EMF and risk of tumours

Rationale for IARC 2B classification of ELF and RF

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IARC Monographs Vol 80 - 2002

- **5.5 Evaluation**
  - There is *limited evidence* in humans for the carcinogenicity of extremely low frequency magnetic fields in relation to childhood leukaemia.
  - There is *inadequate evidence* in humans for the carcinogenicity of extremely low frequency magnetic fields in relation to all other cancers.
  - There is *inadequate evidence* in humans for the carcinogenicity of static electric or magnetic fields and extremely low-frequency electric fields.
  - There is *inadequate evidence* in experimental animals for the carcinogenicity of extremely low-frequency magnetic fields.
  - No data relevant to the carcinogenicity of static electric or magnetic fields and extremely low-frequency electric fields in experimental animals were available.
- **Overall evaluation**
  - Extremely low-frequency magnetic fields are *possibly carcinogenic to humans (Group 2B)*.
  - Static electric and magnetic fields and extremely low-frequency electric fields are *not classifiable as to their carcinogenicity to humans (Group 3)*

Evidence in humans

➢**Ahlbom et al 2000 – pooled analysis of data from 9 studies**

Type of study	0.1–< 0.2 μT	0.2–< 0.4 μT	≥ 0.4 μT	O	E	Continuous analysis
Measurement studies						
Canada (McBride *et al.*, 1999)	1.3 (0.84–2.0)	1.4 (0.78–2.5)	1.6 (0.65–3.7)	13	10.3	1.2 (0.96–1.5)
Germany (Michaelis *et al.*, 1998)	1.2 (0.58–2.6)	1.7 (0.48–5.8)	2.0 (0.26–15)	2	0.9	1.3 (0.76–2.3)
New Zealand (Dockerty *et al.*, 1998, 1999)	0.67 (0.20–2.2)	4 cases/0 controls	0 cases/0 controls	0	0	1.4 (0.40–4.6)
United Kingdom (UKCCSI, 1999)	0.84 (0.57–1.2)	0.98 (0.50–1.9)	1.0 (0.30–3.4)	4	4.4	0.93 (0.69–1.3)
USA (Linet *et al.*, 1997)	1.1 (0.81–1.5)	1.0 (0.65–1.6)	3.4 (1.2–9.5)	17	4.7	1.3 (1.0–1.7)
Calculated field studies						
Denmark (Olsen *et al.*, 1993)	2.7 (0.24–31)	0 cases/8 controls	2 cases/0 controls	2	0	1.5 (0.85–2.7)
Finland (Verkasalo *et al.*, 1993)	0 cases/19 controls	4.1 (0.48–35)	6.2 (0.68–57)	1	0.2	1.2 (0.79–1.7)
Norway (Tynes & Haldorsen, 1997)	1.8 (0.65–4.7)	1.1 (0.21–5.2)	0 cases/10 controls	0	2.7	0.78 (0.50–1.2)
Sweden (Feychting & Ahlbom, 1993)	1.8 (0.48–6.4)	0.57 (0.07–4.7)	3.7 (1.2–11.4)	5	1.5	1.3 (0.98–1.7)
Summary						
Measurement studies	1.1 (0.86–1.3)	1.2 (0.85–1.5)	1.9 (1.1–3.2)	36	20.1	1.2 (1.0–1.3)
Calculated field studies	1.6 (0.77–3.3)	0.79 (0.27–2.3)	2.1 (0.93–4.9)	8	4.4	1.1 (0.94–1.3)
All studies	1.1 (0.89–1.3)	1.1 (0.84–1.5)	2.0 (1.3–3.1)	44	24.2	1.2 (1.0–1.3)

➢**Greenland et al 2000 - pooled estimates from 12 studies:**

OR: 1.7 (1.2 – 2.3) above 0.3 μT

What is new since IARC Monographs Vol 80 ?

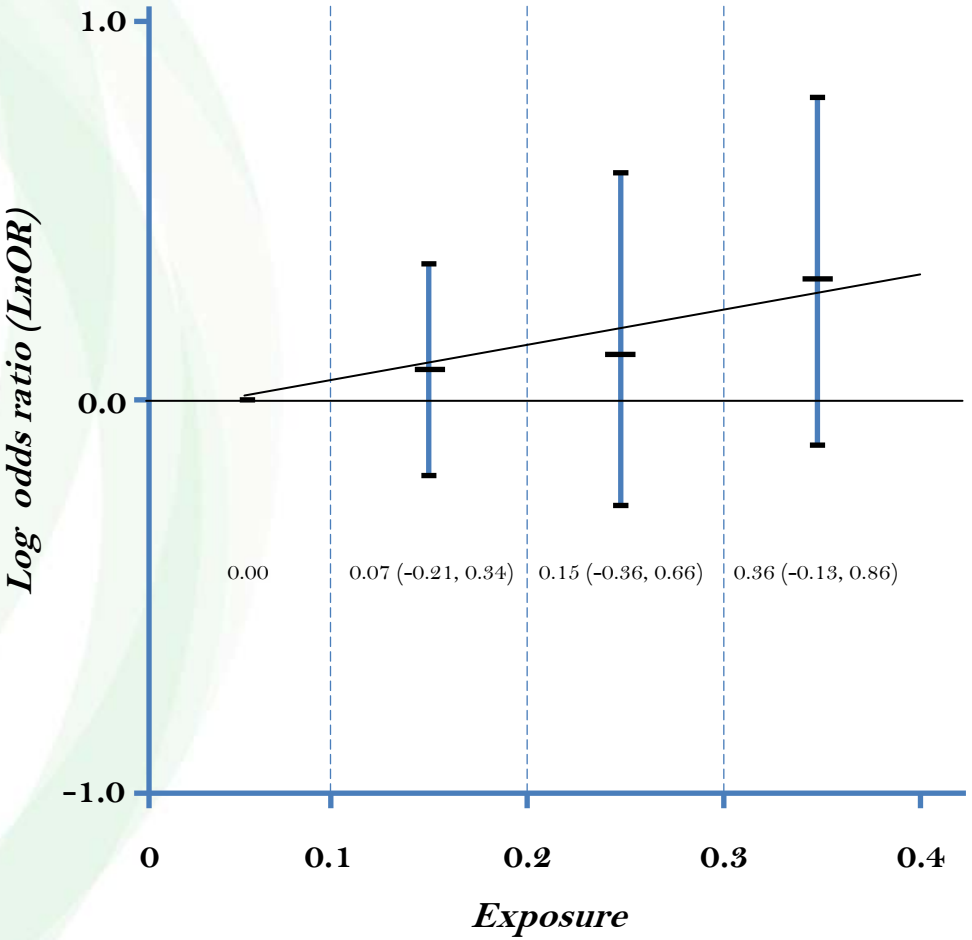
- Recent pooled analysis on newer* studies - *Kheifets et al (2010)*

Germany, 2 Italian studies, Japan, Tasmania, UK

Exposure category (μT)	Number of cases	Number of controls	N	OR (adjusted for age, sex and SES) with 95% CI
<0.1	10,691	12,501	23,192	1.00
0.1-0.2	79	202	281	1.07 (0.81, 1.41)
0.2-0.3	22	53	75	1.16 (0.69, 1.93)
≥0.3	26	50	76	1.44 (0.88, 2.36)

≥0.4 μT : OR 2.02 (0.9–4.7) vs. 2.00 (1.3-3.1) in Ahlbom et al 2000

Continuous exposure-response coefficient derived from summary data



Generalised least squares regression, constrained to origin

Current evidence for ELF and childhood leukaemia

- Kheifets et al (2010)
  - ***We conclude that recent studies on magnetic fields and childhood leukaemia do not alter the previous assessment that magnetic fields are possibly carcinogenic***

- *EFHRAN review (2011)*
  - ***There is limited evidence for an association between magnetic fields and the risk of leukaemia in children.***
  - *This evaluation reflects the current state of knowledge: epidemiological studies have shown an association between residential exposures to power frequency magnetic fields at above approximately 0.3/0.4 μT and a two-fold risk of childhood leukaemia with some degree of consistency, but observed association alone not sufficient to conclude a causal relationship.*
    - ✓ *i) no known mechanistic explanation and none of the hypotheses put forward to explain it has received any convincing support from data;*
    - ✓ *ii) overall, experimental studies do not provide evidence that LF magnetic fields are carcinogenic;*
    - ✓ *iii) a combination of chance, bias and confounding may well have produced a spurious association*
  - *It is unlikely that further epidemiological studies of the same design as used earlier will provide any new insight.*
    - ✓ *New concepts to identify cohorts of children with higher exposures may turn out to be promising. If the hypothesis of a poorer survival of children with leukaemia will be confirmed by other studies, this will increase the biological plausibility of a causal association.*
    - ✓ *Further methodological work investigating the impact of possible biases in studies.*

- *EFHRAN health impact assessment (underway) –*
  - *1-2% childhood leukaemia cases in Europe may be due to ELF if ELF is carcinogenic*

Mobile phones, RF and health

- History of mobile phone use
  - 1st generation – analogue phones
    - ✓ started in early 1980´s
      - – "bag telephones" with antenna on the bag
      - – car phones
      - – mainly 450 MHz range
      - – costs were high and phones unwieldy
    - ✓ late 1980´s – early 1990s …
      - – "Smaller" hand held phones with antennas
      - – 800-900 MHz
      - – still expensive … "businessmen"

Mobile phones, RF and health

- 2nd generation - digital phones
  - started around 1992
  - 800-900 MHz
  - then 1500, 1800-1900 MHz
  - prices decreased
  - subscription prevalence increased
  - ,,, but use still low …
    - ✓100 hours lifetime,
    - ✓2-2.5 hours monthly in Interphone controls (interviewed 2000-2004)

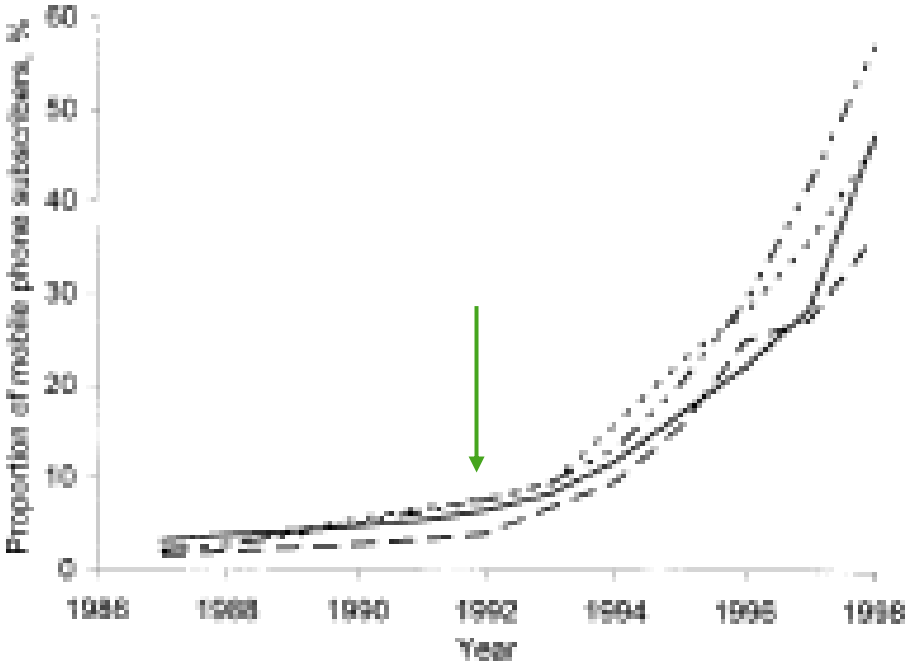


FIGURE 1 – Annual proportion of mobile phone subscribers in four Nordic populations during 1987-98. Denmark is indicated as— —, Finland as– – – –, Norway as —— and Sweden as - - -.

Lönn et al, 2004

Mobile phones, RF and health

- Today …
  - >4.6 billion users in the world
  - Increasingly 3G, 3.5G, 4G
  - Higher frequencies … 2.2 GHz
    though now re-using lower frequencies
  - Prevalence of use still increasing, particularly in young people
  - So is amount of use …

  … not unusual to see young people using phones 1 or more hour a day

What do we know about health effects of RF ?

- Have been reviewed over the years by a number of national and international committees
  - Most reviews have been inconclusive – some suggesting lack of effects at athermal levels

- WHO-IARC Monographs evaluation 31 May 2011
  - based on a critical review of all available peer-reviewed studies, classified RF as *"possibly carcinogenic to humans – 2B"* *

** Baan et al, The Lancet Oncology – epub 22 June 2011*

IARC RF evaluation

- Possibly carcinogenic to humans – 2B
  - Limited evidence of carcinogenicity in human
    - ✓ Main basis are results of Hardell and INTERPHONE studies which show indications of a possible increased risk of glioma and acoustic neurinoma in longer term and/or heaviest users
    - ✓ Interpretation is credible
    - ✓ Bias and/or counfounding cannot however be ruled out

A few members of the Working Group considered the current evidence in humans "inadequate". In their opinion there was inconsistency between the two case-control studies and a lack of an exposure-response relationship in the INTERPHONE study results; no increase in rates of glioma or acoustic neuroma was seen in the Danish cohort study, and up to now, reported time trends in incidence rates of glioma have not shown a parallel to temporal trends in mobile phone use.

IARC RF evaluation

- Limited evidence of carcinogencity in animals
  - ✓None of the chronic bioassays showed an increased incidence of any tumour type in tissues or organs of animals exposed to RF-EMF for 2 years though an increased total number of malignant tumours was found in RF-EMF-exposed animals in one
  - ✓Increased cancer incidence in exposed animals in a small number of studies with tumour-prone animals and in one of 18 studies using initiation-promotion protocols.
  - ✓Four of six co-carcinogenesis studies showed increased cancer incidence after exposure to RF-EMF in combination with a known carcinogen
- Weak mechanistic evidence relevant to RF induced cancer in humans

Epidemiology - different approaches

- Ecologic studies
- Cohort studies
- Case-control studies

.. Each has specific purposes, advantages and limitations

Different epidemiological approaches

- "Ecologic" studies

  correlation between mortality or incidence rates in a population and a measure of exposure at the level of the population

  (e.g. mobile phone subscription rates)…

  - ✓ Geographical correlations
  - ✓ Temporal correlations – time trends

- Helpful surveillance tool
- But interpretation can be difficult – e.g. for mobile phones
  - ✓ most analyses examined trends until the early 2000s only and hence provide little information
    - – if excess risk only manifests more than a decade after phone use begins,
    - – and/or if phone use only affects a small proportion of cases—eg, the most heavily exposed, or a subset of brain tumours.

Different epidemiological approaches

- "Analytical studies"

  …. Information available at individual level

  …. Much more informative for risk evaluation

  - Cohort studies

    Study group defined by its exposure
    and followed up in time to determine disease status

    - ✓ Very useful for surveillance – follow multiple endpoints
    - ✓ Little power for rare outcomes … e.g. Danish cohort study
      - 400 000 subscribers approximately
      - 3.8 million person years of follow-up

      … 356 glioma cases ….
    - ✓ Exposure assessment difficult for large cohorts
      - *Substantial exposure misclassification in Danish cohort*
    - ✓ Potential for selection bias if comparisons with general population
    - ✓ Need many years of follow-up for diseases such as cancer

Different epidemiological approaches

- "Analytical studies" (con'td)
  - Case-control studies

    Study group defined by disease status

    compare level of exposure between cases and controls

    - ✓ Much greater statistical power for rare outcomes:
      - – select all cases from very large geographical areas e.g Interphone: *2 708 glioma cases*
    - ✓ Can collect detailed information for exposure estimation
      - – numbers of subjects limited (thousands vs hundreds of thousands or millions)
    - ✓ No need for very long-term follow-up
      - – Collect cases over a few years
    - ✓ But - by design - focus on only a few outcomes
      - – No information about Alzheimer's in brain tumour study …
    - ✓ Potential for recall bias and error
    - ✓ Potential for selection bias (if poor response rates)

Early case-control studies of brain tumour risk

Reference	Study period	Total number of cases	% users	Long term users		
				Duration of use	Number of cases	RR (95% CI)
Muscat, 2000	94-98	469	18%	≥4 years	17	0.7 (0.4-1.4)
Inskip, 2001	94-98	782	18%	≥5 years	22	0.9 (0.5-1.6)
Auvinen, 2002	96	398	13%	>2 years	18	1.5 (0.9-2.5)

… few exposed cases, short follow-up … …

Swedish case-control study - glioma

- Pooled analysis of two studies (Hardell et al, 2011)
  - 1148 glioma and 2438 controls
  - Cases ascertained 1997–2003 through cancer registries
  - Self-administered questionnaires followed by telephone interviews
  - Response rates high (84-85%)
- ORs for glioma
  - Use 1+ years 1.3 (95% CI 1.1-1.6) 529 cases
  - Use 10+ years 2.5 (95% CI 1.8-3.3) 123 cases
  - >2000 hours 3.2 (95% CI 2.0-5.1) 58 cases
  - OR increased with time since first use and with total call time
  - Ipsilateral use of the mobile phone was associated with higher risk
  - Risk highest for use before age 20
  - Similar findings for use of cordless phones

The INTERPHONE study

- *Objectives*
  - To determine whether mobile phone use increases the risk of cancer, and
  - To examine the association with other known / suspected risk factors
- *Design*
  - Population based case-control studies:
    - ✓ Glioma
    - ✓ Meningioma
    - ✓ Acoustic neurinoma
    - ✓ Parotid gland tumours
  - All persons aged 30-59 years who reside in the study regions (metropolitan areas in most countries)
  - Case diagnoses: 2000 until late 2004

INTERPHONE - study results

- Meningioma: 2409 cases and 2662 controls
- Glioma: 2708 cases and 2972 controls
- Acoustic neuroma (AN): 1105 cases and 2145 controls

- Reduced OR among ever regular users
  - Meningioma: 0.79 (95% CI 0.68-0.91)
  - Glioma: 0.81 (95% CI 0.70-0.94)
  - AN: 0.85 (95% CI 0.69-1.04)

- No increased risk for use 10+ years
  - Meningioma: 0.83 (95% CI 0.61-1.14)
  - Glioma: 0.98 (95% CI 0.76-1.26)
  - AN: 0.76 (95% CI 0.52–1.11)

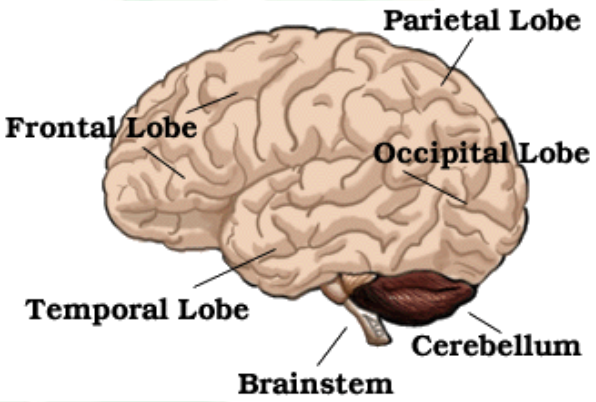
- Overwhelming majority of ORs below 1 … *risks underestimated ?*

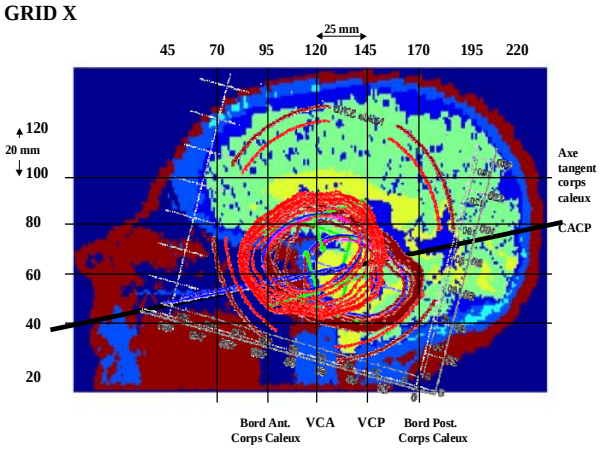
The INTERPHONE Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. IJE 2010

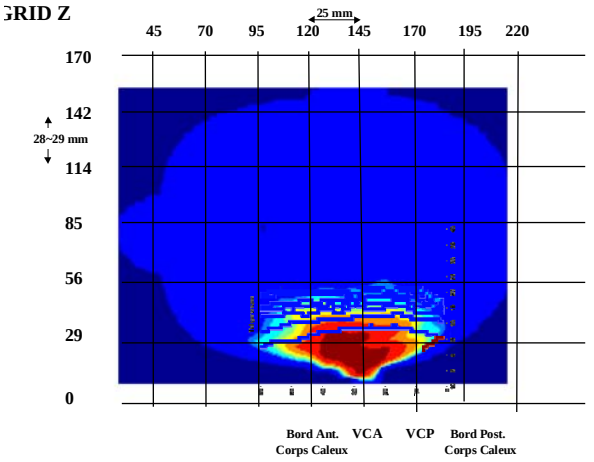
The INTERPHONE Study Group. Acoustic neuroma risk in relation to mobile telephone use: Results of the INTERPHONE international case–control study . Cancer Epidemiol, 2011

INTERPHONE - study results

- No evidence of exposure response relationship but …
- Increased OR in highest users (>= 1640h)
  - Glioma: 1.40 (95% CI 1.03-1.89)
  - Risk highest
    - ✓ On side of head where phone is used 1.96 (1.2-3.2)
    - ✓ For tumours in the temporal lobe 1.87 (1.1-3.2)







INTERPHONE study results

- Recent 5-country analyses with estimated RF dose at the location of the tumour *(Cardis et al, OEM, 2011)*
  - a dose-response relationship for glioma 7+ years before dx
  - no association in short-term users
  - a higher proportion of long term users in tumours in most exposed area of the brain

... Results suggestive, but biases and error prevent a causal

- *Caution needed until more definitive conclusions can be drawn*

CHANGES IN PATTERN OF USE

- Interphone study subjects
  - Light users compared to today
    - ✓ Few used the phone more than 10 years
    - ✓ Median cumulative call time over life: 100 hours
    - ✓ Highest group >=1640 hours: *about 30 min/day over 10 years*
  - Not unusual today for people to speak one hour or more, particularly young people

➢ Need more research, particularly among young people

Mobile phones and brain tumours in young people

- Public and public health interest
  - International recommendations
    - ✓ WHO International EMF Project
    - ✓ EU supported EMF-Net
  - National recommendations

mobi-kids
Tecnologías de la comunicación, medioambiente y tumores cerebrales en la gente joven

Use of mobile phones during childhood and adolescence

- Benefits – non-negligible
  - Emergencies
  - Communication with family
  - Communication with friends
- What are the potential risks ?
  - Cognitive effects
  - Brain and CNS tumours
- Health effects of RF not demonstrated at this point

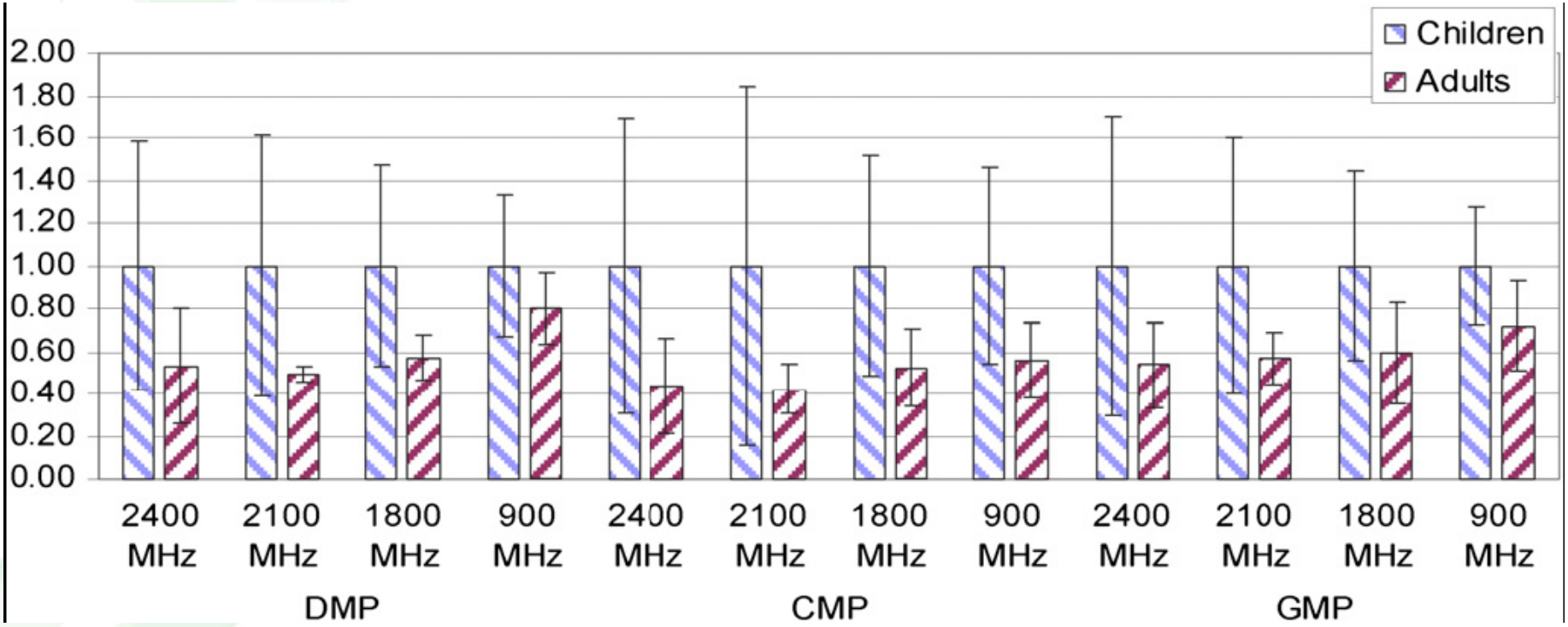
… but if there is a risk, it is likely to be greater for exposures in childhood and adolescence …

Why would the risk be larger?

- Children who start using phones will have much more exposure
  - Many more years of use
  - Greater quantity of use as much cheaper than before
- Children may be more vulnerable

Exposure is greater …

The relative mean MSAR1g tends to be higher in children than in adult brain tissues
(results normalized to children)



Wiart et al, 2008

Brain tumours in young people - CEFALO

- Aydin et al 2011, JNCI
  - 352 cases, 646 controls
  - 7-19 years old, 2004-2008
  - Participation rates - 83% cases, 71% controls
  - Results
    - ✓ Ever regular use (194 cases) OR 1.36 (95% CI 0.92-2.02)
    - ✓ No evidence of increase with duration or amount of use

    …only 52 cases with subscriptions for 4 years or more
  - Interpretation difficult
    - ✓ Relatively small number of subjects
    - ✓ Subjects young – median 13 years
    - ✓ Very few long term or heavy users

      - median years of use 2.7

      - median cumluative hours of use lifetime: 35
    - ✓ Most ORs above 1 …

Mobi-Kids

SEVENTH FRAMEWORK PROGRAMME

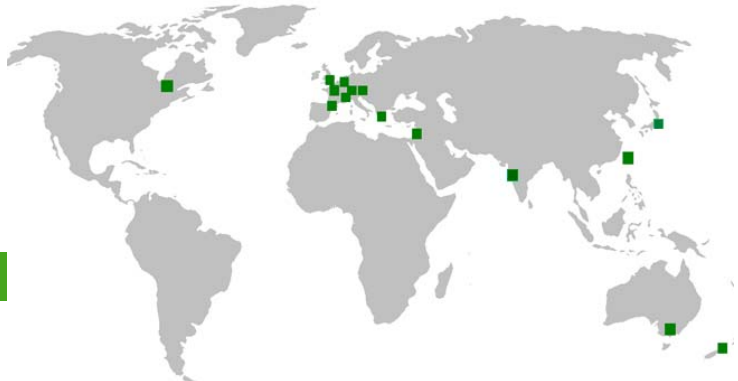
- Overall objective
  - To assess the risk of brain tumours in young people in relation to:
    - ✓ childhood and adolescent exposure to EMF from communication technologies
    - ✓ other potential environmental and host factors

- Case-control study
  - Cases
    - ✓ Benign and malignant brain tumours
    - ✓ Aged 10-24, 2010-2013
    - ✓ Rapid ascertainment from diagnosing and treatment hospitals
  - Controls
    - ✓ 2 per case
    - ✓ Appendicitis controls, to minimise selection bias related to non-participation.
    - ✓ Individually matched on age, sex and region

MobiKids countries – about 2000 cases expected

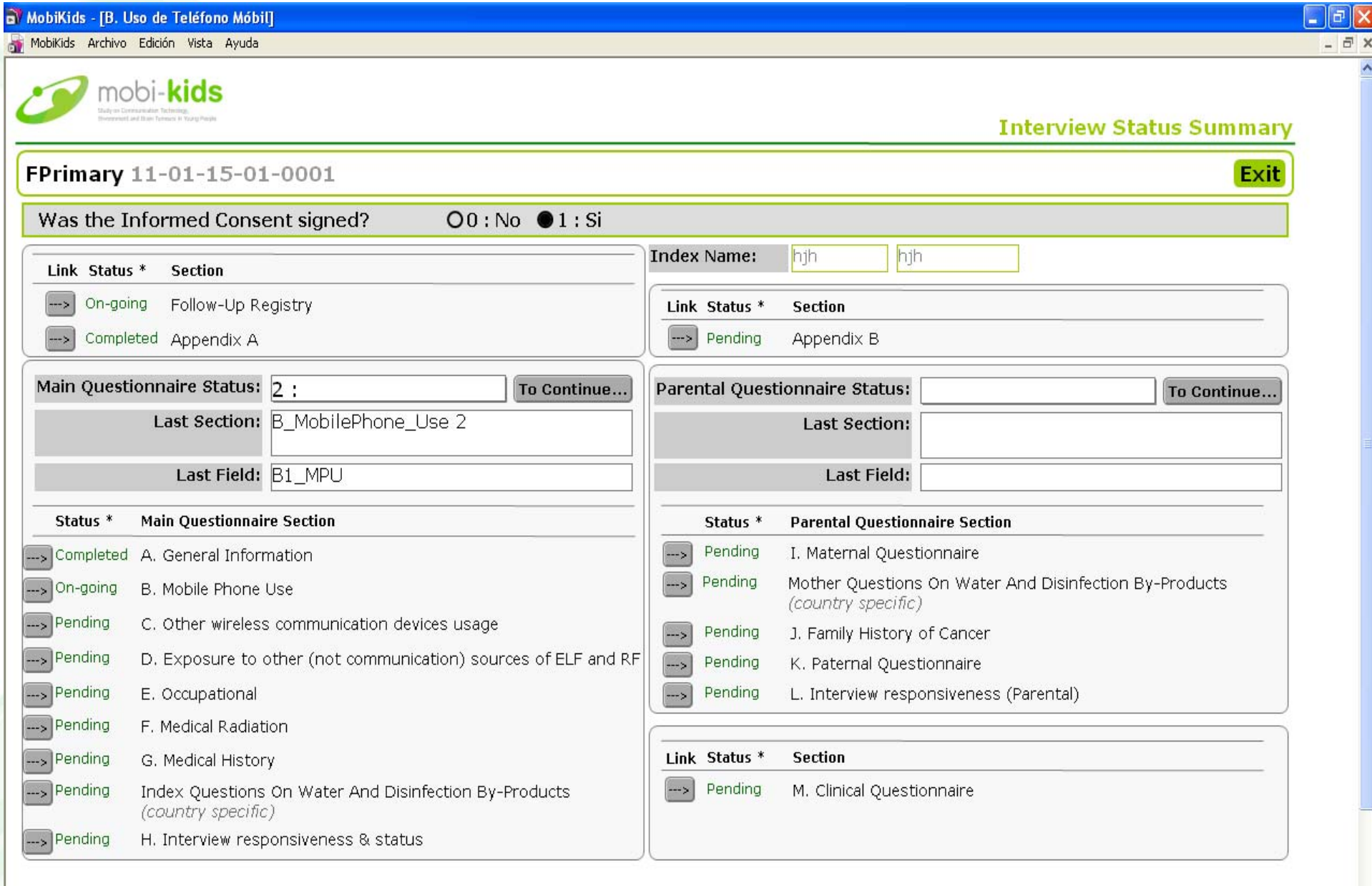
- EU funding
  - Austria
  - France
  - Germany
  - Greece
  - Israel
  - Italy
  - The Netherlands
  - Spain*

- Separate funding
  - Australia
  - New Zealand
  - Canada
  - India
  - Korea
  - Japan
  - *Taiwan*
  - *US ?*



**CREAL coordinator*

Detailed study questionnaire



Validation of self-reported mobile phone use

- Historical traffic/billing records from providers for cases and controls
  - Frequency and duration of voice and data use
  - Identification of phones (in some countries through IMEI)
- Laterality
  - Interview hands a phone to the subject
  - Photograph if not in person
- Software-modified-smartphones (SMSP) study among volunteers
  - Frequency and duration of voice and data use
  - Laterality
  - Hands free
  - Estimated power

  ... Validation and information on use patterns

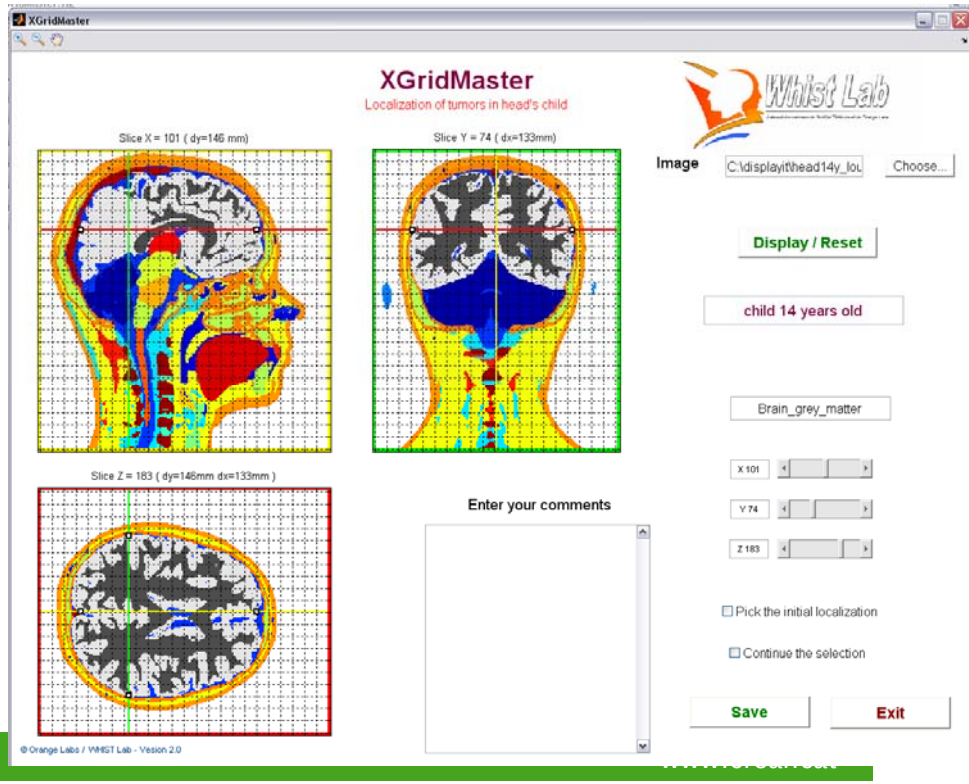
ZonWN

anses
French agency for food, environmental and occupational health & safety

Tumour diagnosis and localisation

- Tumour diagnosis:
  central review of sample of histological slides
  by international panel of neuropathologists to verify diagnosis

- Tumour localisation:
  review of MRI/CT scans - mark precise location of tumour on specially developed grids

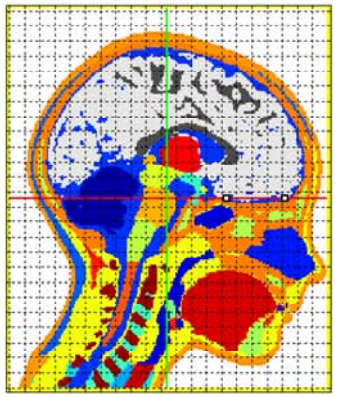


Exposure assessment

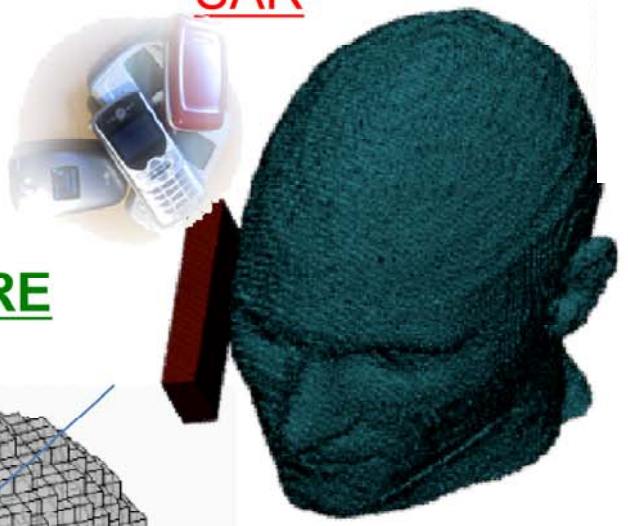
- Exposure assessment subcommittee:
  Myron Maslany, Joe Wiart, Hans Kromhout, Malcolm Sim, Ae-Kyoung Lee, Masao Taki, Elisabeth Cardis
- Exposure assessment - EMF
  - Estimation of RF and ELF exposure at different locations of the brain from mobile and DECT phones and other communications technologies
  - Estimation of EMF exposure from other residential and occupational sources

Objective: characterise the exposure

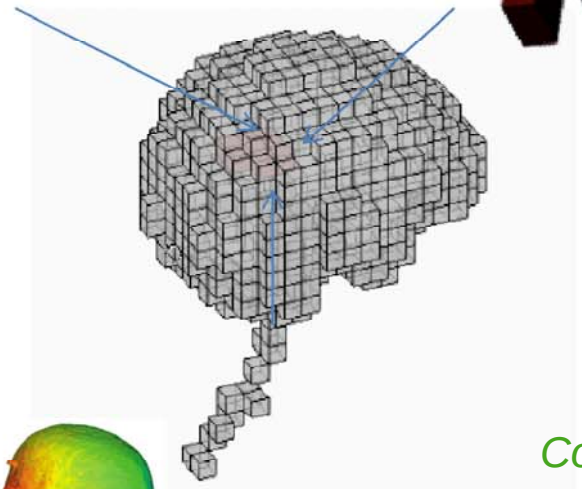
Tumor localisation



SAR

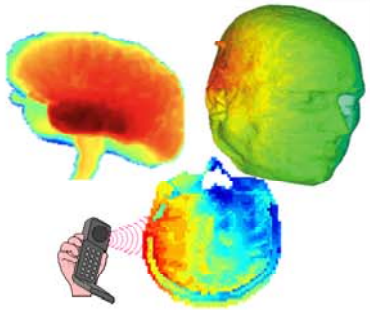


EXPOSURE



SAR distribution in brain :

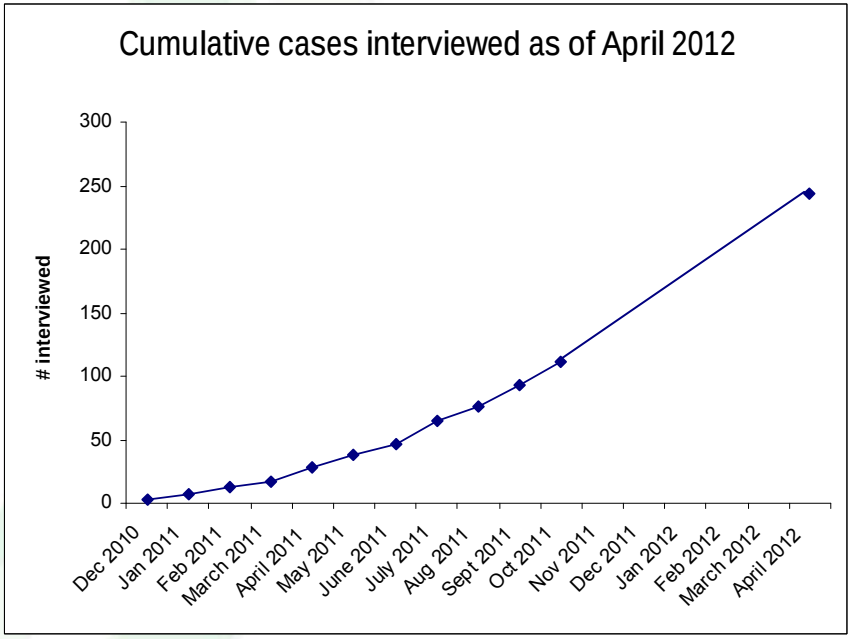
highly localized

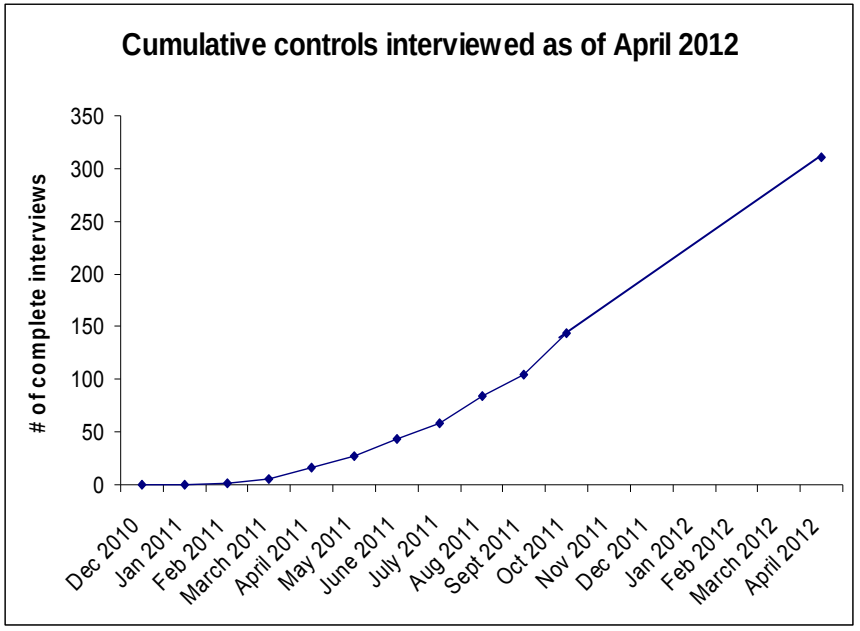


Courtesy: J. Wiart, Whist Labs

Current status

- Ethics approvals:
  - Obtained or ongoing in most countries (hundreds of hospitals !)
- First interviews started early 2011
- New countries about to start





Data collection until Sept 2014 – results 2015/2016

What should we do in the mean time?

- There are easy ways to reduce one's exposure
  - Keeping phone away from the head
    - ✓ SMS
    - ✓ Hands-free kits
    - ✓ Speaker of the phone

… Reasonable to use them until more conclusive evidence

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