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International Agency for Research on Cancer

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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 $B6C3F_1$ 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 μs (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)	Mammary-gland tumours	CDT_{50}	*P < 0.01	Mammary-gland tumours detected only by palpation
			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		
Mouse, *Eμ-Pim1* (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 = 0.006 (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 Jauchem 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, *Eμ-Pim1* and wild-type (C57BL/6NTac) (F) 104 wk Utteridge 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 *Eμ-Pim1*)	Number of tumour-bearing animals: *Lymphoblastic lymphoma* 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 *Non-lymphoblastic lymphoma* 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 *Neurological tumours* 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	*$P = 0.02$ (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, *Eμ-Pim1* (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: *Lymphoma* (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) *Harderian gland adenoma*: (M) – 0 (sham), 0 (0.5 mW/g), 2 (1.4 mW/g), 4 (4.0 mW/g)	Harderian-gland adenoma: $P = 0.0028$ (one-tailed test, trend) (M)	Restrained exposure (Ferris wheel). Mortality was higher ($P < 0.05$) 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; wbSAR: 0.4, 1.3, 4 mW/g for each signal. 2 h/d, 5 d/wk 50 M and 50 F/group	*All tumours* (%) 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)* *Liver adenoma in males* (%) DCS: 22 (sham), 4 (high dose)*; GSM: 30 (sham); 12 (high dose)*	*$P < 0.05$ (decrease)	Restrained exposure (Ferris wheel) Complete histopathology GLP
Mouse, *Ptc1*$^{+/-}$, *Ptc1*$^{+/+}$ (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	*Lymphoma* 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	*Thymic lymphoma* 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	*Malignant neoplasms (all sites)* Sham, 5/100; exposed, 18/100 *Adrenal gland, pheochromocytoma* Sham, 1/100; exposed, 7/100 *Adrenal gland, cortical carcinoma* 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 ± 0.5 mW/g (nominal time-averaged brain SAR) 4 h/d, 5 d/wk 80 M and 80 F/group	*Total No. of tumours* (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; CDT_{50}, 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/cm^2) and group 2 was exposed to infrared radiation at 1.5 W/cm^2. 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/cm^2) or infrared radiation (600 mW/cm^2) 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/cm^2; group 5 was exposed to DMBA plus RF radiation at 333 mW/cm^2 plus TPA; group 6 was exposed to DMBA plus infrared radiation at 600 mW/cm^2; group 7 was exposed to DMBA plus infrared radiation at 600 mW/cm^2 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	Skin squamous cell papilloma or carcinoma (combined), tumour multiplicity		
	Group 1: DMBA + RF-EMF (n = 48)	0/48, 0	NS	
	Group 2: DMBA + sham (n = 48)	0/48, 0	NS	
	Group 3: DMBA + TPA (n = 30)	29/30*, 18.8 ± 13.4*	*$P < 0.001$	
	Group 4: DMBA + cage control (n = 30)	1/30, 0.1 ± 0.5	-	
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 × /wk for 23 wk	*Exp. 1:* Comparable skin tumour incidence and multiplicity in sham-, MMW- or IR-exposed groups. TPA increased incidence and multiplicity of skin tumours.		No SAR given
	Group 1: DMBA + 1.0 W/cm² MMW (n = 55)			
	Group 2: DMBA + 1.5 W/cm² 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 × /wk, 12 wk; TPA, 2 × /wk for 23 wk	*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.		
	Group 1: DMBA + sham			
	Group 2: DMBA + sham + TPA			
	Group 3: sham + TPA			
	Group 4: DMBA + 333 mW/cm² MMW			
	Group 5: DMBA + MMW + TPA			
	Group 6: DMBA + 600 mW/cm² IR			
	Group 7: DMBA + IR + TPA			
	Group 8: sham			
	50/group			

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 *in utero*, 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				Ferris wheel/restrained exposure 25 (M) or 20 (F) sections per brain
		CNS tumours			
		Total [%]	Brain [%]		
	Group 1: sham/sham, *n* = 30 M + 30 F	11.7	8.3	-	
	Group 2: sham/RF, *n* = 30 M + 30 F	3.3	3.3	NS	
	Group 3: ENU/sham, *n* = 30 M + 30 F	16.7	15.0	-	
	Group 4: ENU/RF, *n* = 30 M + 26 F	7.1	3.6	NS	

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/cm²) SAR (wb, av): 75 or 270 mW/kg Exposure started on d 20, 40 or 75 after B[*a*]P initiation 2 h/d, 5 d/wk, 2 wk Group 1, 2: RF 55 μW/cm², 17/17 sham/RF, 20 d after B[*a*]P initiation Group 3, 4: RF 55 μW/cm², 18/18 sham/RF, 40 d after B[*a*]P initiation Group 5, 6: RF 55 μW/cm², 14/17 sham/RF, 75 d after B[*a*]P initiation Group 7, 8: RF 200 μW/cm², 8/9 sham/RF, 40 d after B[*a*]P initiation Group 9: cage control, 6	Small palpable tumours (sarcomas) detectable from d 90–100 onwards. Tumour incidence not reported. No consistent pattern of differences in time to tumour or survival.	NS	Poor and confusing description of experiment and results. The authors stated that tumour onset was "slightly different" ($P = 0.05$) in the sham-exposed group and one of the exposed groups (55 μW/cm², 40 days).
Rat, F344 (M, F) ENU *in utero*, 4 mg/kg bw i.v. on GD 18 24 mo Adey et al. (2000)	836.55 MHz, NADC-modulated Far-field: GD 19–PND 21 (weaning) 2.6 ± 0.50 mW/cm² 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, *n* = 45 M + 45 F: 1.1 / 1.1 Group 2: sham/RF, *n* = 45 M + 45 F: 4.4 / 3.3 Group 3: ENU/sham, *n* = 45 M + 45 F: 22.2 / 18.9 Group 4: ENU/RF, *n* = 38 M + 52 F: 17.8 / 15.6 Group 5: ENU/cage control, *n* = 45 M + 45 F: 14.4 / 14.4 Group 6: cage control, *n* = 45 M + 45 F: 4.4 / 3.3	- 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 (M, F) ENU *in utero*, on GD 15, 0, 2.5 or 10 mg/kg bw i.v. 24 mo Zook & Simmens (2001)	860 MHz, PW or CW, near-field 6 h/d, 5 d/wk, 22 months (starting on PND 57) 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 evidence that PW or CW increased the incidence of tumours in any studied tissues or promoted cranial or spinal or spinal nerve-cord tumours initiated by ENU. No. of rats with brain tumours (M + F combined)	NS (overall)	Restrained exposure of the head in tube (Ferris wheel) GLP 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.

Group	ENU (mg/kg bw)	RF	All	Multiple	Astrocytoma	Oligodendroglioma	Mixed glioma	
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) DMBA, 50 mg/kg bw by gavage 259–334 d Bartsch et al. (2002)	900 MHz GSM signal (217 Hz pulsed; pulse width, 577 µs) Far-field, 100 µW/cm² ± 3 dB; SAR (wb, av), 17.5–70 mW/kg 23 h/d, 7 d/wk Two groups each in three similar experiments performed over 3 years, 60/group	Mammary-gland tumours							Malignant tumours were adenocarcinomas
		Median tumour latency (d)		Cumulative incidence of tumours Last day of observation	[%]				
		Malignant	Benign		Malignant	Benign	Malignant	Benign	
	Exp. 1: Sham	145	316	334	79	90	-	-	
	Exp. 1: Exposed	278	310	334	82	91	$P = 0.009$ (retardation)	NS	
	Exp. 2: Sham	95	> 265	259	84	38	-	-	
	Exp. 2: Exposed	95	221	259	94	60	NS	NS	
	Exp. 3: Sham	216	293	343	91	89	-	-	
	Exp. 3: Exposed	195	321	343	81	92	NS	NS	

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 (M, F) ENU *in utero*, on GD 15, at 6.25 or 10 mg/kg bw i.v. Up to 24 months Zook & Simmens (2002, 2006)	860 MHz PW signal (frame rate, 11.1Hz; slot duration, 15-ms), near-field 6 h/d, 5 d/wk, up to 22 months (starting on PND 52) SAR (brain, av): 1.0 ± 0.2 mW/g 6 groups, 90 M + 90 F/group Group 2: ENU at 6.25 mg/kg bw + PW Group 3: 6.25 mg/kg bw ENU + cage control Group 4: 10.0 mg/kg bw ENU + sham Group 6: 10.0 mg/kg bw ENU + cage control	Neurogenic tumours: PW does not affect incidence, multiplicity or latency. [6.25 and 10.0 mg/kg bw ENU-treated groups combined, M + F combined]:						Restrained exposure of the rat head in tube (Ferris wheel) GLP Study conducted in three phases. Each group included three cohorts of 30 M + 30 F. Euthanasia with 30-days intervals started on PND 171. Tissues that were studied histologically included brain (1-mm step sections), spinal cord, thyroid, pituitary and adrenal glands, liver, kidneys, lungs, spleen, heart, trigeminal nerves and any other tissues that appeared abnormal. The incidence, volume and malignancy grade of neurogenic tumours were increased in the group given ENU at 10 mg/kg bw compared with the group given ENU at 6.25 mg/kg bw. The incidences of tumours outside the nervous system were not associated with ENU treatment and were not increased in PW-exposed rats.
					Oligodendroglioma	*Mixed glioma*		
	PW (360 animals at start)	173	61	1	111	100	NS	
	Sham (360 animals at start)	193	76	5	118	113		
	Cage control (360 animals at start)	180	58	6	106	107		
Rat, Sprague-Dawley (F) DMBA, 10 mg/rat by gavage on d 1 10 d + 9 wk (RF exposure) + 3 wk Anane et al. (2003)	900 MHz, GSM, far-field *Exp. 1*: SAR (wb, av): 0 (sham), 1.4, 2.2, 3.5 mW/g *Exp. 2*: SAR (wb, av): 0 (sham), 0.1, 0.7, 1.4 mW/g 2 h/d, 5 d/wk, 9 wk 16/group in both experiments	Mammary-gland tumours Rate of incidence of malignant tumours: *Exp. 1*: groups exposed at 1.4 and 2.2 mW/g *vs* sham *Exp. 2*: group exposed at 1.4 mW/g *vs* sham *No. of tumours at wk 12* *Malignant*	*Benign*	*No. of rats without tumour*	*No. of rats alive at wk 12*		$P = 0.02$, 0.04 (increase in rate of incidence) $P = 0.04$ (decrease in rate of incidence)	
	Exp. 1: Sham	21	5	5	16	-		
	1.4 mW/g	24	5	2	16	NS		
	2.2 mW/g	24	2	1	15	NS		
	3.5 mW/g	29	6	2	14	-		
	Exp. 2: Sham	17	5	3	14	NS		
	0.1 mW/g	8	11	0	16	NS		
	0.7 mW/g	13	15	4	16	NS		
	1.4 mW/g	4	4	9				

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 *in utero*, 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	Spinal cord				.
		M/F	M/F				
	Group 1: cage control	0/0	0/0				
	Group 2: ENU control	18/18	2/6				
	Group 3: ENU/sham	24/30	2/4			-	
	Group 4: ENU/low (0.67 mW/g)	30/18	0/6			NS	
	Group 5: ENU/high (2.0 mW/g)	22/16	4/4			NS	
	50 M + 50 F/group						
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 (%)	Benign mammary-gland tumours (%)	Mammary-gland hyperplasia (%)		
	Group 1: cage control	60*	37	23*	14	*$P < 0.05$ *vs* sham	
	Group 2: sham	45	37	8	29		
	Group 3: 0.44 mW/g	38	25**	13	24	**$P = 0.058$ *vs* sham	
	Group 4: 1.33 mW/g	41	34	7	15		
	Group 5: 4.0 mW/g	43	38	5	24		
	99–100/group						
Rat, F344 (M, F) ENU *in utero*, 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	Spinal cord				
		M/F	M/F				
	Group 1: cage control	2/2	0/0				
	Group 2: ENU/cage control	16/14	2/0			-	
	Group 3: ENU/sham	8/10	2/0			NS	
	Group 4: ENU/low (0.67 mW/g)	16/10	0/0			NS	
	Group 5: ENU/high (2.0 mW/g)	16/22	2/0			NS	
	5 M + 50 F/group						

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)					NS (RF-exposed *vs* sham-exposed)	Restrained exposure in tube (Ferris wheel) GLP Malignant tumours were mainly adenocarcinomas.
	100/group	Mammary-gland tumour multiplicity or volume					
		Mammary-gland lesions (%)					
		Malignant or benign	Malignant	Benign	Hyperplasia		
	Group 1: cage control	73	45	28	12		
	Group 2: sham	60	30	30	11		
	Group 3: 0.4 mW/g	57	40	17*	19	* $P < 0.05$ *vs* sham (decrease)	
	Group 4: 1.3 mW/g	50	35	15*	22		
	Group 5: 4.0 mW/g	65	47**	18*	9	** $P < 0.05$ *vs* sham (increase)	

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, electromoagnetic 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 ± 0.50 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 $B6C3F_1$ 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/m^2 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/m^2; and group 5 was exposed to UMTS RF radiation at 48 W/m^2. 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 bronchioloalveolar 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/m^2 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 1st 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.

Table 3.3 (continued)

Species, strain (sex) Carcinogen Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, BALB/c (M) *Exp.1*: 1 or 3 mo irradiation before B[*a*]P skin painting on alternate days for 5 mo *Exp. 2*: 5 mo-irradiation simultaneously with B[*a*]P skin painting on alternate days for 5 mo Up to 12 mo Szmigielski et al. (1982)	2 450 MHz MW (far-field condition in an anechoic chamber) 2 h/d, 6 d/wk Confinement-stress controls were provided: mice were located individually in a chronic stress-syndrome compartment for 1–8 mo. *Exp. 1*: sham, 5 mW/cm^2 (1 mo before B[*a*]P), 5 mW/cm^2 (3 mo before B[*a*]P), confinement stress (1 mo before B[*a*]P), or confinement stress (3 mo before B[*a*]P)	*Exp. 1*: No. of mice with skin cancers: 0, 2, 22*, 3, 16* after 6 mo 4, 18*, 29*, 16*, 25* after 8 mo 19, 27**, 36**, 24, 31** after 10 mo	*$P < 0.01$ **$P < 0.05$	Distance from the antenna (vertical 30 × 30 cm horn antenna) to cages: 220 cm. Four cages (30 × 50 cm area cage) containing 10 mice each. Data are poorly presented and difficult to interpret.
	Exp. 2: sham, 5 mW/cm^2, 15 mW/cm^2 or confinement stress SAR: 2–3 mW/g (5 mW/cm^2) or 6–8 mW/g (15 mW/cm^2) 40/group	*Exp. 2*: Number of mice with skin cancers: 0, 12*, 28*, 13* after 6 mo 5, 23*, 33*, 26* after 8 mo 21, 32*, 38*, 31* after 10 mo	*$P < 0.01$	
Mouse, BALB/c (M) *Exp. 1*: 6 mo irradiation simultaneously with B[*a*]P skin painting *Exp. 2*: 1, 2 or 3 mo irradiation before B[*a*]P skin painting on alternate days for 6 mo Up to 12 mo Szudziński et al. (1982)	2 450-MHz MW (far field) 2 h/d, 6 d/wk	Skin carcinoma		
	Exp. 1: 0, 5 or 15 mW/cm^2, SAR: 0, 2 or 6 mW/g	*Exp. 1*: CDT_{50} of 296, 235, 131 days at 0, 5, 15 mW/cm^2	$P < 0.05$ at 15 mW/cm^2	
	Exp. 2: three groups at 10 mW/cm^2 wbSAR: 4 mW/g 100/group	*Exp. 2*: CDT_{50} of 253, 210, or 171 days after 1, 2 or 3 mo of irradiation [Control CDT_{50}: 296 days, see *Exp. 1*]	No *P*-values reported	No concurrent sham control in *Exp. 2*

B[*a*]P, benzo[*a*]pyrene; CNS, central nervous system; CDMA, code-division multiple access; CDT_{50}, cancer development time 50 (i.e. time in which 50% of the mice developed skin carcinoma); d, day; D-AMPS, digital advanced mobile phone service; DCS, Digital Personal Communication System; DEN, diethylnitrosamine; DMBA, 7,12-dimethylbenz[*a*]anthracene; DMH, dimethylhydrazine; EMF, electromagnetic field; ENU, *N*-ethyl-*N*-nitrosourea; FDMA, frequency-division multiple access; GD, gestational day; GSM, Global System for Mobile communication; i.p., intraperitoneal; i.v., intravenously; MMW, millimetre wavelength; mo, month; MW, microwave; NADC, North American Digital Cellular; NS, not significant; ODC, ornithine decarboxylase; PH, partial hepatectomy; p.o., oral administration; PRF, pulsed radiofrequency field; RF, radiofrequency radiation; 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

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.]

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