German Mobile Telecommunication Research Programme

# Report on the

# 5th International Workshop on Long-term Effects

## 11/12 October 2007 in Munich

# Long-term effects

studied

1. in animal models by chronic or repeated exposure
2. in epidemiological studies

endpoints:

ad 1. blood brain barrier, learning and memory,
immune response and stress, tinnitus,
leukaemia and metabolic system,
fertility and development

ad 2. brain tumours, uveal melanoma, childhood leukaemia

# What was the situation before starting the programme?

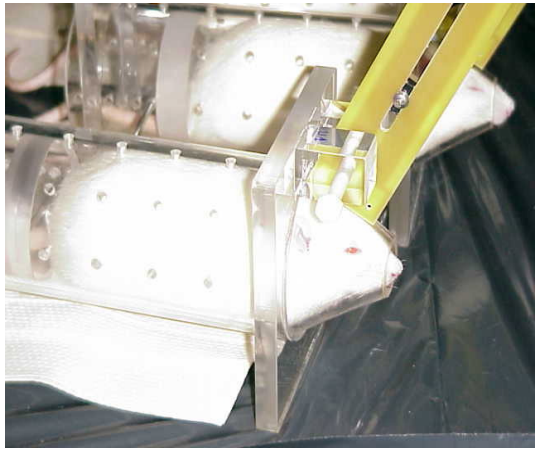
## animal studies:

- some evidence from *in vivo* and *in vitro* studies on increased permeability of the BBB
- chronic exposure of $E_{pim}$-mice showed increased lymphoma incidence
- inconsistent results regarding learning and memory

## epidemiological studies:

- some evidence from occupational exposure on increased cancer risk, cardiovascular disorders, reproduction and cataracts
- some evidence of childhood leukaemia risk near AM/FM transmitters
- some evidence that the use of mobile phones might go along with increased risk for brain tumours or uveal melanoma

# Results – animal studies



## Blood Brain Barrier (3 projects)

*In vivo* study on rats (University Bordeaux)

head exposure (GSM1800, UMTS at 0.026, 0.26, 2.6 and 13W/kg):

- 1 x 2h; analysed immediately or with delay after exposure, max 50 days („Salford reproduction“)
- 2h/d, 5d/w for 4w; analysed immediately or on day 50 after exposure

endpoints: (i) permeability
(ii) dark neurons

results:
- no confirmation of Salford results
- some statistical significant effects, most of them at 13 W/kg, but no plausible pattern, no dose-response relationship
- physio-pathological consequences unlikely

# Results – animal studies

## Blood Brain Barrier (cont.)

*In vivo* study on 3 generations of free-moving rats (LMU Munich)

chronic whole body exposure (GSM1800, UMTS at 0.4W/kg)

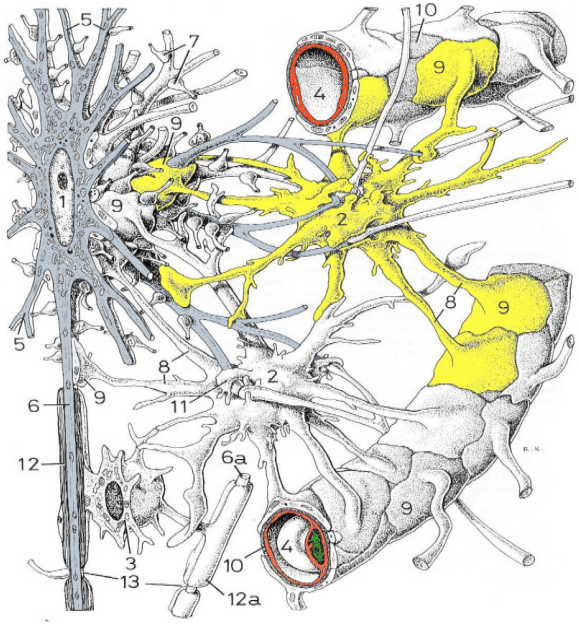
endpoints: (i) permeability under challenging conditions studied by influx for $^{14}$C-saccharose in 7 brain areas
(ii) number of hippocampal CA1-neurons

results: no statistical significant differences between exposed animals versus sham, analysed after 4 or 11 months of exposure

# Results

## Blood Brain Barrier (cont.)

*In vitro* study in a BBB model (University Münster)




endothelial cell cultures from rat brain
exposure (GSM1800, UMTS at 0.4, 1, 3 and 8 W/kg)

endpoints: - differential gene expression (whole genome; Affymetrix GeneChip)
- verification by qRT-PCR (TaqMan-Array)

results: - 13(UMTS) / 5(GSM1800) BBB-relevant genes regulated at least at one SAR, among them tight junction protein claudin-1
- regulations relatively weak
- for none of the genes dose-response relationship

→ results do not point towards patho-physiologically relevant events in human, but identified candidates should be investigated further on protein level

# Results – animal studies

## Multigeneration studies

### 3-generation study on Wistar rats (LMU Munich)

chronic whole body exposure (GSM1800, UMTS at 0.4W/kg)

endpoints: (i) BBB
(ii) learning & memory – studied by operant behavioural tests in computer-controlled skinner boxes
(iii) immune response & stress – studied by analysing antibody production after immunization and corticosteron levels after stimulation

results: - ad learning & memory: no significant differences between exposed animals (including *in utero*) versus sham
- ad immune response & stress: no systematic differences between exposed animals and controls

# Results – animal studies

## Multigeneration studies (cont.)

## 4-generation study on fertility and development in mice

(Jacobs University Bremen)

chronic whole body exposure (UMTS at 0.08, 0.4 and 1.3W/kg)

endpoints: (i) body weight

(ii) *males:* sperm analysis, weight of testis and accessory glands

*females:* number and weight of fetuses, corpora lutea/ovary

*outcomes:* number of pups, developmental observations (eye opening, reflex tests, malformations…)

result: no indication of harmful effects due to chronic exposure over several generations (including *in utero*)

# Results – animal studies

Tinnitus

Free-moving rats
(University Tuebingen)

local exposure (UMTS at 0.02, 0.2, 2 and 20W/kg)

endpoints: (i) behavioural response
(ii) differential gene expression
in cochlea and brain – studies by RT-PCR

results: - no behavioural response
- no influence on gene expression

# Results – animal studies

## Influence of GSM or UMTS-signals on spontaneous leukaemia
(Jacobs University Bremen)

AKR/J-mice as model for studying hematopoietic malignancy

chronic whole body exposure (24h/d): - GSM900, UMTS at 0.4W/kg
- 50Hz at 1, 100 and 1000µT

endpoints: (i) survival rate
(ii) lymphoma incidence
(iii) blood parameter, gross necropsy
(iv) body weight

results: no influence on developing lymphoma, but statistical significant increase in body weight upon GSM-exposure

additional study on metabolism - ongoing -

# Results – epidemiological studies

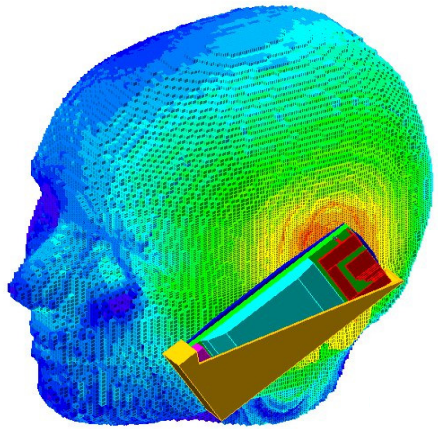
Feasibility of a cohort study on occupationally (highly) exposed groups
(University of Bielefeld and Mainz, DKFZ Heidelberg)

based on literature review and criteria catalogue
3 potential cohorts identified:

(i) workers on dielectric heat sealers
(ii) engineers and technicians on AM/FM transmitters
(iii) amateur radio operators

result: no cohort without substantial problems and
with exposures similar to mobile phones –
cohort study on mobile phone users recommended

# Results – epidemiological studies



Feasibility of a prospective cohort study
on mobile phone users
(University of Bielefeld, Mainz, DKFZ Heidelberg)

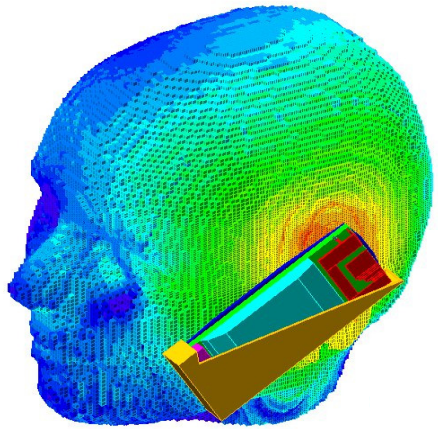
aim: Is participation of Germany within the international cohort study COSMOS possible?

results:

- cooperation with net providers was promising
- exposure assessment is complex, but possible
- complete follow-up for all endpoints difficult
- in pilot study very low participation rate (5% -12%)

participation in the international cohort study (COSMOS) is, in principle, feasible, but too cost-intensive due to too low participation rate

# Results – epidemiological studies



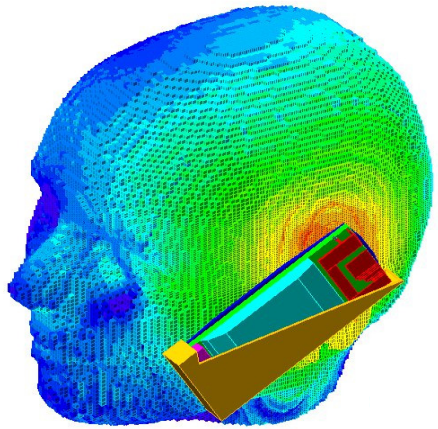
## National INTERPHONE study

(University of Mainz and Bielefeld, DKFZ Heidelberg)

study design:
- case-control study (2000-2003)
- glioma (366), meningeoma (381), acoustic neuroma (97)
- exposure assessment using CAPI (self-reports) – validation study with software-modified mobile phones

results:
- use of mobile phones (< 10 ys) not associated with brain tumour risk (consistent with other national studies)
- statistically non-significant increased risk for glioma among users of 10+ years (too few cases, pooled analysis necessary)
- no increased risk for cordless phone use or high occupational RF-exposure

# Results – epidemiological studies



Estimation of RF-exposure in
INTERPHONE study subjects (IARC, Lyon)

aim: construction of a RF exposure gradient
final goal: correlation of generic SAR-distribution with anatomical tumour location

information needs:
- type of telephone
- network (frequency, signal characteristic, power control)
- amount of phone use (number and duration of calls)
- conditions of use (headside, stationary vs moving,…)

to consider:
- selection bias, recall bias
- uncertainties in dosimetry

→ validation studies and sensitivity analyses

Unlikely, that the international study (pooled analysis) will provide final answers
- still small number of long-term users (10+ years)
- substantial errors possible → COSMOS

# Results – epidemiological studies

## Case-control study on uveal melanoma and RF
(University of Halle-Wittenberg)

aim: does the use of mobile phones increase the risk for uveal melanoma?

study design:
- interview included UV-exposure, pigmentation type, …
- for exposure to mobile phones same CAPI as in INTERPHONE study
- 458 cases, 1194 controls (827 population-, 180 ophthalmologist- and 187 sib-controls)

result: no association between mobile phone use and risk of uveal melanoma (a few increased OR, but based on few subjects, large uncertainties and without consistent pattern)

firm conclusion for long-term mobile phone users (10+ years) not possible

# Results – epidemiological studies

## Case-control study on childhood leukaemia and proximity to radio and television transmitters (University of Mainz, Copenhagen)

study design:

- 16 AM-transmitters and 8 FM/TV-transmitters
- 1,959 cases (1984-2003), 5,848 controls
- individual retrospective exposure assessment based on historic transmitter data, place of residence (1 year before diagnosis)
- validation study → good correlation between calculated and measured fields

result: no association between childhood leukaemia risk and exposure to RF transmitters (total field strength or separately for AM and FM/TV)

# Results – age-dependency

Age-dependent effects of RF-fields based on relevant biophysical and biological parameters (IT´IS Zürich)

aim: investigation of age-dependent RF-absorption in the head

study design:

- 3 MRI-based head models (3, 6 and 11 years), focus on target structures (pineal gland, hypothalamus, hippocampus, eye, skull and bone marrow)
- realistic exposure situations, including temperature measurements in auditory canal and on skin; measurement of pinna thickness

preliminary results:

- age dependencies of dielectric tissue do not seem to have much impact on peak spatial average SAR, but thickness of pinna may have
- exposure of certain regions may be higher in children compared to adults, depending on phone type

- ongoing -

# Final discussion – Questions to the Auditorium - Conclusions

1. What has been achieved by the projects? What are the lessons learned?

Results from chronic (or repeated) exposure to RF-fields
(i) in animal models:
- no health-related effects on BBB
- no induction of tinnitus
- no effect on lymphoma in AKR/J-mice
- 3-generation study in rats: no effect on learning, memory, BBB, CA1 neurons, immune response, stress
- 4-generation study in mice: no effect on fertility and development

(ii) in epidemiological studies:
- no risk for brain tumours or uveal melanoma among mobile phone users (at least up to 10 years)
- no risk for childhood leukaemia near AM/FM transmitters

*in overall, good consistency with results from other national studies*

# Final discussion – Questions to the Auditorium - Conclusions

2. Where do we still have gaps?

*Scientific uncertainties* could be reduced
- hints from previous studies not supported
- no *new* evidence on health-related effects below limits

*Still open*

possible long-term effects (10+ years) for (intensive) mobile phone users, true for adults, but especially for children as a „possible higher sensitivity of children“ is still under exploration

3. Can we define minimum standards for future work?

Ken Foster´s Conclusions from the comments for future work:
- It is time for consolidation
- Do not just continue “because science is nice”
- Persistent gaps: children, combined effects, long-term effects
- Optimization of exposure
- Maintain efforts in risk communication

# Final discussion – Questions to the Auditorium - Conclusions

4. Are there findings that have an impact on guidelines or on standard settings?

**The overall results confirm the current limit values**