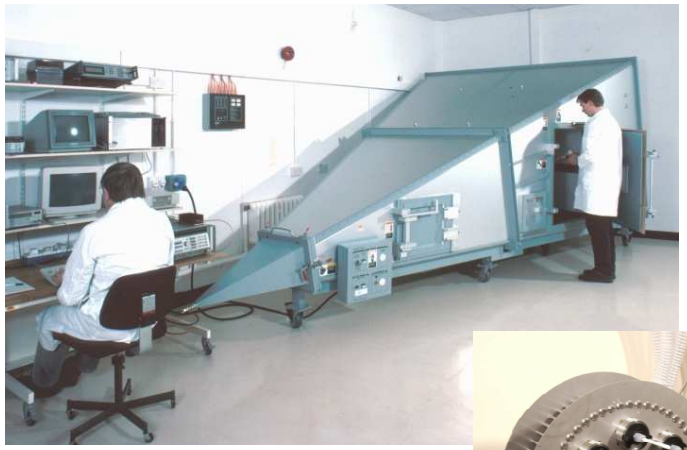
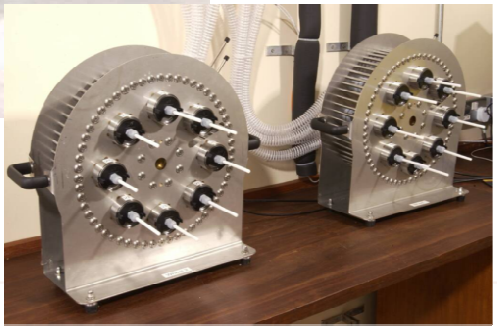
IARC 2B and RF laboratory studies



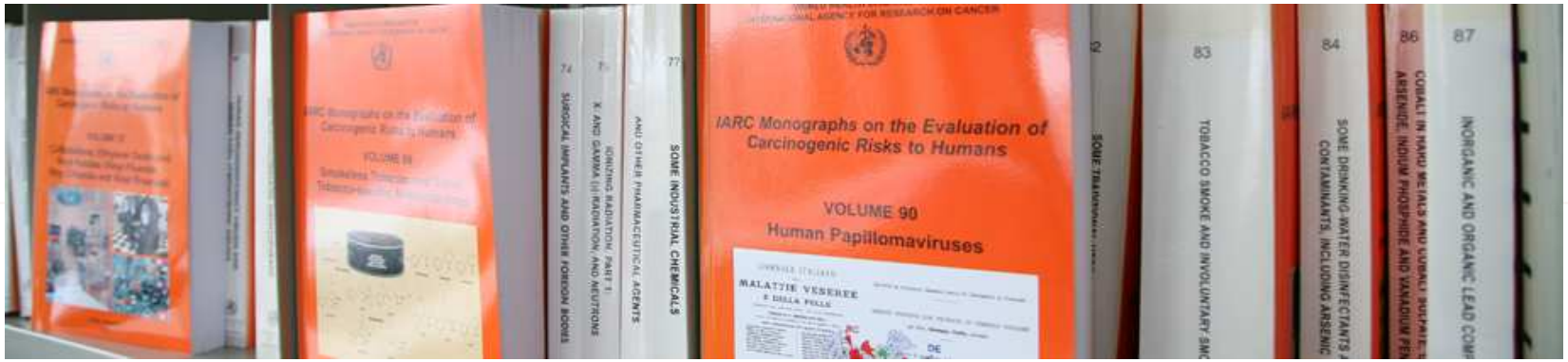


2B, or not 2B,
that is the question….

IARC Monographs

International Agency for Research on Cancer
World Health Organization

- Identify environmental factors that can increase the risk of human cancer. These include chemicals, complex mixtures, occupational exposures, physical agents, biological agents, and lifestyle factors.
- Interdisciplinary working groups of expert scientists review the published studies and evaluate the weight of the evidence that an agent can increase the risk of cancer.
- Since 1971, more than 900 agents have been evaluated, of which more than 400 have been identified as carcinogenic, probably carcinogenic, or possibly carcinogenic to humans



IARC assessment: Human data

Sufficient evidence of carcinogenicity

- causal relationship established, chance, bias ruled out

Limited evidence

- causal relationship credible, chance, bias not ruled out

Inadequate evidence

- no conclusions possible due to insufficiencies in data

Evidence suggesting lack of carcinogenicity

- studies consistently show no positive association

IARC assessment: Animal data

Sufficient evidence for carcinogenicity

- causal relationship established in 2 or more species

Limited evidence

- data suggest effect, but unresolved questions about studies

Inadequate evidence

- no conclusions possible due to limitations/absence of data

Evidence suggesting lack of effects

- not carcinogenic in 2 or more species

IARC assessment: Other relevant data

Supporting evidence

- genetics and related effects
- metabolism and biokinetics
- tumour pathology

Mechanism of carcinogenic action

- weak, moderate or strong
- does it operate in humans?
- levels in tests compared to human exposures

Overall evaluation by IARC

Group 1 - is carcinogenic to humans

- sufficient evidence in humans, animals

Group 2a - is probably carcinogenic

- limited evidence in humans, sufficient in animals

Group 2b - is possibly carcinogenic

- limited evidence in humans, less than sufficient in animals
- inadequate evidence in humans, sufficient in animals

Group 3 - is not classifiable

- inadequate evidence in humans, limited/inadequate in animals

Group 4 – is probably not carcinogenic

- evidence of lack of carcinogenicity in humans, animals

Numbers of evaluations

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

Group 1 - is carcinogenic to humans

- 114 agents: arsenic, benzene, ionizing radiation, UVR

Group 2a - is probably carcinogenic

- 69 agents: creosotes, diesel engine exhaust, trichloroethylene

Group 2b - is possibly carcinogenic

- 283 agents: carbon tetrachloride, chloroform, coffee, petrol engine exhaust, talc-based body powder, magnetic fields, RF fields

Group 3 - is not classifiable

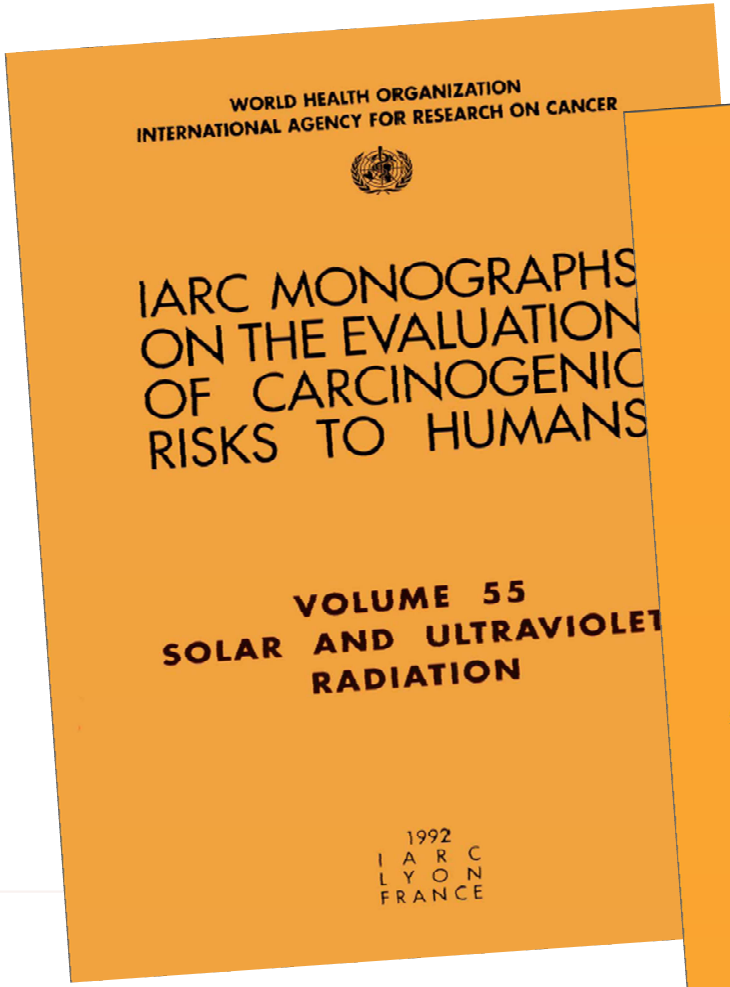
- 504 agents: acrylic fibres, caffeine, chloral hydrate, fluorescent lighting, tea, electric fields

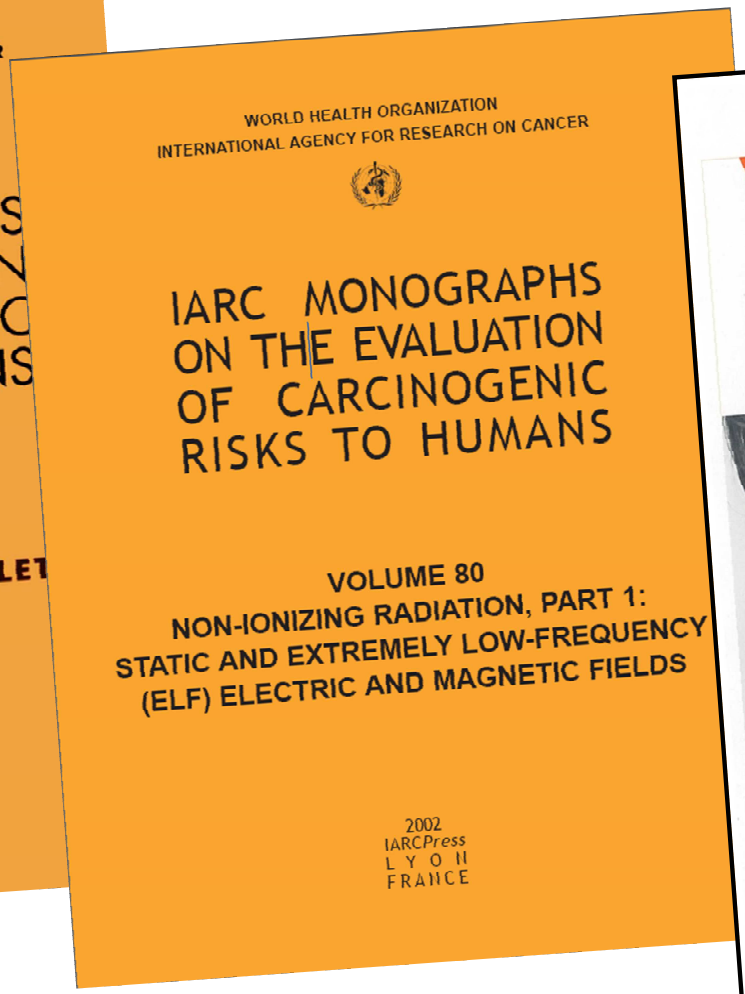
Group 4 – is probably not carcinogenic to humans

- 1 agent: caprolactam

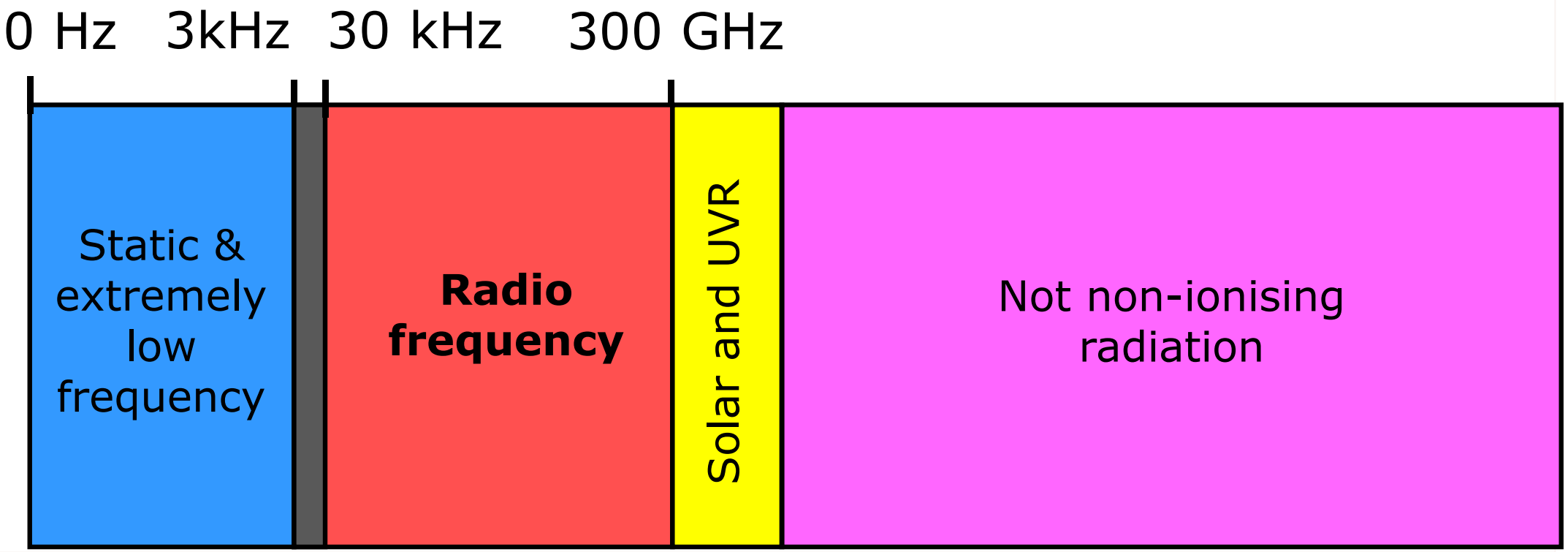
- 971 evaluations as of 25th July 2014

Monographs on NIR





Definitions used



Starting perspective

Investigated for > 50 years

- many thousand studies
- much information on many endpoints
- not just mobile phone frequencies

Technically challenging subject

- metrology and dosimetry complex
- large scope for artefact/errors

Paucity of replicable effects of weak fields

- close to limits of detection

Experimental studies

Laboratory-based investigations using volunteers, animals, embryos, tissues, cells, molecules

- high degree of control of conditions
- detailed exposure history
- known genetic background
- specific endpoints studied
- can investigate mechanisms
- positive controls possible

Limitations of laboratory studies

Humans	• short-term physiological effects
Animals	• extrapolation necessary to humans • ethical concerns
Tissues, cells, molecules	• in isolation, without rest of body • relevance to health less clear

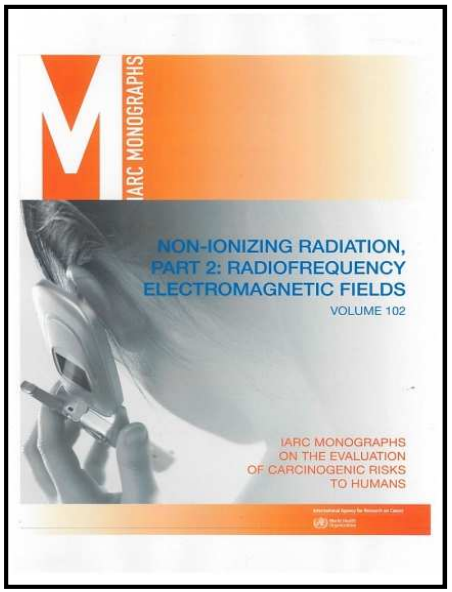
Representative exposure, usually single frequency

Quality of published studies

Very wide variation in quality

- some very good, some very poor
- older studies tend to be less reliable
- journals may not have appropriate referees
- publishing bias for positive studies

IARC Conclusion on RF fields



6.2 Cancer in Experimental Animals

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

6.3 Overall Evaluation

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

Overview of *in vivo* studies

Many negative results

- spontaneous tumours in normal/prone animals
- chemically-induced tumours
- lifespan not reduced
- immune function unaffected

But some positive studies

- increase in lymphomas in transgenic mouse

Overview of *in vitro* studies

Many negative results

- not mutagenic
- no reproducible damage to chromosomes

But some positive studies

- apoptosis
- growth/division enzyme (ODC) activity
- cell membrane changes
- gene/protein expression

In vivo and other data considered by IARC

Animal cancer studies

- long-term bioassays
- transgenic and tumour-prone models
- initiation-promotion studies
- co-carcinogenesis

Other relevant data

- genetic effects
- immune function
- ‘omics and signalling pathways
- mechanistic endpoints

1. Long-term bioassays

No significant increase in incidence of any benign or malignant tumour in any organ, male or female rats or mice, repeated, daily exposures to RF fields for 24 + months; complete pathology. No effects on body weight, survival

- SD rats, pulsed 2.45 GHz, 800 pps, 10 µs pulse width, 21.5 h/day, 7 days/week, at 0.4 W/kg (younger) and 1.5 W/kg (older) (Chou et al, 1992)

  total malignant tumours all sites increased following pooling of data

- SD rats, 900 MHz GSM, 23 h/day. 7 days/week, up to 37 months, at 0.03-0.13 W/kg (younger) to 0.015-0.06 W/kg (older) (Bartsch et al, 2010)

  4 experiments: sporadic differences on survival, decreases in pituitary or mammary tumours; lack of complete pathology

Studies using Ferris wheel exposure system, animals restrained

- F344 rats, 835 MHz FDMA, 847 MHz CDMA, 4 h/day, 5 days/week at 1.3 W/kg in brain (La Regina et al, 2003)
- F344 rats, 1620 MHz, 2 h/day, 7 days/week from gestation day 19 to weaning then from day 36, 2 h/day, 5 days/week at 0.16 or 1.6 W/kg in brain (Anderson et al, 2004)
- Wistar rats, 902 MHz GSM, 1747 MHz DCS, 2h/day, 5 days/week at 0.4, 1.3 or 4 W/kg (Smith et al, 2007)
- B6C3F mice, 902 MHz GSM, 1727 MHz DCS, 2 h/day, 5 days/week, at 0.4 1.3, or 4 W/kg (Tillmann et al, 2007)

decreases in liver adenoma in males at highest SAR, both signals

Conclusions on long-term bioassays

Overall, 6 studies evaluated

- 0 of 4 studies with mobile phone signals gave positive result

  1 study not included due to incomplete pathology
- 1 of 1 study with pulsed RF signals gave increased incidence of total malignant tumours ONLY after pooling of non-significant changes at several sites – *of limited biological significance*

It was concluded that "the results of 2-year cancer bioassays provided no evidence that long-term exposure to RF radiation increases the incidence of any benign or malignant neoplasm in standard-bred mice or rats"

- awaiting full results of US NTP study at IIT Research Institute with interest

2. Transgenic and tumour prone models

***Eμ-Pim 1* mouse: incidence of lymphoma**

- 900 MHz GSM basic, 2x30 min/day, 7 days/week for 18 months, at 0.13-1.4 W/kg (Repacholi et al, 1997)

  significant (twofold) increase of non-lymphoblastic/all lymphomas increased; surviving mice not examined; no pathology data

- 898 MHz GSM, 1 h/day, 5 days/week for 2 y, at 0.25, 1, 2 or 4 W/kg (Utteridge et al, 2002)

  no significant increases in lymphoma

- 900 MHz GSM, 2x30 min/day, 5 days/week for 18 months, at 0.5, 1.4 or 4 W/kg (Oberto et al, 2007)

  no significant increases in lymphoma; survival shorter in all males, females at 0.5 W/kg; incidence of Harderian gland tumours higher in males; incidence of lymphoma in control group comparable to exposed group in 1997 study (43%)

AKR mouse: lymphomas, haematopoietic malignancies

- 900 MHz GSM, 24 h/day, 7 days/week for 40 weeks at 0.4 W/kg (Sommer et al, 2004)

  no significant increases in lymphoma or survival; body weight gain increased

- 1966 MHz UMTS, 24 h/day, for 43 weeks at 0.4 W/kg (Sommer et al, 2007)

  no significant increases in lymphoma or survival or body weight

- 1950 MHz and 849 MHz, 45 min/day, 5 days/week for 42 weeks at 2 x 2 W/kg (Lee et al, 2007)

  no significant increases in lymphoma or survival or body weight

OF1 mouse: lymphoid tissue tumours

- 800 MHz, 1h/week for 4 months (Anghileri et al, 2005)

  earlier onset, formation of lymphoblastic ascites, extra nodal tumours; no dosimetry, no pathology, not included

Patched1$^{+/-}$ mouse: brain (medulloblastoma) tumours

- 900 MHz GSM basic, 2x30 min/day, from postnatal day 2 to 6 at 4 W/kg (Saran et al, 1997)

  no significant increase in any tumour type; short exposure period

C3H mouse: mammary gland tumours

- C3H/HeA mice, CW 2.45 GHz, 6 weeks to 12 month old at 2-3 W/kg or 6-8 W/kg (Szmigielski et al, 1982)

  more rapid appearance, significant increase in incidence of tumours, no pathology

- C3H/HeJ mice, pulsed 435 MHz, 1 ps, 1 kHz pulse rate, 22 h/day, 7 days/week for 21 months at 0.32 W/kg (Toler et al, 1997)

  no significant increases in incidence, latency or growth rate, or survival or body weight

- C3H/HeJ mice, CW 2.45 GHz, 20h/day, 7 days/week for 18 months at 0.3 W/kg (Frei et al, 1998a)

  no significant increases in incidence, latency or growth rate, or survival or body weight

C3H mouse: mammary gland tumours

- C3H/HeJ mice, CW 2.45 GHz, 20h/day, 7 days/week for 78 weeks at 1 W/kg (Frei et al, 1998b)

  no significant increases in incidence, latency or growth rate, or survival or body weight

- C3H/HeJ mice, UWB pulses, 176 ps rise time, 2 min/week for 42 weeks at 40 kV/m (0.001 W/kg) (Jauchem et al, 2001)

  no significant increases incidence, latency or growth rate or survival or body weight; limited exposure

Conclusions on transgenic and tumour-prone models

Overall, 12 studies evaluated with 4 mouse models

- 1 of 3 lymphoma in *Eμ-Pim1*
- 0 of 3 lymphoma in AKR
- 0 of 1 of brain tumours in *Patched1*$^{+/-}$
- 1 of 5 of mammary tumour in C3H/HeA

] studies gave positive results

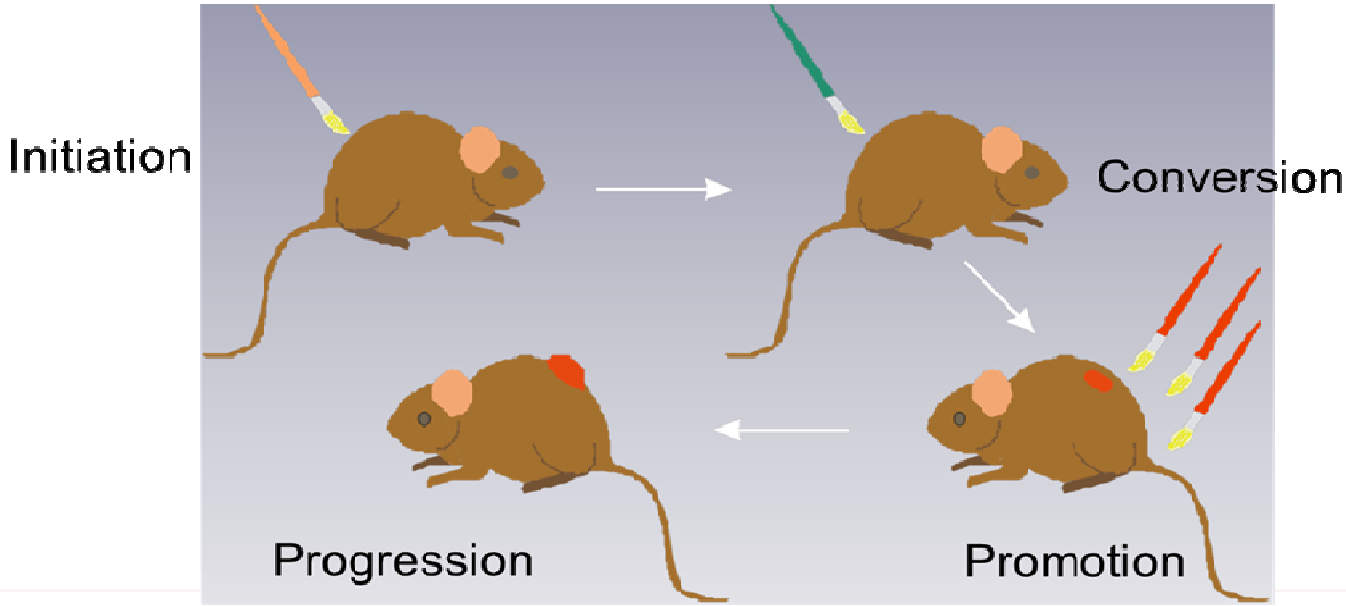
It was concluded that "the results of three tumour-prone animal models … do not support the hypothesis that the incidence of tumours in the brain or lymphoid tissue would increase as a result of exposure to RF radiation"

3. Initiation-promotion studies

Can exposure to a RF field promote tumorigenic effects of known chemical carcinogens?

Areas of study

- skin tumours
- mammary tumours
- brain tumours
- lymphoma



3a. Skin tumour studies

No increase with single dose of DMBA painted on skin/injected followed by repeated exposure to RF fields, post mortem examination

- ICR mice: 1.5 GHz PDC, 90 min/day, 5 days /week for 19 weeks, 2 W/kg in skin, 0.08 W/kg average (Imaida et al, 2001)
- SENCAR mice; 94 GHz CW at 10 W/m^2 for 10s, or at 3 W/m^2 for 10 s 2/week for 12 weeks. Plus no co-promoting effects with repeated 12-O-tetradecanoylphorbol 13-acetate (TPA) (Mason et al, 2001)
- ICR mice: 848 or 1762 CDMA, 2 x 45 min/day, 5 day/week for 19 weeks, 0.4 W/kg (Huang et al, 2005)
- Swiss albino mice: 112 MHz AM at 16 Hz at 0.75 W/kg or 2.45 GHz at 0.1 W/kg, 2 h/day, 3 day/week for 16 weeks (Paulraj and Behari, 2011)
- SD rats; 900 MHz GSM, 2 h/day, 5 days/week for 2 weeks, at 0.075 or 0.27 W/kg, on day 20, 40 or 75 after single 2 mg s.c. (Chagnaud et al, 1999)

3b. Brain tumour studies

No increase with prenatal injection of *N*-ethylnitrosourea (ENU) followed by daily exposure, post mortem pathology

- Fischer 344 rats: 836 MHz TDMA pulsed, continuous gd19 until day 21 (far field) and 7.5 min on/off, 2h/day, 4 days/week for up to 680 days after day 31, 2 h/day, 4 days/week for almost 2 y (near field) 1.4 W/kg peak in brain (Adey et al, 1999)
- Fischer 344 rats: 836 MHz FM at 12.5 kHz, continuous gd19 until day 21 (far field) and 2 h/day, 4 days/week from day 31 for 2 y (near field) 1-1.2 W/kg peak in brain (Adey et al, 2000)
- Fischer 344 rats: 1.4 GHz TDMA or 1.9 GHz WCDMA, 90 min/day, 5 day/week for 2 y, 0.67 and 2 W/kg, head-only (Shirai et al, 2005, 2007))
- SD rats: 860 MHz MIRS signals, 6 h/day, 5 days/week from 50 days old until almost 1 y,1 W/kg, head-only (Zook and Simmens, 2001, 2006)

3c. Mammary tumour studies

No consistent changes, significant increases in one study, in SD female rats with single dose of 7,12- dimethylbenz(a)anthracene (DMBA) by gavage, followed by repeated exposure to 900 MHz mobile phone signals, post mortem pathology

- Nearly continuous for 1 y, 0.02 - 0.07 W/kg (Bartsch et al, 2002)
  results inconsistent between 3 experiments
- 2h/day. 5 days/week for 9 weeks, 0.1 - 3.5 W/kg (Anane et al, 2003)
  more rapid growth in one experiment, decrease incidence in other
- 4 h/day, 5 day/week for 26 weeks, 0.4, 1.3 or 4 W/kg (Yu et al, 2006)
  no significant effects
- 4 h/day, 5 day/week for 26 weeks, 0.4 1.3 or 4 W/kg (Hruby et al, 2008)
  significant increase in rats with malignant tumours and decrease in benign tumours at 4 W/kg, but comparable to values in cage controls

3d. Lymphoma

No significant increase in CBA/S mice following X-rays plus repeated, daily exposure, post mortem pathology

- 4 Gy X-rays (3 x 1.3 Gy weekly) then 902.5 MHz NMT at 1.5 W/kg or 900 MHz GSM at 0.35 W/kg for 1.5 h/day, 5 days/week for 78 weeks, (Heikkinen et al, 2001)

Conclusions on initiation/promotion models

Overall, 16 studies evaluated

- 0 of 5 skin cancer
- 0 of 6 of brain cancer
- 1 of 4 of mammary tumour
- 0 of 1 lymphoma

studies gave positive results

It was concluded that “the evidence failed to demonstrate a consistent pattern of enhancement of carcinogenesis by exposure to RF radiation in any of the tissues studied”

4. Co-carcinogenesis studies

Skin tumour studies with 3,4 benzo[a]pyrene (BaP)

- BALB/c mice: repeated BaP every other day for 5 months, 2.45 GHz CW at 2-3 or 6-8 W/kg, 2 h/day, 6 day/week for up to 5 months either before or with BaP (Szmigielski et al,1982)

  accelerated development; poor design; difficult to interpret; result comparable to confinement stress

- BALB/c mice: 2.45 GHz CW, 2 h/day, 6 day/week for 1,2,3 or 6 months at 2, 4 or 6 W/kg plus repeated BaP at sub-carcinogenic dose (Szudzinski et al, 1982)

  accelerated development; decreased in lifespan; poor design

Tumourigenesis with mutagen MX (3-chloro-4-(dichloromethyl)-5-hydroxy-2(*5H*)-furanone) in drinking water during exposure

- Wistar rats: 900 MHz GSM, 2 h/day, 5 days/week for 2 y, at 0.3 or 0.9 W/kg, animals restrained (Heikkinen et al, 2006)

  no effect on mortality, body weight; increased incidence of vascular tumours in lymph nodes at 0.9 W/kg; unusual model

Tumourigenesis with prenatal ENU (gestational day 14)

- B6C3F1 mice: 1.9 GHz UMTS from gestational day 6, 20 h/day for 2 y, up to 48 W/m^2 (5 W/kg peak) (Tillmann et al, 2010)

  increases in bronchiolo-alveolar carcinoma and hepatocellular adenoma incidence; unusual model

Colon cancers with dimethylhydrazine (DMH)

- BALB/c mice with weekly injection of DMH plus 2.45 GHz, 3 h/day, 6 day/week for 5 month at 10-12 W/kg (Wu et al, 1994)

  no effects on tumour incidence

Skin cancers with ultraviolet radiation (UVR)

- K2 mice (ODC transgenic and wild-type) with 3/week UVR plus 848 MHz D-AMPS or 902 MHZ GSM, 1.5 h/day, 5 day/week for 52 weeks at 0.5 W/kg (Wu et al, 1994)

  no effects on body weight, survival, skin tumour incidence

Conclusions on co-carcinogenesis

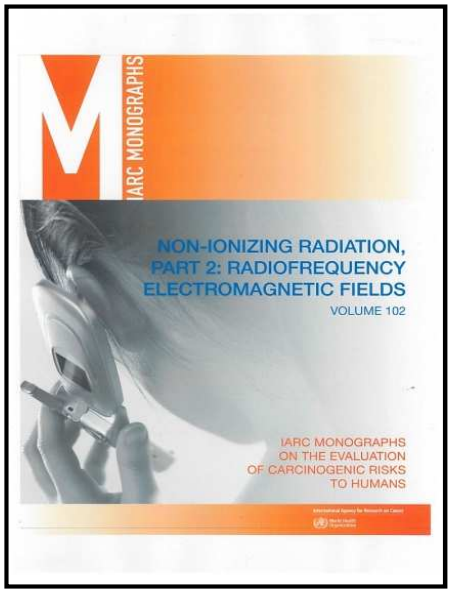
Overall, 6 studies evaluated with 5 models

- 2 with skin tumours/BaP
- 1 with vascular tumours/ MX in drinking water
- 1 with lung, liver tumours/prenatal ENU injection

} studies gave positive results

It was concluded that these studies “provide some additional evidence supporting the carcinogenicity of RF radiation in experimental animals”

IARC Conclusion on RF fields

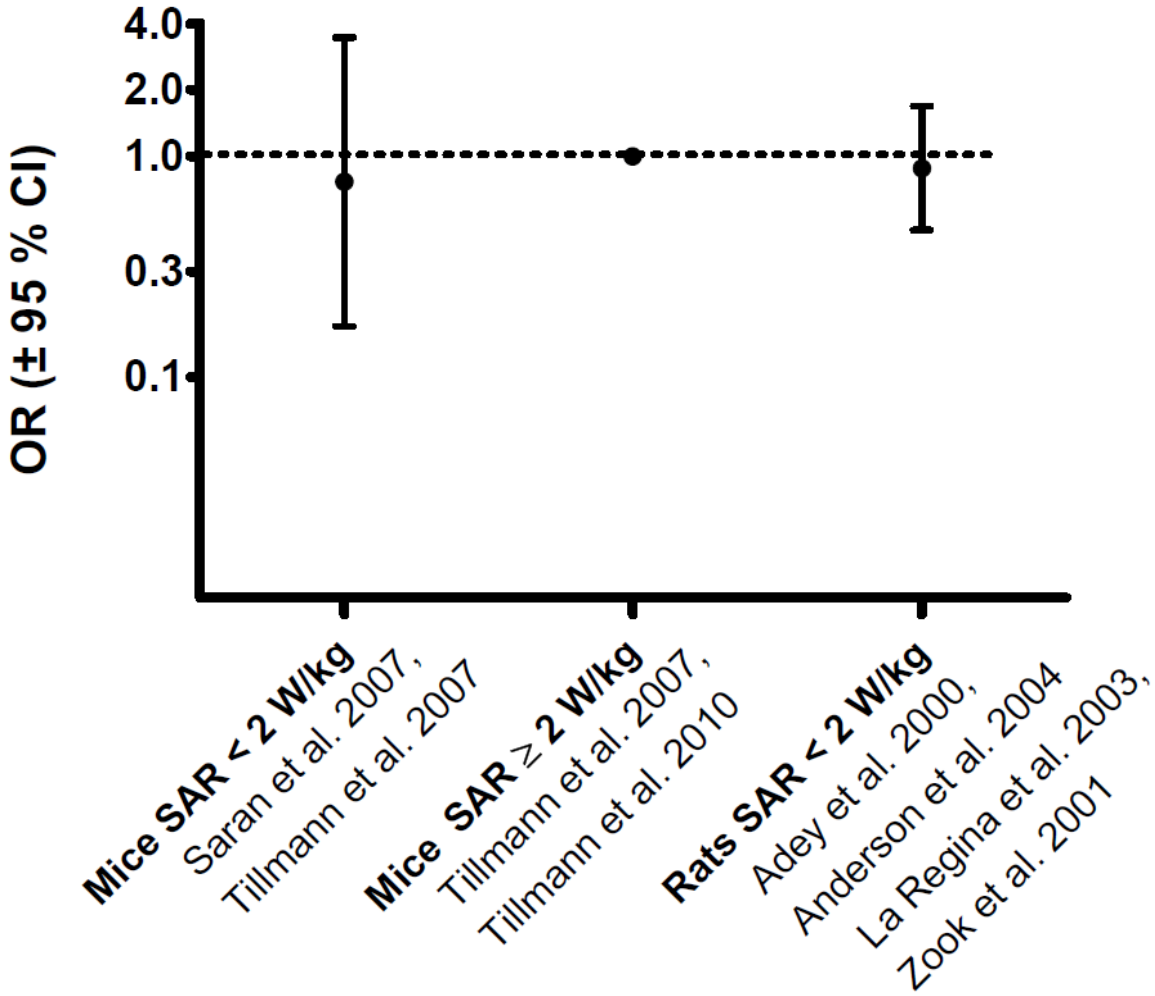


6.2 Cancer in Experimental Animals

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

where *limited evidence* means data suggest effect, but unresolved questions about studies

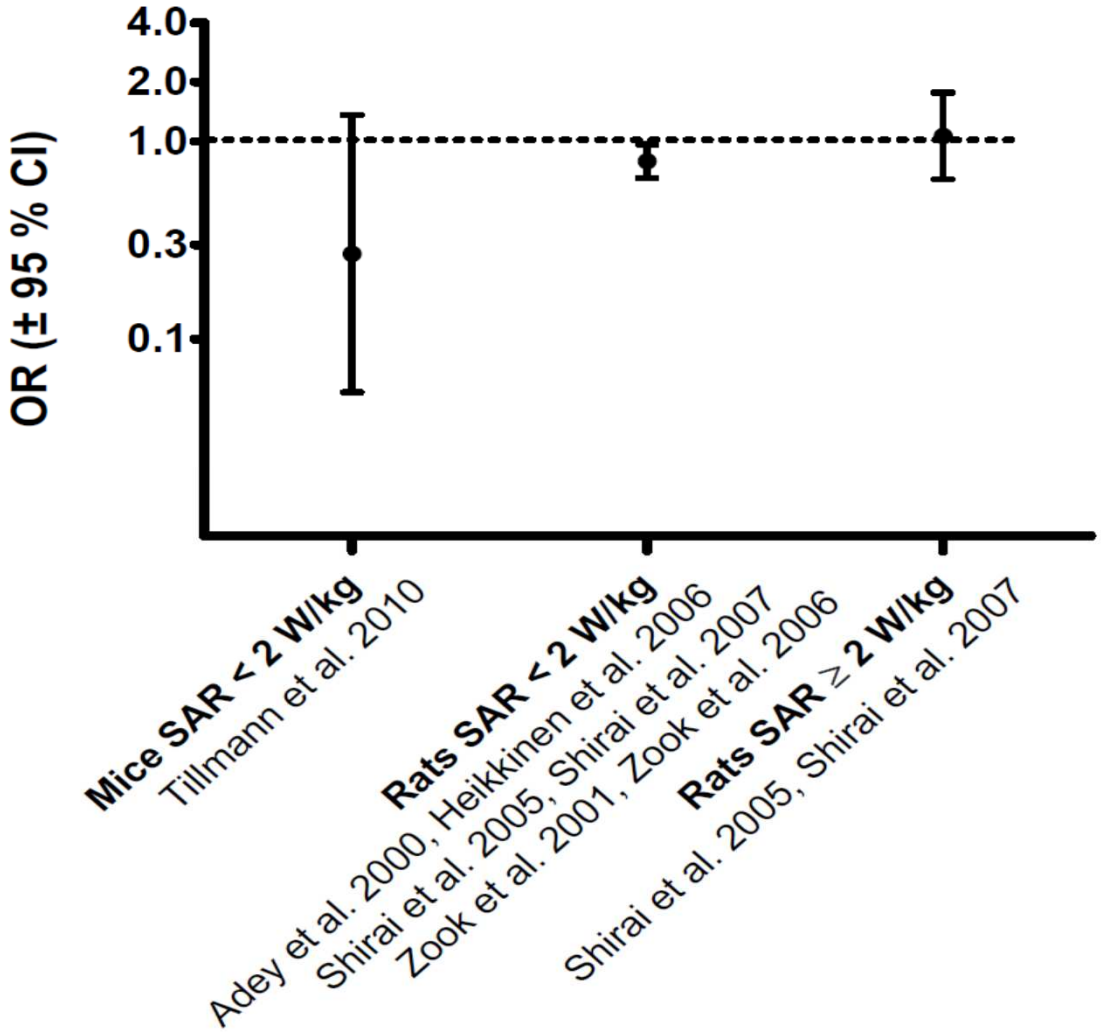
Spontaneous brain tumour studies in animals



Repacholi et al, 2011

Brain tumour promotion studies in animals

Repacholi et al, 2011



Other relevant data (*in vivo* and *in vitro*)

Genetic and related effects of exposure

- *much negative data but limitations and methodological flaws with many studies, confounding not addressed in occupational studies, contradictory results in animals, thermal effects possible* in vitro, but *DNA single-strand breaks, chromosome numbers, spindle disturbances*

Weak evidence that RF radiation is genotoxic, no evidence for mutagenicity

Reaction of the immune system

- *variable results in humans plus small groups sizes, relevance of reported changes in animals unclear, variable responses* in vitro*, lack of dosimetry*

Insufficient evidence to indicate effects on immune function

Other relevant data

Genes, proteins and signalling pathways

- *unreliable, methodological shortcomings, mixed results, with no consistent pattern of response, but some studies showed gene/protein, signal transduction pathways changes in some cell lines*

Weak evidence of effects, no mechanistic information relevant to cancer in humans

Other mechanistic endpoints

- *possibility of changes in cerebral blood flow, otherwise conflicting*, *negative of very limited data, many* in vivo *and* in vitro *studies have methodological or other shortcomings*

Weak evidence on oxidative stress, blood-brain barrier, cell division

Conclusions

International Agency for Research on Cancer

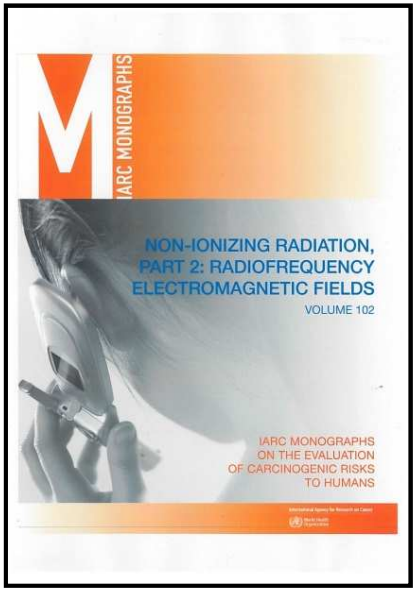
World Health Organization

IARC considered and evaluated an extensive and diverse literature

There was no clear, unequivocal evidence from these studies to suggest that exposure to RF fields may cause or enhance carcinogenesis

Overall, data from animal studies was *limited* and the supporting evidence was *weak*

Other groups have expressed different opinions



And finally, thanks for listening

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