Health Council of the Netherlands

Mobile phones and cancer

Part 2. Animal studies on carcinogenesis

Health Council of the Netherlands

Mobile phones and cancer

Part 2. Animal studies on carcinogenesis

Gezondheidsraad
Health Council of the Netherlands

Aan de staatssecretaris van Infrastructuur & Milieu

Onderwerp : Aanbieding advies *Mobile phones and cancer. Part 2. Animal studies on carcinogenesis*
Uw kenmerk : -
Ons kenmerk : U-8204/EvR/ts/673-N2
Bijlagen : 1
Datum : 5 september 2014

Geachte staatssecretaris,

Hierbij bied ik u het advies *Mobile phones and cancer. Part 2. Animal studies on carcinogenesis* aan. Het advies is opgesteld door de Commissie Elektromagnetische velden en getoetst door de Beraadsgroep Gezondheid en omgeving van de Gezondheidsraad.

Het gebruik van het radiofrequente deel van het elektromagnetisch spectrum voor mobiele telecommunicatie toepassingen biedt vele voordelen voor het dagelijks leven. De daarmee gepaard gaande blootstelling aan elektromagnetische velden leidt echter ook tot zorgen, bijvoorbeeld dat er een verhoogde kans is op het krijgen van kanker.

De Commissie Elektromagnetische velden heeft systematische literatuurstudies uitgevoerd van de epidemiologische en dierexperimentele gegevens over de relatie tussen blootstelling aan radiofrequente elektromagnetische velden en kanker. In ons advies dat in juni 2013 is uitgebracht zijn de epidemiologische gegevens besproken. Het huidige advies bevat de analyse van de dierexperimentele studies. De commissie concludeert op grond van deze gegevens dat het uiterst onwaarschijnlijk is dat blootstelling aan radiofrequente elektromagnetische velden bij proefdieren kanker kan veroorzaken of de ontwikkeling van kanker kan stimuleren.

Bezoekadres
Rijnstraat 50
2515 XP Den Haag
E-mail: E.van.Rongen@gr.nl
Telefoon (070) 340 57 30

Postadres
Postbus 16052
2500 BB Den Haag
www.gr.nl

Gezondheidsraad
Health Council of the Netherlands

Onderwerp : Aanbieding advies *Mobile phones and cancer. Part 2. Animal studies on carcinogenesis*
Ons kenmerk : U-8204/EvR/ts/673-N2
Pagina : 2
Datum : 5 september 2014

In een derde advies zal de commissie de bevindingen uit de eerste twee adviezen integreren en bespreken in het licht van de classificatie van radiofrequente elektromagnetische velden door het International Agency for Research on Cancer (IARC) van de Wereldgezondheidsorganisatie als "mogelijk kankerverwekkend bij mensen". Dat advies wordt begin volgend jaar verwacht.

Met vriendelijke groet,

prof. dr. J.L. Severens,
vicevoorzitter

Bezoekadres
Rijnstraat 50
2515 XP Den Haag
E-mail: E.van.Rongen@gr.nl
Telefoon (070) 340 57 30

Postadres
Postbus 16052
2500 BB Den Haag
www.gr.nl

Gezondheidsraad
Health Council of the Netherlands

To the State Secretary for Infrastructure and the Environment

Subject : Advisory report *Mobile phones and cancer. Part 2. Animal studies on carcinogenesis*
Your reference : -
Our reference : U-8204/EvR/ts/673-N2
Enclosure(s) : 1
Date : September 5, 2014

Dear State Secretary,

I have the pleasure of presenting you the advisory report *Mobile phones and cancer. Part 2. Animal studies on carcinogenesis*. It has been drafted by the Electromagnetic Fields Committee of the Health Council and reviewed by its Standing Committee on Health and the Environment.

The use of the radiofrequency part of the electromagnetic spectrum for mobile telecommunication purposes offers many benefits for daily life. The associated exposure to electromagnetic fields, however, also leads to concerns, for instance on an increased risk of cancer.

The Electromagnetic Fields Committee has performed systematic reviews of the epidemiological data and the data from animal experiments on the relation between exposure to radiofrequency electromagnetic fields and cancer. A report that was published in June 2013 discussed the epidemiological data. The current report contains the analysis of the studies on animal experiments. The Committee concludes from this evidence that it is highly unlikely that exposure to radiofrequency electromagnetic fields can cause or stimulate the development of cancer in animals.

P.O.Box 16052
NL-2500 BB The Hague
The Netherlands
Telephone +31 (70) 340 57 30
E-mail: E.van.Rongen@gr.nl

Visiting Address
Rijnstraat 50
NL-2515 XPThe Hague
The Netherlands
www.healthcouncil.nl

Gezondheidsraad
Health Council of the Netherlands

In a third report the Committee will integrate the findings from the two previous reports and discuss them in the light of the classification of radiofrequency electromagnetic fields by the International Agency for Research on Cancer (IARC) of the World Health Organization as "possibly carcinogenic to humans". That report is expected early next year.

Kind regards,
(signed)
Prof. dr. J.L. Severens
Vice President

P.O.Box 16052
NL-2500 BB The Hague
The Netherlands
Telephone +31 (70) 340 57 30
E-mail: E.van.Rongen@gr.nl

Visiting Address
Rijnstraat 50
NL-2515 XPThe Hague
The Netherlands
www.healthcouncil.nl

Mobile phones and cancer

Part 2. Animal studies on carcinogenesis

to:

the State Secretary for Infrastructure and the Environment

the Minister of Economic Affairs

the Minister of Health, Welfare and Sport

No. 2014/22, The Hague, September 2014

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

The Health Council of the Netherlands is a member of the European Science Advisory Network for Health (EuSANH), a network of science advisory bodies in Europe.

This report can be downloaded from www.healthcouncil.nl.

Preferred citation:
Health Council of the Netherlands. Mobile phones and cancer: Part 2. Animal studies on carcinogenesis. The Hague: Health Council of the Netherlands, 2014; publication no. 2014/22.

ISBN: 978-94-6281-012-9

Contents

Samenvatting

Waarom dit rapport?

De blootstelling aan radiofrequente elektromagnetische velden (RF EMV) is de afgelopen tientallen jaren aanzienlijk veranderd als gevolg van de snelle groei van mobiele telecommunicatie, draadloos internet en andere bronnen. Parallel hieraan is de ongerustheid over mogelijk nadelige effecten op de gezondheid van die blootstelling toegenomen. De classificatie door het *International Agency for Research on Cancer* (IARC, een agentschap van de Wereldgezondheidsorganisatie) van RF EMV als 'mogelijk kankerverwekkend bij mensen' heeft die ongerustheid verder doen toenemen. Deze classificatie was vooral gebaseerd op de resultaten van epidemiologische onderzoeken, aangevuld met die van onderzoeken aan proefdieren.

De commissie Elektromagnetische velden van de Gezondheidsraad heeft besloten om een onafhankelijke systematische analyse uit te voeren van zowel de epidemiologische als de experimentele gegevens. Hierbij wordt rekening gehouden met de wetenschappelijk kwaliteit van de onderzoeken. De analyse van de epidemiologische gegevens is gepubliceerd in een rapport dat in 2013 is uitgebracht. Het huidige rapport bevat de analyse van de gegevens over carcinogenese in proefdieren.

Systematisch onderzoek

De systematische zoektocht die de commissie heeft uitgevoerd leverde 54 proefdier onderzoeken naar carcinogenese door blootstelling aan RF velden op. In 23 onderzoeken is gekeken naar het effect van blootstelling aan alleen RF velden. Daarbij is een verscheidenheid aan diermodellen en tumortypen gebruikt, evenals een aantal verschillende typen RF velden, hoewel de nadruk wel lag op het type signalen zoals dat wordt gebruikt in de huidige mobiele telecommunicatie. In de onderzoeken is gekeken naar blootstelling variërend van enkele weken tot twee jaar, en de gezondheidstoestand van de dieren is doorgaans levenslang gevolgd. Daarnaast zijn er 24 onderzoeken waarin een mogelijke beïnvloeding van blootstelling aan RF velden is onderzocht op de carcinogenese door verschillende bekende kankerverwekkende stoffen. En verder zijn er nog zeven onderzoeken waarin het effect van blootstelling aan RF velden op de groei van geïmplanteerde tumoren is onderzocht. Deze gegevens hebben bij elkaar betrekking op een breed scala van experimentele omstandigheden en kunnen dus een redelijk goed inzicht geven in de mogelijke effecten van blootstelling aan RF EMV op carcinogenese in knaagdieren.

Geen effecten in de meeste onderzoeken

De kwaliteit van de onderzoeken is geanalyseerd door na te gaan of de interne of externe validiteit van de onderzoeken beïnvloed zou kunnen zijn. Uit deze analyse bleek dat de meeste onderzoeken goed opgezet zijn. Bij zeven onderzoeken leidden verschillende oorzaken tot een negatieve waardering en die onderzoeken zijn derhalve verder niet meegenomen in de analyse. In vijf van de resterende 47 onderzoeken werd een toename gevonden van verschillende typen tumoren. Vier van deze onderzoeken waren nauw verwant en uitgevoerd door dezelfde onderzoeksgroep. Deze gebruikte tamelijk hoge blootstellingsniveaus en de auteurs konden niet uitsluiten dat er een invloed was van warmteontwikkeling. In het vijfde onderzoek werd een toename gevonden van chemisch opgewekte longtumoren, maar in het onderzoek ontbrak de juiste controlegroep. De auteurs beschouwen het als een voorlopig onderzoek dat herhaald moet worden. De commissie heeft het in de analyse een laag gewicht gegegeven. In drie andere onderzoeken is een lager aantal tumoren gevonden in dieren die aan RF EMV waren blootgesteld in vergelijking met de controle groep. Hiervoor is geen logische verklaring te geven, en deze gegevens worden daarom als toevalstreffers beschouwd. Dat kan ook de verklaring zijn voor de positieve bevindingen in de

eerder beschreven onderzoeken. In het merendeel van de onderzoeken, 39 in totaal en met een scala aan tumortypen en verschillende soorten proefdieren, is echter geen effect van blootstelling aan RF EMV gevonden op carcinogenese.

Conclusies

Op grond van de resultaten van de proefdieronderzoeken die in deze systematische analyse zijn opgenomen concludeert de Commissie dat het hoogst onwaarschijnlijk is dat langdurige continue of herhaalde blootstelling aan RF EMV de ontwikkeling van van kanker kan veroorzaken of bevorderen.

De Commissie vindt het op dit moment niet nuttig om voorstellen te doen voor nader proefdieronderzoek naar carcinogenese door radiofrequente elektromagnetische velden. Er is momenteel een groot, goed opgezet onderzoek hiernaar gaande in de Verenigde Staten. Voordat er mogelijk nieuwe voorstellen voor onderzoek worden gedaan moeten de resultaten van dit onderzoek, die naar verwachting in 2016 worden gepubliceerd, worden afgewacht.

Summary

Why this report?

Exposure to radiofrequency electromagnetic fields (RF EMF) has considerably changed in the past decades, as a result of the fast growth of mobile telecommunication, wireless internet access and other sources. This has increased general anxiety about possible adverse health effects of such exposures. The classification of RF EMF as 'possibly carcinogenic in humans' by the International Agency for Research on Cancer (IARC) in 2012 has further sparked these fears. This classification was primarily based on epidemiological data, with additional support from animal studies.

The Electromagnetic Fields Committee of the Health Council of the Netherlands decided to perform an independent systematic review of both the epidemiological and experimental data, taking into account the scientific quality of the studies. The analysis of the epidemiological data has been published in a report issued in 2013. The current report contains the analysis of the data on carcinogenesis in experimental animals.

Systematic search

The systematic literature search performed by the Committee revealed a substantial body of 54 animal studies on the carcinogenesis of exposure to RF

fields. In 23 studies the effect of exposure to RF EMF alone has been investigated. A variety of animal models and tumour types has been used, as well as a number of different types of RF signals, although the focus has been on the types of signals used in modern mobile telecommunication. Exposure has been from several weeks up to two years, and the follow-up time generally lifelong. In addition, 24 studies investigated the modulating effects of RF exposure on carcinogenesis induced by various well-known carcinogenic compounds, and another seven studies the effect of RF exposure on the growth of implanted tumours. These data cover a wide range of experimental situations and may thus provide a reasonably well insight into the effects of RF exposure on carcinogenesis in rodents.

No effect in most studies

The analysis of the quality of the studies, as reflected in the possibility that the internal or external validity of the studies could be affected, showed that most of the studies are of adequate design. However, in seven studies various issues resulted in a negative appraisal and these studies were consequently excluded from the overall analysis. Of the remaining 47 studies, five showed an increase in the incidence of several types of tumours. Four of these were closely linked and performed by the same research group. They used rather high exposure levels and could not exclude thermal effects. The fifth study found an increased incidence of chemically-induced lung tumours, but lacked a proper control group. The authors consider it to be a preliminary study that needs to be replicated. The Committee has given it a low weight in the overall analysis. A further three studies found a decreased rate of tumour growth in RF EMF exposed animals. There is no logical explanation for this, and therefore these are considered to be chance results. This might also be the case for the positive associations observed in the studies described above. In the majority of the studies, however, 39 in total, describing experiments on a range of tumour types and in different species, no effect on carcinogenesis has been observed.

Conclusions

This has led the Committee to conclude that, on the basis of the results of the animal studies presented in this systematic review, it is highly unlikely that long-term continuous or repeated exposure to RF EMF may have initiating or promoting effects on the development of cancer.

The Committee considers it not useful at this time to propose further animal studies into RF carcinogenesis. There is currently a large, well-designed animal carcinogenesis study ongoing in the USA. Before recommending further research, the outcome of this study, expected in 2016, has to be awaited.

Chapter 1

Introduction

The fast and extensive growth of mobile telephony and the resulting change in exposure of people to radiofrequency electromagnetic fields (RF EMF) has sparked the fear of possible adverse effects resulting from such exposure. Especially dreaded are possible carcinogenic effects. Many studies into this have been performed in the past decades, and on the basis of the available results the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) has classified RF EMF in 2010 as 'possibly carcinogenic for humans' (class 2B).[1] This classification was primarily based on the results of epidemiological studies into the relation between mobile phone use and the risk of various types of brain tumours, and on some data of experimental studies with animals.[2]

The Electromagnetic Fields Committee of the Health Council of the Netherland (designated further in this report as 'the Committee') decided to perform its own, independent, systematic review of the literature on this subject. In a first report it has described the epidemiological data[3], while the present report discusses the outcomes of experimental animal studies. Data collection, extraction, and analysis have been done in a predetermined systematic way.

Exposure

Exposure to RF EMF is usually expressed in terms of the SAR, the Specific Absorption Rate. This is the rate of energy absorption by an exposed object per unit of mass. It is expressed in watts per kilogram (W/kg). Energy absorption in the body can lead to heating, and too much heating can be a health hazard. Therefore exposure limits have been developed. In the Netherlands generally the limits of the International Commission for Non-ionizing Radiation Protection (ICNIRP) are observed.[62] The exposure limits for the frequency range of 100 kHz - 10 GHz are based upon limitation of heating of the body, and therefore expressed in terms of SAR. For exposure of the entire body, the limit for the general population is an SAR of 0.08 W/kg. This roughly compares to the amount of heating induced by drinking a cup of hot liquid every 2 hours and will not lead to an increase in the core temperature of the body. For local exposure, higher SAR values are allowed. The most relevant for the use of a mobile phone is the SAR limit of 2 W/kg for exposure of the head. Use of a mobile phone will lead to an increase in SAR which is highest close to the antenna of the phone. The SAR specifications of a mobile phone provide the maximum SAR that can be obtained averaged over a 10 g volume of tissue, when the phone is operating at maximum power. Sustained exposure to an SAR of 2 W/kg (a situation that in practice virtually never occurs) will lead to a local temperature increase in the head of approximately 0.2 °C.[63] Whole body exposure of rodents to an SAR of 2-5 W/kg can lead to the induction of thermoregulatory mechanisms[64], but due to differences between rodents and humans in temperature regulation, dimensions and frequency-dependent resonance effects this cannot be easily extrapolated to humans.

This report

In Chapter 2 the literature search is described. Chapter 3 provides the methods used in the data analysis. In Chapter 4 the results are presented, and Chapter 5 contains the discussion of the results.

The composition of the Committee at the time of writing of this report is given in Annex A.

Annex B contains the items used in the validity assessment. In Annex C the experimental details of the included studies are provided. Annex D gives a list of the abbreviations used in this report.

Chapter 2

Literature search

A literature search in PubMed was performed into the effect of exposure to radiofrequency electromagnetic fields on the formation and growth of cancer, using the following search strategy:

(radiofrequency OR radio waves OR radio-waves OR cellphone* OR cell phone* OR cellular *phone* OR mobile phone* OR cellular phone[MeSH Terms] OR telephone, cellular[MeSH Terms]) AND (animal OR rat OR mouse OR rats OR mice OR murine) AND (cancer OR carcinogen* OR tumour* OR tumor* OR neoplasm* OR benign OR malignant OR malignancy) NOT ("in vitro"[Publication Type] OR "in vitro"[All Fields] OR hyperthermia OR ablation OR imaging)

There were no restrictions on date and language. The search was performed on September 13, 2012.

The total number of papers retrieved was 376. An additional search using Related papers in PubMed brought up another 4 papers, which increased the total number of papers to 380. Of these, 42 were on in vitro studies, 95 on therapy, 42 were reviews, 144 dealt with other subjects, 1 was in Chinese with only an abstract available in English, 5 were comments, 1 was a reanalysis of another paper, and 1 was a background paper. This left 49 papers to be included in the analysis.

A search in the EMF Portal using the key words 'Mobile Phone', 'cancer' and 'animal' did not produce any thus far undetected studies.

A search in Web of Science using the same keywords as with PubMed resulted in 132 papers. Of these, 10 were on in vitro studies, 1 was on therapy, 32 were reviews, 6 were conference proceedings, 1 was a book and 51 were classified as 'other'. That left 31 relevant papers, of which 30 had already been retrieved with PubMed.

One paper was obtained from another source.

So the total number of papers included in the analysis of this report is 51, divided over different tumour types as listed in Table 1 (one paper includes two separate studies).

Table 1 Number of studies per tumour type.

Type of tumour	Number of studies using wildtype animals and no chemical or UV induction	Number of studies using wildtype animals and chemical or UV induction	Number of studies using tumour-prone animals (wildtype and transgenic)	Number of studies using implanted tumours in wildtype animals	Total number of studies
Lymphoma			10		10
Skin tumour	1	6	1	1	9
Mammary tumour	1	4	3		8
Liver tumour		2			2
CNS tumour	2	6		3	11
Sarcoma		2		1	3
Colon tumour		1			1
Multiple tumours	5	2	1		8

Chapter 3

Data analysis

The studies were extracted and analysed using the Gold Standard Publication Checklist (GSPC) as basis.[4,5] The GSPC addresses a large number of items, many of which were not considered relevant by the Committee for the current analysis, while some items that are relevant for the specific type of RF EMF carcinogenesis studies in this report are missing from the GSPC. The Committee therefore added a number of items, in particular several pertaining to the dosimetry. Table 2 lists the items that were extracted from the papers.

Table 2 Items extracted from the studies.

Background information	
Funding sources	
Conflicts of interest	
Methods	
Quarantine and acclimatisation period after transportation to animal facility	
Species	(wildtype or tumour-prone)
Sex	
Age at the start of the experiment	(alternative: animal weight)
Number of animals per experimental group	(also power and sample size calculations)
Sham, cage and positive controls	
Intervention	
Day and time of intervention within experiment	
Type of intervention	(RF alone or RF + carcinogenic agent or effect modifier)
Source of RF exposure	(including frequency, pulsed or continuous wave)

Exposure duration and schedule	
Exposure system used	(dedicated to exposed target or whole body)
Exposure level	(local or whole-body SAR; external field strength)
Determination of exposure level	(measured or predicted (calculated))
Account for movement, growth in exposure level	
Drugs	(carcinogenic agent or effect modifier)
Restraint	(similar in exposed and control animals?)
Outcome	
Description of parameters of interest	(are all parameters mentioned in the Introduction and Material and Methods sections described?)
Blinding of staff to treatment modality	
Description of the statistics used	
Results	
Blinding of staff in analysis	
Description of the main results	
Excluded animals	(number, and reasons why they were excluded)

Validity assessment

Internal validity

These data were used to assess the internal validity of the studies according to five topics:

- Allocation to groups
- Blinding
- Data loss
- Reporting bias
- Other bias.

The assessment was performed by considering for each topic a number of questions on the information presented in each publication. These questions, that were formulated by the authors of the GSPC, are listed in Table B1 in Annex B.

External validity

The external validity is used to indicate to what extent the results of the studies can be extrapolated to humans. For the external validation the Committee developed a table with items to be considered for two topics: Animal characteristics and Exposure. An important part of this evaluation is the

assessment of the quality of the exposure and exposure characterization. For instance, if the exposure is not well-described or the exposure level is not reported, it is difficult or even impossible to evaluate the study in terms of relevance to the situation in humans. In the appraisal of the quality of the dosimetry the Committee has taken into consideration that there has been considerable progress in the past decades in the possibilities to accurately measure and calculate the exposure. So the criteria for older studies were more lenient than for more recent ones. This information is provided in Table B2 in Annex B.

Both the internal and the external validity were assessed by two independent assessors, and conflicts were solved by a third party. For each of the five topics for internal validity and for each of the two topics for external validity the chance that they would influence the outcome of the assessment of the results of the study was estimated as either *high*, *low* or *unknown*. In the next step, these estimations were combined into an overall assessment for each individual study of whether there is a chance that either the internal or the external validity would influence the conclusions of the study. The results of these assessments were used in the overall appraisal of the entire dataset.

A brief description of each study is given in Chapter 4 and the agreed scores for the validity assessments are summarized in Table 3 in Chapter 5. They give an impression of the internal and external validity of each of the studies.

Chapter 4

Results

In this chapter a brief description is given of the results of each of the selected studies, organized first per treatment modality (RF alone, RF + carcinogenic agent or implanted tumours) and then per tumour type and per type of animal (wildtype, tumour-prone or transgenic). More details of the studies are provided in Table C1 in Annex C. The reason for the primary organization per treatment modality is because there is a fundamental difference between treatment with RF alone, where the carcinogenic potential (cancer induction) of RF is investigated, and treatment with RF and a carcinogenic agent or RF exposure of an implanted tumour. The latter studies investigate the modulating potential of RF (cancer modulation). Some studies fall in more than one category, either because they investigate more than one tumour type, or because they study both exposure to RF alone and exposure to a carcinogenic agent and RF. These studies are discussed under each heading.

4.1 RF alone

4.1.1 Lymphoma

Transgenic tumour-prone animals

Repacholi et al. (1997)[6] exposed transgenic lymphoma-prone female C57BL/6NTac (strain ppG64 transgenic for Eμ-*Pim1*) mice to a GSM 900 MHz signal.

The animals were free roaming in their cages during exposure and the individual SAR could vary (~500-fold!) from 0.008-4.2 W/kg. An increase in lymphoma incidence was observed in the exposed group, with an odds ratio of 2.4 (95% confidence interval: 1.3-4.5). [The Committee notes that histopathology of lymphoma was only performed on animals that died before the end of the experiment. The lymphoma incidence in surviving animals is unknown, and this is thus also the case for the overall lymphoma incidence.]

Two repetition studies were performed. These studies were not exact replications, since in these studies the mice were restrained to obtain a more uniform and better defined exposure and histopathological analysis was performed on all animals. Utteridge et al. (2002)[7] exposed female mice of the same transgenic strain and of a wildtype strain to a GSM 900 MHz signal. Instead of two exposure sessions of 30 min per day they had only one session of 1 h, because of the effort to put the animals in the restrainers and the stress this imposed on the mice. Exposure was at four SAR levels: 0.25, 1.0, 2.0 and 4.0 W/kg, neither of which resulted in any effects on lymphoma incidence in either transgenic or wildtype mice.

The second repetition study was by Oberto et al. (2007).[8] They exposed male and female mice from again the same transgenic strain to a GSM 900 MHz signal using SARs of 1.4 or 4.0 W/kg. No effect on survival and on the incidence of lymphomas or other tumours was observed.

Non-transgenic tumour-prone animals

Sommer et al. (2004)[9] exposed non-transgenic female AKR/J mice with a high spontaneous lymphoma incidence to a GSM 900 MHz signal. The animals were free roaming and the SAR of 0.4 W/kg therefore had rather large variations of ± 40%. No effect of exposure was observed on lymphoma incidence and survival.

Using a similar study design, Sommer et al. (2007)[10] exposed female AKR/J mice to an UMTS signal, also at an SAR of 0.4 W/kg ± 40%. Again no difference in lymphoma incidence and survival was observed.

Lee et al. (2011)[11] also used the same mouse strain and exposed them simultaneously to a CDMA and a WCDMA signal. The SAR was 4.0 W/kg, but since the animals were free roaming, there was likely a considerable variation. They also observed no difference in lymphoma incidence and survival.

Anghileri et al. performed several studies using female Ico:OFI mice, a non-transgenic strain with a high spontaneous lymphoma incidence. In the first study (Anghileri et al., 2005)[12] they exposed the mice to a GSM 800 MHz signal and observed a decreased survival and increased lymphoma incidence.

In the second study (Anghileri et al. 2006)[13] they exposed the mice to GSM 800 MHz or to a ferric–ATP complex (FeATP). FeATP is used by this group as a promoter of carcinogenesis because it increases cellular calcium ion influx. A similar acceleration of carcinogenesis by RF EMF and by FeATP was observed.

In the third study (Anghileri et al, 2009)[14] the animals were injected with calcium chloride, aluminium lactate or aluminium citrate and exposed to a GSM 800 MHz signal. The chemical substances influenced the intracellular calcium ion balance. A decreased survival and more lymphoma were observed in animals exposed to RF and each of the substances, compared to exposure to the substances alone. [The Committee notes that important data such as the exposure level is missing from these studies; they are therefore difficult to interpret.]

4.1.2 *Skin tumour*

Non-transgenic animals

Sanchez et al. (2006)[15] exposed hairless female rats (IFFA Creda) to GSM 900 or 1800 MHz signals, at SARs of 2.5 and 5 W/kg. In contrast to the control group that was exposed to UV radiation, no histological alterations were observed in the skin of the RF exposed animals.

In an experiment that was primarily aimed at studying the effect of RF exposure on chemically-induced skin cancer (see 4.2.2), Paulraj and Behari (2011)[16] exposed male Swiss mice to either 112 MHz EMF, amplitude modulated at 16 Hz, at an SAR of 0.75 W/kg, or to 2.54 GHz at an SAR of 0.1 W/kg without the chemical induction. Neither type of exposure resulted in any effect on skin tumours. [The Committee notes that the number of animals in this study is not clear: the authors use an unspecified 'effective' number of animals in their analysis.]

4.1.3 *Mammary tumour*

Non-transgenic tumour-prone animals

Szmigielski et al. (1982)[17] exposed female C_3H/HEA mice with a high spontaneous mammary cancer incidence to 2450 MHz RF fields with a power density of 5 or 15 mW/cm^2, corresponding to whole-body SAR levels of 2-3 and 6-8 W/kg, respectively. They observed a dose-dependent acceleration of mammary cancer development resulting in shortening of life time. The authors could not exclude thermal effects. [The Committee notes that whole-body

exposure to the highest SAR level can certainly result in heating of the animals, but also an SAR of 2 W/kg is already a significant systemic challenge.]

Three publications from the same US research group report on experiments with mammary tumour-prone female C_3H/HeJ mice. Toler et al. (1997)[18] exposed them to pulsed 435 MHz EMF at an SAR of 0.32 W/kg, Frei et al. (1998)[19] and Frei et al. (1998)[20] to 2,450 MHz EMF at SARs of 0.3-1.0 W/kg. No effects on the number and growth of tumours were observed.

Jauchem et al. (2001)[21] exposed the same mammary tumour-prone female C_3H/HeJ mice to an ultra wide band signal with a 40 kV/m peak, but an SAR of only 0.0098 W/kg. They observed no effects of this exposure on mammary tumour incidence and survival.

4.1.4 *Central nervous system (CNS) tumour*

Wildtype animals (not tumour-prone)

Adey et al. (1999)[22] exposed male and female Fischer 344 rats before and after birth to an NADC 835 MHz signal at SARs of 0.33-0.53 W/kg. They observed a reduced incidence of CNS tumours in the RF-exposed group.

In similar experiments but using another type of signal, FM 836 MHz at SARs of 1.0 or 1.2 W/kg, Adey et al. (2000)[23] did not observe any effect of RF exposure on survival and CNS tumour incidence.

In an experiment primarily aimed at studying the effect of chemically-induced neurogenic tumours (see below) Zook and Simmens (2001)[24] exposed male and female Sprague Dawley rats without the inductive agent to 860 MHz pulsed or continuous-wave RF EMF, at SARs of 1.0 ± 0.2 W/kg. They observed no effect of this exposure on the incidence of neurogenic or other tumours.

La Regina et al. (2003)[25] investigated exposure of male and female Fischer 344 rats to an FDMA 835 MHz or CDMA 847 MHz signal at SARs of 1.3 ± 0.5 W/kg in the brain. No effect of either signal on CNS and other tumours was observed.

Anderson et al. (2004)[26] exposed male and female Fischer 344 rats before and after birth to an 1.6 GHz Iridium* signal, at an SAR in the brain of 0.16 W/kg (perinatal) and 0.16 or 1.6 W/kg (postnatal). No effect on survival was observed in males, but in females survival was lower in the cage-controls. No effects were observed on brain or other tumours.

* Iridium: a mobile telecommunication signal used by the Iridium satellite system.

4.1.5 *Multiple tumours*

Wildtype animals (not tumour-prone)

Chou et al. (1992)[27] exposed male Sprague Dawley rats to 2450 MHz pulsed EMF at SARs of 0.15-0.4 W/kg. They observed no overall effect on tumour development, but found somewhat more primary malignant tumours in exposed animals. There was no effect on benign tumours and on overall survival.

Ivanov et al. (2005)[28] exposed inbred albino mice and adult C57Bl/6 mice (sex not specified) to 37 GHz RF EMF, at a power density of <10 mW/cm^2. They observed a decreased survival in C57Bl/6 adults and offspring, and tumour formation in albino mice. [The Committee notes that important information is missing, such as the exposure level and why some animals are not included in the analysis. Some groups had been exposed in previous, unspecified experiments. Therefore this study cannot be interpreted.]

Smith et al. (2007)[29] exposed male and female Han Wistar rats to GSM 900 MHz or DCS 1800 MHz signals at SARs of 0.44, 1.33 or 4.0 W/kg. They observed no effect on survival and carcinogenesis.

Tillmann et al. (2007)[30] exposed male and female B6C3F1/Crl BR mice to GSM 902 MHz or DCS 1747 MHz signals at SARs of 0.4, 1.3 or 4.0 W/kg. They observed no effect of the GSM signal, but a decreased number of tumours after DCS exposure. These were, however, within the tumour rates of historical controls.

Jin et al. (2011)[31] exposed male and female Sprague Dawley rats simultaneously to CDMA 848.5 MHZ and WCDMA 1950 MHz signals. The SAR for each signal was 2 W/kg, so the combined SAR was 4 W/kg. There was no effect of this exposure on carcinogenesis.

Transgenic animals

Saran et al. (2007)[32] exposed transgenic, X-ray tumour-prone mice (CD-1 heterozygous for *Patched1*) to GSM 900 MHz fields at a SAR of 0.4 W/kg. No effect on survival and carcinogenesis was observed.

4.2 RF + carcinogenic agent

Unless indicated, studies listed in this section are all using non-transgenic animals.

4.2.1 *Lymphoma*

RF + X-rays

Heikkinen et al. (2001)[33] exposed female CBA/S mice to X-rays to induce lymphomas and other tumours. Restrained animals were subsequently exposed to an NMT 902 MHz signal at an SAR of 1.5 W/kg, or to a GSM 902 MHz signal at an SAR of 0.35 W/kg. No effects of these exposures on X-ray induced lymphomas, other neoplasms or survival were observed.

4.2.2 *Skin tumour*

RF + 3,4 benzopyrene (BAP)

Szmigielski et al. (1982)[17] exposed male Balb/c mice treated with the skin carcinogen 3,4 benzopyrene (also known as benzo(a)pyrene) (BAP) to 2450 MHz RF fields with a power density of 5 or 15 mW/cm^2, corresponding to whole-body SARs of 2-3 and 6-8 W/kg, respectively. They observed acceleration of skin cancer growth and mortality with both SAR levels. For simultaneous treatment with RF fields and BAP this was dose-dependent. For treatment with RF fields 3 months prior to BAP treatment dose-dependence is not clear. The authors could not exclude the occurrence of thermal effects. [Whole-body exposure to the highest SAR level can certainly result in heating of the animals, but also an SAR of 2 W/kg is already a significant systemic challenge.]

Szudinski et al. (1982)[34] apparently reported the same data as Szmigielski et al. (1982)[17] of exposures to power densities of 5 or 15 mW/cm^2 (corresponding to SARs of 2-3 and 6-8 W/kg) during BAP application, and additionally exposed groups of male Balb/c mice to a power density of 10 mW/cm^2 (corresponding to an SAR of 4 W/kg) during 1, 2 or 3 months before BAP application. They report an exposure duration-dependent acceleration of skin cancer development. [The Committee notes that the highest SAR level could have resulted in heating of the animals, but also an SAR of 2 W/kg is already a significant systemic challenge.]

RF + 7,12-dimethybenz[a]anthracene (DMBA)

A number of studies investigated the effect of RF exposure on skin cancer induced by DMBA.

Imaida et al. (2001)[35] exposed female CD-1 mice to a 1.5 GHz TDMA signal at an SAR of 2.0 W/kg and found no effect of this treatment on skin tumours.

Mason et al. (2001)[36] treated female SENCAR mice with single or repeated very short (10 sec) exposures to high-power 94 GHz fields (0.333 or 1 W/cm^2). No effect of these RF treatments on skin tumours were observed.

Huang et al. (2005)[37] exposed male ICR mice to a 849 or 1763 MHz signal at an SAR of 0.4 W/kg. They also found no effect on skin tumours.

In an experiment of which the RF-alone exposure has been described above, Paulraj and Behari (2011)[16] exposed DMBA-treated male Swiss mice to either 112 MHz EMF, amplitude modulated at 16 Hz, at an SAR of 0.75 W/kg, or to 2.54 GHz at an SAR of 0.1 W/kg. Neither type of exposure resulted in any effect on skin tumours. [The number of animals in this study is not clear: the authors used an unspecified 'effective' number of animals in their analysis.]

RF + ultraviolet (UV) radiation

Heikkinen et al. (2003)[38] studied female K2 mice, either wildtype or transgenic for ornithine decarboxylase (ODC), an enzyme involved in carcinogenesis. The transgenic strain had been shown to be more sensitive to chemical tumour promotion.[39] The animals were exposed to two different types of signal: GSM or DAMPS. The SAR in both cases was 0.5 W/kg. They observed a non-significant acceleration of growth of skin tumours induced by UV radiation, especially in the non-transgenic mice.

4.2.3 *Mammary tumour*

RF + 7,12-dimethylbenz[a]anthracene (DMBA)

Mammary tumours can be induced in rats by administration of DMBA. Using this paradigm, Bartsch et al. (2002)[40] exposed female Sprague Dawley rats to GSM 900 MHz signals at an SAR of maximally 0.08 W/kg. No effects on tumour latency and incidence were observed. [The authors observed a significant effect in the first of three series of experiments, but could not reproduce that in subsequent experiments.]

Anane et al. (2003)[41] exposed female Sprague Dawley rats to GSM 900 MHz EMF, at SARs of 0.1, 0.7, 1.4, 2.2 or 3.5 W/kg. They observed no effect on tumour latency, volume, and multiplicity. In the first of two experiments they found an inverse dose relation for tumour incidence which could not be satisfactorily explained.

Yu et al. (2006)[42] exposed female Sprague Dawley rats to GSM 900 MHz signals at SARs of 0.44, 1.33 or 4.0 W/kg. They observed no effect on tumour latency, size, multiplicity and incidence; the incidence and latency were higher in the cage controls than in the sham controls and the exposed groups.

Hruby et al. (2008)[43] used a GSM 902 MHz signal to expose female Sprague Dawley rats to SARs of 0.4, 1.3 or 4.0 W/kg. They found inconsistent effects on tumour number and incidence. Also in this study the tumour incidence was higher in cage controls than in the sham controls and the exposed groups.

4.2.4 *Liver tumour*

RF + diethylnitrosamine

Imaida et al. (1998) performed two experiments with liver tumours induced in male and female Fischer 344 rats by application of diethylnitrosamine. In the first study the animals were exposed to a 929 MHz TDMA signal at SARs of 1.7-2.0 W/kg.[44] In the second study exposure was to a 1439 MHz TDMA signal at SARs of 0.937-1.91 W/kg.[45] In both cases they observed no effect on the number and size of liver foci, but they did found an increase in serum hormones. The increase in adrenocorticotropic hormone (ACTH) and corticosterone could in part be explained by stress due to the confinement during exposure, but the increase in melatonin was unexpected and unexplained by the investigators.

4.2.5 *Central nervous system (CNS) tumour*

RF + ethylnitrosourea (ENU)

In a study described above, where Adey et al. (1999)[22] exposed male and female Fisher 344 rats before and after birth to an NADC 835 MHz signal at SARs of 0.33-0.53 W/kg, they also induced CNS tumours by injection of ENU. As with the spontaneous CNS tumours, they also observed a reduction in the incidence of ENU-induced tumours in the RF-exposed group.

In similar experiments (also described above) but using another type of signal, FM 836 MHz at SARs of 1.0 or 1.2 W/kg, Adey et al. (2000)[23] did not observe any effect of RF exposure on survival and the incidence of ENU-induced CNS tumours.

Zook and Simmens (2001)[24] treated pregnant female Sprague Dawley rats with ENU and exposed the offspring to 860 MHz pulsed or continuous-wave RF

EMF, at SARs of 1.0 ± 0.2 W/kg. They observed no effect of exposure on ENU-induced neurogenic or other tumours.

In a replication of the previous study, Zook and Simmens (2006)[46] exposed the offspring of ENU-treated Sprague Dawley rats to 860 MHz pulsed fields at an SAR of 1.0 ± 0.2 W/kg. Again, no effect of this exposure on the incidence of neurogenic tumours was observed.

Shirai et al. (2005)[47] exposed male and female Fischer 344 rats born from ENU-treated mothers to a 1439 MHz TDMA signal at SARs of 0.67 or 2.0 W/kg. They observed a lower incidence of pituitary tumours in males after the higher SAR, but no other RF effect on neurogenic (including CNS tumours) or other tumours and serum hormones.

In a study with a similar design but another type of signal, 1.95 GHz WCDMA at SARs of 0.67 or 2.0 W/kg, Shirai et al. (2007)[48] found no effects of exposure on neurogenic or other tumours.

4.2.6 *Colon tumour*

RF + demethylhydrazine (DMH)

Wu et al. (1994)[49] investigated DMH-induced colon tumours in male and female Balb/c mice. They exposed the animals to 2450 MHz RF EMF at SARs of 10-12 W/kg but did not observe any effects.

4.2.7 *Sarcoma*

RF + 3,4 benzopyrene (BAP)

Chagnaud et al. (1999)[50] treated female Sprague Dawley rats injected with BAP to induce sarcomas with a GSM 900 MHz signal at SARs of 0.075 ± 0.025 or 0.27 ± 0.09 W/kg. No effects on tumour development or growth, on survival and on serum autoantibodies were observed.

4.2.8 *Multiple tumours*

Heikkinen et al. (2006)[51] investigated in female Wistar rats the effect of combined exposure to the mutagen 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX) and a GSM 900 MHz signal at SARs of 0.3 or 0.9 W/kg. No effects of RF EMF exposure on survival and carcinogenesis were seen.

Tillmann et al. (2010)[52] exposed female B6C3F1 mice before and after birth to ethylnitrosourea (ENU), ENU + an UMTS signal at a power density of 4.8 W/m^2, or an UMTS signal of 48 W/m^2. They observed an increased number of malignant lung tumours and benign liver tumours in the UMTS+ENU group compared to the ENU-only group. High rates of benign liver tumours were found in all groups and might be related to infection with *Helicobacter hepaticus*. The lack of an ENU+sham exposure group makes it difficult to draw definitive conclusions . No effect were seen for other tumours.

4.3 Implanted tumours

4.3.1 Skin tumour

Santini et al. (1988)[53] exposed female C57Bl/6J mice with an implanted melanoma to pulsed or continuous 2450 MHz RF EMF. The SAR was 1.2 W/kg. No effect was observed on melanoma growth and on survival.

4.3.2 Central nervous system (CNS) tumour

Salford et al. (1993, 1997)[54,55] pairwise implanted male and female Fischer 344 rats with brain tumour cells. One animal was sham exposed and one exposed to a 915 MHz RF field either continuous or pulse modulated at 4, 8, 16, 50 or 200 Hz. The output of the pulses was kept constant, therefore the SAR varied from 0.0077 to 1.67 W/kg. In some pairs tumour growth in the exposed animal was faster than in the sham control, but overall there was no significant effect of exposure on tumour growth. [The animals used in these studies were not well-defined; they had a range of body weights and presumably of ages. The use of inoculated cells with varying viability resulted in a large variation in tumour growth. Consequently the experimental conditions show too much variation for a meaningful analysis.]

Higashikubo et al. (1999)[56] implanted male Fischer 344 rats with CNS tumour cells and exposed them to an 835 MHz continuous wave FM signal or a 847 MHz CDMA signal at SARs of 0.75 ± 0.25 W/kg. They observed no effect of RF exposure on survival, independent of the number of cells injected.

4.3.3 Ascites tumour

Paulraj and Behari (2011)[16] injected ascites carcinoma cells in male Swiss mice and subsequently exposed them to either 112 MHz EMF, amplitude modulated at

16 Hz, at an SAR of 0.75 W/kg, or to 2.54 GHz at an SAR of 0.1 W/kg. Neither type of exposure resulted in any effect on the growth of the ascites tumour.

4.3.4 *Sarcoma*

Preskorn et al. (1978)[57] injected sarcoma cells in male and female CWF mice that had been repeatedly exposed in utero and, in one experiment, also after birth to thermal levels of 2450 MHz fields. They observed a lower tumour incidence and longer survival in animals both with and without tumour.

Szmigielski et al. (1982)[17] intraveneously injected lung sarcoma cells in male Balb/c mice and exposed them to 5 or 15 mW/cm^2 2450 MHz RF fields, corresponding to SAR levels of 2-3 and 6-8 W/kg, respectively. They observed a dose-dependent increase in the number of sarcoma nodules in the lungs. The authors could not exclude the occurrence of thermal effects. [Whole-body exposure to the highest SAR level can certainly result in heating of the animals, but also an SAR of 2 W/kg is already a significant systemic challenge.]

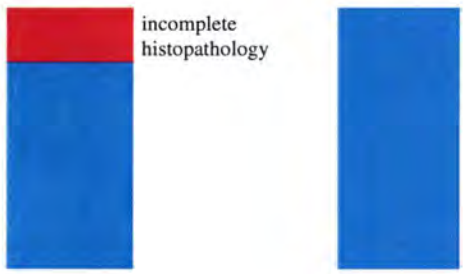
Chapter 5

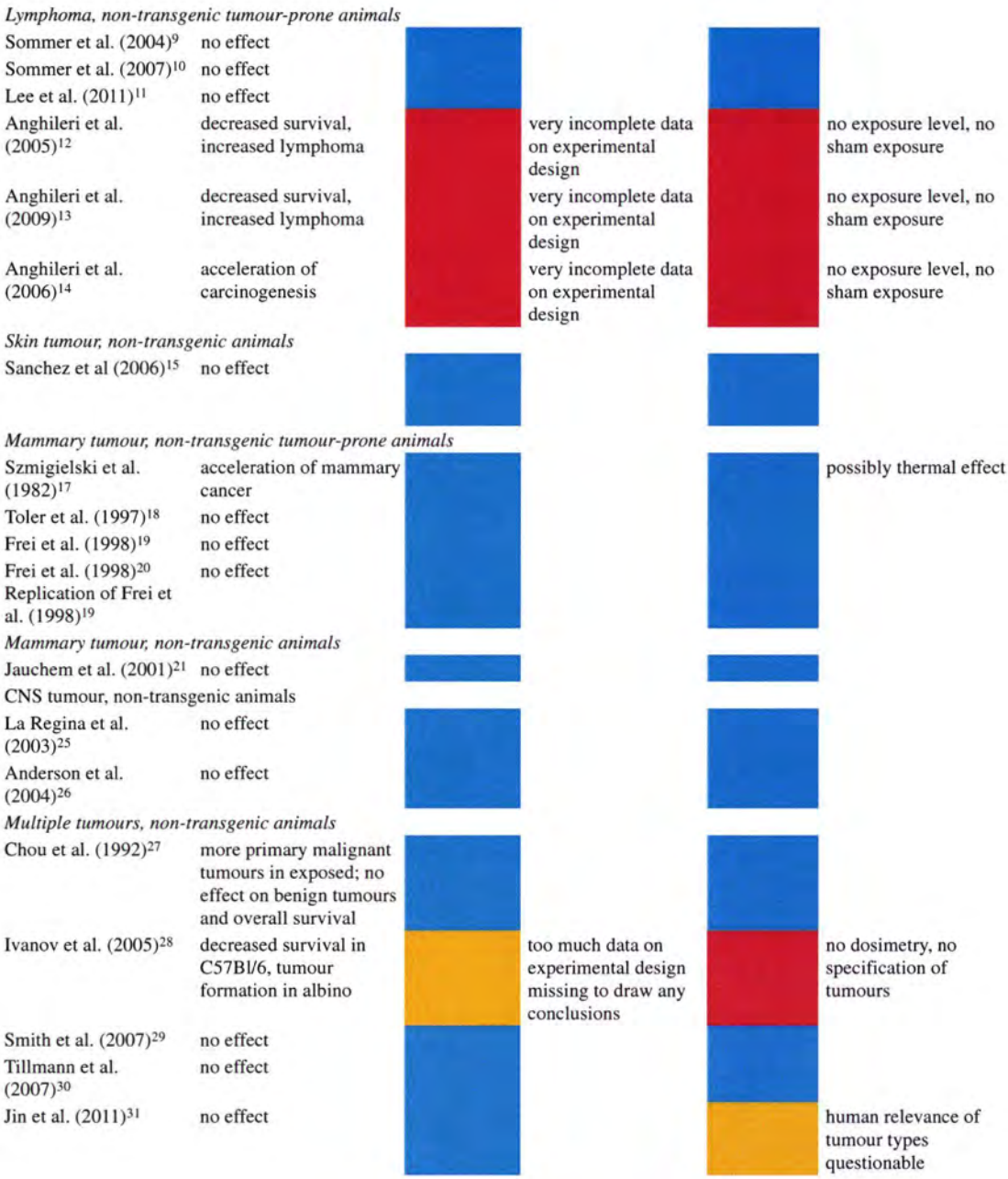
Quality assessment

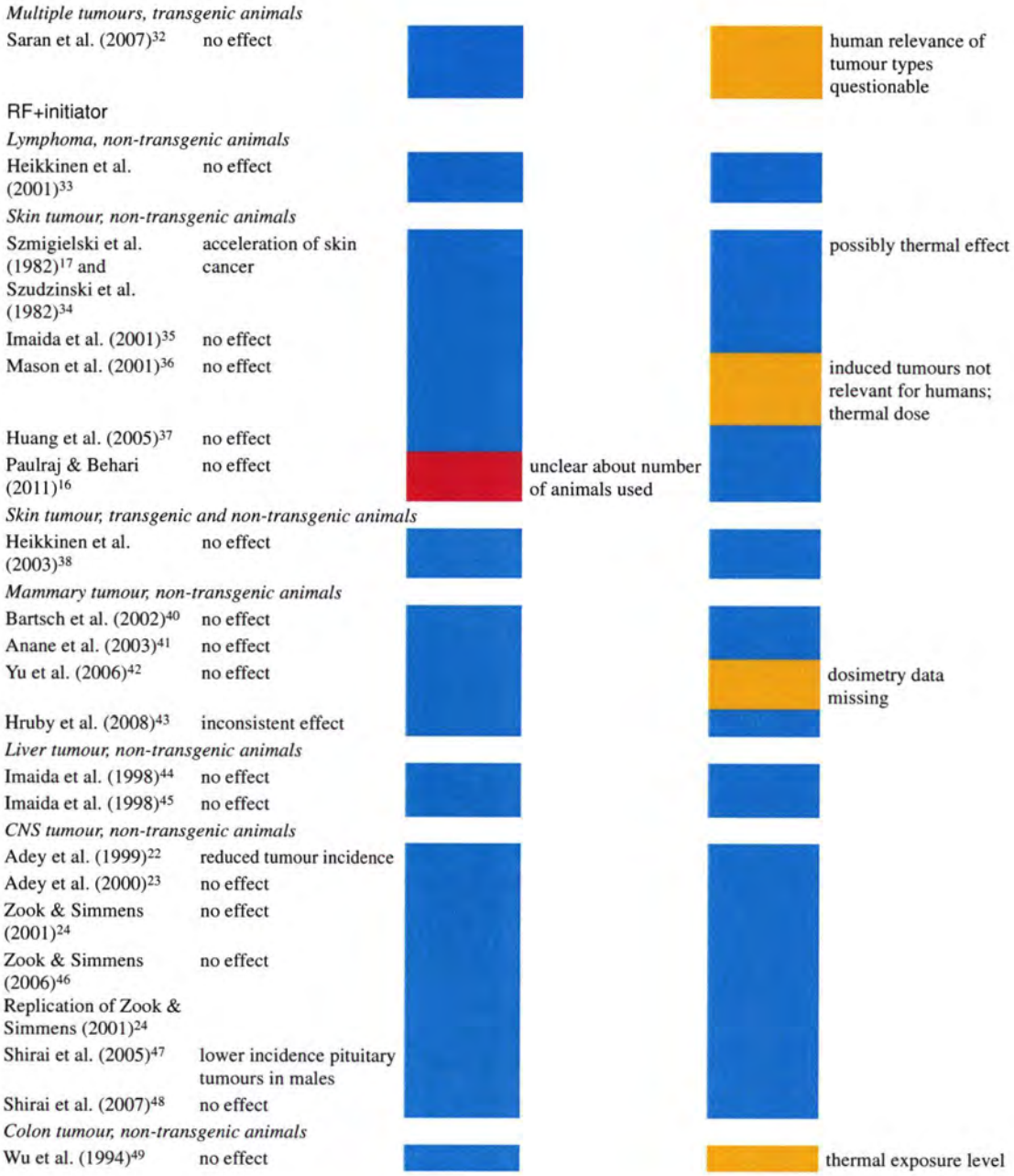
The agreed scores for the assessment of the internal and external validity of the included studies is presented in Table 3. For each study, threats to the internal or external validity were estimated as either high (coded red), low (coded blue) or unknown (coded yellow). Studies that considered multiple endpoints and that are described in different sections of the preceding chapter are listen only once in the table, except for the paper by Paulraj and Behari (2011)[16], that describes two very distinct experiments.

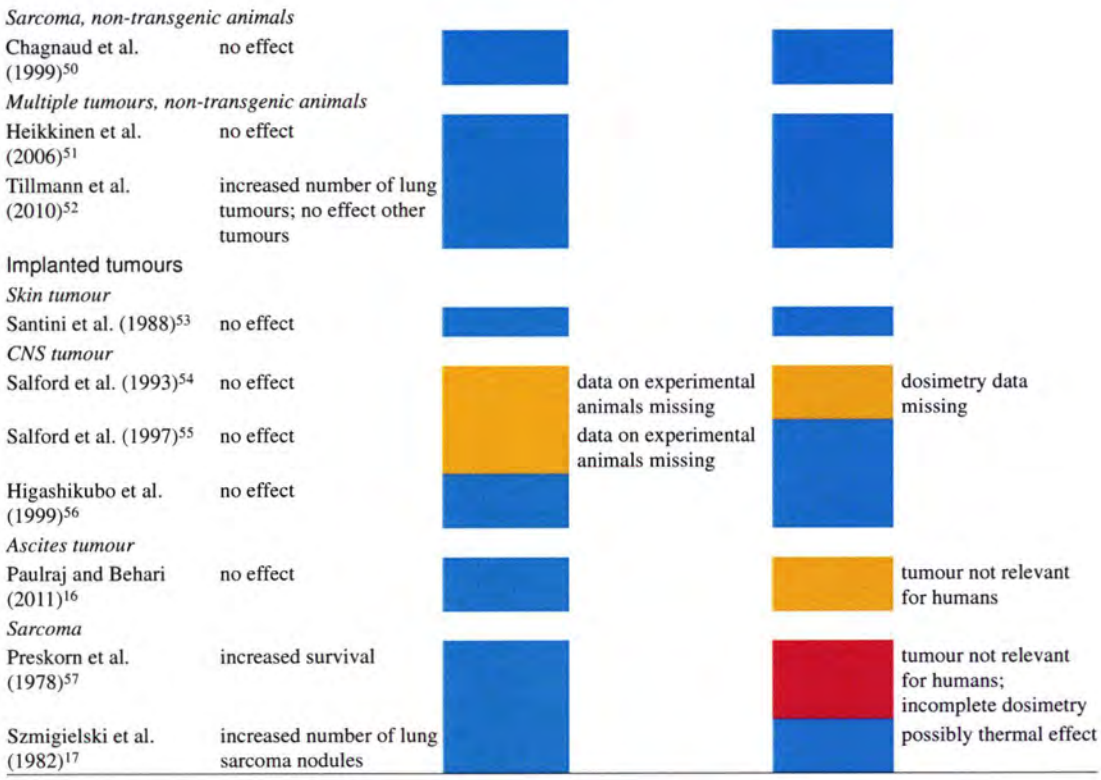
Table 3 Overview of the scores for the internal and external validity of each of the studies.

Authors	Brief results	Internal validity		External validity	
		Influence	Comment	Influence	Comment
RF alone					
Lymphoma, transgenic tumour-prone animals					
Repacholi et al. (1997)[6]	increased lymphoma		incomplete histopathology		
Utteridge et al. (2002)[7] Replication of Repacholi et al. (1997)[6]	no effect				
Oberto et al. (2007)[8] Replication of Repacholi et al. (1997)[6]	no effect				




Lymphoma, non-transgenic tumour-prone animals
Sommer et al. (2004)[9] no effect
Sommer et al. (2007)[10] no effect
Lee et al. (2011)[11] no effect
Anghileri et al. (2005)[12] decreased survival, increased lymphoma
very incomplete data on experimental design
no exposure level, no sham exposure
Anghileri et al. (2009)[13] decreased survival, increased lymphoma
very incomplete data on experimental design
no exposure level, no sham exposure
Anghileri et al. (2006)[14] acceleration of carcinogenesis
very incomplete data on experimental design
no exposure level, no sham exposure
Skin tumour, non-transgenic animals
Sanchez et al (2006)[15] no effect
Mammary tumour, non-transgenic tumour-prone animals
Szmigielski et al. (1982)[17] acceleration of mammary cancer
possibly thermal effect
Toler et al. (1997)[18] no effect
Frei et al. (1998)[19] no effect
Frei et al. (1998)[20] no effect
Replication of Frei et al. (1998)[19]
Mammary tumour, non-transgenic animals
Jauchem et al. (2001)[21] no effect
CNS tumour, non-transgenic animals
La Regina et al. (2003)[25] no effect
Anderson et al. (2004)[26] no effect
Multiple tumours, non-transgenic animals
Chou et al. (1992)[27] more primary malignant tumours in exposed; no effect on benign tumours and overall survival
Ivanov et al. (2005)[28] decreased survival in C57Bl/6, tumour formation in albino
too much data on experimental design missing to draw any conclusions
no dosimetry, no specification of tumours
Smith et al. (2007)[29] no effect
Tillmann et al. (2007)[30] no effect
Jin et al. (2011)[31] no effect
human relevance of tumour types questionable


Multiple tumours, transgenic animals
Saran et al. (2007)[32] no effect
human relevance of tumour types questionable
RF+initiator
Lymphoma, non-transgenic animals
Heikkinen et al. (2001)[33] no effect
Skin tumour, non-transgenic animals
Szmigielski et al. (1982)[17] and Szudzinski et al. (1982)[34] acceleration of skin cancer
possibly thermal effect
Imaida et al. (2001)[35] no effect
Mason et al. (2001)[36] no effect
induced tumours not relevant for humans; thermal dose
Huang et al. (2005)[37] no effect
Paulraj & Behari (2011)[16] no effect
unclear about number of animals used
Skin tumour, transgenic and non-transgenic animals
Heikkinen et al. (2003)[38] no effect
Mammary tumour, non-transgenic animals
Bartsch et al. (2002)[40] no effect
Anane et al. (2003)[41] no effect
Yu et al. (2006)[42] no effect
dosimetry data missing
Hruby et al. (2008)[43] inconsistent effect
Liver tumour, non-transgenic animals
Imaida et al. (1998)[44] no effect
Imaida et al. (1998)[45] no effect
CNS tumour, non-transgenic animals
Adey et al. (1999)[22] reduced tumour incidence
Adey et al. (2000)[23] no effect
Zook & Simmens (2001)[24] no effect
Zook & Simmens (2006)[46] no effect
Replication of Zook & Simmens (2001)[24]
Shirai et al. (2005)[47] lower incidence pituitary tumours in males
Shirai et al. (2007)[48] no effect
Colon tumour, non-transgenic animals
Wu et al. (1994)[49] no effect
thermal exposure level


Sarcoma, non-transgenic animals
Chagnaud et al. (1999)[50]
no effect
Multiple tumours, non-transgenic animals
Heikkinen et al. (2006)[51]
no effect
Tillmann et al. (2010)[52]
increased number of lung tumours; no effect other tumours
Implanted tumours
Skin tumour
Santini et al. (1988)[53]
no effect
CNS tumour
Salford et al. (1993)[54]
no effect
data on experimental animals missing
dosimetry data missing
Salford et al. (1997)[55]
no effect
data on experimental animals missing
Higashikubo et al. (1999)[56]
no effect
Ascites tumour
Paulraj and Behari (2011)[16]
no effect
tumour not relevant for humans
Sarcoma
Preskorn et al. (1978)[57]
increased survival
tumour not relevant for humans; incomplete dosimetry
Szmigielski et al. (1982)[17]
increased number of lung sarcoma nodules
possibly thermal effect

Chapter 6

Conclusions

The systematic literature search performed by the Committee revealed a substantial body of animal studies on the carcinogenesis of exposure to RF fields. A total of 23 studies have been published that investigated the effect of exposure to RF EMF alone. A variety of animal models and tumour types has been investigated, as well as a number of different types of RF, although the focus has been on the types of signals used in modern mobile telecommunication. Exposure has been from several weeks up to two years, and the follow-up time generally lifelong.

In addition, 24 studies investigated the modulating effects of RF exposure on carcinogenesis induced by various well-known carcinogenic compounds and another seven studies the effect of RF exposure on the growth of implanted tumours.

These data cover a broad range of experimental situations and may thus provide a reasonably well insight into the effects of RF exposure on carcinogenesis in rodents. An overview is presented in Figure 1. Studies in which an effect was observed and studies in which this was not the case are presented separately and are ordered by type of exposure (RF only, RF + effect modifier or RF and implanted tumour). In four studies the effect observed was a positive one, i.e. a decrease in tumour incidence or an increase in survival. This is indicated as an inhibiting effect. The colour codes indicate the score for the internal (upper) and external validity (lower). Red means that there is a chance that the outcome of the study has been influenced by the issues discussed with the internal and

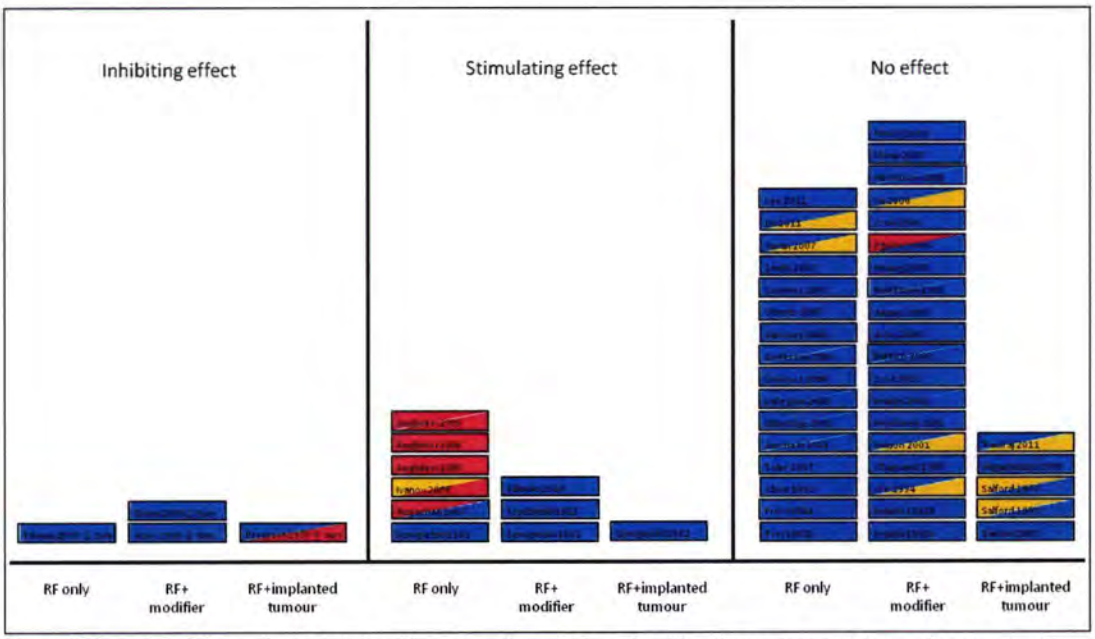


Figure 1 Overview of the studies included in this systematic analysis, ordered by effect outcome and type of exposure, and colour coded for internal (upper) and external validity (lower).

external validity. Such studies have not been included in the overall appraisal by the Committee. A blue colour means that the chance for an influence of the internal or external validity issues on the outcome is minimal or absent and yellow means that this is unknown. Studies that are coded with blue and yellow are included in the overall appraisal.

Some issues warrant a further discussion here. The first one is the Repacholi et al. (1997)[6] study in which the authors found an effect of a mobile phone-type signal on lymphoma incidence. However, histopathology was only performed on animals that died before the end of the experiment. It is thus unknown whether there was any non-fatal lymphoma in the surviving animals, and thus the overall lymphoma incidence is also unknown. This is the main reason for concluding that the outcome might have been influenced by the study design and thus for giving a red code for the internal validity. No effects have been found in studies designed as repetitions of the Repacholi study. These studies were no exact replications because the animals were restrained instead of free roaming in order to improve dosimetry and the daily exposure was given in one session instead of

two for practical reasons. Other studies applying lifelong exposure to free roaming or restrained animals with SAR values up to 4 W/kg did not find any effect on lymphoma incidence or survival. In view of the flaws in the Repacholi study and the results of the repetition studies, the conclusion of the Committee is that an effect of long-term exposure to mobile phone signals on the incidence of lymphomas has not been demonstrated. Also, since transgenic animals were used in these studies with an increased spontaneous lymphoma incidence, the direct relevance of this model for humans is questionable.

No effects of various types of RF signals on skin tumour development or growth have been observed, with the exception of the results of the research group of Szmigielski and colleagues.[17,34] However, they employed exposures with SAR levels of 2-8 W/kg and it cannot be excluded that the growth-accelerating influence of exposure at the these levels could be explained by thermal effects[58,59], although not all tumours seem to respond similarly to moderate heating.[60] Even a whole-body SAR of 2 W/kg is a significant systemic challenge to a mouse with a metabolic rate of 4-7 W/kg under thermal neutral conditions.

With respect to mammary tumours, the study by Szmigielski et al. (1982)[17] was again the only one showing acceleration of tumour development. They exposed the animals for 2 hours per day to SAR levels that may result in increased body temperatures. Studies of two other groups exposing the animals of the same mouse strain to various frequencies for up to 22 hours per day, but to a maximum SAR of 1 W/kg, did not observe any influence on mammary tumour development.[18-20] The committee considers it likely that the effects observed by Szmigielski et al. were the result of thermal challenge and not a direct effect of the RF field.

There are only few data on the influence of RF EMF on liver tumours, and they come from only one research group, but they do not indicate any effect.

There are no indications that exposure to RF EMF has any influence on the development or growth of CNS or other neurogenic tumours. Although Adey et al. (1999)[22] observed less CNS tumours after longterm RF exposure, and Shirai et al. (2005)[47] found less pituitary tumours after RF exposure of male offspring from mothers that had been treated with a carcinogen, there is no rational biological explanation for these observations, and they might be chance results.

Even at very high SAR levels that could induce thermal effects, no influence of RF EMF on colon tumour growth was observed. However, these data only come from one single publication.

Long-term exposure to RF EMF up to a SAR of 4 W/kg does not seem to have any effect on other spontaneous or carcinogen-induced tumours, with the

exception of an increase in ENU-induced lung tumours observed by Tillman et al. (2010)[52] after UMTS exposure. This is, however, a single study that has not been followed up or replicated. It also lacks an ENU-sham exposed control group.The Committee therefore gives it a low weight in the overall analysis.

The systematic analysis of the quality of the studies, reflected in the indications of the internal and external validity, has shown that most studies are of sufficient quality and can be included in the overall analysis. There are some studies, however, that suffer from a very poor description of the experimental design and/or poor dosimetry. They are, therefore, of limited or no value in the overall analysis.

Overall the studies discussed in this report show that no effects of long-term exposure to RF EMF on the development or growth of tumours in general, or on specific types of tumours, have been demonstrated in rodents. The findings of the few studies that did indicate effects have either not been observed in repetition studies, or might be explained by thermal effects. It is also possible that they were chance findings. This can also only be the conclusion for the few observed protective effects of RF exposure.

An important issue is also whether the animal models and exposures used in these studies have predictive value for the situation in humans. In general the exposure of small laboratory animals to RF fields results in a different energy deposition than in humans. Because of their smaller size, the exposure of rats and mice results much easier in whole-organ or whole-body exposure. This means that the action of any compensating mechanisms will be much reduced compared to in humans, where only parts of the body and organs will be exposed when using communication devices such as mobile phones. Whole-body exposure does occur in humans, of course, by the RF fields emanating from mobile phone base stations and other antennas, but the exposure levels in such situations are considerably lower than in the animal studies, that tend to employ as much as possible worse-case situations. This can also be said of the animal models that use either transgenic animals with an increased spontaneous incidence of tumours, or models that use chemical or physical carcinogens. These create also worse-case situations that – except for UV exposure – people usually do not encounter in daily life. So in general the animal studies provide worse-case situations with respect to RF exposure, and when no effects are observed on the induction or promotion of tumours in such models the Committee considers this a strong indication that such effects are improbable in humans.

The final conclusion of the Committee is therefore that, on the basis of the results of the animal studies presented in this systematic review, it is unlikely that long-term continuous or repeated exposure to RF EMF may have initiating or promoting effects on the development of cancer.

The Committee deems further animal studies into RF carcinogenesis not useful at this time. There is currently a large, well-designed animal carcinogenesis study ongoing in the USA in which two species, rats and mice, are being long-term exposed to various levels of RF fields.[61] Before recommending further research, the outcome of this study, expected in 2016, has to be awaited.

In general, the Committee wishes to make the point that, for experimental studies to be of value, the design has to be well-conceived and described, the tumour model and exposure schedule used should be relevant for humans, and there should be a good description of the dosimetry and exposure levels. Following the recommendations of the Gold Standard Publication Checklist[4,5] can be helpful.

References

1 Baan R, Grosse Y, Lauby-Secretan B, e.a. Carcinogenicity of radiofrequency electromagnetic fields. Lancet Oncol, 2011; 12(7): 624-626.

2 IARC - International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Non-ionizing radiation, Part 2: Radiofrequency electromagnetic fields. Volume 102. Internet: http://monographs.iarc.fr/ENG/Monographs/vol102/index.php. Access date 23-4-2013.

3 HCN - Health Council of the Netherlands. Mobile phones and cancer. Part 1: Epidemiology of tumours in the head. The Hague: Health Council of the Netherlands, 2013; Publication nr 2013/11.

4 Hooijmans CR, Leenaars M, and Ritskes-Hoitinga M. A gold standard publication checklist to improve the quality of animal studies, to fully integrate the Three Rs, and to make systematic reviews more feasible. Altern Lab Anim, 2010; 38(2): 167-182.

5 Hooijmans CR, de Vries R, Leenaars M, e.a. Improving planning, design, reporting and scientific quality of animal experiments by using the Gold Standard Publication Checklist, in addition to the ARRIVE guidelines. Br J Pharmacol, 2011; 162(6): 1259-1260.

6 Repacholi MH, Basten A, Gebski V, e.a. Lymphomas in Em-Pim1 transgenic mice exposed to pulsed 900 MHz electromagnetic fields. Radiat Res, 1997; 147(5): 631-640.

7 Utteridge TD, Gebski V, Finnie JW, e.a. Long-term exposure of E-μ-Pim1 transgenic mice to 898.4 MHz microwaves does not increase lymphoma incidence. Radiat Res, 2002; 158(3): 357-364.

8 Oberto G, Rolfo K, Yu P, e.a. Carcinogenicity study of 217 Hz pulsed 900 MHz electromagnetic fields in Pim1 transgenic mice. Radiat Res, 2007; 168(3): 316-326.

9 Sommer AM, Streckert J, Bitz AK, e.a. No effects of GSM-modulated 900 MHz electromagnetic fields on survival rate and spontaneous development of lymphoma in female AKR/J mice. BMC Cancer, 2004; 4: 77.

10 Sommer AM, Bitz AK, Streckert J, e.a. Lymphoma development in mice chronically exposed to UMTS-modulated radiofrequency electromagnetic fields. Radiat Res, 2007; 168(1): 72-80.

11 Lee HJ, Jin YB, Lee JS, e.a. Lymphoma development of simultaneously combined exposure to two radiofrequency signals in AKR/J mice. Bioelectromagnetics, 2011; 32(6): 485-492.

12 Anghileri LJ, Mayayo E, Domingo JL, e.a. Radiofrequency-induced carcinogenesis: cellular calcium homeostasis changes as a triggering factor. Int J Radiat Biol, 2005; 81(3): 205-209.

13 Anghileri LJ, Mayayo E, Domingo JL, e.a. Evaluation of health risks caused by radio frequency accelerated carcinogenesis: the importance of processes driven by the calcium ion signal. Eur J Cancer Prev, 2006; 15(3): 191-195.

14 Anghileri LJ, Mayayo E, and Domingo JL. Aluminum, calcium ion and radiofrequency synergism in acceleration of lymphomagenesis. Immunopharmacol Immunotoxicol, 2009; 31(3): 358-362.

15 Sanchez S, Masuda H, Billaudel B, e.a. Effect of GSM-900 and -1800 signals on the skin of hairless rats. II: 12-week chronic exposures. Int J Radiat Biol, 2006; 82(9): 675-680.

16 Paulraj R and Behari J. Effects of low level microwave radiation on carcinogenesis in Swiss Albino mice. Mol Cell Biochem, 2011; 348(1-2): 191-197.

17 Szmigielski S, Szudzinski A, Pietraszek A, e.a. Accelerated development of spontaneous and benzopyrene-induced skin cancer in mice exposed to 2450 MHz microwave radiation. Bioelectromagnetics, 1982; 3: 179-191.

18 Toler JC, Shelton WW, Frei MR, e.a. Long-term, low-level exposure of mice prone to mammary tumors to 435 MHz radiofrequency radiation. Radiat Res, 1997; 148(3): 227-234.

19 Frei MR, Berger RE, Dusch SJ, e.a. Chronic exposure of cancer-prone mice to low-level 2450 MHz radiofrequency radiation. Bioelectromagnetics, 1998; 19(1): 20-31.

20 Frei MR, Jauchem JR, Dusch SJ, e.a. Chronic, low-level (1.0 W/kg) exposure of mice prone to mammary cancer to 2450 MHz microwaves. Radiat Res, 1998; 150(5): 568-576.

21 Jauchem JR, Ryan KL, Frei MR, e.a. Repeated exposure of C3H/HeJ mice to ultra-wideband electromagnetic pulses: lack of effects on mammary tumors. Radiat Res, 2001; 155(2): 369-377.

22 Adey WR, Byus CV, Cain CD, e.a. Spontaneous and nitrosourea-induced primary tumors of the central nervous system in Fischer 344 rats chronically exposed to 836 MHz modulated microwaves. Radiat Res, 1999; 152(3): 293-302.

23 Adey WR, Byus CV, Cain CD, e.a. Spontaneous and nitrosourea-induced primary tumors of the central nervous system in Fischer 344 rats exposed to frequency-modulated microwave fields. Cancer Res, 2000; 60(7): 1857-1863.

24 Zook BC and Simmens SJ. The effects of 860 MHz radiofrequency radiation on the induction or promotion of brain tumors and other neoplasms in rats. Radiat Res, 2001; 155(4): 572-583.

25 La Regina M, Moros EG, Pickard WF, e.a. The effect of chronic exposure to 835.62 MHz FDMA or 847.74 MHz CDMA radiofrequency radiation on the incidence of spontaneous tumors in rats. Radiat Res, 2003; 160(2): 143-151.

26 Anderson LE, Sheen DM, Wilson BW, e.a. Two-year chronic bioassay study of rats exposed to a 1.6 GHz radiofrequency signal. Radiat Res, 2004; 162(2): 201-210.

27 Chou CK, Guy AW, Kunz LL, e.a. Long-term, low-level microwave irradiation of rats. Bioelectromagnetics, 1992; 13(6): 469-496.

28 Ivanov VB, Subbotina TI, Khadartsev AA, e.a. Exposure to low-intensive superhigh frequency electromagnetic field as a factor of carcinogenesis in experimental animals. Bull Exp Biol Med, 2005; 139(2): 241-244.

29 Smith P, Kuster N, Ebert S, e.a. GSM and DCS wireless communication signals: combined chronic toxicity/carcinogenicity study in the Wistar rat. Radiat Res, 2007; 168(4): 480-492.

30 Tillmann T, Ernst H, Ebert S, e.a. Carcinogenicity study of GSM and DCS wireless communication signals in B6C3F1 mice. Bioelectromagnetics, 2007; 28(3): 173-187.

31 Jin YB, Lee HJ, Seon LJ, e.a. One-year, simultaneous combined exposure of CDMA and WCDMA radiofrequency electromagnetic fields to rats. Int J Radiat Biol, 2011; 87(4): 416-423.

32 Saran A, Pazzaglia S, Mancuso M, e.a. Effects of exposure of newborn patched1 heterozygous mice to GSM, 900 MHz. Radiat Res, 2007; 168(6): 733-740.

33 Heikkinen P, Kosma VM, Hongisto T, e.a. Effects of mobile phone radiation on X-ray-induced tumorigenesis in mice. Radiat Res, 2001; 156(6): 775-785.

34 Szudzinski A, Pietraszek A, Janiak M, e.a. Acceleration of the development of benzopyrene-induced skin cancer in mice by microwave radiation. Arch Dermatol Res, 1982; 274(3-4): 303-312.

35 Imaida K, Kuzutani K, Wang J, e.a. Lack of promotion of 7,12-dimethylbenz[a]anthracene-initiated mouse skin carcinogenesis by 1.5 GHz electromagnetic near fields. Carcinogenesis, 2001; 22(11): 1837-1841.

36 Mason PA, Walters TJ, DiGiovanni J, e.a. Lack of effect of 94 GHz radio frequency radiation exposure in an animal model of skin carcinogenesis. Carcinogenesis, 2001; 22(10): 1701-1708.

37 Huang TQ, Lee JS, Kim TH, e.a. Effect of radiofrequency radiation exposure on mouse skin tumorigenesis initiated by 7,12-dimethybenz[alpha]anthracene. Int J Radiat Biol, 2005; 81(12): 861-867.

38 Heikkinen P, Kosma VM, Alhonen L, e.a. Effects of mobile phone radiation on UV-induced skin tumourigenesis in ornithine decarboxylase transgenic and non-transgenic mice. Int J Radiat Biol, 2003; 79(4): 221-233.

39 Halmekytö M, Syrjänen K, Jänne J, e.a. Enhanced papilloma formation in response to skin tumor promotion in transgenic mice overexpressing the human ornithine decarboxylase gene. Biochem Biophys Res Commun, 1992; 187(1): 493-497.

40 Bartsch H, Bartsch C, Seebald E, e.a. Chronic exposure to a GSM-like signal (mobile phone) does not stimulate the development of DMBA-induced mammary tumors in rats: results of three consecutive studies. Radiat Res, 2002; 157(2): 183-190.

41 Anane R, Dulou PE, Taxile M, e.a. Effects of GSM-900 microwaves on DMBA-induced mammary gland tumors in female Sprague-Dawley rats. Radiat Res, 2003; 160(4): 492-497.

42 Yu D, Shen Y, Kuster N, e.a. Effects of 900 MHz GSM wireless communication signals on DMBA-induced mammary tumors in rats. Radiat Res, 2006; 165(2): 174-180.

43 Hruby R, Neubauer G, Kuster N, e.a. Study on potential effects of "902-MHz GSM-type Wireless Communication Signals" on DMBA-induced mammary tumours in Sprague-Dawley rats. Mutat Res, 2008; 649(1-2): 34-44.

44 Imaida K, Taki M, Yamaguchi T, e.a. Lack of promoting effects of the electromagnetic near-field used for cellular phones (929.2 MHz) on rat liver carcinogenesis in a medium-term liver bioassay. Carcinogenesis, 1998; 19(2): 311-314.

45 Imaida K, Taki M, Watanabe S, e.a. The 1.5 GHz electromagnetic near-field used for cellular phones does not promote rat liver carcinogenesis in a medium-term liver bioassay. Jpn J Cancer Res, 1998; 89(10): 995-1002.

46 Zook BC and Simmens SJ. The effects of pulsed 860 MHz radiofrequency radiation on the promotion of neurogenic tumors in rats. Radiat Res, 2006; 165(5): 608-615.

47 Shirai T, Kawabe M, Ichihara T, e.a. Chronic exposure to a 1.439 GHz electromagnetic field used for cellular phones does not promote N-ethylnitrosourea induced central nervous system tumors in F344 rats. Bioelectromagnetics, 2005; 26(1): 59-68.

48 Shirai T, Ichihara T, Wake K, e.a. Lack of promoting effects of chronic exposure to 1.95-GHz W-CDMA signals for IMT-2000 cellular system on development of N-ethylnitrosourea-induced central nervous system tumors in F344 rats. Bioelectromagnetics, 2007; 28(7): 562-572.

49 Wu RY, Chiang H, Shao BJ, e.a. Effects of 2.45-GHz microwave radiation and phorbol ester 12-O-tetradecanoylphorbol-13-acetate on dimethylhydrazine-induced colon cancer in mice. Bioelectromagnetics, 1994; 15(6): 531-538.

50 Chagnaud JL, Moreau JM, and Veyret B. No effect of short-term exposure to GSM-modulated low-power microwaves on benzo(a)pyrene-induced tumours in rat. Int J Radiat Biol, 1999; 75(10): 1251-1256.

51 Heikkinen P, Ernst H, Huuskonen H, e.a. No effects of radiofrequency radiation on 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone-induced tumorigenesis in female Wistar rats. Radiat Res, 2006; 166(2): 397-408.

52 Tillmann T, Ernst H, Streckert J, e.a. Indication of cocarcinogenic potential of chronic UMTS-modulated radiofrequency exposure in an ethylnitrosourea mouse model. Int J Radiat Biol, 2010; 86(7): 529-541.

53 Santini R, Hosni M, Deschaux P, e.a. B16 melanoma development in black mice exposed to low-level microwave radiation. Bioelectromagnetics, 1988; 9(1): 105-107.

54 Salford LG, Brun A, Persson BRR, e.a. Experimental studies of brain tumor development during exposure with continuous and pulsed 915 MHz radiofrequency radiation. Bioelectrochem Bioenerget, 1993; 30(1-3): 313-318.

55 Salford LG, Brun A, and Persson BR. Brain tumor development in rats exposed to electromagnetic fields used in wireless communication. Wireless-Netw, 1997; 3: 463-469.

56 Higashikubo R, Culbreth VO, Spitz DR, e.a. Radiofrequency electromagnetic fields have no effect on the in vivo proliferation of the 9L brain tumor. Radiat Res, 1999; 152: 665-671.

57 Preskorn SH, Edwards WD, and Justesen DR. Retarded tumor growth and greater longevity in mice after fetal irradiation by 2450-MHz microwaves. J Surg Oncol, 1978; 10(6): 483-492.

58 Dickson JA. The effects of hyperthermia in animal tumour systems. Recent Results Cancer Res, 1977; (59): 43-111.

59 Wile AG, Nahabedian MY, and Mason GR. Enhanced tumor growth in experimental whole body hyperthermia. J Surg Oncol, 1983; 24(2): 119-123.

60 Sen A, Capitano ML, Spernyak JA, e.a. Mild elevation of body temperature reduces tumor interstitial fluid pressure and hypoxia and enhances efficacy of radiotherapy in murine tumor models. Cancer Res, 2011; 71(11): 3872-3880.

61 NIEHS - National Institute of Environmental Health Services. Cell Phones. Internet: http:// www.niehs.nih.gov/health/topics/agents/cellphones/index.cfm. Access date 24-6-2014.

62 ICNIRP - International Commission on Non-Ionizing Radiation Protection. Guidelines for limiting exposure to time-varying electric, magnetic, and electromagnetic fields (up to 300 GHz). Health Phys, 1998; 74(4): 494-522.

63 Leeuwen G van, Lagendijk JJW, van Leersum B, e.a. Calculation of change in brain temperature due to exposure to a mobile phone. Phys Med Biol, 1999; 44: 2367-2379.

64 Ebert S, Eom SJ, Schuderer J, e.a. Response, thermal regulatory threshold and thermal breakdown threshold of restrained RF-exposed mice at 905 MHz. Phys Med Biol, 2005; 50(21): 5203-5215.

Annexes

Annex **A**

The Committee

The membership of the Electromagnetic Fields Committee at the time of preparation of this advisory report was as follows:

- Prof. G.C. van Rhoon, *chair*
  Professor of Physical Aspects of Electromagnetic Fields and Health, Erasmus University Medical Centre Rotterdam
- Prof. A. Aleman
  Professor of Cognitive Neuropsychiatry, University of Groningen
- Prof. H. Kromhout
  Professor of Epidemiology of Health Effects from Exposure to Electromagnetic Fields, Institute for Risk Assessment Sciences, University of Utrecht
- Prof. F.E. van Leeuwen
  Professor of Cancer Epidemiology, Free University of Amsterdam, Epidemiologist, Netherlands Cancer Institute, Amsterdam
- Prof. H.F.J. Savelkoul
  Professor of Cell Biology and Immunology, Wageningen University
- Prof. W.J. Wadman
  Professor of Neurobiology, University of Amsterdam

- D.H.J. van de Weerdt, physician
  Toxicologist and specialist in environmental medicine, Central Gelderland Municipal Health Services (GGD), Arnhem
- Prof. A.P.M. Zwamborn
  Professor of Electromagnetic Fields and Health, Eindhoven University of Technology; Physicist, TNO (Netherlands Organisation for Applied Scientific Research), The Hague
- Prof. R.A. Woutersen
  Professor of Translational Toxicology, Wageningen University; Toxicologic pathologist, TNO (Netherlands Organisation for Applied Scientific Research), Zeist
- Dr. G. Kelfkens, *advisor*
  Physicist, National Institute for Public Health and the Environment, Bilthoven
- Prof. I.A. Kreis, *advisor*
  Epidemiologist and specialist in social medicine, Health Council of the Netherlands, The Hague
- Prof. E. Lebret, *observer*
  Professor of Environmental Health Impact Assessment, Institute for Risk Assessment Sciences, Utrecht University, and Chairman Science forum, Knowledge Platform Electromagnetic Fields, Bilthoven
- Dr. M.J.M. Pruppers, *observer*
  Physicist, Deputy Executive Director, Knowledge Platform Electromagnetic Fields, Bilthoven
- J. Robijns, *observer*
  Ministry of Economic Affairs, The Hague
- R.P.R. Schutte, *observer*
  Ministry of Infrastructure and the Environment, The Hague
- Dr. E. van Rongen, scientific secretary
  Radiobiologist, Health Council of the Netherlands, The Hague

Assistence with the scoring system for the internal and external validity of the studies and its further development was provided by dr. C.R. Hooijmans and Prof. M. Ritskes-Hoitinga, Radboud University Medical Centre, Nijmegen.

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **B**

Items used in the validity assessment

Table B1 Items used in the assessment of the internal validity and the chance of influencing the outcome.

Allocation to groups			
Was the allocation sequence adequately generated and applied?	Yes (low chance): The investigators describe a random component in the sequence generation process such as referring to a random number table, or using a computer random number generator.	No (high chance): The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: • allocation by judgement or preference of the investigator • allocation based on the results of a laboratory test or a series of tests • allocation by availability of the intervention • sequence generated by odd or even date of birth • sequence generated by some rule based on animal number/ cage number.	Unknown: Insufficient information about the sequence generation process to permit judgement of 'Low chance' or 'High chance.

Were the groups similar at baseline or adjusted for confounders?	Yes (low chance): The investigators show / describe an equal distribution of all relevant baseline characteristics and or confounders. Usually such a description contains: • the gender, age or weight of the animals • baseline values of the outcomes which are of interest in the study.	No (high chance): The authors show that there is an unequal distribution of relevant baseline characteristics and/or confounders and do not adjust for this imbalance.	Unknown: Not reported or insufficient information about the distribution of baseline characteristics or confounders to permit judgement.
Blinding Were the care givers / and or investigators during the course of the experiment adequately blinded from knowledge of which intervention each animal received?	Yes (low chance): All of the following: • blinding of care givers and investigators ensured, and unlikely that the blinding could have been broken • ID cards of individual animals, or cage/animal labels are coded and of identical appearance • another person than the investigator prepares the intervention • the circumstances during the intervention are specified and similar in both groups (**see next entry**) • housing conditions of the animals during the experiment are randomized within the room.	No (high chance): Any one of the following: • no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding • blinding of investigators and animal care givers attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding. For example: • coloured cage labels (red for group A, yellow group B) • expected differences in visible effects between control and experimental groups • housing conditions of the animals during the experiment are not randomized within the room • the person who prepares the experiment is the same as the one who conducts and analyses the experiment • circumstances during the intervention are not similar in both groups (**see next entry**).	Unknown: Insufficient information to permit judgement of 'Low chance' or 'High chance'.

Additional criteria to score the similarity of the circumstances during the intervention.	Similar (low chance): The reviewers judge that the intervention is as similar as possible between the experimental and control groups. For example: • timing of the intervention was similar; • the control group received a correct sham treatment; • technique and duration needed to conduct the intervention is exactly the same in the experimental groups.	Not similar (high chance): The reviewers judge that the circumstances during the intervention differ in such a way that they increase the risk of performance bias. For example: • timing of administration of real and sham exposure are different • instruments used to conduct the experiment differ between real and sham exposed groups.	Unknown: Insufficient information to permit judgement of 'Low chance' or 'High chance'.

Was the outcome assessment adequately blinded (with regard to the subjective outcomes)?	Yes (low chance):
	
	Any one of the following
	• no blinding or incomplete blinding, but the outcome is not likely to be influenced by lack of blinding, e.g. mortality
	• blinding of outcome assessment ensured, and unlikely that the blinding could have been broken:
	• methods for outcome assessment are the same in both groups
	• animals were selected at random during outcome assessment.
		No (high chance):
		
		Any one of the following:
		• no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding
		• blinding of outcome assessment might be attempted, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding:
		  • methods for outcome assessment are not the same in both groups
		  • animals were not selected at random during outcome assessment.
			Unknown:
			
			Insufficient information to permit judgement of 'Low chance' or 'High chance'.

Data loss Were incomplete outcome data adequately addressed?	Yes (low chance): Any one of the following: • no missing outcome data • reasons for missing outcome data unlikely to be related to true outcome • missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups • missing data have been imputed using appropriate methods.	No (high chance): Any one of the following: • reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups • high proportion of missing outcomes • potentially inappropriate application of simple imputation.	Unknown: Insufficient reporting of attrition/exclusions to permit judgement of 'Low chance' or 'High chance' (e.g. number randomized not stated, no reasons for missing data provided).

Reporting bias			
Are reports of the study free of selective outcome reporting?	Yes (low chance): Any one of the following: • the study protocol is not available, but the outcomes of interest as mentioned by the investigators in the introduction and material and methods sections are similar with the outcome measures described in the results section • the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes thaat are of interest in the review have been reported in the pre-specified way.	No (high chance): Any one of the following: • not all the study outcomes as specified in introduction and material and methods sections of the paper are described in the results section • not all of the study's pre-specified primary outcomes have been reported • one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified in the protocol • one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect) • the study report fails to include results for a key outcome that would be expected to have been reported for such a study.	Unknown: Insufficient information to permit judgement of 'Low chance' or 'High chance'.
Other bias			
Was the study apparently free of other problems that could put a high risk of bias?	Yes (low chance): The study appears free of other biases.	No (high chance): There is at least one important risk of bias. For example: • the study suffered from extreme baseline imbalance (evidence for failed randomization) • the conduct of a study is affected by interim results • author has been claimed to have been fraudulent • inappropriate influence of funders • incorrect statistical methods or unit of analysis error. For example data or animals are assumed to be independent, but they are not • some design specific risks of bias: • multi-arm study in which different outcomes are presented per group (selective outcome reporting) • multi-arm study in which results of different arms are combined (all data should be presented per group).	Unknown: There may be a risk of bias, but there is either: • insufficient information to assess whether an important risk of bias exists; or • insufficient rationale or evidence that an identified problem will introduce bias.

Table B2 Items used in the assessment of the external validity and the chance of influencing the outcome.

	High chance	Low chance	Unknown chance
Animal characteristics			
Age	--	Age characteristic for age in humans for cancer type	Non-characteristic age
Cancer type	Cancer type predominantly found in animals	Cancer type typically found in humans	--
Exposure			
Exposure: whole body or local	--	Relevant for cancer type	Not relevant for cancer type
Exposure: source and level	Not typical for exposure of humans	Typical for exposure of humans	--
Exposure protocol	--	Typical for exposure of humans (e.g. low level continuous, or higher level intermittent, simulating mobile phone conversations)	Not typical for exposure of humans
Exposure: level	Not typical for exposure of humans (non-thermal level, comparable to exposure with use of mobile phone or near antenna)	Typical for exposure of humans	--
Exposure: quality of dosimetry, rated on a scale of 0 (very poor) - 5 (excellent)	0-1	2-5	1-2

Annex **C**

Experimental details

Table C1 Details of the included studies.

Authors	Animal normal / transgenic Age at start (+: acclimatization period) Other tumours	Carcinogen	Exp source Exp time Exp level	Exp level: correction for growth	Exp free / restrained	Controls	Group size	Blinded	Results
RF alone									
Lymphoma, transgenic tumour-prone animals									
Repacholi et al. (1997)[6]	female C57BL/ 6NTac mice, transgenic for Eμ-Pim1, lymphoma prone 4-6 wk + 10 d	none	GSM 900 MHz 2x30 min/d, 24 mo 0.008-4.2 W/kg (individual) 0.13-1.4 W/kg (in cage)	yes	free 5 / cage	sham	101 (contr.: 100)	exposure and analysis	higher risk in exposed OR=2.4 (1.3-4.5)
Utteridge et al. (2002)[7] Replication of Repacholi et al. (1997)[6]	female C57BL/ 6NTac mice, transgenic for Eμ-Pim1, lymphoma prone & wildtype 4-6 wk + 10 d	none	GSM 898 MHz 1 h/d, 5 d/wk, 104 wk 0.25, 1.0, 2.0, 4.0 W/kg	no	restrained	sham, cage control, positive control	120 (exp, sham, cage contr.); 30 (positive contr.)	exposure and analysis	no effect in either transgenic or normal mice

Oberto et al. (2007)[8] Replication of Repacholi et al. (1997)[6]	male and female C57BL/6NTac mice, transgenic for Eμ-Pim1, lymphoma prone 6 wk + 20 d multiple tumours	none	GSM 900 MHz 1 h/d, 7 d/wk, 18 mo 0.5, 1.4, 4.0 W/kg	yes	restrained	sham, cage control	100 (50 m, 50 f)	yes	no effect on survival, lymphomas and other tumours
Lymphoma, non-transgenic tumour-prone animals									
Sommer et al. (2004)[9]	female AKR/J mice, wildtype, but with high lymphoma incidence 4-5 wk	none	GSM 900 MHz continuous, 46 wk 0.4 W/kg ± 40%	no	free 6-7 / cage	sham	160	exposure and analysis	no difference in lymphoma incidence, survival
Sommer et al. (2007)[10]	female AKR/J mice, wildtype, but with high lymphoma incidence 8 wk	none	UMTS continuous, 43 wk 0.4 W/kg ± 40%	no	free 6-7 / cage	sham, cage control	160	exposure and analysis	no difference in lymphoma incidence, survival
Lee et al, (2011)[11]	female AKR/J mice, wildtype, but with high lymphoma incidence 5 wk	none	CDMA, WCDMA 45 min/d, 5 d/wk, 42 wk 4.0 W/kg	no	free 5 / cage	sham	40	exposure and analysis	no difference in lymphoma incidence, survival
Anghileri et al, (2005)[12]	female Ico:OFI mice, wildtype, but with high lymphoma incidence 4-5 wk	none	GSM 800 MHz 1 h/wk, 4 mo exposure level not provided	no	free	sham	20	no	decreased survival and more lymphoma in exposed
Anghileri et al. (2009)[13]	female Ico:OFI mice, wildtype, but with high lymphoma incidence 2 mo	CaCl, Al lactate	GMS 800 MHz 1 h/wk, 16 wk exposure level not provided	no	free	sham	10	no	decreased survival and more lymphoma in exposed
Anghileri et al. (2006)[14]	female Ico:OFI mice, wildtype, but with high lymphoma incidence 4-5 wk	FeATP	GSM 800 MHz 1 h/wk, 4 mo exposure level not provided	no	free	sham	20	no	similar acceleration of carcinogenesis by RF & FeATP

Skin tumour, non-transgenic animals									
Sanchez let al. (2006)[15]	female IFFA Creda rats, hairless 5 wk + 1 wk	none	GSM 900 MHz, 1800 MHz 2 h/d, 5 d/wk, 12 wk 2.5, 5 W/kg	yes	restrained	sham, positive control (UV), cage control	8	histological analysis	no effect RF on skin histology
Mammary tumour, non-transgenic tumour-prone animals									
Szmigielski et al. (1982)[17]	female C_3H/HEA mice, wildtype with high mammary cancer incidence 6 wk	none	2450 MHz 2 h/d, 6 d/wk, 10.5 mo 2-3, 6-8 W/kg	no	free 10 / cage	sham	40	no	dose-dependent acceleration of mammary cancer
Toler et al. (1997)[18]	female C3H/HeJ mice, wildtype with high mammary cancer incidence 3-4 wk + 1 mo	none	435 MHz pulsed 22 h/d, 7 d/wk, 21 mo 0.32 W/kg	no	free	sham	200	histological analysis	no effect on number and growth of tumours
Frei et al. (1998)[19]	female C3H/HeJ mice, wildtype with high mammary cancer incidence 3-4 wk + 10 d	none	2450 MHz 20 h/d, 7 d/wk, 18 mo 0.3 W/kg	no	free	sham	100	histological analysis	no effect on number and growth of tumours
Frei et al (1998)[20] Replication of Frei et al. (1998)[19]	female C3H/HeJ mice, wildtype with high mammary cancer incidence 3-4 wk + 10 d	none	2450 MHz 20 h/d, 7 d/wk, 78 wk 0.3-1.0 W/kg	no	free	sham	100	histological analysis	no effect on number and growth of tumours
Jauchem et al. (2001)[21]	female C3H/HeJ mice, 3-4 wk + 10 d	none	UWB 2 min/wk, 12 wk 40 kV/m peak; 0.0098 W/kg	no	free	sham	100	histological analysis	no effect on tumour incidence, survival
CNS tumour, non-transgenic animals									
La Regina et al. (2003)[25]	male and female Fischer 344 rats, wildtype 4+2 wk CNS & other tumours	none	FDMA 835 MHz, CDMA 847 MHz 4 h/d, 5 d/wk, 2 y 1.3 ± 0.5 W/kg (brain)	no	restrained	sham	160 (80 m, 80 f)	histological analysis	no effect of either signal on brain or other tumours

Anderson et al. (2004)[26]	male and female Fischer 344 rats, wildtype 4 d before birth brain and other tumours	none	Iridium 1.6 GHz 2 h/d, 7 d/wk (perinatal); 2 h/d, 5 d/wk, 2 y (postnatal) brain: 0.16 W/kg (perinatal); 0.16, 1.6 W/kg (postnatal)	yes	free	sham, cage control	exp.: 180 (90 m, 90 f) contr.: 160 (80 m, 80 f)	postnatal exposure, histological analysis	males: no effect survival; females: lower survival cage-controls; no effect brain or other tumours
Multiple tumour, non-transgenic animals									
Chou et al. (1992)[27]	male Sprague Dawley rats, wildtype 3 + 5 wk	none	2450 MHz, pulsed 21.5 h/d, 25 mo 0.15-0.4 W/kg	yes	free	sham	100	histological analysis	no overall effect on tumour development; more primary malignant tumours in exposed; no effect on benign tumours and overall survival
Ivanov et al. (2005)[28]	inbred albino mice and adult C57Bl/6 mice (sex not specified); wildtype adults & progeny age not provided	none; some groups exposed in previous experiments	37 GHz repeatedly f or 1 mo, total exposure 3.5 h <10 mW/cm^2	no	unknown	cage control	unknown	no	decreased survival in C57Bl/6 adults and F1; tumour formation in albino
Smith et al. (2007)[29]	male and female Han Wistar rats, wildtype 4-5 + 2 wk	none	GSM 900 MHz, DCS 1800 MHz 2 h/d, 5 d/wk, 104 wk 0.44, 1.33, 4.0 W/kg	no	restrained	sham, cage control	130 (65 m, 65 f)	yes	no effect on survival and carcinogenesis
Tillmann et al. (2007)[30]	male and female B6C3F1/Crl BR mice, wildtype 4-5 + 4 wk	none	GSM 902 MHz, DCS 1747 MHz 2 h/d, 5 d/wk, 24 mo 0.4, 1.3, 4.0 W/kg	yes	restrained	sham	130 (65 m, 65 f)	yes	no effect GSM, decreased number of tumours after DCS

Jin et al. (2011)[31]	male and female Sprague Dawley rats, wildtype 5 + 1 wk	none	CDMA, WCDMA 45 min/d, 5 d/wk, 12 mo 4.0 W/kg	no	free	sham	40 (20 m, 20 f)	yes	no difference in tumour incidence
Multiple tumours, transgenic animals									
Saran et al. (2007)[32]	CD-1 mice heterozygous for Patched1, transgenic, X-ray tumour prone 2 d	none	GSM 900 MHz 2x0.5 h/d, 5 d 0.4 W/kg	yes	restrained	sham	50-63 (m+f)	yes	no effect on survival and carcino-genesis
RF+ initiator									
Lymphoma, non-transgenic animals									
Heikkinen et al. (2001)[33]	female CBA/S mice, wildtype 3-5 wk lymphomas and other tumours	X-ray	NMT 902 MHz, GSM 902 MHz 1.5 h/d, 5 d/wk, 78 wk NMT: 1.5 W/kg; GSM: 0.35 W/kg	yes	restrained	sham, cage control	50	histological analysis	no effect on X-ray induced lympho-mas, other neoplasms or survival
Skin tumour, non-transgenic animals									
Szmigiel-ski et al. (1982)[17]	male Balb/c mice, wildtype 6 wk	BAP	2450 MHz 2 h/d, 6 d/wk, 10.5 mo 2-3, 6-8 W/kg	no	free, 10 / cage	sham	40	no	dose-dependent acceleration of skin cancer
Szudzin-ski et al. (1982)[34]	male Balb/c mice, wildtype adult, age not provided	BAP	2450 MHz 2 h/d, 6 d/wk, 1, 2, 3, 6 mo 2-3, 6-8 W/kg during BAP; 4 W/kg 1, 2, 3 mo before BAP	no	free, 10 / cage	BAP + sham	100	no	dose-dependent acceleration of skin cancer; in part same data as Szmigiel-ski et al. (1982)
Imaida et al. (2001)[35]	female CD-1 mice, wildtype 5 wk	DMBA	TDMA 1.5 GHz 1.5 h/d, 5 d/wk, 19 wk 2.0 W/kg	no	restrained	sham, positive control (TPA), cage control	30, 48	no	no effect RF on skin tumour
Mason et al. (2001)[36]	female SENCAR mice, wildtype 4-5 wk + 10 d	DMBA	94 GHz 10 s (1 W/cm^2); 10 s, 2/wk, 12 wk (0.333 W/cm^2)	no	restrained	sham, positive control (TPA), infrared, cage control	27-55	no	no effect RF on skin tumour

Huang et al. (2005)[37]	male ICR mice, wildtype 6 wk	DMBA	849, 1763 MHz 2x45 min/d, 5 d/wk, 19 wk 0.4 W/kg	no	free	sham, positive control (TPA)	20	histological analysis	no effect RF on skin tumour
Paulraj & Behari (2011)[16]	male Swiss mice, wildtype 7-8 wk skin, ascites tumour	DMBA	112 MHz, 16 Hz AM; 2.54 GHz 2 h/d, 3 d/wk, 16 wk 112 MHz: 1 mW/cm², 0.75 W/kg; 2.54 GHz: 0.34 mW/cm², 0.1 W/kg	no	free	sham	18	no	no effect RF on skin and ascites tumour
Skin tumour, transgenic and non-transgenic animals									
Heikkinen et al. (2003)[38]	female K2 mice, wildtype and ODC transgenic mice 12-15 wk	UV	GSM, DAMPS 1.5 h/d, 5 d/wk, 52 wk 0.5 W/kg	yes	restrained	sham, cage control	45-49, cage contr.: 20	RF sham: histological analysis	non-significant acceleration of tumour growth
Mammary tumour, non-transgenic animals									
Bartsch et al. (2002)[40]	female Sprague Dawley rats, wildtype 38+13 d; 43+8 d;34+17 d	DMBA	GSM 900 MHz continuously max 0.08 W/kg	no, but decline in SAR taken in consideration	free	sham	60	histological analysis ; animal control in experiment 3	no effect on tumour latency and incidence
Anane et al. (2003)[41]	female Sprague Dawley rats, wildtype 55 d	DMBA	GSM 900 MHz 2 h/d, 5 d/wk. 9 wk 0.1, 0.7, 1.4, 1.4, 2.2, 3.5 W/kg	no	restrained	sham, cage control	16 (cage contr.: 8)	histological analysis	no effect on tumour latency, volume, multiplicity; in 1st of 2 experiments inverse dose relation for incidence
Yu et al. (2006)[42]	female Sprague Dawley rats, wildtype 36 + 12 d	DMBA	GSM 900 MHz 4 h/d, 5 d/wk, 26 wk 0.44, 1.33, 4.0 W/kg	no, but variation of 1.93 dB noted	restrained	sham, cage control	100	exposure, histological analysis	no effect on tumour latency, size, multiplicity, incidence; incidence and latency higher in cage controls

Hruby et al. (2008)[43]	female Sprague Dawley rats, wildtype 5 wk + 12 d	DMBA	GSM 902 MHz 4 h/d, 5 d/wk, 6 mo 0.4, 1.3, 4.0 W/kg	no, but lifetime variation of 1.0 dB noted	restrained	sham, cage control	100	exposure, histological analysis	inconsis-tent effect on tumour number, incidence; incidence higher in cage controls
Liver tumour, non-transgenic animals									
Imaida et al. (1998)[44]	male and female Fischer 344 rats, wildtype 5 + 1 wk	DEN	TDMA 929 MHz 1.5 h/d, 5 d/wk, 6 wk 1.7-2.0 W/kg	no	restrained	sham, cage control	48	no	no effect on foci number, size, but increase in serum ACTH, cortico-sterone, melatonin
Imaida et al. (1998)[45]	male and female Fischer 344 rats, wildtype 5 + 1 wk	DEN	TDMA 1439 MHz 1.5 h/d, 5 d/wk, 6 wk 0.937-1.91 W/kg	no	restrained	sham, cage control	48	no	no effect on foci number, size, but increase in serum ACTH, cortico-sterone, melatonin
CNS tumour, non-transgenic animals									
Adey et al. (1999)[22]	male and female Fischer 344 rats , wildtype gestation d 15 + 3 d	ENU	NADC 835 MHz 2 h/d, 7 d/wk (prenatal), 4 d/wk (postnatal), 2 y 0.33-0.53 W/kg	yes	free (prenat.), restrained (postnat.)	sham	236	histological analysis	reduced incidence spontaneou s and ENU-induced tumours
Adey et al. (2000)[23]	male and female Fischer 344 rats, wildtype gestation d 15 + 3 d	ENU	FM 836 MHz 2 h/d, 7 d/wk (prenat.), 4 d/wk (postnat.), 2 y 1.0, 1.2 W/kg	yes	free (prenat.), restrai-ned (postnat.)	sham	90	histological analysis	no effect of RF on survival, tumour incidence
Zook & Simmens (2001)[24]	male and female Sprague Dawley rats, wildtype 57 ± 4 d	ENU (mothers)	860 MHz pulsed, CW 6 h/d, 5 d/wk, 22 mo 1.0 ± 0.2 W/kg	no	restrained	sham, cage control	60	histological analysis	no RF effect on neurogenic or other tumours

Zook & Simmens (2006)[46] Replication of Zook & Simmens (2001)[24]	male and female Sprague Dawley rats, wildtype 52 ± 2 d	ENU (mothers)	860 MHz pulsed 6 h/d, 5 d/wk, 325 d 1.0 ± 0.2 W/kg	no	restrained	sham, cage control	30 (serial killing experiment)	histological analysis	no RF effect on neurogenic tumours
Shirai et al. (2005)[47]	male and female Fischer 344 rats, wildtype gestation d 18	ENU	TDMA 1439 GHz 90 min/d, 5 d/wk, 104 wk 0.67, 2.0 W/kg	yes	restrained	sham, cage control	100	histological analysis	lower incidence pituitary tumours in males after high dose RF, no other RF effect on neurogenic or other tumours and serum hormones
Shirai et al. (2007)[48]	male and female Fischer 344 rats, wildtype gestation d 18	ENU	WCDMA 1.95 GHz 90 min/d, 5 d/wk, 104 wk 0.67, 2.0 W/kg	yes	restrained	sham, cage control	100	histological analysis	no RF effect on neurogenic or other tumours
Colon tumour, non-transgenic animals									
Wu et al. (1994)[49]	male and female Balb/c mice, wildtype 4-5 wk	DMH	2450 MHz 3 h/d, 6 d/wk, 5 mo 10-12 W/kg	no	restrained	sham	26-32	no	no RF effect
Sarcoma, non-transgenic animals									
Chagnaud et al. (1999)[50]	female Sprague Dawley rats, wildtype 2 mo	BAP	GSM 900 MHz 2 h/d, 2 wk 0.075 ± 0.025, 0.27 ± 0.09 W/kg	no	restrained	sham	6 (contr.), 7-9 (exp.)	no	no effect on tumour development or growth, on survival and on serum autoantibodies
Multiple tumours									
Heikkinen et al. (2006)[51]	female Wistar rats, wildtype 7 wk	MX	GSM 900 MHz 2 h/d, 5 d/wk, 104 wk 0.3, 0.9 W/kg	no	free	sham, cage control	72	histological analysis	no effect on survival and carcinogenesis

Tillmann et al. (2010)[52]	female B6C3F1 mice, wildtype 6 d post conception	ENU	UMTS continuously 24 mo 0, 4.8, 48 W/m²	yes	free	sham, ENU cage control	54-60	yes	increased number of malignant lung tumours and benign liver tumours; no effect other tumours; no ENU +sham control
Implanted tumours									
Skin tumour									
Santini et al. (1988)[53]	female C57Bl/ 6J mice, wildtype, implanted melanoma 5 wk	none	2450 MHz, pulsed, CW 2.5 h/d, 6 d/ wk, lifelong 1.2 mW/kg	no	free, 15 / cage	sham	15	no	no effect melanoma tumour growth, survival
CNS tumour									
Salford et al (1993)[54]	male and female Fischer 344 rats, wildtype age not provided, weight 150-250 g	none	915 MGz CW and pulsed 4, 8, 16, 50, 217 Hz 7 h/d, 5d/wk, 2-3 wk 4 Hz: 0.0077 W/kg; 8 Hz: 0.016 W/kg; 16 Hz: 0.030 W/kg; 50 Hz: 1 W/kg; 217 Hz: 0.4 W/kg; CW: 1.67 W/kg	no	restrained	sham	37	histological analysis	overall no effect of exposure on tumour growth; large variation due to use of inoculated cells
Salford et al. (1997)[55]	male and female Fischer 344 rats, wildtype age, weight not provided,	none	915 MHz CW and pulsed 4, 8, 16, 50, 217 Hz 7 h/d, 5d/wk, 9-15 d 4 Hz: 0.0077 W/kg; 8 Hz: 0.016 W/kg; 16 Hz: 0.030 W/kg; 50 Hz: 1 W/kg; 217 Hz: 0.4 W/kg; CW: 1.67 W/kg	no	restrained	sham	4-29	histological analysis	overall no effect of exposure on tumour growth; large variation due to use of inoculated cells, probably includes results from 1993 study

Higashi-kubo et al. (1999)[56]	male Fischer 344 rats, wildtype 28 d	none	FM CW 835 MHz, CDMA 847 MHz 4 h/d, 5 d/wk, 4 wk 0.75 ± 0.25 W/kg	no	restrained	sham	12-67 (sham), 10-49 (FMCW), 22-38 (CDMA), groups from 2 exp. com-bined	histological analysis	no effect of RF on survival, indepen-dent of number of cells injected
Ascites tumour									
Paulraj and Behari (2011)[16]	male Swiss mice, wildtype 7-8 wk	none	112 MHz, 16 Hz AM; 2.54 GHz 2 h/d, 3 d/wk, 16 wk 112 MHZ: 1 mW/cm^2, 0.75 W/kg; 2.54 GHz: 0.34 mW/cm^2, 0.1 W/kg	no	free	sham	8	no	no effect
Sarcoma									
Preskorn et al. (1978)[57]	male and female CWF mice, wildtype d 11 gestation	none	2450 MHz 20 min/d, 3(pre)+36 d (postnatal); 4 d prenatal 35 W/kg	no	free	sham	12	palpation and histological analysis	lower incidence and longer survival with/ without tumour after prenatal exposure
Szmigiel-ski et al. (1982)[17]	male Balb/c mice, wildtype 6 wk	none	2450 MHz 2 h/d, 6 d/wk, 3 mo 2-3, 6-8 W/kg	no	free, 10 / cage	sham, confine-ment stress	not provi-ded	no	dose-dependent increased number of sarcoma lung nodules

Abbreviations: OR: odds ratio; SAR: specific absorption rate
Carcinogens: UV: ultraviolet; BAP: benzo(a)pyrene; DMBA: 7,12-dimethybenz[a]anthracene; TPA: 12-O-tetradecanoylphorbol-13-acetate; DEN: diethylnitrosamine; ACTH: adrenocorticotrope hormone; ENU: ethylnitrosourea; DMH: ethylnitrosourea; MX: 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone; CaCl: calcium chloride; Fe-ATP: ferric-adenosine triphosphate complex; Al lactate: aluminum lactate
RF sources: GSM: Global System for Mobile ommunication; UMTS: Universal Mobile Telecommunications Signal; CDMA: Code Division Multiple Access; WCDMA: Wideband Code Division Multiple Access; NMT: Nordic Mobile Telephony; CW: continuous wave; TDMA: Time Division Multiple Access; DAMPS: Digital Advanced Mobile Phone System; UWB: ultra wide band; FDMA: Frequency-Division Multiple Access; NADC: North American Digital Cellular; FM: Frequency Modulation; DCS: Digital Communication Signal.

Annex **D**

Abbreviations

BAP	benzo(a)pyrene or 3,4 benzopyrene, a skin carcinogen
CDMA	Code Division Multiple Access – a second generation or 2G type of signal used in mobile telephony (predominantly in the USA and Japan)
CNS	Central Nervous System
DAMPS	Digital Advanced Mobile Phone System – a second generation or 2G type of signal used in mobile telephony in the USA and Canada
DCS	Digital Communication Signal – a second generation or 2G type of signal used in mobile telephony (similar to GSM, but with a higher frequency)
DMBA	7,12-dimethybenz[a]anthracene, a carcinogen
DMH	dimethylhydrazine, a carcinogen
EMF	electromagnetic fields
ENU	ethylnitrosourea, a carcinogen
FDMA	Frequency Division Multiple Access – a type of signal used in mobile telephony, especially in satellite communication
FM	Frequency Modulation: information is transmitted by variations in the basic frequency of the carrier wave signal
GHz	gigahertz: 10^9 Hz
GSM	Global System For Mobile Communication – a second generation or 2G type of signal used in mobile telephony

GSPC	Gold Standard Publication Checklist
Hz	hertz, unit of frequency; 1 Hz equals one cycle per second
IARC	International Agency for Research on Cancer
Iridium	a mobile telecommunication signal used by the Iridium satellite system
MHz	megahertz: 10^6 Hz
MX	3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone, a mutagen
NADC	North American Digital Cellular – a third generation or 3G type of signal used in mobile telephony in the USA
NMT	Nordic Mobile Telephony – a first generation or 1G type of signal used in mobile telephony
ODC	ornithine decarboxylase, an enzyme involved in carcinogenesis
RF	radiofrequency
SAR	Specific Absorption Rate – the rate of absorption of radiofrequency electromagnetic energy in a body; used as a measure of RF EMF exposure
TDMA	Time Division Multiple Access – a type of signal used in mobile telephony; GSM and DAMPS are TDMA signals
UMTS	Universal Mobile Telecommunications Signal – a third generation or 3G type of signal used in mobile telephony
UV	ultraviolet (radiation)
WCDMA	Wideband Code Division Multiple Access – a third generation or 3G type of signal used in mobile telephony; similar to UMTS
WHO	World Health Organization
W/kg	Watt per kilogram, the unit in which the SAR is expressed

Health Council of the Netherlands

Advisory Reports

The Health Council's task is to advise ministers and parliament on issues in the field of public health. Most of the advisory reports that the Council produces every year are prepared at the request of one of the ministers.

In addition, the Health Council issues unsolicited advice that has an 'alerting' function. In some cases, such an alerting report leads to a minister requesting further advice on the subject.

Areas of activity

Optimum healthcare
What is the optimum result of cure and care in view of the risks and opportunities?

Prevention
Which forms of prevention can help realise significant health benefits?

Healthy nutrition
Which foods promote good health and which carry certain health risks?

Environmental health
Which environmental influences could have a positive or negative effect on health?

Healthy working conditions
How can employees be protected against working conditions that could harm their health?

Innovation and the knowledge infrastructure
Before we can harvest knowledge in the field of healthcare, we first need to ensure that the right seeds are sown.

www.healthcouncil.nl