; SAR, 5–200 W/kg; 2 h	Bleomycin, for 1 h before irradiation	RF radiation (200 W/kg) increased <i>Hprt</i> mutation frequency by itself, and increased bleomycin-induced <i>Hprt</i> mutations (100 and 200 W/kg). Effects may be due to hyperthermia	Koyama et al. (2007)
Chinese hamster ovary cells; SCE	2450 MHz, pulsed-wave; 490 W/m ² ; SAR, 33.8 W/kg; 2 h	Simultaneous exposure to adriamycin	No effect of RF radiation alone. No effect on adriamycin-induced SCE	Ciaravino et al. (1991)
C3H10T½ mouse fibroblasts; micronucleus formation	835.6 MHz CW; FDMA and 847.7 MHz CW, CDMA; SAR, 3.2 and 5.1 W/kg	-	No increase in frequency of micronucleus formation	Bisht et al. (2002)
Chinese hamster V79 cells; micronucleus formation	7700 MHz; 30 mW/cm ² ; 15, 30, 60 min	-	Increased micronucleus formation	Garaj-Vrhovac et al. (1991)
Chinese hamster ovary CHO-K1 cells; micronucleus formation	2450 MHz; SAR, 13, 39, 50, 78, 100 W/kg; 18 h	Bleomycin	Increased micronucleus frequency after RF radiation, and potentiation by RF radiation of bleomycin-induced micronucleus formation, both at SARs ≥ 78 W/kg	Koyama et al. (2003)
Chinese hamster ovary CHO-K1 cells; micronucleus formation	2450 MHz; SAR, 5, 10, 20, 50, 100, 200 W/kg; 2 h	Bleomycin	Increased micronucleus formation at SARs of 100 and 200 W/kg. No combined effect of RF and bleomycin	Koyama et al. (2004)
Chinese hamster V79 cells; micronucleus formation	1800 MHz; CW or pulse-wave; continuous and intermittent (5 min on, 10 min off), 1–24 h; SAR, 2 W/kg	-	No effect found. This study was aimed at replicating earlier findings.	Speit et al. (2007)
Bovine lymphocytes; micronucleus formation	9000 MHz, 70 W/kg CW; 10 min	MMC	Increased micronucleus frequency after RF radiation; significant increase by RF radiation of MMC-induced micronuclei.	Scarfi et al. (1996)

Table 4.7 (continued)

Test system, end-point	Exposure conditions	Genotoxic agent	Results and comments	Reference
Mouse m5S cells; chromosomal aberrations	2450 MHz CW or PW; SAR, 5, 10, 20, 50, 100 W/kg; 2 h	-	No effect	Komatsubara et al. (2005)
Chinese hamster V79 cells; chromosomal aberrations	7700 MHz, 300 mW/cm ² ; 15, 30, 60 min	-	Induction of chromosomal aberrations	Garaj-Vrhovac et al. (1990b)
Chinese hamster ovary cells; chromosomal aberrations	2450 MHz pulsed-wave; 490 mW/cm ² , SAR, 33.8 W/kg, 2 h	Simultaneous exposure to adriamycin or MMC	No effect of RF radiation alone No effect by RF radiation on aberrations induced by adriamycin or MMC	Kerbacher et al. (1990)
Chinese hamster V79 cells; chromosomal aberrations (structural)	7700 MHz, 30 mW/cm ² , 15, 30, 60 min	-	Increased frequency of chromosomal aberrations, including dicentric and ring chromosomes	Garaj-Vrhovac et al. (1991)
Chinese hamster ovary cells; cell-cycle progression	2450 MHz pulsed-wave; 490 mW/cm ² , SAR, 33.8 W/kg, 2 h	Simultaneous exposure to adriamycin	No effect of RF radiation alone No influence on cell-cycle progression caused by adriamycin	Ciaravino et al. (1991)
Chinese hamster V79 cells; cell growth (cell count, microtubule structure)	935 MHz; SAR: 0.12 W/kg; 1, 2, 3 h	-	Alteration of microtubule structure after a 3-h exposure; significantly decreased growth was noted in cells exposed for 3 h, at 3 d after exposure	Pavacic & Trosic. (2008)
Chinese hamster V79 cells; cell-proliferation kinetics, analysis of microtubule structure, mitotic index	935 MHz CW; SAR, 0.12 W/kg; 1, 2, 3 h	-	Alteration of microtubule structure; no effect on mitotic index. Cell proliferation was reduced at 72 h after exposure in cells exposed for 3 h. Slower cell-division kinetics	Trosic & Pavacic (2009)
Chinese hamster V79 cells; survival	7700 MHz; 0.5, 10, 30 mW/cm ² ; 10, 20, 30, 60 min	-	After 8 days of post-incubation: reduced cell survival related to power density and exposure time	Garaj-Vrhovac et al. (1991)

4-NQO, 4-nitroquinoline 1-oxide; CA, chromosomal aberrations; CDMA, code-division multiple access; CHP, cumene hydroperoxide; CPA, cyclophosphamide; CW, continuous wave; DSB, DNA double-strand breaks; FDMA, frequency-division multiple access; h, hour; *Hprt*, hypoxanthine-guanine phosphoribosyl transferase gene; min, minute; MMC, mitomycin C; MMS, methylmethane sulfonate; MN, micronuclei; SA, sodium azide; SCE, sister-chromatid exchange; SSB, DNA single-strand breaks

The alkaline comet assay and a test for chromosome aberrations *in vitro* were used to investigate the effects of 835 MHz RF radiation (4 W/kg), alone and in combination with the clastogens cyclophosphamide (CP), 4NQO and ethylmethane sulfonate (EMS), in L5178Y *Tk*^{+/−} mouse-lymphoma cells (to assess DNA breakage) and in Chinese hamster lung fibroblasts (to measure chromosome aberrations). In the latter cells, no effect was observed from RF radiation, alone or in combination with CP or EMS, but in the mouse-lymphoma cells a potentiating effect was noted on DNA strand-break induction after exposure to RF radiation following treatment with CP or 4NQO (Kim *et al.*, 2008a).

V79 Chinese hamster cells were exposed for 1, 2, or 3 hours to RF radiation at 935 MHz, generating an electric field-strength of 8.2 ± 0.3 V/cm and an average SAR of 0.12 W/kg. The microtubule structure in these cells was analysed by use of an immunocytochemical method. After 3 hours of exposure, microtubules in exposed cells were found to be altered compared with those in unexposed control cells. Three days after exposure, cell proliferation was significantly decreased in samples that had been exposed for 3 hours. Exposure to RF radiation at 935 MHz affects the structure of microtubule proteins, which consequently may obstruct cell growth (Pavicic & Trosic, 2008; Trosic & Pavicic, 2009).

(ii) 2450 MHz

The assay for forward mutation at the thymidine kinase locus in L5178Y mouse lymphoma cells was used to investigate the effects of a 4-hour exposure to RF radiation at 2450 MHz (power density, 48.8 mW/cm²; SAR, 30 W/kg), alone and in the presence of the chemical mutagen MMC (0.1, 0.2, 0.3 µg/ml). Exposure to RF radiation alone was not mutagenic, and it did not alter the effects of MMC with regards to cell proliferation or mutation induction (Meltz *et al.*, 1989). A similar experiment involving exposure to RF radiation combined with proflavin – a

DNA-intercalating drug – gave similar results (Meltz *et al.*, 1990).

In a cytogenetic study, CHO cells were exposed to pulsed-wave RF radiation at 2450 MHz (SAR, 33.8 W/kg), for 2 hours in the absence or presence of MMC (0.075 or 0.1 µg/ml) or adriamycin (0.175 µg/ml). The experimental conditions resulted in a maximum temperature increase of 3.2 °C. With respect to the induction of chromosomal aberrations, no effect was found that could be ascribed to the exposure to RF radiation (Kerbacher *et al.*, 1990).

CHO cells were exposed simultaneously to adriamycin (10^{−6} M) and pulsed-wave RF radiation at 2450 MHz (SAR, 33.8 W/kg) for 2 hours, or to adriamycin only. There was no effect of exposure to RF radiation on adriamycin-induced changes in cell progression or SCE frequency (Ciaravino *et al.*, 1991).

Micronucleus formation in Chinese hamster ovary (CHO) K1 cells was measured after exposure of the cells to RF radiation at 2450 MHz in four different scenarios: (1) exposure for 18 hours at average SARs of 13, 39 or 50 W/kg (input power, 7.8 W), which had no effect on micronucleus formation; (2) exposures corresponding to SARs of 78 or 100 W/kg (input power, 13 W), which produced a significant increase ($P < 0.01$) in micronucleus frequency; (3) treatment with the clastogenic compound bleomycin alone, or with bleomycin followed by irradiation for 18 hours at SARs of 25, 78 or 100 W/kg, which resulted in enhancement by RF radiation (at SAR values of 78 and 100 W/kg) of the effect of bleomycin alone; and (4) incubation at 39 °C for 18 hours as a high-temperature control; this last experiment also showed an increase in micronucleus frequency, albeit less strong than that after exposure to RF radiation. In a subsequent study, the authors reported a significant increase in micronucleus formation in cells exposed to RF radiation at 2450 MHz at SARs of 100 or 200 W/kg for 2 hours, but no effect of the combined exposure to RF radiation and bleomycin. Sham-exposures

at higher temperatures (38–42 °C) also increased the frequency of micronuclei, which indicates that the effects at the high SAR levels may have been thermal in nature ([Koyama et al., 2003, 2004](#)).

C3H 10T½ mouse fibroblasts were exposed to continuous-wave RF radiation at 2450 MHz (SAR, 1.9 W/kg) for 2 hours and processed for measurement of alkali-labile DNA damage and/or DNA–protein or DNA–DNA crosslinks. No effect was noted for any of these end-points ([Lagroye et al., 2004b](#)).

The induction of chromosomal aberrations was investigated in murine m5S cells exposed to continuous- or pulsed-wave RF radiation at 2450 MHz (average SARs of 5, 10, 20, 50 or 100 W/kg) for 2 hours. No significant differences were observed following exposure at any SAR compared with sham-exposed controls. There was also no difference between exposure to continuous-wave and pulsed-wave RF radiation ([Komatsubara et al., 2005](#)).

CHO-K1 cells were exposed to RF radiation at 2450 MHz (SAR, 5–200 W/kg) for 2 hours, after which *Hprt* gene mutations were scored. There was no mutation induction by exposure to RF radiation alone. An increase in the mutation frequency was found in cells exposed to RF radiation (SAR, 100 or 200 W/kg) in combination with bleomycin, but this may have been a thermal effect ([Koyama et al., 2007](#)).

(iii) 7000–9000 MHz

Cultured V79 Chinese hamster cells were exposed to continuous-wave RF radiation at 7700 MHz (power density, 30 mW/cm²) for 15, 30, or 60 minutes. In comparison with the controls, there was a higher frequency of specific chromosome lesions and a reduction in the incorporation of [³H]thymidine, showing inhibition of entry into S-phase ([Garaj-Vrhovac et al., 1990b](#)).

In a further study, the same authors reported a decrease in the number of V79 cell colonies, which was related to the power density and

the duration of exposure. Significantly higher frequencies of specific chromosomal aberrations – dicentrics, ring chromosomes – and micronuclei were observed in the exposed cells ([Garaj-Vrhovac et al., 1991](#)).

Cultures of bovine (*Bos taurus* L.) peripheral blood lymphocytes were exposed to RF radiation at 9000 MHz (SAR, 70 W/kg) for 10 minutes. To evaluate possible cooperative effects with a chemical mutagen, some exposed cultures were also treated with MMC. Exposure to RF radiation induced a statistically significant increase in micronucleus formation, both in the presence ($P < 0.01$) and absence ($P < 0.001$) of MMC ([Scarfi et al., 1996](#)).

(e) Non-mammalian cells

See [Table 4.7](#)

Mutagenic or recombinogenic effects of RF radiation at 900 MHz (GSM; SAR, 0.13 and 1.3 W/kg) were investigated in the yeast *Saccharomyces cerevisiae*. Mutation rates were monitored with a widely used gene-specific assay for forward mutation in the *CAN1* gene, which encodes arginine permease (gene-inactivating mutations lead to canavanine resistance) and with an assay measuring induction of respiration-deficient “petite” clones (small colonies) that have lost mitochondrial function. The recombinogenic effect of RF radiation was investigated with an assay for intrachromosomal deletion and an assay for intragenic recombination at the *ADE2* gene, which encodes an enzyme involved in purine (adenine) biosynthesis. Exposure of *S. cerevisiae* to RF radiation under these conditions did not result in recombinogenic or mutagenic effects ([Gos et al., 2000](#)).

The effects of a 40-minute exposure to pulsed-wave RF radiation at 8800 MHz (SAR, 1.6 W/kg; pulse width, 180 ns; peak power, 65 kW; repetition rate, 50 Hz) were investigated in erythrocytes of the frog *Xenopus laevis* by means of the alkaline comet assay. The temperature rise in the blood samples at steady-state was 3.5 ± 0.1 °C.