



**INTERNATIONAL AGENCY FOR RESEARCH ON CANCER
WORLD HEALTH ORGANIZATION**

**INTERPHONE
International Case Control Study of Tumours
of the Brain and Salivary Glands**

Protocol, *rev. 1*

Prepared by:

Elisabeth Cardis and Monique Kilkenny

***International Agency for Research on Cancer
Lyon, 2001***

IARC INTERNAL REPORT 01/002

LIST OF PARTICIPATING INSTITUTIONS

Australia

- Cancer Control Information Centre, New South Wales Cancer Council, Sydney

Canada

- University of Ottawa, Faculty of Medicine, Epidemiology and Community Medicine
- Institut Armand Frappier, Université du Québec, Laval, Québec
- Cancer Control Research, British Columbia Cancer Agency, Vancouver

Denmark

- Danish Cancer Society, Division for Cancer Epidemiology, Copenhagen

Finland

- Finnish Centre for Radiation and Nuclear Safety, Helsinki

France

- Institut de Médecine du Travail, Lyon

Germany

- Dep. of Epidemiology and Medical Statistics, School of Public Health, University Bielefeld
- Division of Epidemiology, DKFZ German Cancer Research Centre, Heidelberg
- Institut für Medizinische Statistik und Dokumentation, Johannes Gutenberg-Universität, Mainz

Israel

- Chaim Sheba Medical Centre, Tel-Hashomer

Italy

- Istituto Superiore di Sanità, Rome

New Zealand

- Wellington School of Medicine, University of Otago, Wellington South

Japan

- National Cancer Center Research Institute, Tokyo
- Keio University School of Medicine, Tokyo, Japan
- Ministry of Posts and Telecommunications, Tokyo

Norway

- Norwegian Radiation Protection Authority, Osteras

Sweden

- Karolinska Institute, Institute of Environmental Medicine, Division of Epidemiology, Stockholm

UK

- Unit of Epidemiology and Health Services Research, Leeds University, Leeds
- National Radiological Protection Board, Didcot
- Scottish Cancer Intelligence Unit, NHS, Scotland
- Section of Epidemiology, Institute of Cancer Research, Sutton

International Organisations

- International Agency for Research on Cancer (IARC), Lyon, France

Table of contents

| | |
|--|----|
| I. INTRODUCTION | 1 |
| A. BACKGROUND | 1 |
| B. STUDY OUTCOMES | 3 |
| C. CRITERIA FOR INCLUSION OF STUDY CENTRES IN THE INTERNATIONAL STUDY | 4 |
| II. OBJECTIVE..... | 5 |
| III. STUDY DESIGN..... | 5 |
| A. STUDY REGIONS | 5 |
| B. STUDY POPULATION | 5 |
| C. STUDY PERIOD..... | 6 |
| D. DEFINITION OF CASES | 6 |
| E. CASE ASCERTAINMENT | 7 |
| F. DEFINITION OF CONTROLS | 8 |
| G. INFORMED CONSENT | 9 |
| H. COLLECTION OF INFORMATION | 9 |
| I. DATA COLLECTION..... | 12 |
| J. EXPOSURE ASSESSMENT | 12 |
| K. ANALYSES | 14 |
| IV. ORGANISATION OF THE STUDY | 16 |
| A. STUDY PROTOCOL..... | 16 |
| B. THE STUDY GROUP | 16 |
| C. SUBCOMMITTEES..... | 17 |
| D. CO-ORDINATION..... | 18 |
| E. USE OF DATA | 18 |
| F. PUBLICATIONS..... | 19 |
| G. FINANCIAL ASPECTS..... | 19 |
| V. TIMETABLE..... | 20 |
| VI. ACKNOWLEDGEMENTS | 20 |
| VII. REFERENCES | 20 |
| APPENDIX A – DISTRIBUTION OF SAR IN HEAD FROM DIFFERENT TYPES OF MOBILE TELEPHONES..... | 21 |
| APPENDIX B – CODING OF TUMOURS AND ELIGIBILITY CRITERIA..... | 22 |
| APPENDIX C – PROCEDURES FOR TUMOUR LOCALISATION FOR EXPOSURE ASSESSMENT PURPOSES | 25 |
| APPENDIX D – PROTOCOL OF VALIDATION STUDY | 33 |
| APPENDIX E – COMMITTEE MEMBERSHIP | 41 |

I. INTRODUCTION

A. Background

On 20-21 November 1996, an international symposium “Biological effects of non-thermal pulsed and amplitude modulated RF-electromagnetic fields and related health hazards” was held in Munich, Germany. The objectives of this symposium were to address the health effects of low-level (non-thermal and athermal) exposure to radio frequency (RF) radiation in the range 100 kHz to 300 GHz and to review the state of current research in relation to exposure assessment, in vivo and in vitro studies and epidemiology. It concluded that it is unlikely that RF produce genotoxic effects and the most likely mechanism in relation to carcinogenesis, if any, is a possible promotion or progression effect (Repacholi, 1998). An EU expert group also recently reviewed the state of knowledge about RF (McKinlay, 1997).

In view of the current limited state of knowledge concerning the possible adverse health effects of RF exposure, and of the increasingly widespread use of portable telephones in many countries, both the Munich meeting and the EU expert group recommended that, research – in particular epidemiological studies – be carried out to determine whether radiotelephones could cause adverse health effects. The conclusions of these groups in terms of research priorities for epidemiological studies are similar and include:

1. Studies of the relationship between use of hand-held mobile phones and the incidence of (a) brain tumours (b) salivary gland tumours, acoustic neurinomas and other head and neck tumours (c) leukaemia and lymphomas
2. Cohorts with high occupational exposure should be followed with respect to cancer e.g.: members of military forces, plastic heat sealers and physiotherapists
3. Adverse pregnancy outcomes in various highly exposed occupational groups should be followed in cohort studies

As a result of these recommendations, on 8 and 9 October 1997, a meeting was held in London – as a joint initiative of the International Agency for Research on Cancer (IARC) in Lyon and the Leukaemia Research Fund (LRF) in Leeds. The objective of the meeting was to discuss the possibility of carrying out a multi-centric study of adult brain, head and neck tumours to assess whether RF radiation emitted by mobile telephones could be carcinogenic. The meeting recommended that, "in a first phase, a study be carried out to:

- evaluate the feasibility of conducting a case-control study that would be informative concerning the existence of a cancer risk from RF from mobile telephones
- and, if appropriate, to devise a common core protocol for this study".

The advantage of setting up a large-scale multicentric study if the feasibility study were successful would be to maximise statistical power, and in turn, increase the probability of detecting any health effect from this exposure. Although mobile telephone use is now very prevalent, it was much more rare five to ten years ago. Only by carrying out a well-targeted multi-centric study focusing on areas and populations (restricted age range) with longest phone use would sufficient power be achieved to test the hypothesis that RF exposures at these levels may promote the risk of cancer in the organs most exposed (the acoustic nerve, salivary glands and parts of the brain – mainly the meninges and the glial cells).

A multinational feasibility study was therefore set-up and carried out between March 1998 and December 1999. Fourteen countries participated in the feasibility study: Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden, UK and the United States. The objectives of the feasibility study were to collect and analyse the information necessary to assess the feasibility of a multi-centric study of Adult Head and Neck Tumours

(including brain tumours) and Mobile Telephones. The specific aims of the feasibility study were as follows:

- *Collection of exposure information from companies:* Service providers and network operators were to be approached to describe the history of the mobile phone industry in each country and determine the nature and availability of historical records on mobile phone use. In particular, the feasibility and possible costs of accessing billing records were to be evaluated.
- *Collection of information on exposure profile of the population:* The results of market surveys were to be accessed or, if not available, a population survey (possibly in collaboration with telephone companies) was to be carried out to determine the age and sex distribution of phone use over time in the target populations.
- *Collection of information on age-sex-period specific incidence of tumours of interest:* Information on incidence in the study areas (or nearby regions when unavailable) was to be collected as well as, where appropriate, on number of cases treated in the hospitals to be included in the study
- *Evaluation and testing of the data collection procedures:* Procedures to be followed in the national case-control studies, with special reference to mechanisms of case identification and ascertainment and control selection, were to be tested in order to inform final decisions concerning the health outcomes to be considered in the study.
- *Testing of the study questionnaire:* The draft study questionnaire was to be translated – where appropriate – and tested on a limited number of individuals (possibly a convenience sample including some mobile phone subscribers). Validation of the answers on mobile phone use was also to be carried out with the help of records from phone companies.
- *Power calculations.* Information on the historical use of mobile phones and incidence of the tumours of interest in the target areas in participating countries was to be used to calculate the necessary sample size for the case-control study to be informative.

The conclusion of the study was that there was sufficient use of mobile telephones in the past in the participating regions for an international study, based on *2 years of case ascertainment to have nearly 100% power to detect, with 95% confidence, a 1.5 fold increase in risk in the tumours of interest associated with use of mobile phones 5 years in the past** (Cardis and Kilkenny, 1999). For use 8 or more years in the past, the power of the study for some tumour types is slightly less, as indicated below.

| Tumour | Case-control ratio | Number of study subjects | | Estimated power (%) | |
|----------------------|--------------------|--------------------------|----------|---------------------|----------|
| | | Cases | Controls | 5 years | 8+ years |
| Brain tumours | 1:1 | 7420 | 7420 | 100 | 100 |
| Acoustic neurinoma | 1:2 | 1080 | 2415 | 99.3 | 87.2 |
| Parotid gland tumour | 1:3 | 796 | 2175 | 98.7 | 74.8 |
| Acute Leukaemia | 1:3 | 1298 | 3294 | 99.7 | 85.1 |

A decision was therefore made to go ahead with an international study, based on a “core” protocol describing common procedures to be followed in all participating countries. National studies, however, might have specific features or a wider scope than the international study (e.g., covering a wider age range or more types of brain tumours).”

* Note: As mentioned above, the EU and WHO expert groups concluded that the *most likely mechanism in relation to carcinogenesis, if any, is a possible promotion or progression effect*. On that basis, one would expect the latent period (time between an exposure and the subsequent cancer associated with it) to be shorter than if RF were acting as an initiating agent. Thus, the effect of exposure could possibly be seen within 5 – 10 years of exposure.

The current document is the core protocol for this study.

B. Study outcomes

Relative RF exposure to various tissues during mobile phone use – general considerations

As no biological mechanism for the carcinogenic effect – if any – of RF radiation has been identified, the "dosimetric quantity" of interest is not known. At much higher levels of exposure, where tissue heating is the outcome of concern, the relevant dosimetric quantity is the specific absorption rate (SAR) in the target tissue, which is defined as the power absorbed per second by 1 kg of biological tissue. It is often assumed that the SAR is also the relevant quantity for long-term health effects, although there is no evidence of this and other parameters of exposure may be more appropriate. The relevant dosimetric quantity could be, for example, cumulative RF energy absorption in an (unknown) etiologically relevant time window, peak SAR or the proportion of time with SAR's above a certain level. A continuous exposure resulting in 10 J may therefore not necessarily have the same effect as 10 different calls resulting in a cumulative absorbed energy of 10 J.

In order to define the study outcomes of interest, however, the tissues exposed to RF from mobile telephones must be identified. Relevant levels of exposure due to mobile phone use are received only in the immediate vicinity (within 2 cm) of the handset and consist mainly of RF of the frequency of operation (around 450, 900, 1800 and 1900 MHz) and, to a far lesser extent, ELF in the 10-20 Hz range.

Most (over 50%) of the absorbed energy (itself about 50% of the emitted energy) from mobile telephone use is absorbed by the head in a cube of 5 cm³. Of this, most is absorbed by the skin, the salivary glands and the external ear; only 20-30% is absorbed by the brain as a whole. This is illustrated by the figures from (Rothman et al, 1996) in Appendix A. The first two figures show the position of the phone in relation to the head during a normal phone call using a classic "banana" mobile phone (Figure 3) and a hand-held portable "flip" mobile telephone (Figure 4) and the specific absorption rate (SAR) recorded at several locations on the head during this exposure. From Figure 4 we see that with the flip phones the highest SARs (1.1 and 0.9mW, respectively) are seen in front of the ear and directly over the ear with considerably lower SARs along the cheek and directly behind the ear. Figure 5 shows the attenuation of exposure with tissue depth. The exposure to brain tissue closest to the surface of the head is lower by up to a factor of 2 than the peak exposure to the surface of the face and is attenuated by over 90% at 5 cm depth (Rothman et al, 1996).

Thus, absorbed energy is relatively high only for that small fraction of glial and meningeal tissue which is located at the outermost surface of the lower anterior portion of the parietal lobe, and only on the side of the head where the telephone is used. Any active marrow in the flat bones of the cranium directly over this region would also be exposed. SARs would be relatively high at the surface of the vestibular portion of the eighth cranial nerve (acoustic nerve) where acoustic neurinoma arise. SARs may be similarly high at the parotid gland, which is located in the cheek directly below the ear starting at a depth of about 1 cm. SARs would be expected to be considerably lower at other head and neck locations including the cerebellum, midbrain, eyes and thyroid gland.

These observations, along with the unique characteristics of several types of cancers and/or tumours and other factors such as biological plausibility, latency considerations, prevalence, severity, prognosis etc. should be the deciding factors in what tissues are of greatest concern in terms of RF exposure. The following tumours should be considered for inclusion in the case control studies: tumours of the brain and cranial meninges, in particular acoustic neurinomas, tumours of the parotid gland and leukaemia.

C. Criteria for inclusion of study centres in the International Study

At the outset, the following minimum set of criteria that must be met by each proposed study centre to be accepted for participation in the study was established by the epidemiology subcommittee:

1. *Sufficiently high prevalence of past mobile telephone use:* The prevalence in the study population in each country should be at least 5% five years before the beginning of the study and 0.5% eight years before. Lower prevalence would make the study inefficient.
2. *Sufficient numbers of cases should be available,* at least 100 cases for the study of brain tumours.
3. *Highly complete population-based ascertainment of cases.*
4. *Satisfactory diagnostic confirmation available for a high percentage of diagnosed cases (see below)*
5. *Use of an appropriate non-biased control group.*
6. *Non-biased methods for data collection applied in the same way to cases and controls.*
7. *Personal interview for data collection.*
8. *Availability of recorded exposure data for the validation study.*
9. *Willingness of investigators to use the agreed study questionnaire for data collection (whether or not they also include further questions of their own), to follow the general study design agreed by the group, to enter data into combined analyses, and to follow agreed mechanisms to prevent inappropriate preliminary publications.*

II. OBJECTIVE

The primary objective of the study is to assess whether radio frequency (RF) radiations emitted by mobile telephones are carcinogenic.

The secondary objective of the study is to assess whether the use of mobile telephones increases the risk of cancer.

III. STUDY DESIGN

The study is designed as a **population-based case-control study**

A case-control approach was chosen – over the cohort study – as the most cost-efficient epidemiological design to address this issue at the international level. A prospective cohort study design was also considered, but this approach was rejected at the international level because of logistic and ethical constraints in many of the interested countries and because of the extremely large cost which would be required to carry out a study with the same statistical power as a multicentric case-control study (the study population would need to cover millions of persons, with individual exposure estimates, who would need to be followed-up prospectively for years).

The outcomes under study are as follows:

- Brain tumours (particularly gliomas and meningiomas)
- Salivary gland tumours (particularly tumours of the parotid gland)
- Acoustic neurinomas

In most countries/study regions investigators will focus on either two or three outcomes (brain tumours, salivary gland tumours and acoustic neurinomas). Although a small number of centres also planned to study acute leukaemia, this outcome is not included in the current protocol; a separate protocol will be prepared if funding for this study can be found. The tumour types included in each country/region are specified in the country-specific section of the Procedures Document.

A. Study regions

In most countries, the study population has been restricted to **major metropolitan areas** for the following reasons:

- As mobile telephone use was first introduced in these areas, these are the regions with the highest prevalence of mobile telephone use in the general population in the past;
- The major treatment centres for the diseases of interest are concentrated in these areas and the population of these areas is unlikely to go out of the region for diagnosis and treatment, thus ensuring nearly complete ascertainment of the cases;
- By focusing the study area on these populations, it facilitates face-to-face interviews, as distances to be travelled by interviewers are not unreasonable.

The study regions are given, by country, in the country-specific section of the Procedures Document.

B. Study population

The study population consists of **all persons** (men and women) **aged 30 to 59 who reside in the study regions**.

The study population is restricted to this age range in order to maximise the informativeness of the study with respect to assessing the role of mobile telephones and RF radiations in the aetiology of these cancers. Mobile telephone use is a relatively new phenomenon in the regions and countries under study. In the beginning, for economic and social reasons, mobile telephone use was mainly restricted to “business aged” persons (25-54) in many of the countries under study.

As the study assumes a latency period of at least five years, these persons will mostly be in the age range 30-59 during the study period. Inclusion of younger and older ages in all countries would considerably increase the sample size of the study, without materially adding to its power (Cardis and Kilkenny, 1999), as well as lead to the inclusion of tumours with recognised different aetiology.

C. Study period

Two phases are foreseen:

- In the first phase, to be started in 1999 or 2000 (once funding is obtained), case and control ascertainment will cover a period of **2 to 3 years** depending on the study and region: recruitment will generally be over 2 years for the brain tumour case-control study and 3 years for the other studies.
- Depending on the outcome of the first phase, a second phase is envisaged, to be started about five years later (2004-2005), in order to investigate the possibility of a carcinogenic risk with a longer (10 years or more) latency period.

D. Definition of cases

The cases are **all patients** with one of the following **histologically confirmed** diagnoses¹:

- primary glioma or meningioma of the brain (benign or malignant),
- acoustic neurinoma (neuroma)
- malignant tumours of the parotid glands

who are diagnosed during the study period in the study regions and who meet the following criteria:

- possess the intellectual and language skills necessary to complete the interview;
- have given informed consent.

The eligibility criteria for cases, related to the timing and mode of diagnosis, are listed in Appendix B, *Coding of tumours and eligibility criteria*.

Inclusion of Proxies – For deceased cases and for cases who are too ill to be interviewed, a proxy respondent will be interviewed. The proxy will be chosen from the subject's close family, in the following order: 1: spouse (partner if not married); 2: oldest child (at least 18), if no spouse; 3: closest relative with knowledge of the subject's habit, if no child – this will preferably be a brother or sister (at least 18) or parent (spouse, sibling, parent) –; or 4: a close friend. While recruitment methods for proxy subjects may vary between centres, the choice of the proxy should preferably be one who has spent the most time with the subject during the exposure period, that is, while the subject was using a mobile telephone. The quality of information on variables of interest that could be obtained from proxies is uncertain, however, and response rates among relatives of deceased cases may be quite low. The objective of including proxies is to evaluate the possibility of a bias arising from the exclusion of deceased and very ill subjects. The questionnaire used with proxy respondents will be an abbreviated form of the full questionnaire. Interviews of proxies for living subjects will also be carried out in a number of countries (see Procedures Document) to test the accuracy of information obtained from proxies.

¹ Diagnoses may be confirmed histologically, or on the basis of imaging (see below)

E. Case Ascertainment

Brain tumour case-control study

Source

Case ascertainment should be rapid so that interviews can be scheduled as soon as possible after diagnosis, in order to minimise the number of cases whose participation may be restricted by death or deteriorating health. In the case of gliomas, the interval from diagnosis to ascertainment should be within three weeks. Interviews should take place as soon as possible after that time.

The **primary source** for ascertainment of cases of brain tumours will be the appropriate departments (pathology, surgery, radiology, etc) of the **participating health institutions** (see country specific section of Procedures document). Where population-based cancer registries exist, they will be used as a secondary source to ensure the completeness of the case ascertainment for malignant tumours (and benign tumours where they are registered).

Verification

All cases should be histologically confirmed – either from surgery or biopsy material – and the histopathology report should be available. Cases that are diagnosed on the basis of unequivocal imaging results¹ will be included also in the study – copies of the radiology report should be retained. These will be examined by study team members (or appropriate local experts) to determine the eligibility of the cases.

The classifications to be used are listed in Appendix B, *Coding of tumours and eligibility criteria*.

Localisation of tumours

It is important that the exact location of all brain tumours is recorded as accurately as possible, using copies of CT scans, MRIs or other imaging procedures. Study centres may require the services of a specialist neuro-radiologist to ensure that high-quality tumour location data are collected.

An international review group has been established to check the quality and comparability of these data. The procedures for the localisation are included as Appendix C. Study centres will meet the costs of obtaining copies of CT or MRI scans from 10% of cases, and sending these to the co-ordinator institution.

Acoustic neurinoma case-control study

Source

Case ascertainment does not need to be rapid, as acoustic neurinoma will generally have a good prognosis; inclusion of retrospective cases (up to 6 months) is therefore possible. The **primary source** for ascertainment of cases of acoustic neurinoma will be the appropriate departments (pathology, surgery, radiology, etc) of the **participating health institutions** (see country specific section of Procedures Document). Where population-based cancer registries exist and register benign tumours, they will be used as a secondary source to ensure the completeness of the case ascertainment for acoustic neurinomas.

Verification

For acoustic neurinomas, all cases should be histologically confirmed – either from surgery or biopsy material – and the histopathology report should be available. Cases that are diagnosed on the basis of unequivocal scanning results¹ will be included also in the study – copies of the radiology

¹ Criteria for diagnosis by imaging will be agreed by an International panel before recruitment of cases begins

report should be retained. These will be examined by study team members (or appropriate local experts) to determine the eligibility of the cases.

The exact location of the tumour (side of the head) will be recorded, using copies of CT scans, MRIs or other imaging procedures.

The classifications to be used are listed in Appendix B, *Coding of tumours and eligibility criteria*.

Parotid gland tumour case-control study

Source

Case ascertainment does not need to be rapid, as these tumours will generally have a good prognosis; inclusion of retrospective cases (up to 6 months) is therefore possible. Because parotid gland tumours may be treated in a very large number of institutions, it will be logistically difficult to ensure complete ascertainment in most regions and it will generally be preferable to restrict the ascertainment to malignant tumours, registered in cancer registries.

The **primary source** for ascertainment of cases of malignant parotid gland tumours will be **population-based cancer registries**, in regions where they exist (see country-specific section of Procedures Document), or departments of surgery in the participating health institutions.

Verification

All cases should be histologically confirmed – either from surgery or biopsy material – and the histopathology report should be available. These should be examined by study team members (or appropriate local expert) to determine the eligibility of the cases.

The exact location of the tumour (side of the head) will be recorded, using copies of CT scans, MRIs or other imaging procedures.

The classifications to be used are listed in Appendix B, *Coding of tumours and eligibility criteria*.

Representativity

Ideally, case ascertainment should be **population-based** in order to ensure that all cases in the study population have the opportunity to be included in the study.

For logistic reasons, in some countries it will be **hospital-based** (or, if no hospitalisation is involved, based on notification from the diagnosing physicians); in regions where most (90% or more) cases in the study population would be referred to the participating hospitals and physicians, this will not pose a problem. In some regions, however, because of the very large numbers of treatment institutions and clinicians involved, complete ascertainment of cases from the study population will not be possible and only a limited number of treatment institutions will participate. In these regions, a "study population" will be defined objectively as a community (or set of communities) in which individuals would be highly likely to be referred to those institutions if they became cases. All participating study regions must be able to define the population from which their cases have arisen, with reasonable certainty (See guidelines in procedures document).

The procedures for ascertainment of cases are summarised by country and region in the country-specific section of the Procedures Document.

F. Definition of controls

For each brain tumour case, 1 control will be selected, while 2 will be selected for each acoustic neurinoma and 3 for each parotid gland tumour cases.

Controls will be either individually or frequency matched on age (within 5 year categories), sex and study region. Some study regions may also match on ethnic status or geographical region (see country specific section of Procedures Document).

Representativity

Study regions must be able to select controls from the population in which their cases have arisen. Selection of controls must be carried out in a manner that provides as far as possible a representative picture of mobile telephone use in the entire study population.

In some countries, the best strategy will be to recruit controls from population lists. Where these lists do not exist, or are deficient in some respect, investigators may use other means, including selection of controls from hospitals. In all instances, investigators must provide detailed information on how controls are chosen, and what steps will be taken to minimise bias.

Control selection should be **population-based** in order to be representative of the entire study population. In countries where, for logistic reasons, control selection will be hospital-based, controls should be selected at random from all of the medical institutions to which individuals in the "study population" would be highly likely to be referred if they became ill.

The procedures for identifying the controls are summarised by country and region in the country specific section of the Procedures Document.

G. Informed consent

All cases and controls will be contacted, informed about the study and given the opportunity of refusing to participate. The number of subjects who refused and their reasons for refusal – when available – will be documented. In order to assess the magnitude of a possible non-responder bias, in some countries, where Ethical Committees agree, subjects who refuse to participate in the full study will be asked whether they are willing to answer immediately (or later by telephone if more convenient) a short questionnaire (this will be the same as that used for proxies – see below).

The IARC Ethical Review Committee has approved the study and will require written informed consent from all participating subjects in each centre. Although the forms may differ slightly in each participating country in order to meet the requirements of local Institutional Ethics Committees regarding consent procedures, they should be similar. Individual participating centres will inform the IARC secretariat when ethical approval has been obtained and forward a copy of the consent forms used.

The procedures for contacting the subjects and obtaining their informed consent are summarised by country and region in the Procedures Document.

H. Collection of information

Information on factors of interest will be obtained from the following sources:

- the Computer Assisted Personal Interview (CAPI) study questionnaire
- records of mobile telephone companies (operators, service providers, base station providers and phone manufacturers)
- phone bills and memory of mobile telephones
- blood samples – for study centres participating in the Study of inherited susceptibility and gene-environment interactions

Study questionnaire

The study questionnaire concerns information on the following factors:

- **Demographic factors**, including sex, date of birth, level of education, current address.
Note: identifying information such as name and address, which is necessary at the national level for linkage of information to medical and phone company records, should not be sent to IARC.

- **Mobile telephone use:** this section contains an ‘event history calendar’ for the period of mobile telephone use. The calendar will be structured, for each subject, according to factors, such as changes in residence, occupation and the mobile telephone they used most often, which may have affected their pattern of use. For each stable period of mobile telephone use, more specific questions about RF exposure are asked. This includes questions concerning the average duration and number of calls made and received by the study subjects with their mobile telephones, use of hands-free devices and other characteristics of use that may influence the level of RF exposure from mobile telephones.
- **Use of other communication devices:** the aim of this section is to identify subjects who may have received RF exposures through the use of communication devices (including ham/CB radios, two-way portable radios, satellite telephones) other than mobile telephones.
- **Occupational exposures to EMF and known risk factors:** this section contains questions concerning occupations in which exposure to EMF (ELF, LF and RF) radiations and known risk factors for the tumours of interest (ionising radiation and loud noise) may have taken place.
- **Smoking history:** this section contains questions concerning lifetime smoking history.
- **Medical history:** in this section, information is sought on potential risk factors and confounding factors for the tumours of interest; this includes the subject’s history of various diseases (including allergies, hearing loss and other cancers) and diagnostic and therapeutic procedures involving ionising radiation to the head and neck.
- **Family history of diseases:** this section contains questions about a number of diseases that may be associated with the tumours of interest in familial syndromes.

A shortened version of the questionnaire will be used for proxies and for subjects not agreeing to participate in the full interview but willing to answer a few questions. This questionnaire will seek basic information on whether or not the subject used such a mobile telephone and, if so, the approximate dates of beginning and of mobile phone use; current or most recent occupation and information about use of other portable communications equipment, work with industrial electric machinery or as an electrician and family history of brain tumours.

Type of interview

A trained interviewer will administer this questionnaire during a **face-to-face interview** using a computer assisted personal interview system (CAPI). This type of interview is required because of the complexity of the information that needs to be obtained, the length of the interview and the state of health of some of the cases.

As far as possible, interviews should be carried out in the **same setting for both cases and controls** to minimise the risk of bias (subjects may be more eager to participate while hospitalised than in their homes or elsewhere).

Timing of interview for cases: as soon as possible after ascertainment – ideally within 4 weeks after diagnosis of brain tumours (benign and malignant) and within 3 months of diagnosis of acoustic neurinoma and parotid gland tumours.

When the study subject cannot complete the interview in one sitting (too tired or ill, etc...), the interviewer will make another appointment to complete at a later time.

The interview should not last for more than 45 minutes.

The type of interviewer and location of the interview are described, for each of the participating centres, in the country-specific section of the Procedures Document.

Records of mobile telephone companies

All study regions should plan to compare reported and recorded phone use for a 10% sample of their study subjects. If historic records are not available these comparisons should be made on

current or very recent use. This validation will be carried out only if written approval has been obtained from the study subject.

Those study regions that have access to billing records covering the entire study period will use these to validate questionnaire responses of some or all study subjects¹.

Wherever possible, billing records will be used also to validate responses provided by proxies.

The information to be obtained from records of mobile telephone companies includes:

- Average duration of calls per month (both incoming and outgoing)
- Average number of calls per month (both incoming and outgoing)
- The phone system (analogue or digital)

Other sources of information for validating answers to the questionnaire concerning number and duration of calls include:

- for past history of phone use – the subjects' phone bills (if they have been kept and if the subscription was in the name of the subject) and
- for recent calls – the memory of the telephones or SIM cards (on many recent phones the phone or the card records duration and number of calls)

Study subjects will be asked if they have kept their own billing records and where these exist and access is granted, they will be used to check questionnaire estimates of the average number and duration of calls. The purpose of on-going validation using billing records held either by study subjects or telephone companies is to monitor the extent to which the different measures of exposure diverge. The correlation between billing records and questionnaires will be compared with that obtained in the prior validation study (see section J), and if there are appreciable differences, appropriate adjustments will be applied in the statistical analysis.

Biological samples

In some countries (see country-specific section of Procedures Document), blood samples (buffy coat and sera) will be collected from cases and controls, as well as tumour specimens to enable future analyses as follows:

- to investigate risks associated with familial aggregation of tumours,
- to identify multiplex families (those with multiple first-degree relatives characterised by occurrence of brain tumours and possibly selected other malignancies) and families with unusual occurrence of cancer for further detailed study to potentially identify major underlying heritable syndromes and/or germline mutations,
- to examine genetic polymorphisms that may be linked with specific morphologic or molecularly-defined subtypes of gliomas,
- to assess potential gene-environment or gene-gene interactions in relation to specific morphologic or molecularly-defined subtypes of gliomas.

The requirements are as follows:

- i. blood collection: 27 ml of whole blood in:
 1. one 10 ml serum separator tube (SST),
 2. two 8.5 ml acid citrate dextrose (ACD) tubes

¹ In most countries where this is possible, the amount of work involved in obtaining records on a sample will be similar to that involved in obtaining information on the full study population. Therefore it will be preferable to include records for all participants.

- ii. Processing of sample:
 1. SST tube: centrifugation in a table-top clinical centrifuge for 20 minutes. After refrigeration, aliquot four 1 ml serum samples into four cryovials and freeze at -70Y C.
 2. ACD tubes: centrifugation of both tubes in a table-top clinical centrifuge for 20 minutes. Place each buffy coat into separate 2 ml cryovials. Freeze at -70Y C.
- iii. Shipment: Split samples from each subject into two equal batches. Half will be kept in the study centre. Half will be shipped at regular intervals (procedures to be determined) to a central repository (NCI or IARC).

I. Data collection

IARC will develop data collection procedures manuals, code books, procedures for checking the accuracy and completeness of the data collected and of the coding (for example, random samples of records will be reabstracted and validated) in consultation with national Study Group members.

A computer assisted personal interview (CAPI) will be used to collect data from personal interview. The questionnaire and CAPI design (including country specific modifications and translations) will be managed centrally (by the UK group led by Dr P. McKinney) in conjunction with the IARC secretariat in order to ensure compatibility in questionnaires and data files between countries.

Workshops will be held in order to train interviewers from each study centre in administering the questionnaire and for using the CAPI system. The costs of travel and accommodation for interviewers will met by study regions.

Once data have been collected, national Study Group members will provide copies of the linked computer files to IARC in a standard form suitable for analyses. For confidentiality reasons, identifying information such as name, not necessary for analysis, will be excluded from the IARC copy of the data.

J. Exposure assessment

Development of an exposure gradient

In the absence of clear and consistent data from laboratory or animal studies, there is no definite idea of the most appropriate physical quantity to be related to possible health effects of electromagnetic fields (EMF) radiated from mobile phones. However, it seems reasonable to quantify the exposure in terms of the total energy delivered to the user's body. This energy, in turn, depends on the time of use of the phone, and on the SAR (specific absorption rate, i.e. the energy delivered per second to the unit mass of tissue).

While the duration of use can be deduced from user's interview, or from traffic data provided by the operators, the power actually absorbed in the body depends on several factors: some are technical, others are related to the way of use of the phone. The importance of these factors will be investigated; they include:

- power actually radiated from the antenna, depending on the link with the base station;
- fraction of power delivered to the user's body due to the antenna (position and type);
- fraction of power delivered to the user's body due to the position of the handset (i.e. the way it is held);
- fraction of the conversation time during which power is actually emitted (depending on technical characteristics such as DTMA, DTX, etc.);
- technology (analogue vs. digital).

The main goal of the exposure assessment project will be to develop and implement one (or more) exposure index(es) for each case-control study (i.e. for each tumour of interest) based on these factors. To achieve this, the following steps will be carried out:

- assessment of the relative importance of the above factors and derivation of weighting factors;
- estimate of uncertainties in the numerical values of the factors;
- estimate of variability of the factors among users;

The following activities are proposed to achieve this goal:

- collection of data from operators and manufacturers on technical parameters affecting exposure;
- analysis of data on power collected by software modified telephones used in different settings;
- experimental measurements of power radiated from cellular phones in different environments (indoor, outdoors in urban areas, outdoors in rural areas, etc.) with the use of specialised equipment (dedicated phones) and software;
- survey of power absorption in the user's body in different conditions, with the use of specialised equipment: dosimetric phones specially designed for dosimetry;
- definition of the location and boundaries of the tissue regions of interest based on reanalyses of experiments (measurement or modelling based approaches);
- analysis of the relative importance and distribution of the above factors;
- development of correction factors and uncertainties for each of the parameters affecting SAR.

Validation studies

The purpose of the validation studies is to investigate the accuracy of self-reported use of mobile phones. The "use of mobile phones" includes all determinants of exposure to RF from this source that respondents can reasonably recall (for example, type of phone and average frequency and duration of calls). The purpose of the validation studies is to compare reported and actual phone use, in quantitative terms if possible, to assist the planning and execution of the case control studies, and to guide interpretation of the findings.

Two validation studies are proposed, both to be carried out before or at the beginning of the case control studies. In addition to these studies, and as part of the case-control studies, it will also be necessary at a later time to check the accuracy of self-reported use of a sample of participants, probably by comparison of questionnaires with network records.

The first (the "retrospective" study) will compare participants' responses to questions about mobile telephone use in the distant past (ideally 5 years or more) with records of network operators and, where these are available, bills and other records that the user holds.

In the second, the "prospective study", phone use will be recorded prospectively for a period of one month using a software modified telephone (SMP - which records number and duration of calls, as well as characteristics of the power distribution during the calls) and over a period of three months by network operators. The subjects recent recall will then be tested by administering a questionnaire several months later (interval to vary between 3 months and one year) about phone use during the recording period and comparing the answers of the subjects with the information recorded by the phone and the operators. The detailed protocol of the prospective validation study is included as Appendix D.

The validation studies will be conducted in a number of geographical regions, as the populations involved in the case-control studies are likely to vary with regard to a number of variables that may affect the accuracy of self-reported phone use. For example, in the past, prevalence of mobile telephone use varied considerably between countries (eg it was much greater in Nordic countries than in France or Germany), and industry deals offering a certain number of hours of free communication (which could make it less, or more, likely subscribers will pay close attention to the

duration of their calls) were introduced at different times in different countries. The location of the validation studies will be determined by the availability of network records.

Ideally prospective studies should be conducted in every country that is participating in the case control studies. It is proposed that the retrospective study take place in (at least) Canada, Italy and Australia. These are countries in which phone companies have been identified which keep accessible records on mobile phone use of subscribers over a substantial period of time (at least 5 years or more). In some instances, both incoming and outgoing calls are included. The countries cover a range of geography, languages and cultures, and varying patterns of mobile phone use.

K. Analyses

Analyses will be carried out in parallel at the region/country level by the national study investigator and internationally and at IARC. Separate analyses will be carried out for the following outcomes:

- All brain tumours, as well as the following subtypes:
- Gliomas
- Meningiomas
- Malignant and benign brain tumours separately
- Parotid gland tumours
- Acoustic neurinomas

Number of subjects who refused to participate and reasons for refusal will be analysed by sex, age, region and case/control status.

The primary goal of the international analyses is to assess whether there exists an association between RF exposure from mobile telephones and the risk of the diseases of interest. The data will be analysed using standard case-control analytical methods, i.e. logistic regression. The exposure measure will be taken to denote exposure level accumulated by time $t - x$, where x is a specified lag period introduced to account for a minimal latency period. The data will be analysed using computer programmes such as STATA, EGRET and EPICURE.

The effects of RF exposure from mobile telephones will be modelled. Variables to be considered include:

- Categorical index of exposure for each tissue of interest (see section on exposure gradient above)
- Number of years of use (accumulated by time $t - x$)
- Average duration of calls over the period of use
- Average number of calls over the period of use

The primary analyses will be based on a lag x of 5 years. Supplementary analyses, using lags of 2 and 8 years will also be carried out.

The effects of age, sex, education level and region will be taken into account systematically. In addition, the effects of other possible risk factors and confounding variables will be taken into account where appropriate and possible. These include:

- Use of other RF communication devices
- Occupational exposure to RF
- Occupational exposure to other risk factors for the diseases of interest
- Smoking history
- Medical history
- Family history of diseases

Separate analyses for each region will also be carried out and formal tests for heterogeneity of risk will be performed to minimise the risk of reporting false positive associations. Explanations of

inconsistencies between regions will be sought through detailed examination of available information on study design and exposure.

Unless strong heterogeneity is found which can be explained by differences in methods or levels of exposure, results of combined analyses will be presented, using random effects models to take into account heterogeneity.

The Exposure Assessment Subcommittee (see below) will provide estimates of systematic and random errors in the exposure classifications. These will be taken into account in the statistical analyses.

IV. ORGANISATION OF THE STUDY

A. Study Protocol

The current document represents the common core protocol for the International Case-Control Study.

B. The Study Group

A collaborative group of scientists (the Study Group), consisting of one representative per national/regional study (one epidemiologist or statistician), and the IARC principal investigator .

IARC will serve as secretariat and co-ordinating agency. The national Study Group members will be actively involved in the planning and carrying out of the study in their own country and will serve as contact between IARC staff and the persons responsible for the data and analyses locally. Although at a national level the study may be based on a number of different regions and several different studies may be set-up, at the international level, collaboration will be established with representatives of national/regional study groups rather than with specific institutions.

The Study Group as a whole will be responsible for the progress of the study, the choice of analyses to be conducted, and the interpretation and preparation of publications of results. All the decisions about the study will rest on the Study Group, which will decide on a consensus basis. The Study Group, at its meetings, will identify the tasks to be carried out between its meetings by a subgroup of the full Study Group - the *Epidemiology Subcommittee* - and nominate its members. This Subcommittee will have the responsibility of recommending to the full Study Group changes to the protocol and procedures (as appropriate), monitoring progress and difficulties, discussing relations with funding bodies, planning analyses, outlining publications.

The phrase “participating country” refers to countries in which one or more groups of investigators have stated their agreement to participate in principle. They will send official notification to IARC of their willingness to participate in the International Study.

Official participation entails:

1. Acceptance and adherence to the current common core protocol;
2. Collaboration with IARC in the development of detailed procedures for the study and implementation of these procedures in data collection;
3. Sending non-identifiable individual data, in the form requested in this protocol, for combined analyses to be carried out at IARC in consultation with the Study Group.

Each country will notify IARC if there are any changes in the composition of its delegation to the Study Group.

National Study Group members, in collaboration with the appropriate local bodies (hospitals, cancer registries, mobile telephone companies, etc.) will be in charge of:

- Ensuring that the appropriate ethical procedures have been followed for carrying out the study at the national level and for release of data to IARC, and for informing IARC that this has been done;
- Ascertaining cases and controls according to the principles and procedures described in the current document;
- Supervising the data collection and transfer of information to a standard data base worked out in consultation with IARC;
- Working out guidelines, in consultation with IARC, and carrying out checks on the validity of the data collected and on the case and control ascertainment procedures;
- Ensuring the proper flow of information about the progress of the study within their country.

The IARC Secretariat is composed of IARC staff members (epidemiologists, statisticians, physicists/engineers and technical assistants) who work on the organisation and conduct of the study. IARC functions will be:

- To take the responsibility for the co-ordination of the International Study;
- In collaboration with national Study Group members, to provide guidelines on the collection of data from the required sources in the various countries;
- To assist participating countries in the supervision of data collection in individual mobile telephone companies, where necessary;
- In consultation with participating countries, to provide guidelines for checking the accuracy and completeness of the data collected and of the case ascertainment procedures;
- To maintain the international database;
- To take responsibility for carrying out the statistical analyses of the combined data in consultation with the Study Group;
- Wherever necessary, to provide statistical and programming assistance at the national level;
- To organise meetings of the Study Group and its SubCommittees to discuss on-going problems of the study, results, preparation of reports and publications;
- To select further countries to participate in the study and provide a link among the participating countries between the meetings of the Study Group
- To co-ordinate the publication of results of the international study;
- To keep national investigators informed of study progress via national Study Group members;
- To submit the current protocol to the IARC Ethical Committee.

C. Subcommittees

Exposure assessment SubCommittee

A team of RF exposure assessment experts will be formed in order to provide guidelines for the collection of information on RF exposures of the subjects from mobile telephones and other devices, for the development of exposure metrics to be used in the statistical analyses of the data, for the characterisation of errors in these metrics and to ensure the comparability of the exposure information collected in the different countries. Appendix E lists the current membership of the Exposure Assessment SubCommittee.

Epidemiology SubCommittee

A subcommittee of epidemiologists/statisticians will be set-up. Membership will be *ad-hoc*, depending on the expertise needed at a particular time during the study. The first task of this SubCommittee will be to provide guidelines for the design of the study in each country, taking into account local circumstances. Other issues to be referred to this SubCommittee include data collection problems arising in the course of the study and details of analyses. Appendix E lists the current membership of the Epidemiology SubCommittee.

Panel of neuro-radiologists

An international panel of neuro-radiologists will be set-up to establish criteria for localising tumours based on imaging and to review CT or MRI scans in order to verify the localisation of all brain tumours in order to ensure high quality tumour location data are collected.

Other SubCommittees

Ad-hoc SubCommittees, consisting of members of the Study Group, possibly supplemented by mutually acceptable experts, will be set-up if and as needed.

Other parties

Other parties may also be involved in the Study Group as observers or consultants. These may include representatives of industry, other concerned organisations such as consumer's groups, as

well as individuals whose skills are considered to be valuable for the progress of the study. Participation of such persons at the meetings of the Study Group or at parts of these (such as single days) must be agreed in advance by members of the Study Group. Proceedings of the Study Group will be confidential and all parties should retain in confidence information, such as preliminary results, presented at the meetings.

D. Co-ordination

Reports

IARC will prepare, with the help of rapporteurs, and circulate to the Study Group members, reports of Subcommittee and Study Group meetings, updates of the Procedures Document (as needed) and, biannually, a report outlining the progress of the study. The report will be posted on the INTERPHONE private working website.

National Study Group members will prepare and circulate to national collaborators and to the IARC co-ordinator progress reports every 6 months; a letter requesting this will be sent from IARC a month before.

Site visits and exchange of expertise

One to two site visits will be carried out by IARC staff to each participating country, as needed, for example one during the data collection phase and the other during the period of validation and analyses of data.

In addition, IARC staff and members of the ad-hoc SubCommittees (see above) will provide assistance to the National Study Group members, as needed, with problems of data collection and analysis. In particular, National Study Group members may choose to come to IARC, or send one of their collaborators, in order to set-up or carry-out part of the analyses of their data.

For the international combined analyses, collaborators/consultants agreed by the Study Group with special expertise (for example on random effects models, adjustment for errors in exposure) may have access to the combined data set at IARC (no data will be transferred to third parties), to carry out part of the analyses outlined in the previous section, under the conditions of confidentiality and data use stipulated below.

Meetings

Meetings of the Study Group and ad-hoc Subcommittees will be held as necessary, to discuss its developments, approaches to the analysis and interpretation of results, as well as to prepare publications. A provisional timetable is given below:

Meetings of the ad-hoc groups

A panel of neuro-radiologists will assemble once in Lyon after all brain cases have been ascertained and necessary CT or MRI scans have been obtained in order to verify the location of brain tumours on a sample of cases. This panel will also meet at the beginning of the study to establish criteria for localising tumours based on imaging.

Meetings of ad-hoc subgroups will be organised as needed.

E. Use of data

The use of the combined data is the prerogative of the Study Group. The use of each local or national data set is the prerogative of local or national investigators.

Access to the combined data set for further analyses may be provided to a local or national investigator or a third party for a well-described and specified purpose, only if written consent is obtained from all Study Group members. Analyses by such third parties will be performed at IARC

(no data will be sent out) in collaboration with the Study Group, and the interpretation of results will be discussed before any result is published. Such analyses will be permitted only if they do not pre-empt or duplicate work to be done by the Study Group.

F. Publications

IARC Secretariat will be responsible for preparing a detailed report of the final results of the study. This report will appear as an IARC Technical Report (if approved by the IARC Publications Committee) or as an IARC Internal Report and will contain detailed overall results as well as results by participating country.

Results from both the epidemiological analyses and the exposure assessment group will be published in the international scientific literature. Authorship will be as follows: individual with the greatest involvement in the co-ordination and carrying out of the study and in the writing of the report will be listed first; all other members of the Study Group will be listed in alphabetical order. IARC has the responsibility of providing working drafts of the papers. These papers will present overall combined results and, where there is scientific merit, results of specific subgroups. No result will be published that will allow identification of a particular country without the approval of the appropriate Study Group members.

Overall publications will be outlined during a meeting of the Study Group. The finalisation of the publications will be made through correspondence between IARC and national Study Group members. Intensive efforts will be made (including if necessary a meeting of the full Study Group) to obtain consensus on the contents of the publications. In the event a consensus is not obtained, the report will contain clear statement of any dissenting view. No withdrawal of data will be permitted after the beginning of the combined analyses.

The results will remain strictly confidential until publication. However, representatives of industry and other concerned organisations such as consumer's groups shall be informed shortly (maximum of seven days) before publication, in a co-ordinated fashion, under the same terms of confidentiality as the members of the Study Group, with prior agreement from the journal in which the publication will appear.

Each participating country will retain the right to perform and publish results from its own epidemiological and exposure assessment data.

G. Financial aspects

IARC will seek financial support for the co-ordination of the overall study. If such support is obtained, IARC will cover the expenses of meetings of the Study Group and co-ordination of the study.

In principle, each participating country will cover its own expenses for the conduct of the study at the local or national level.

IARC secretariat and national Study Group members will closely co-operate to co-ordinate applications for the financial support of the study in the different participating countries. Such co-operation may include exchange of draft grant applications, advice on specific aspects and joint grant applications.

V. TIMETABLE

The international case-control study is scheduled to last five to six years from the time funding is ascertained and the study is started in participating countries. Subject to modifications, the timetable is as follows:

| Time period | Activities |
|-------------|--|
| Years 1-4 | <ul style="list-style-type: none">• Ascertainment and verification of cases; selection of controls• Interview of study subjects• Collection of information from mobile telephone companies and other appropriate organisations• Validation and checking of completeness (while data collection is on-going). |
| Years 4-5 | <ul style="list-style-type: none">• Receipt of data at IARC as early as possible (completed parts of the final data set should be submitted as soon as they are ready)• International consistency checks;• Analyses to be carried out in parallel between national groups and IARC• Reporting of individual regional and national case-control study results by national investigators as their analyses are completed. |
| Years 5-6 | <ul style="list-style-type: none">• Completion of the international combined analyses;• Preparation of final report and publication of results. |

VI. ACKNOWLEDGEMENTS

The preparation of this protocol was made possible thanks to a grant from the National Radiological Protection Board, Chilton, United Kingdom.

The authors would like to thank the members of the feasibility study group and their national colleagues for helpful advice in the evaluation of the feasibility of the present study and all members of the International Study Group for their assistance in the development of the protocol of the present study.

VII. REFERENCES

- Cardis, E and Kilkenny, M., International Case Control Study of Cancers of Brain and Salivary Gland. Report of the Feasibility Study. 1999. IARC Internal Report 99/004, International Agency for Research on Cancer, Lyon
- McKinlay et al. Possible Health Effects Related to the Use of Radiotelephones. *Radiol Protect Bull* 1997; **187**: 9-16.
- Repacholi, M.H. Low level exposure to Radiofrequency Electromagnetic Fields: Health Effects and Research Needs. *Bioelectromagnetics*, 1998; **19**: 1-19.
- Rothman, KJ., Chou, C.K., Morgan, R., Balzano, Q., Guy, A.W, Funch, D., Preston-Martin, S., Mandel, J., Steffens, R., Carlo, G. Assessment of radiofrequency exposure for epidemiologic studies of wireless communications. *Epidemiology*, 1996; **7**: 291-298.

APPENDIX A – DISTRIBUTION OF SAR IN HEAD FROM DIFFERENT TYPES OF MOBILE TELEPHONES

APPENDIX B – CODING OF TUMOURS AND ELIGIBILITY CRITERIA

I. DIAGNOSTIC ELIGIBILITY CRITERIA FOR CASES TO BE INCLUDED IN THE INTERPHONE STUDY

A. *Brain and CNS tumours*

Definition of cases

All subjects fulfilling the age and regional residence criteria, and diagnosed with a primary glioma, meningioma, acoustic or trigeminal neurinoma on or after the “LOCAL DATE FOR START OF STUDY” (see table below for ICD codes).

Definition of date of diagnosis:

The date of diagnosis will be the date on which the first positive investigative procedure was carried out which led to diagnosis. For example:

- If the diagnosis was initially made on radiological evidence and subsequent pathology confirmed and refined this diagnosis, the date of diagnosis is the date that the radiology was carried out.
- If preliminary radiological procedures did not lead the clinician to make a diagnosis of tumour and the pathology report was the first written evidence of diagnosis, then the date of diagnosis will be the date of surgery.

Note: The diagnosis date is the date of the biopsy or radiological procedures, as appropriate, not the date of the report.

Eligible dates for inclusion in the study

Cases who have had diagnostic investigations before the date of start of the study will be included only if the diagnosis was actually made during the study period, i.e. any previous investigation was inconclusive.

Diagnosis

As the specific diagnosis of a case may change in the months following the identification of the tumour, for analyses purposes, the final diagnosis, i.e. that posed at the conclusion of all diagnostic procedures, will be taken.

B. *Parotid gland:*

Definition of cases

All subjects fulfilling the age and regional residence criteria, and a histologically confirmed diagnosis of malignant parotid gland tumour (see ICD classifications in table below).

II. CODES OF TUMOURS ELIGIBLE FOR INCLUSION IN THE INTERPHONE STUDY

The following table provides the ICD codes for those sites to be included in the International Study. Radiological reports including site and laterality will be requested for each case. If histologically confirmed, a copy of the diagnostic histology report will be requested from the treating centre for each case registered in the study.

| TUMOURS | TOPOGRAPHY | | MORPHOLOGY |
|---------------------------------------|--------------------|-------------------------------|---|
| Classifications | ICD-9 ¹ | ICD-O (EUROCIM ²) | ICD-O (EUROCIM ²) ³ |
| Meningiomas (Benign and malignant) | 192.1 | C70.0 | 9530-9539 |
| | 225.2 | C70.9 | |
| Gliomas (Benign and malignant) | 191.0-191.9 | C71.0-C71.9 | 9380-9384, 9390-9394, 9400-9401, 9410-9411 9420-9424, 9430, 9440-9443, 9450-9451, 9460, 9480-9481 |
| | 225.0 | | |
| Acoustic neurinoma | 225.1 | C72.4 | 9540-9541, 9550, 9560-9562, 9570 |
| Parotid gland tumours (malignant) | 142.0 | C07.9 | 8020, 8041, 8050, 8070, 8082, 8140, 8147, 8200, 8290, 8410, 8430, 8450, 8480, 8500, 8550, 8562, 8940, 8941, 8982 |
| Trigeminal | 192.0 | C72.5 | |

1. These topography codes were selected from ICD-9 [WHO (World Health Organization) (1977) International Classifications of Diseases, 1975 Revision, Geneva, World Health Organization]
2. This is the classification used by EUROCIM (European Network of Cancer Registries) database, which is based on ICD-O (International Classifications of Diseases for Oncology).
3. This is the Histological typing of salivary gland tumours [WHO (World Health Organization) (1991) International Classifications of Diseases, (second edition). Seifert G. in collaboration with pathologists]

III. EXAMPLES OF CASES ELIGIBLE AND NOT ELIGIBLE FOR INCLUSION IN THE STUDY.

↓ ↓
Start of study date *End of study date*

| | | | | |
|---------------|--------------------------------|--------------------------------|------------------------------|---|
| Case 1 | imaging based diagnosis | path confirmation biopsy | | exclude |
| Case 2 | | imaging based diagnosis | path confirmation biopsy | include |
| Case 3 | | | path diagnosis biopsy | include |
| Case 4 | inconclusive imaging | path diagnosis biopsy | | include |
| Case 5 | | | inconclusive imaging | path diagnosis biopsy exclude |
| Case 6 | | Imaging based diagnosis | | path confirmation biopsy include |

**APPENDIX C – PROCEDURES FOR TUMOUR LOCALISATION FOR EXPOSURE
ASSESSMENT PURPOSES**



INTERNATIONAL AGENCY FOR RESEARCH ON CANCER
WORLD HEALTH ORGANIZATION

INTERPHONE Study

PROCEDURES FOR THE LOCALISATION OF BRAIN TUMOURS

DOCUMENT FOR NEURO-RADIOLOGISTS

1. INTRODUCTION

In view of the increasingly widespread use of portable telephones in many countries, the international collaborative INTERPHONE study is being carried out to determine whether mobile telephones or their emitted radio-frequency radiation may be related to cancer risk.

In order to optimise the power of the INTERPHONE study to detect an increase in risk linked to exposure to radio-frequency radiation, it is essential to collect data as precise as possible on both the exposure levels of all study subjects, and on the disease for the cases. Indeed, each source of uncertainty in the data reduces the magnitude of the detectable risk and the power of the study. Concerning the exposure (RF radiation from mobile phone use), individual information is currently obtained from interviews with the subjects. This document deals with the second aspect of the collection of high quality data, namely the description of the disease in the eligible cases, and in particular, procedures for the localisation of the brain tumours.

The core protocol of the INTERPHONE Study indicates that the exact location of all brain tumours should be recorded as accurately as possible, using either copies of CT scans, MRIs or other imaging procedures. This will require the collaboration of a specialist neuro-radiologist to ensure the highest quality of data collected. The review of a 10 % sample of all images by an international group of expert neuro-radiologist is planned to check the quality and comparability of the localisation of the tumours.

This document outlines the procedures envisaged for the localisation of brain tumours by participating neuro-radiologists.

A. Pilot Study

In 2001, an expert working group of neuro-radiologists and physicists was convened to examine the feasibility of the proposed tumour localisation procedure. The group included neuroradiologists and neurosurgeons from France (Drs Hermier and Turak), the UK (Dr Britton) and Italy (Dr Vidiri), a physicist, Dr Wiart, who had worked on developing a suitable mapping system of the brain, and epidemiologists Dr Cardis of IARC and Dr Hours of the University of Lyon.

A pilot test involving the members of the expert working group was conducted. The methods for generating the maps, localising the tumour and obtaining qualitative

information from the neuro-radiologists were refined. The methods and results of the pilot test are described in the full protocol that can be obtained from the study centre coordinator.

IV. OBJECTIVE

The goal is to record the probable location of the origin of the tumour and its contours, for all eligible brain tumour cases of the INTERPHONE Study.

V. WHAT WE ARE ASKING OF THE NEURO-RADIOLOGISTS

A. Study population

All eligible cases with brain tumours (Glioma and Meningioma, malignant and benign).

B. Procedures for the localisation of tumours

If the subject's scans are available

If the subject's scans are available, the neuro-radiologist will mark the location of the tumour (probable origin and contours) on copies of standardised cuts and fill in the case information form (documents provided by IARC). Details are described below.

- Where to mark the origin and the contours of the tumour

The atlas containing cuts from a reference standardised phantom head is provided by IARC. The sets of acquisitions, spaced 1 cm and spanning the 3 directions (axial, coronal and sagittal) have been superimposed with a 1 cm grid. These 3 sets constitute the atlas (see Atlas and Annex 1). It is up to the discretion of the neuro-radiologist to choose the most appropriate cuts to indicate the origin and 3-dimensional extent of the tumour. Copies of the three sets of cuts will be provided and the neuro-radiologist will have to select only the view or views corresponding most closely to local practises for scanning. In general, it will only be necessary to use one of the imaging planes. For instance, it may be appropriate to use the axial plane in one case but in another the coronal plane will be simpler to use. In a few cases it may be necessary to use more than one view. A residual inaccuracy in tumour localisation will be accepted because tumour growth may deform the structure of the brain.

- How to mark the origin and the contours of the tumour

It is recognised that estimating the origin of a tumour which extends diffusely along white matter tracts rather than gradually expanding like a balloon is very difficult. In a high grade glioma with a central area of irregular ring enhancement it can be assumed that the area of enhancement identifies the origin of the lesion. In low grade, non-enhancing gliomas the origin is more difficult to estimate. It should also be remembered that in a meningioma the origin should lie somewhere on the meninges. Whilst recognising the limitations the neuro-radiologist is to make his or her best educated guess.

Annex 1 shows an example of a completed grid indicating the possible origin (by a cross) and the extent of the tumour (by diagonal marks). As far as possible, only one cell of the grid should be indicated as the estimated origin. If this is not possible, the cross should be put on the intersection of the cells where the origin is judged to be located, but this should be avoided, if at all possible.

- How to fill in the case information form

The case information form, reproduced in *Annex 2*, records technical details about the patient, the scan used, the tumour and the tumour localisation. The Study ID number identifying the patient within the INTERPHONE study will be recorded on the case information form. The neuro-radiologist will identify him/herself by his/her initials. Copies of the case information forms will be provided.

If the scans are not available

Medical records may be used for the tumour localisation if it is not possible to obtain the scans of a patient. Please indicate the source used on the case information form. The same instructions as under 3.2.1 apply to localisation from records.

Technical aspects and data to be transmitted to IARC

In order to ensure that the information recorded on the completed grids can be entered into the study database:

- The modalities for obtaining scans, completing the review and returning the information to the local study centre will be determined by the study centre coordinator and the neuro-radiologist.
- The grids and the case information form must have a label with the INTERPHONE Study ID number affixed
- The grid sheets used should have the neuro-radiologist's initials
- The case information form should have the initials of the neuro-radiologist and the name of the hospital clearly identified
- Nominal information about the case should not appear on either the grid sheets or the case information form
- Staple together the completed grids and case information form for each subject

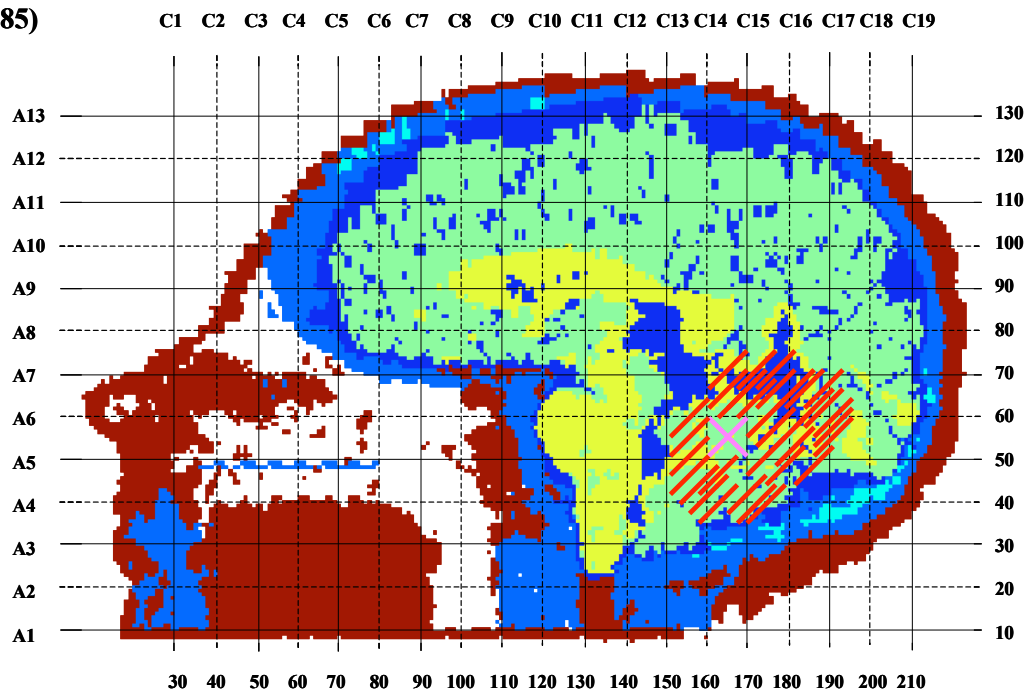
C. Material for the localisation of tumours

- This procedure document
- Atlas: IARC has prepared an atlas for each centre. This atlas contains colour reproductions of 3 sets of cuts (axial, sagittal and coronal). The atlas is intended to serve as a reference in the evaluation.
- Grids: Copies of each of the images in the Atlas have been provided for use by the radiologist. The 1cm grid has been superimposed on each image/cut. It is up to the discretion of the neuro-radiologist to select the view(s) corresponding most closely to local practises for scanning. The evaluation for each patient will be made however many grids may be necessary. The atlas can be photocopied to provide further grids as required.
- Case information form: this is a brief form to be completed by the neuro-radiologist for each patient, concerning the type of tumour, type of scan/records used and difficulty involved in making the evaluation.
- Labels: containing each patient study ID number.

ANNEXES

Annex 1: Example of the method to locate the probable origin (cross) and the extent of the tumour (diagonals marks); in this case, a sagittal median cut

S7_{median}
(X=85)



Annex 2: Case information form

INTERPHONE

**Brain tumour localisation
Case information form**

Please answer the following questions for each case reviewed:

Case Identification No _____

Reviewer Initials _____

Hospital _____

- Have you filled in the grid(s) based on a CT/CAT scan, MRI scan, surgery records, radiology records, or other source (tick more than one box as appropriate) ?

CT scan [] pre-operative [] post-operative []

MRI [] pre-operative [] post-operative []

Surgery records []

Radiology records []

Other : _____

- Which cuts were used for the original scan?
Axial [] Coronal [] Sagittal []

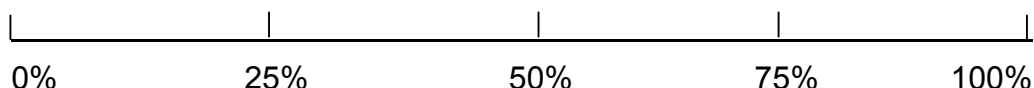
- At what stage was the tumour?

Low grade glioma [] High grade glioma []

Low grade meningioma [] High grade meningioma []

- How would you quantify your confidence in assessing the location of the origin of the tumour?

Please mark an X on the following scale where 0% means absolutely no confidence in your estimate, 100% means absolute confidence in your estimate, and 50% means that chances are even that you correctly identified the origin of the tumour.



APPENDIX D – PROTOCOL OF VALIDATION STUDY



INTERPHONE Study

Protocol for the prospective study to validate self-reported use of mobile phones¹

I. INTRODUCTION

A. Rationale

Research into the possible health effects of the use of mobile phones is relatively recent. Very little evidence is currently available on the validity of self-reported use of mobile phones. How much weight is given to the findings of the INTERPHONE study will depend to a large extent on how well the study can account for inaccuracies in self-reported phone use. *The core protocol for the INTERPHONE study indicates that study centres should carry out validation studies to assess the accuracy of questionnaire responses on cell phone use.*

The ideal way to estimate validity of questionnaire responses concerning past phone use is retrospectively, by comparing the responses with the actual historical billing records. Such investigations are limited to those countries in which historical records of phone use are available over long time periods - at present, this includes Australia, Canada, Italy and New Zealand.

Prospective studies (and short-term retrospective studies) provide another means of testing the validity of questionnaire data. Using this approach, details on current phone use are collected from network records (and possibly complemented by data from software modified phones) over a defined period of time. At a later date, following the period of monitoring of phone use, a questionnaire is administered and the responses are compared to the information obtained from the monitoring mechanism.

This document is the core protocol for the prospective studies, recognising that some details will vary from one study centre to another.

B. What is currently known about recall of phone use

In a study of mobile telephone users in the USA, Funch et al (1996) reported that there was a high correlation ($r = 0.74$) between reported cellular telephone use and the data recorded on the billing records. In this study, subjects reported their use (mobile telephone or fixed car phone, minutes of use per week, laterality) at the conclusion of a 3-month period. Funch's paper also

¹ Prepared by Alistair Woodward, Angus Cook, Elisabeth Cardis, Lucia Ardoino, Lesley Richardson

indicated that there was little variation between reported and actual cellular telephone use by geographical area, age or gender. The number of telephones owned was associated with accuracy of recall, with accuracy falling as the number of telephones owned increased.

There are limitations in the study with regard to its applicability to the INTERPHONE study. First, although subjects were chosen from four geographical areas, the study was limited to users who lived in the United States. The relationship between reporting reliability and variables such as age, gender, and number of telephones owned needs to be explored in other studies in different locations. Factors not explored by Funch that may affect the reliability of the subjects' reported telephone use include:

- whether or not the subject is self-employed. (Self-employed subjects may monitor their expenditures for telephone use more closely and thus have a clearer recollection of their level of use.)
- the total duration of use of cellular telephones. (The ability to judge extent of use and the reliability of reporting may differ between longer-term users of cellular telephones and short-term users.)
- whether or not subjects are the account holders of the cellular telephones they use. (Account holders may be more conscious of the time they spend on the telephone if they receive - and must pay for - the telephone bills.)
- the frequency with which the subject has changed telephone brands or companies
- whether or not the subject speaks one of the major languages of their country of residence
- whether or not the subject has suffered from symptoms which they attributed to cellular telephone usage, such as headaches or sleep disturbances. (People who have suffered symptoms which they attribute to telephone usage, or who associate use of the telephone with discomfort, may overestimate the amount of time they spend on the telephone compared with people who are 'symptom-free'.)

C. Aims of the prospective validation studies in the INTERPHONE study

The Interphone Study aims to collect information on lifetime use of mobile phones. Since these devices have been widely available since the late 1980s (even earlier in some Nordic countries), subjects may be required to recall information about use over a fairly lengthy period of time.

The prospective validation studies aim to determine how accurately individuals *drawn from the same population as the cases and controls in each of the national studies*, can respond to questions about recent cell phone use. For most of the participating countries this question is more amenable to study than use in the distant past, because information about actual use can be obtained prospectively from the telephone companies/network operators and from software modified phones (SMPs).

The obvious disadvantage is that the elapsed time between "actual" and "reported" phone use is much less than will generally be the case in the case-control study. As a consequence, the comparison of subjects' reports and independently recorded information in the validation study is likely to provide an optimal measure of reporting accuracy, because the details of use have undergone relatively little decay in the subject's memory. Subjects' memories of potential determinants of RFR exposure may also be of lower salience in the case-control study, amongst the controls at least. (It is unclear what effect tumour diagnosis will have on the recall of phone use by cases.)

II. STUDY DESIGN

A. Objectives

The goal is to carry out a prospective validation study in each study centre. There are essentially two sources of information available for comparison with questionnaire responses. These are the records held by network operators, and logs of calls made on special software modified phones (SMPs). Using one (and preferably both) of these sources, the validation studies will attempt to verify the accuracy of the subjects' responses to questions about potential determinants of RFR exposure. This verification will be attempted by:

- i. direct comparison of subjects' responses with information recorded by the network operator and the SMPs.
- ii. indirect estimation of the accuracy of subjects' responses, using information recorded by the operator and the SMPs. (For example, the first and last base stations used by a subject during a call (information obtained from network traffic records) may be used to estimate whether the subject was moving or stationary when the call was made, and whether the phone was being used in a rural or urban setting.)

B. Validation study population

It is proposed that a specially constituted cohort of individuals who are mobile phone users be asked to participate in the validation study by: 1) authorising the network providers to prospectively record and release information on actual phone use patterns, and 2) agree to be interviewed at some point following the end of the monitoring period by the network operators. *If possible, a sample of the cohort should also be willing to use an SMP for a period of one month.*

The participants in the validation study will generally be distinct from those taking part in the INTERPHONE case control study. The objective is to recruit at least 100-150 persons in each study centre (50 of them would use the SMPs). Ideally this would be a random sample of cell phone users. If this is not possible, then attempts should be made to gather a convenience sample that is broadly representative of the INTERPHONE study population with respect to:

- Gender
 - Urban and sub-urban/rural residence¹
 - Socio-economic status
- Subjects for the validation studies should:
- be aged between 30-59 years
 - possess sufficient language abilities to consent to participation in the study and to complete the questionnaire(s)
 - be resident in the study locality until the end of the validation study
 - be likely to use a mobile telephone at least once a week for the duration of the study period
 - be the main user of the nominated telephone for the majority of the time (i.e. the subject will be the individual responsible for >50% of calls with the nominated telephone)
 - use only the nominated telephone for the majority of his or her mobile telephone calls (i.e. the subject will use the nominated telephone for >50% of mobile telephone calls)
 - consent in writing to the network operator providing details of phone use to the investigators
- Further, volunteers who agree to use the SMPs should have mobile phones provided through pre-payment or contact arrangements and be able to transfer their usual SIM cards into a SMP. Within each country, the group of 50 users should be chosen to include people involved in a variety of different work and leisure activities, resident in both urban and suburban/rural areas and equally

¹ Note: the SMP users should be evenly distributed between urban and rural

distributed between the available network operators. Usage whilst in motion, either in a train or car, should be covered, as well as stationary usage in an office and at home.

C. Information to be obtained from the subjects

The subjects will be asked to agree to 3 months of prospective network monitoring of their mobile phone use – as described in section D. Six months after the monitoring period is completed, the appropriate part of the mobile phone section of the CAPI questionnaire used in the case-control study will be administered in an interview. Additional questions to be asked are as follows:

- whether the individual was the primary user of the telephone
- whether any other cellular telephones were used during the period
- whether any other types of telephone (e.g. hands-free devices) were used during the period
- the subject's first language(s) or preferred language of use – in countries where this is appropriate
- whether or not the subject has suffered from symptoms which he or she attributes to cellular telephone usage, such as headaches or sleep disturbances

In addition, it may be important to anticipate that some subjects will spend time in other countries (e.g. as part of their business), and therefore may use cellular telephones/telecommunications companies which are not contributing to the traffic or billing records. It is important to ensure that subjects report any travel to other countries and use of any extraterritorial operators during the study period.

D. Information collected by network operators (network monitoring)

The network operators will be asked to record prospectively the following information for a period of 3 months:

For each call made or received

- Date
- Incoming or outgoing
- Start and finish time
- First and last base station used¹
- Type of call (voice, text)
- Telephone used

The base station data will be used to judge whether the call was made while moving (ie in a train or car) or stationary, and to categorize the call as "urban", "suburban" or "rural".

E. Information that can be derived from the use of software modified phones (SMPs)

As part of the exposure assessment activities of the INTERPHONE case-control study, each country/region where GSM networks (or 1900 MHz) are used, will take a turn using software modified phones to collect information on the power outputs of different models of phones in different settings. The characteristics and use of the SMPs are described in a separate document. They will be useful for validating information on date, time and duration of calls.

¹ Note: as the references of the base stations may be difficult to understand, the study members should negotiate to obtain either the reference coordinates (for example GIS) of the base stations or to have information provided in a grouped way (by area within and around the cities – specific definition to be discussed between the study group members and the operators).

F. Why use the SMPs within the validation study?

Ideally each centre would combine the two studies, i.e. ask 50 of the participants in the validation study to use the SMPs for one of the 3 months during which information will be recorded by the operator. This will result in fewer subjects to be contacted and fewer interviews than if the SMPs were used in a separate study.

This will also be important for the exposure assessment, as the information recorded, together with information from the networks and the questionnaire will allow the evaluation of differences in average power emitted by the telephones in different circumstances (study regions, urban vs suburban and rural use, moving vs. stationary).

G. Determination of sample size

Unfortunately, determining an appropriate size for validation studies is not straightforward because this depends on the measures being considered (multiple measures which differ between studies), and their variation between and within studies. One example of a successful validation study is that of Funch et al (1996) which involved more than 5 000 telephone users, but such a study size is unlikely to be realistic for the validation studies considered here. Funch et al considered the association between minutes per week of use reported by respondents and the average weekly use calculated from billing data and found a correlation of 0.74 overall, and 0.79 for those with only one cellular phone. Assuming that these estimates apply to comparative measures in the prospective validation study, then it would be desirable to be sure that, given an observed correlation of 0.8, that the "true" correlation was at least 0.6. The number of participants needed to detect this difference can be calculated based on the standard one sample formula for sample size using Fisher's Z transformation of correlation coefficients (Willett, 1998). This yields an estimated sample size of about 100-150 persons in each study centre, although more would obviously be desirable.

H. Analysis of results

The agreement between self-reports and the information from the network operators and the SMPs will be evaluated, and factors that may be associated with varying degrees of mis-reporting will be identified.

Analyses will be carried out in each study centre and at IARC in parallel.

III. RESOURCES

It is expected that the network operators will be able to provide traffic or billing records prospectively without charge.

IV. TIMELINES

The validation studies should be started as soon as possible once the ethical approvals and agreements with the operators have been obtained. As the number of SMPs is limited, they can only be used in two countries at a time. The INTERPHONE Study Coordinator will contact each study group member to discuss the timing of the distribution of the SMPs.

V. REFERENCES

Rothman KJ, Chou C, Morgan R, Balzano Q et al. Assessment of Cellular Telephone and Other Radio Frequency Exposure for Epidemiologic Research. *Epidemiology* May 1996; 7:291-298

Funch D, Rothman K et al. Utility of Telephone Company Records for Epidemiologic Studies of Cellular Telephones. *Epidemiology* May 1996; 7:299-302

Willett W. *Nutritional epidemiology*. Oxford: Oxford University Press, 1998

APPENDIX E – COMMITTEE MEMBERSHIP

The current (updated 2006) membership is as follows:

A. Epidemiology SubCommittee

Dr Bruce Armstrong
Dr Maria Feychting
Dr Christoffer Johansen
Dr Patricia McKinney
Dr Joachim Schüz
Dr Anthony Swerdlow
Dr Paolo Vecchia

B. Exposure assessment SubCommittee

Dr Bruce Armstrong
Dr Joseph Bowman
Dr Simon Mann
Dr Louise Nadon
Dr Masao Taki
Dr Tore Tynes
Dr Paolo Vecchia
Dr Joe Wiart