

# **Final Report IMBA**

## **Workpackage 1 (WP1):**

**What gaps and what uncertainties exist in the  
ELF- and RF-EMF cancer risk assessment ?**

**RF-EMF and Genotoxicity**

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## 1. Introduction

On occasion of the IMBA kick-off meeting on June 12th 2006 in Berlin, the main goals of IMBA were discussed in detail. The significance of the broad interdisciplinary background and expertise of the participating members (life sciences, social sciences and risk sciences) and organizations enables a communication of the results to health agencies, politics and the interested public.

The emphasis of the project lies on the identification and description of the main uncertainties in the current assessment of human health risks in the field of radiation protection, with special focus on non-ionizing radiation (100 KHz - 300 GHz). Within workpackage 1 (WP1) the Charité Group, Berlin, focussed on in vitro genotoxic effects associated with RF-EMF (radiofrequency electromagnetic fields) and on the identification and a critical review of the main gaps and uncertainties with respect to potential genotoxic effects of RF-EMF. By intensifying research efforts to close these gaps this could optimally result in better exposure assessments, in reduction of uncertainties for risk assessments, and in the development of individualized human health risk assessments.

In published studies however, some gaps regarding genotoxicity effects were occasionally mentioned. These are for instance the lack of a confirmed mechanistic model, the possibility of window effects, the suspected distinctive effect of pulsed EMF's and the assumed special susceptibility of children (see ICNRIP 2005). These issues as well as others have to be systematically compiled. In general, however, a systematic review of the gaps and uncertainties in EMF risk assessment is still missing. The goal of IMBA, especially of Workpackage 1 (WP1), is to perform such systematic review to be able to evaluate in the following Workpackages, if these open gaps and uncertainties could be successfully be approached by toxicogenomics. This approach should enable to advise, if further research in this area is meaningful and should be recommended for further funding.

This report covers two parts: in the first part a comprehensive literature review of the research on in vitro genotoxicity of RF-EMF is given. Additionally an evaluation of cause-effect relationship between RF EMF exposure and the endpoint in vitro genotoxicity is performed (pro-arguments vs. con-arguments). Additional arguments to support or attenuate the respective arguments should be discussed. Summarizing these arguments, conclusions in order to describe a potential cancer risk through RF-EMF should be drawn. Remaining gaps and uncertainties in these conclusions should be identified as well as the underlying gaps in knowledge.

In the second part of the report all identified gaps, uncertainties and inconsistencies should be discussed with respect to four major aspects: (1) exposure assessment, (2) mode of action and (3) susceptibility.

The results from WP1 will be subsequently used in WP2, which will focus on the expected contribution of toxicogenomics to fill/bridge these gaps.

WP1 started after the kick-off meeting. Duration of WP1 was determined from June 2006 to January 2007, but as the actual start had to be postponed, duration was extended to May 2007.

## **2. Strategy of Workpackage 1 (WP1)**

### **2.1 Goal of the study**

Goal of the study was to identify gaps and uncertainties in current knowledge regarding possible genotoxic effects of radiofrequency electromagnetic fields (RF-EMF). The focus lied on genotoxicity induced in vitro in human cells by means of a literature survey from 2000 to 2007, including the most extensive peer-reviewed recent literature databases available.

In a first step a categorization of peer-reviewed studies on RF-EMF associated genotoxicity was performed. The second step included an extensive literature review based on a defined literature search strategy.

Human genotoxic effects are defined as damage in the genomic material exerted by a noxious agent (chemical, biological or physical). Such damages f.e. include DNA strand breaks in one or both of the poly-5'-nucleotide strands of the DNA molecule. To a certain extent such alterations occur permanently after interactions of biological organisms with the environment and thereafter, under physiological conditions, undergo repair by cell-specific repair mechanisms. Structural alterations of DNA, obliterated in such a way, have no harmful effects on the cell. Though, if cellular repair systems are malfunctioning, disturbances of intercellular communication, alterations in cell division rates or induction of apoptosis may result, opening ways to damage the entire organism and to development of chronic diseases such as neurodegenerative diseases or cancer, respectively.

### **2.2 State of knowledge in the year 2000**

In 2000 the German Radiation Protection Committee (SSK) stated with respect to genotoxic effects of RF-EMFs:

“Experiments investigating potential genotoxic effects of radiofrequency electromagnetic fields can hardly be compared with one another due to different exposure parameters like exposure frequency, signal modulation and field strength. Results of experiments with applied field strengths clearly higher than the limits show no uniformity. So far, no hints for a

genotoxic potential of such RF-fields (continuous wave, amplitude- or frequency-modulated) applied in cell phone communication technologies can be extracted from the experiments performed.”

The Independent Expert Group on Mobile Phones (IEGMP) stated in 2000:

“Several different assays of genotoxicity have failed to produce clear evidence that RF radiation is genotoxic at non-thermal levels. The most consistent results come from observations of micronucleus formation, but these are not simple to interpret and have uncertain implications for health.”

### **2.3 Basic approach within IMBA**

To be able to identify gaps and uncertainties in genotoxicity studies for RF-EMF risk assessment, in a first step a comprehensive literature survey had to be performed. RF-EMF genotoxicity studies investigating *in vitro* effects on cells were classified. Classification criteria are described in detail in section 2.4. The following literature databases used for analysis:

PubMed (<http://www.ncbi.nlm.nih.gov>), Femu database / RWTH Aachen (<http://wbldb.femu.rwth-aachen.de>), WHO database (<http://www10.who.int/peh-emf/emfstudies/IEEEdatabase.cfm>)

Basis of the comprehensive literature survey over the years 2000 to 2004 was the collaborative risk assessment study together with MUT (Gminski et al., 2005). Within the IMBA project this basis was further extended up to the year 2007.

### **2.4 Classification criteria for the literature survey**

The published *in vitro* studies on RF-EMF associated genotoxicity were classified in the following categories :

**group 1:** studies using human cells, with investigation of cell proliferation

**group 2:** studies using human cells, without investigation of cell proliferation

**group 3:** studies using animal cells

### 3. Results

#### 3.1 Literature search on RF-EMF associated genotoxicity – Summary

The literature search on RF-EMF associated genotoxicity revealed the following summarized results for the years 2000 to 2007. References from year 2000 to 2004 are shown in black, those from 2005 to 2007 in red. Detailed data are compiled in **table 1**. Informations on cell type of the study, exposure conditions (duration, frequency, SAR, additional characteristics), detection methods / genotoxic endpoints, information on cell proliferation / cell growth and results of the studies are described comprehensively in **table 1**.

group 1	group 2	group 3
Vijayalaxmi et al. 2001 a	Maes et al. 2000	Li et al. 2001
Vijayalaxmi et al. 2001 b	Vijayalaxmi et al. 2000	Bisht et al. 2002
d'Ambrosio et al. 2002	Zotti-Martelli et al. 2000	Park and Kim 2002
Tice et al. 2002	Maes et al. 2001	Koyama et al. 2003
Miyakoshi et al. 2002	Unknown (WHO meeting on	Lagroye et al. 2004
Zeni et al. 2003	EMF Biological Effects,	Komatsubara et al., 2005b
McNamee et al. 2003	Seoul, Korea), 2001	Diem et al., 2005
Hook et al. 2004	Miyakoshi et al. 2002	Nikolova et al., 2005
REFLEX 2004	McNamee et al. 2002a	Speit et al. 2007
Zotti-Martinelli et al., 2005	McNamee et al. 2002b	
Komatsubara et al., 2005a	Zhang et al. 2002	
(Journal not peer-reviewed)	Rudiger et al. 2003	
Zeni et al., 2005	Mashevich et al. 2003	
Vijayalaxmi, 2006	Diem et al., 2005	
Stronati et al., 2006	Baohong et al., 2005	
Scarfi et al., 2006	Chemeris et al., 2006	
	Sakuma et al., 2006	
	Speit et al. 2007	

**Fig. 1: Summary of results of the literature search on RF-EMF associated genotoxicity for the years 2000 to 2007**

Within group 1 (studies on human cells with investigation of cell proliferation) 15 studies were published within the time period defined. Of those 15 studies 11 showed negative and 4 showed positive findings on RF-EMF associated genotoxicity. For details of the analysis see table 1. These 4 studies with positive findings are compiled below:

- **d'Ambrosio et al., 2002:** human peripheral blood samples, small but statistically significant effect in MN induction following exposure to phase modulated field
- **Tice et al., 2002:** human blood leukocytes and lymphocytes, under extended exposure conditions and certain RF-signals a statistically significant MN effect was found at SAR 5 and 10 W/kg
- **REFLEX 2004:** HL-60 cells (micronucleus assay, Comet assay, cell growth, apoptosis, cell cycle kinetics, cytotoxicity, cell viability) data on human fibroblasts belong to Group 2, no data on cell proliferation provided
- **Zotti-Martinelli et al., 2005:** whole human blood samples; micronucleus assay, small but statistically significant increase of MN frequencies in human lymphocytes in dependency on exposure time and power flux

Within group 2 (studies on human cells without investigation of cell proliferation) 16 studies were published within the time period defined. Of those 16 studies 12 showed negative and 4 showed positive findings on RF-EMF associated genotoxicity. For details of the analysis see table 1. These 4 studies with positive findings are compiled below:

- **Zotti-Martinelli et al., 2000:** human peripheral blood lymphocytes, MN induction at 2.45 and 7.7 GHz, 30 mW/cm<sup>2</sup>, 30 and 60 min exposure
- **Rudiger et al., 2003:** cultured human fibroblasts, 16 and 24 h exposure, 1.2 and 2 W/kg, different signals, Comet formation as detected in alkaline and neutral Comet assay
- **Machevich et al., 2003:** primary human lymphocytes, analysis of chromosome replication/aneuploidy, linear increase with exposure level and aneuploidy of chromosome 17, threshold at SAR  $2.9 \pm 0.35$  W/kg
- **Diem et al., 2005:** cultured human fibroblasts, 1.2 and 2 W/kg, 16 h exposure; Comet formation as detected in alkaline and neutral Comet assay. **Study not reproducible independently: Speit et al., 2007.**

Within group 3 (studies on animal cells) 9 studies were published within the time period defined. Of those 9 studies 6 showed negative and 3 showed positive findings on RF-EMF associated genotoxicity. For details of the analysis see table 1. These 3 studies with positive findings are compiled below:

- **Koyama et al., 2003:** CHO cells, RF-EMF exposure at 78 W/kg and higher induce micronuclei
- **Diem et al., 2005:** transformed rat granulosa cells GFSH-R17, 1.2 and 2 W/kg, 16 h exposure; Comet formation as detected in alkaline and neutral Comet assay
- **Nikolova et al., 2005:** murine embryonal stem cells ES-1 cells, short-term RF-EMF exposure at 1.5 W/kg for 6 h caused transient increase in DNA double strand breaks

### 3.2 Further analysis of group 1

As cell growth and cell proliferation gives important hints with respect to the relevance of genotoxic effects for cellular systems with respect for potential adverse health effects of RF-EMF further analysis of the studies belonging to group 1 was performed with respect to the following classifications:

- flow chart for risk assessment / evidence scheme
- conclusions
- open questions, remaining uncertainties, knowledge gaps

The flow chart for risk assessment of RF-EMF associated effects with pro and contra arguments for the studies of group 1 is shown below. This flow chart leads to the subsections “Conclusions” and “Remaining Uncertainties”:

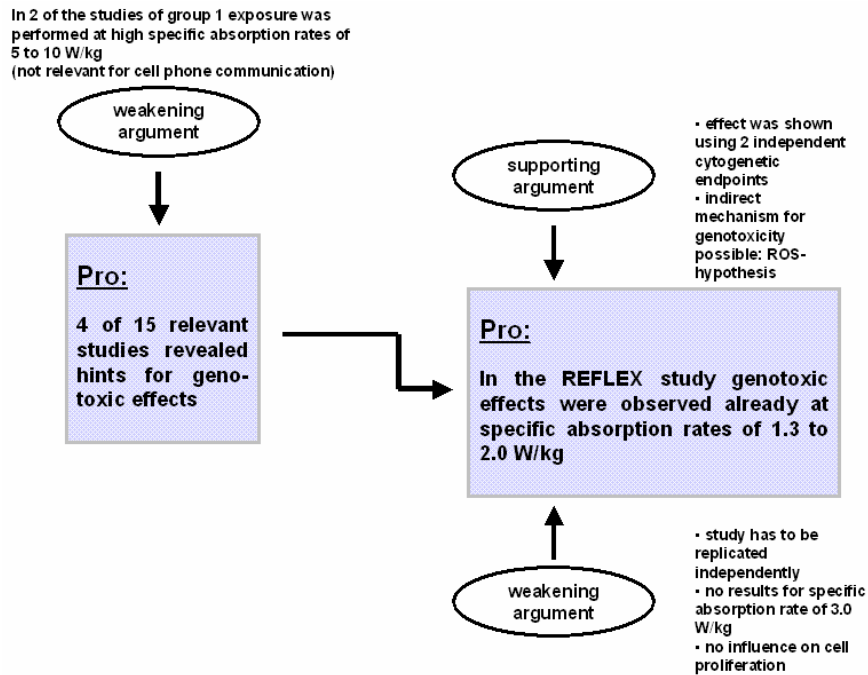


Fig. 2: evidence scheme of human *in-vitro* genotoxic effects (part 1), basis of evidence: 40 peer-reviewed studies, of which 15 are relevant with respect to inclusion of cell proliferation (group 1)

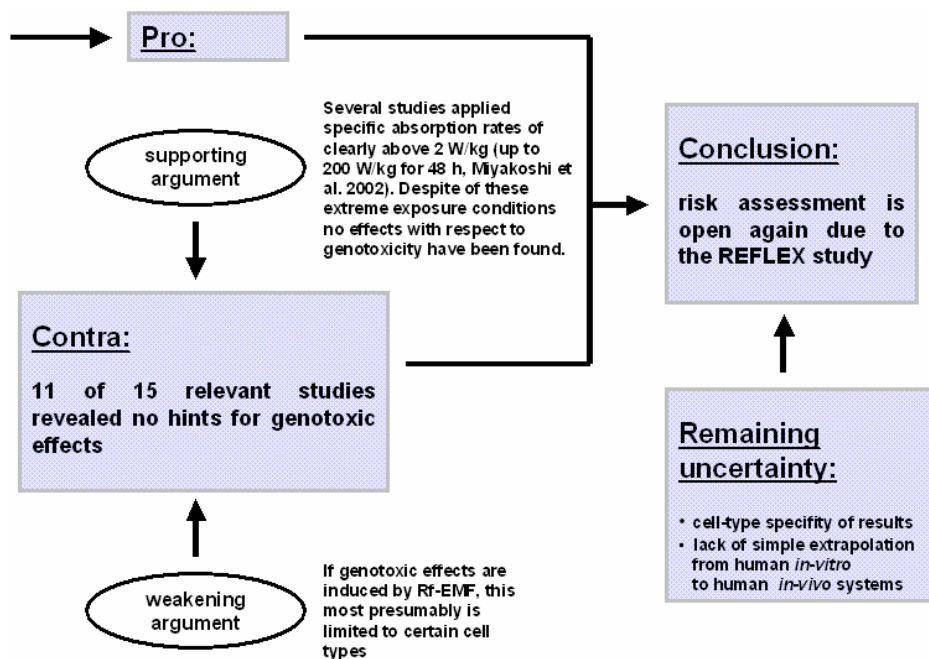


Fig. 3: evidence scheme of human *in-vitro* genotoxic effects (part 2), basis of evidence: 40 peer-reviewed studies, of which 15 are relevant with respect to inclusion of cell proliferation (group 1)

### **3.2.1 Presentation of pros and contras for genotoxic effects exerted by RF-EMF with deduction of knowledge gaps**

The evidence scheme for evaluation of human *in-vitro* genotoxic effects is divided in a contra and pro. The later is sub-divided in 2 steps in order to emphasize the meaning of the REFLEX study particularly for evaluation of pros and cons (fig. 2 and fig. 3).

The REFLEX study (Risk evaluation of potential environmental hazards from low-energy electromagnetic field (EMF) exposure using sensitive in vitro methods) reflects an international multicenter study, consisting of several parts, in which not only the effect of extremely low frequency electromagnetic fields (ELF) but also radiofrequency electromagnetic fields (RF-EMF) on cells, especially on the genome was evaluated. The project was funded by the European Union within the 5<sup>th</sup> Framework Programme (Programme "Quality of Life and Management of Living Resources", Key Action 4 "Environment and Health": QLK4-CT-1999-01574, REFLEX, [http://www.verum-foundation.de/www2004/html/pdf/euprojekte01/REFLEX\\_Final%20Report\\_Part%201.pdf](http://www.verum-foundation.de/www2004/html/pdf/euprojekte01/REFLEX_Final%20Report_Part%201.pdf))

#### ***Pro in-vitro genotoxic effects***

As shown in fig. 1, four of fifteen studies performed with human cells, also investigating cell proliferation, point to an evidence for genotoxic effects (D'Ambrosio et al. 2002, Tice et al. 2002, Reflex 2004, Zotti-Martinelli et al., 2005). Importantly, an alteration of cell proliferation, considered as essentially for risk assessment by the reviewers, could not be observed in any of the three studies.

The pro was weakened by the fact that two of the four studies performed exposure with high specific absorption rates (SARs) of between 5 to 10 W/kg and therefore were clearly above cell-phone technology relevant exposure conditions (D'Ambrosio et al. 2002; Tice et al. 2002).

By this argumentation an extrapolation for risk assessment of cell phone technology is hardly possible.

The second pro is strengthened by the finding of genotoxic effects in the REFLEX study in the cell phone relevant range of between SAR 0.3 to 2.0 W/kg.

This argument is supported on the one hand by the fact, that in the REFLEX study an influence of 1800 MHz exposure on genomic integrity in the sense of genotoxicity was detected by means of not only one but two independent methods: beside DNA single and double strand breaks an increased formation of micronuclei was detected. These results are reinforced by the fact that a free-radical hypothesis could be brought in close context with DNA damage following RF-EMF exposure. The proof for induction of reactive oxygen species by RF-EMF allowed a mechanistic explanation for alterations on the DNA level for the first time. The lack of such an explanation so far was limiting in interpreting described

genotoxic endpoints following RF-EMF exposure. This was especially due to the fact that energy of RF-EMF is too low to break chemical bonds within the DNA molecule.

In the REFLEX study an increase of reactive oxygen species during RF-EMF exposition could be shown for promyelocytic leukaemia HL-60 cells. An induction of DNA breaks by RF-EMF associated generation of free radicals appears possible.

The results of the REFLEX study are weakened by 2 aspects:

- (1) So far for HL-60 cells no independent repetitions of the genotoxic effects in the cell systems examined are available, data on fibroblasts could not be reproduced independently.
- (2) Beside the genotoxic effects observed, no influence of RF-EMF exposition on cell proliferation and cell cycle have been detected.
- (3) For the increase of micronucleus formation in HL-60 cells induced by RF-EMF the dose-response-curve appears not in a classical manner and therefore is hard to interpret. For expositions with 0.2 and 1.0 W/kg micronucleus formation differs not significantly from that of sham-exposed cells. At specific absorption rates of 1.3 W/kg micronucleus formation rapidly increases to decrease again slowly at 1.6 and further at 2.0 W/kg. Micronucleus levels of 1.3, 1.6 and 2.0 W/kg statistically significantly differ from sham-exposure. At higher specific absorption rates of 3.0 W/kg again no difference between RF- and sham-exposed cells is detected with respect to micronucleus formation. Comet formation follows the identical dose-response curve. Taking the ROS-hypothesis into account, a non-monotonic dose-response curve appears mechanistically plausible under the presumption that reactive oxygen species effects show their maximum at 1.3 W/kg. Assuming as a balance of the level of free radicals and effects of cellular repair mechanisms with different effect optima could explain complex and non-linear dose-responses.

### ***Contra in-vitro genotoxic effects***

Eleven of fifteen studies with human cells, also investigating effects on cell proliferation, showed no hints for genotoxic effects (Hook et al 2004, Komatsubara et al., 2005a, McNamee et al. 2004, Miyakoshi et al. 2002, Stronati et al., 2006, Scarfi et al., 2006, Vijayalaxmi et al. 2001a, 2001b, 2006 und Zeni et al. 2004, 2005 ). This argument is supported by the fact that in several studies specific absorption rates of partly clearly more than 2 W/kg (up to 200 W/kg over 48 hours of exposure, Miyakoshi et al. 2002) no genotoxic effects have been found. The contra is weakened by the reviewers appraisal that genotoxic effects of RF-EMF most presumably are limited to specific cell types and not in cells of the peripheral blood. Insofar lack of genotoxicity in lymphocytes or leukocytes following RF-EMF exposure cannot be generalized to other cell types. A new metaanalysis by Vijayalaxmi,

which is not yet published, gives further weight to the weakening arguments (Vijayalaxmi, in press).

If a clear correlation of genotoxic DNA damage with human exposure to radiofrequency electromagnetic fields could be proven, this would provide a sincere evidence for a hazard to human health. The other way around, negative results for genotoxicity in human cells would indicate that diseases, induced by cellular damage, especially damage on the DNA level, are unlikely to be correlated with the influence of RF-EMF exposure. However it has to be pointed out, that not mainly the damage of cells has to be considered of utmost importance for risk assessment, but rather the impact of such alterations on the cell cycle and cell proliferation. This is due to the fact that cellular damage can be repaired and just the damage, that has influence on the cell cycle in the sense of an enhanced cell proliferation, is an indicator for a risk to human health, so f.e. tumor development.

### 3.3 Evaluation of data on one possible underlying mechanism: ROS hypothesis

As it is generally accepted that RF-EMF energy is too low to break atom bonds within the DNA molecule directly, indirect effects such as generation of reactive oxygen species during RF-EMF exposure, addition to DNA and consecutive fragmentation of DNA have to be evaluated. The database literature search on ROS induction associated with RF-EMF exposure was performed in analogy to RF-EMF associated genotoxicity literature search and revealed the following summarized results. Detailed data are compiled in table 2. Informations on cell type of the study, exposure conditions (duration, frequency, SAR, additional characteristics), detection methods / genotoxic endpoints, information on cell proliferation/cell growth and results of the studies are described comprehensively in **table 2**. As just few studies exist and none fits into group 1, all studies published were included into the overview.

Group 1	Group 2	Group 3
-	Kiel et al., 1984	Kiel et al., 1986
	Stopczyk et al., 2002	Deng et al., 2000
	Stopczyk et al., 2005	Zmyslony et al., 2004
	Lantow et al., 2006a	Lantow et al., 2006b
	Lantow et al., 2006b	Zeni et al., 2007
	Simko et al., 2006	

**Fig. 4: Summary of all results of the literature search on induction of reactive oxygen species associated with RF-EMF associated genotoxicity**

Within group 2 (studies on human cells without investigation of cell proliferation) 4 studies with positive findings on ROS formation associated with RF-EMF exposure were published within the time period defined. These 4 studies are compiled below:

- Kiel et al., 1984
- Stopczyk et al., 2002
- Stopczyk et al., 2005
- Lantow et al., 2006b

Within group 3 (studies on human cells without investigation of cell proliferation) 2 studies with positive findings on ROS formation associated with RF-EMF exposure were published within the time period defined. These 2 studies are compiled below:

- Kiel et al., 1986
- Deng et al., 2000

### **3.4 Gaps and uncertainties in genotoxicity studies identified in group 1 (in vitro studies, human cells, with analysis of cell growth)**

With the increasing application of RF-EMF in technical devices such as telecommunication, medical diagnostics and the use of cellular phones, increasing numbers of studies on health risks of RF-EMF, especially of genotoxic effects have been published. While the majority of data provides only hints for genotoxic effects, some studies describe effects of RF-EMF on genomic integrity. Most of the reviews on health effects of EMF's do not focus on existing gaps and uncertainties – usually their focal point is the available scientific evidence for health effects (IEGMP 2000, SSK 2001, BUWAL 2003, NRPB 2004). However, some gaps are often mentioned: for instance, the lack of a confirmed mechanistic model, the possibility of window effects, the suspected distinctive effect of pulsed EMF's and the assumed special susceptibility of children (ICNRIP 2005). These issues as well as others should be systematically compiled. In general, however, a systematic review of the gaps and uncertainties in EMF risk assessment is still missing.

The aim of this study was to analyze knowledge gaps and uncertainties in this field based on the data provided by peer reviewed publications. The focus lied on *in vitro studies*, using

human cells with investigation of cell growth characteristics (group 1). Considering genotoxic effects in human cells with analysis of the influence of RF-EMF on cellular growth characteristics facilitates the most realistic risk assessment for human individuals. Analyzing gaps and uncertainties evident from peer-reviewed studies, the emphasis of further necessary research can be identified to be able to provide a better exposure assessment, a reduction of uncertainties for risk assessments, and the development of individualized human health risk assessments.

The following central knowledge gaps have been identified by analysis of the generated literature survey covering the years 2000 to 2007:

***Are there different cellular susceptibilities ? Is there a cell-type specificity of the genotoxic answer ?***

In the studies published different cell types have been used. Most frequently human lymphocytes were investigated, for example by Baohong (2005), Maes et al. (2000, 2001), Stronati et al., (2006) and Vijayalaxmi et al., (2000, 2001a, 2001 b, 2006). Fibroblasts have been investigated by Diem et al. (2005), Lagroye et al., (2004), Malayapa et al. (1997a), Speit et al. (2007). Stem cells were studied by Nikolova et al. (2005). Beside these cells many more cell types have been examined with different results.

In the majority of lymphocyte studies concludingly no genotoxic effects exerted by RF-EMF are described. A few studies indicate small genotoxic effects in lymphocytes, but most of them occur under specific exposure conditions not relevant for cellular phone use (for details see in f.e. group 1 studies of d'Ambrosio et al. 2002, Tice et al. 2002, Zotti-Martinelli et al., 2005 in table 1).

In the REFLEX study reported in 2004, RF-exposure of HL-60 cells, cultured human fibroblasts and granulosa cells suggested a genotoxic For HL-60 cells no changes were found in cell proliferation kinetics, cell cycle, cellular growth and apoptosis after exposure to CW (for details see table 1, group 1 HL-60 cells, group 2 fibroblasts, and group 3 rat granulosa cells, REFLEX 2004, Diem et al., 2005).

In the study published by Speit et al., 2007 results obtained by Diem et al., 2005 within the REFLEX project could not be reproduced independently.

Controversial results have been published with respect to RF-EMF induced genotoxicity by different researchers. As long as no mechanistic explanation can be given for the genotoxic effects described, cell-type specific answers cannot be definitely excluded. Cell-type specific answers could for example be explained by different genetically determined repair mechanisms of DNA lesions.

***Which biochemical mechanism could explain the genotoxic effects found in association with RF-EMF exposure (f.e. ROS-hypothesis) ?***

Here directly caused genotoxic effects have to be distinguished from indirect caused genotoxic effects. To the momentary knowledge and as a general interdisciplinary consensus the energy of RF-EMF is too low to directly break atom bonds within the DNA molecule. Therefore other mechanisms have to be found for explaining disruption of genetic stability. One hypothesis, which so far could not be substantiated, is the so called receptor hypothesis. A putative receptor at the cellular surface could theoretically transmit the RF-EMF signal into the cell and translate it to biochemical signals. So far no such receptor has been identified.

What is well known from toxicology is the fact, that reactive oxygen species (ROS) are capable to lead via definite DNA adducts, which are instable and occur as intermediates, to DNA fragmentation.

This hypothesis is also discussed for RF-EMF and examined in studies with different cell types such as human platelets, human erythrocytes, monocytes and lymphocytes as well as monocytic cell lines (Stopczyk et al., 2002, Stopczyk et al., 2005, Lantow et al., 2006a, b, Simko et al., 2006, Kiel et al., 1984). In group 2 (human cells without investigation of cell growth) Stopczyk et al. described in 2002 and 2005 an effect of RF-EMF on human platelet SOD activities and MDA concentrations. Lantow et al., 2006b showed for human monocytes a significant generation of ROS following C.W. and intermittent GSM-DTX exposure at 2 W/kg. Kiel et al., 1984 described in human erythrocytes a perturbation of the thermal threshold for oxidative hyperthermic hemolysis associated with RF-EMF.

In animal cells (group 3) Deng et al., 2000 investigated pig retinal pigment (RPE) epithelial cells and published an induction of lipid peroxide damage in RPE cells. Additionally SOD activity decreased significantly as compared with control group.

If reactive oxygen species were induced within cells by RF-EMF, the underlying mechanism of this generation is unclear. Induction of ROS-inducing enzymes or the repression of ROS-detoxifying enzymes may be causative. Still, mechanisms, how a physical signal like RF-EMF, could lead to biological answers like enzyme induction or repression, remains speculative.

***How can controversial results using the same cellular systems be explained ?***

Confusingly, controversial results with respect to induction of genotoxicity in human cells have been described within the same cell types. Beside biological especially technological causes have to be discussed. Using the cellular system peripheral human lymphocytes, a different interindividual susceptibility for RF-EMF could be the case. This could explain different findings in different experiments. As these cells are primary cells and isolated

lymphocytes just undergo cell division (when to be tested for cytogenetic changes) after stimulation, reproduction of experiments using the identical cellular bias is impossible.

Other potential causes for different results in different laboratories using the same cell lines, are methodological shortcomings using genotoxicity assays. Parallel interlaboratory analysis of genotoxic effects on RF-exposed cells therefore appear one important approach to ensure and substantiate positive and negative findings. Such RF-EMF related studies are momentary ongoing but not yet published.

One obvious, already published discrepancy in the genotoxicity results using the identical cell line in different laboratories with comparable exposure setups (Kuster, ITIS Zurich) are the data provided by Diem et al., 2005 and Speit et al., 2007.

Additionally, in genotoxicity studies the reliability and reproducibility of results highly depend on the quality of the exposure setup available. For in vitro studies the most widely used setup for the last years is the setup designed by Kuster et al. (Schönborn et al., 2000), which rarely gives room to improvement. In older studies sometimes insufficient other setups have been used. Additionally, peer-reviewed publications in biological journals often do not provide detailed technical details on the setups. Complete and exact data on the technical background are rarely provided in such a way that an identical technical basis for replication studies can be designed. This may complicate interpretation and appraisal of the study quality retrospectively.

#### **4. Summary and discussion: Knowledge gaps and uncertainties regarding RF-EMF associated genotoxic effects of *in vitro* systems**

Summarizing the results of the comprehensive literature survey on RF-EMF associated genotoxicity within the time period year 2000 to 2007, the following knowledge gaps and uncertainties can be defined:

- Are there different cellular susceptibilities ?  
Is there a cell-type specificity of the genotoxic answer ?
- Which mechanism could explain the genotoxic effects found in association with RF-EMF exposure (f.e. ROS-hypothesis) ?
- How can controversial results using the same cellular systems be explained (exposure setup, methodological differences between laboratories, in the experimental system of human lymphocytes: different interindividual susceptibilities, and others) ?

With respect to these gaps further clarification in scientific studies appears worthwhile.



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## 6. Tables

Attached to the Final Report of the Charité Group are the detailed tables on RF-EMF associated genotoxicity examined in *in vitro* systems (**table 1**) as well as on RF-EMF associated induction of reactive oxygen species (ROS) in *in vitro* systems (**table 2**). In these tables the respective study, the cell type examined, the exposure conditions, the detection methods for the corresponding genotoxic endpoint, information on cell proliferation and cell growth characteristics and the results are summarized.

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## **WP1:**

What gaps and what uncertainties exist in the  
ELF- and RF-EMF cancer risk assessment ?

► RF-EMF and genotoxicity

**Tabelle 1:**

citation	cell type	exposure conditions (duration, frequency, SAR, additional characteristics)	detection methods / endpoints	information on cell proliferation / cell growth (analytical method)	results
<b>group 1</b>	<b>human cells</b>			<b>data on cell growth included</b>	
<b>Vijayalaxmi et al. 2001a</b>	peripheral blood samples collected from four healthy nonsmoking human volunteers	847.74 MHz radiofrequency (RF) radiation (continuous wave), a frequency employed for cellular telephone communications. A code division multiple access (CDMA) technology, exposure times 24 h with a nominal net forward power of 75 W and a nominal power density of 950 W/m <sup>2</sup> (95 mW/cm <sup>2</sup> ). Mean specific absorption rate (SAR) 4.9 or 5.5 W/kg. Blood aliquots sham-exposed or exposed in vitro to 1.5 Gy of gamma radiation as controls. Temperatures of medium during RF-radiation and sham exposures in the Radial Transmission Line facility	genetic damage was assessed from the incidence of chromosome aberrations and micronuclei	the extent of alteration in the kinetics of cell proliferation was determined from the mitotic indices in 48-h cultures and from the incidence of binucleate cells in 72-h cultures	no significant differences between RF-radiation-exposed and sham-exposed lymphocytes with respect to mitotic indices, frequencies of exchange aberrations, excess fragments, binucleate cells, and micronuclei. Thus there was no evidence for induction of chromosome aberrations and micronuclei in human blood lymphocytes exposed in vitro for 24 h to 847.74 MHz RF radiation (CDMA)

		were controlled at $37 \pm 0.3$ °C			at SARs of 4.9 or 5.5 W/kg
<b>Vijayalaxmi et al. 2001b</b>	freshly collected peripheral blood samples from four healthy human volunteers	24 h to 835.62 MHz radiofrequency (RF) radiation, a frequency employed for customer-to-base station transmission of cellular telephone communications. An analog signal was used, and the access technology was frequency division multiple access (FDMA, continuous wave). A nominal net forward power of 68 W was used, and the nominal power density at the center of the exposure flask was $860 \text{ W/m}^2$ . Mean specific absorption rate in the exposure flask was 4.4 or 5.0 W/kg. 1.50 Gy of gamma radiation as positive control	genetic damage was assessed from the incidence of chromosome aberrations and micronuclei	the extent of alteration in the kinetics of cell proliferation was determined from the mitotic indices in 48 h cultures and from the incidence of binucleate cells in 72 h cultures	no significant differences between RF-radiation- and sham-exposed lymphocytes with respect to mitotic indices, incidence of exchange aberrations, excess fragments, binucleate cells, and micronuclei. Thus, under the experimental conditions tested, there is no evidence for the induction of chromosomal aberrations and micronuclei in human blood lymphocytes exposed in vitro for 24 h to 835.62 MHz RF radiation at SARs of 4.4 or 5.0 W/kg
<b>d'Ambrosio et al. 2002</b>	human peripheral blood cultures	1.748 GHz, either continuous wave (CW) or phase only modulated wave (GMSK), for 15 min. The maximum specific absorption rate (approximately 5 W/kg) was higher than that occurring in the head of mobile phone users	cytokinesis block micronucleus assay	cell proliferation kinetics, proliferation index	no changes were found in cell proliferation kinetics after exposure to either CW or GMSK fields. As far as genotoxicity is concerned, the micronucleus frequency

					result was not affected by CW exposure; however, a statistically significant micronucleus effect was found following exposure to phase modulated field. These results would suggest a genotoxic power of the phase modulation per se
<b>Tice et al. 2002</b>	leukocytes and lymphocytes	the signals were voice modulated 837 MHz produced by an analog signal generator or by a time division multiple access (TDMA) cellular telephone, 837 MHz generated by a code division multiple access (CDMA) cellular telephone (not voice modulated), and voice modulated 1909.8 MHz generated by a GSM-type PCS cellular telephone. Cells were exposed at 37± 1 °C, for 3 or 24 h at average SARs of 1.0-10.0 W/kg	strand breaks/alkali labile sites, alkaline (pH>13) single cell gel electrophoresis (SCG) assay. Cytokinesis-block micronucleus assay	leukocyte viability, binucleated cell index (BC), replicative index (RI)	exposure for either 3 or 24 h did not induce a significant increase in DNA damage in leukocytes, nor did exposure for 3 h induce a significant increase in micronucleated cells among lymphocytes. However, exposure to each of the four RF signal technologies for 24 h at an average SAR of 5.0 or 10.0 W/kg resulted in a significant and reproducible increase in the frequency of micronucleated lymphocytes. The magnitude of the response

					(approximately four fold) was independent of the technology, the presence or absence of voice modulation, and the frequency (837 vs. 1909.8 MHz). This research demonstrates that, under extended exposure conditions, RF signals at an average SAR of at least 5.0 W/kg are capable of inducing chromosomal damage in human lymphocytes
<b>Miyakoshi et al. 2002 (Principal invest.)</b>	human glioma cells MO54	2.4 GHz (CW) and 1.5 GHz (PDC) exposure at high SARs (up to 200 W/kg) for 2 days in a circular waveguide	sister chromatid exchange, chromosome aberrations, micronucleus formation, COMET assay, and genetic mutation	cell cycle, signal transduction, transformation, and cell division	preliminary findings reported at the BEMS meeting in 2002 showed exposure at up to 50 W/kg had no effect on HGPRT locus mutations, and exposure at up to 100 W/kg had no effect on DNA strand breaks using an alkaline COMET assay. Additional studies are ongoing using 2.4 GHz (CW) and 1.5 GHz (PDC)

					exposure and analysis of sister chromatid exchange, chromosome aberrations, micronucleus formation, DNA damage, and genetic mutation as well as cell cycle, signal transduction, transformation, and cell division
<b>Zeni et al. 2003</b>	experiments were performed on peripheral blood from 20 healthy donors	several conditions were tested by varying the duration of exposure, the specific absorption rate (SAR), and the signal [continuous-wave (CW) or GSM (Global System of Mobile Communication) modulated signal]. (1) CW intermittent exposure (SAR = 1.6 W/kg) for 6 min followed by a 3-h pause (14 on/off cycles); (2) GSM signal, intermittent exposure as described in (1); (3) GSM signal, intermittent exposure as described in (1) 24 h before stimulation with phytohemagglutinin (8 on/off cycles); (4) GSM signal, intermittent exposure (SAR = 0.2 W/kg) 1 h per day for 3 days. The SARs were estimated numerically	cytokinesis-block micronucleus assay	cytotoxicity was also investigated using the cytokinesis-block and proliferation index	no statistically significant differences were detected in any case in terms of either micronucleus frequency or cell cycle kinetics

<b>McNamee et al. 2003</b>	human blood cell cultures, leukocytes	24-h continuous-wave (CW) and pulsed-wave (PW) 1.9 GHz RF-field exposures. Mean specific absorption rates (SARs) ranged from 0 to 10 W/kg, and the temperature within the cultures was maintained at $37.0 \pm 1.0$ °C for the duration of the 24-h exposure period	primary DNA damage (alkaline COMET assay) and micronucleus induction	proliferation index	no significant differences in primary DNA damage were observed between the sham-treated controls and any of the CW or PW 1.9 GHz RF-field-exposed cultures when processed immediately after the exposure period by the alkaline COMET assay. No significant differences in the incidence of micronuclei, incidence of micronucleated binucleated cells, frequency of binucleated cells, or proliferation index between sham-treated controls and any of the CW or PW 1.9 GHz RF-field-exposed cultures. In conclusion: no evidence of 1.9 GHz RF-field-induced genotoxicity in human blood cell cultures after 24-h exposure
<b>Hook et al. 2004</b>	Molt-4 T	four types of frequency/modulation	single-cell gel	The annexin V affinity	no statistically significant

	lymphoblastoid cells	forms were studied: 847.74 MHz code-division multiple-access (CDMA), 835.62 MHz frequency-division multiple-access (FDMA), 813.56 MHz (iDEN), and 836.55 MHz time-division multiple-access (TDMA). Exponentially growing cells were exposed to RF radiation for periods up to 24 h using a radial transmission line (RTL) exposure system. Specific absorption rates were 3.2 W/kg for CDMA and FDMA, 2.4 or 24 mW/kg for iDEN, and 2.6 or 26 mW/kg for TDMA	electrophoresis assay. Positive control: 1 Gy <sup>117</sup> Cs gamma rays and 44°C for 20 min	assay was used to detect apoptosis	difference in the level of DNA damage or apoptosis between sham-treated cells and cells exposed to RF radiation for any frequency, modulation or exposure time. Exposure of Molt-4 cells to CDMA, FDMA, iDEN or TDMA modulated RF radiation does not induce alterations in level of DNA damage or induce apoptosis
<b>REFLEX 2004</b>	HL-60 cells, cultured human fibroblasts from both young and old donors, granulosa cells	24 hours to 1900 MHz (GSM) and 1800 MHz (GSM) at 0.3 to 2 W/kg. wave guide system sXc1800, Temperature: 37 ± 0.1 °C	COMET assay, Micronuclei induction, chromosome aberrations. Detection of reactive oxygen species (ROS)	was assessed using Annexin V-affinity assay and TUNEL assay. Determination of cell cycle and cellular growth	results suggested an effect of 1.8 GHz and 1.9 GHz exposure on inducing single and double strand breaks in HL-60 cells, cultured human fibroblasts and granulosa cells and micronuclei frequencies. For HL-60 cells no changes were found in cell proliferation kinetics, cell cycle, cellular growth and apoptosis after exposure to CW. Detection of ROS

<b>Zotti-Martinelli et al., 2005</b>	whole blood samples	waveguides 1800 MHz at room temperature (21-22°C) a) C.W. for 1h, 2h and 3h, power flux density 5 mW/cm <sup>2</sup> b) C.W. for 1h, 2h and 3h, power flux density 10 mW/cm <sup>2</sup> c) C.W. for 1h, 2h and 3h, power flux density 20 mW/cm <sup>2</sup>	in vitro micronucleus assay	lymphocyte proliferation index	small but statistically significant increase of micronuclei frequencies in dependency on exposure time and power flux density; short term exposure and mean power flux densities are capable of induction of micronuclei in human lymphocytes, a wide inter-individual variability was found  the experiments have been reproduced 3 months later with the same results
<b>Komatsubara et al., 2005a (Journal not peer-reviewed)</b>	human glioma MO54 cells	waveguides 2450 MHz, C.W. for 2 h at SAR 5, 10, 20, 50, 100 and 200 W/kg  controls: sham-exposure, bleomycin-treated positive control, thermal controls at 39, 41 and 44°C	alkaline COMET assay	cell viability (trypan blue exclusion assay)	no significant COMET formation as compared to sham-exposure and temperature controls
<b>Zeni et al., 2005</b>	human peripheral blood lymphocytes	waveguide 900 MHz, GSM signal (pulsed, 217 Hz) at 0.3 and 1 W/kg for 2 h  controls: sham-exposure, positive control methyl methanesulfonate	alkaline COMET assay  chromosomal aberrations CA  sister chromatid	mitosis index	no statistically significant difference in any parameter tested for RF-EMF exposure as compared to sham-exposure

		MMS for COMET assay and mitomycin C MMC for chromosomal aberrations, sister chromatid exchange tests	exchange SCE		
<b>Vijayalaxmi, 2006</b>	human peripheral blood samples	2450 MHz Pulsed-wave 2450 MHz and 8200 MHz radiofrequency (RF) radiation for 2 h. The RF radiation was generated with a net forward power of 21 W (2450 MHz) or 60 W (8200 MHz) and transmitted from a standard gain rectangular antenna horn in a vertically downward direction. The average power density at the position of the cells in the flask was 5 mW/cm <sup>2</sup> (2450 MHz) and 10 mW/cm <sup>2</sup> (8200 MHz) . The mean specific absorption rate, calculated by finite difference time domain analysis, was 2.135 ± 0.005 W/kg (2450 MHz) and 20.71± 0.08 W/kg (8200 MHz). Aliquots of the same blood sample were either sham-exposed or exposed in vitro to an acute dose of 1.5 Gy gamma-radiation to serve as unexposed and positive controls.	Chromosomal aberration micronucleus formation	mitosis index (percentage of binucleated lymphocytes)	no significant difference between RF-Exposed and unexposed control could be detected neither in the 2450 nor in 8200 MHz exposure experiments. Also no difference was found in the response of unstimulated and PHA-stimulated lymphocytes when exposed to 8200 MHz RF-EMF. Positive controls subjected to gamma radiation exhibited significantly more damage than RF- and sham-exposed lymphocytes

<b>Stronati et al., 2006</b>	human peripheral blood samples	continuous exposure to a GSM basic 935 MHz signal for 24 h at 1 W/kg and 2 W/kg alone or in combination with a 1 min exposure to 1 Gy (250 kVp) immediately before or after RF-EMF	alkaline COMET assay chromosomal aberrations sister chromatid exchange Cytokinesis-block micronucleus assay	nuclear division index	no effect of RF-EMF alone on any assay endpoint Additionally no RF-EMF modulation of the gamma radiation effect Summarizing: no genotoxic or epigenetic effect
<b>Scarfi et al., 2006</b>	human peripheral blood lymphocytes  interlaboratory study	wire patch cells WPC Continuous exposure to 900 MHz / 217 Hz pulsed (GSM signal) for 24 h at SAR 1, 5, 10 W/kg positive control: mitomycin C (0.0333 µg/ml) sham exposure	cytokinesis-block micronucleus assay	cell cycle kinetics Proliferation index	no evidence for existence of genotoxic or cytotoxic effects in the SAR range investigated 2 independent research groups confirmed each others results
<b>group 2</b>	human cells			<b>no data on cell growth</b>	
Maes et al. 2000	human lymphocytes	455.7 MHz microwave-exposed human lymphocytes and in lymphocytes that were subsequently exposed to MMC or X-rays. The exposure was performed by placing the cells at 5 cm from the antenna of a car phone. In this way the specific absorption ratio was approximately 6.5 W/kg. The temperature and humidity was kept constant during the experiments	chromosome aberration and sister chromatid exchange frequency		no statistically significant difference was found between microwave-exposed and unexposed control samples. When the microwave exposure was followed by exposure to MMC, some differences were found between the combined treatments and the MMC treatments alone.

					<p>However, there was no consistency in the results. Combined treatments with X-rays did not provide any indication of a synergistic action between the RF fields and X-rays, either. The data therefore do not support the hypothesis that RF fields act synergistically with chemical or physical mutagens</p>
<b>Vijayalaxmi et al. 2000</b>	human peripheral blood samples	pulsed-wave 2450 MHz radiofrequency (RF) radiation for 2 h. The RF radiation was generated with a net forward power of 21 W and transmitted from a standard gain rectangular antenna horn in a vertically downward direction. The average power density at the position of the cells in the flask was 5 mW/cm <sup>2</sup> . The mean specific absorption rate, calculated by finite difference time domain analysis, was 2.135 (± 0.005 SE) W/kg. Aliquots of whole blood that were sham-exposed or exposed in vitro to 50 cGy of ionizing radiation from a	primary DNA damage (single-strand breaks and alkali-labile lesions) using the alkaline COMET assay with three different slide-processing schedules. 1) cells immediately after the exposures and at 4 h after incubation of the exposed blood at 37 ± 1 °C to allow time for rejoining of any		<p>at either time, the data indicated no significant differences between RF-radiation- and sham-exposed lymphocytes with respect to the comet tail length, fluorescence intensity of the migrated DNA in the tail, and tail moment. The conclusions were similar for each of the three different COMET assay slide-processing schedules examined. Thus, under the experimental conditions tested, there is</p>

		<sup>137</sup> Cs gamma-ray source were used as controls	strand breaks present immediately after exposure, i.e. to assess the capacity of the lymphocytes to repair this type of DNA damage		no evidence for induction of DNA single-strand breaks and alkali-labile lesions in human blood lymphocytes exposed in vitro to pulsed-wave 2450 MHz radiofrequency radiation, either immediately or at 4 h after exposure
<b>Zotti-Martelli et al. 2000</b>	human peripheral blood lymphocytes in vitro	different frequencies (2.45 and 7.7GHz) and power density (10, 20 and 30mW/cm <sup>2</sup> for three times (15, 30 and 60min).  <b>Power density, not SAR ?</b>	micronucleus (MN) assay		the results showed for both radiation frequencies an induction of micronuclei as compared to the control cultures at a power density of 30mW/cm <sup>2</sup> and after an exposure of 30 and 60min. Our study would indicate that microwaves are able to cause cytogenetic damage in human lymphocytes mainly for both high power density and long exposure time.
<b>Maes et al. 2001</b>	cultured human lymphocytes	900 MHz radiation, TEM cell. Three different modes of exposure (continuous, pseudo-random and	chromosome aberration and sister chromatid exchange		Investigation of possible effects of the 900 MHz radiation alone as well as

		dummy burst) were studied for different power outputs (0, 2, 8, 15, 25, 50 W). The specific absorption rates varied between 0 and 10 W/kg	frequency methods		of combined exposure to the chemical or physical mutagens mitomycin C and X-rays. Overall, no indication was found of a mutagenic, and/or co-mutagenic/synergistic effect of this kind of nonionizing radiation.
<b>Unknown (WHO meeting on EMF Biological Effects, Seoul, Korea, 2001</b>	Jurkat (human T-cells), WI-38 (human fibroblasts), DO11.10 (mouse T cells), and C3H10T1/2 (mouse fibroblasts)	1.765 GHz CDMA for up to 72 hours at 1.5 or 75 W/kg.	chromosome aberration		no chromosome effects were observed as a result of RF exposure, even at 75 W/kg
<b>Miyakoshi et al. 2002</b>	human glioma cells MO54	2.54 GHz exposure at high SARs (50 and 100 W/kg) for 2 h in a TE <sub>01</sub> circular waveguide.	COMET assay		exposure up to 100 W/kg had no effect on DNA strand breaks using the alkaline COMET assay
<b>McNamee et al. 2002a</b>	granulocytes	1.9 GHz pulse-modulated radiofrequency (RF) field for 2 h using a series of six circularly	DNA damage was quantified in leukocytes by the		when compared to the sham-treated controls, no evidence of increased

		polarized, cylindrical waveguides. Mean specific absorption rates (SARs) ranged from 0 to 10 W/kg, and the temperature within the cultures during the exposure was maintained at 37.0 ± 0.5 °C.	alkaline COMET assay and the cytokinesis-block micronucleus assay.		primary DNA damage was detected by any parameter for any of the RF-field-exposed cultures when evaluated using the alkaline COMET assay. Furthermore, no significant differences in the frequency of binucleated cells, incidence of micronucleated binucleated cells, or total incidence of micronuclei were detected between any of the RF-field-exposed cultures and the sham-treated control at any SAR tested
<b>McNamee et al. 2002b</b>	human blood cultures (cultured human leukocytes)	1.9 GHz continuous-wave (CW) radiofrequency (RF) field for 2 h using a series of six circularly polarized, cylindrical waveguides. Mean specific absorption rates (SARs) of 0.0, 0.1, 0.26, 0.92, 2.4 and 10 W/kg. were achieved, and the temperature within the cultures during a 2-h exposure was maintained at 37.0 ± 0.5 °C. Concurrent negative (incubator) and	DNA damage was quantified immediately after RF-EMF exposure using the alkaline COMET assay, and four parameters (tail ratio, tail moment, comet length and tail length) were used to assess DNA		no evidence of increased primary DNA damage was detected by any parameter for RF-field-exposed cultures at any SAR tested. There was no significant difference in the binucleated cell frequency, incidence of micronucleated binucleated cells, or total incidence of

		positive (1.5 Gy, <sup>137</sup> Cs gamma radiation) control cultures were run for each experiment	damage for each comet. The formation of micronuclei in the RF-EMF-exposed blood cell cultures was assessed using the cytokinesis-block micronucleus assay		micronuclei between any of the RF-field-exposed cultures and the sham-exposed controls at any SAR tested. These results do not support the hypothesis that acute, nonthermalizing 1.9 GHz CW RF-field exposure causes DNA damage in cultured human leukocytes
<b>Zhang et al. 2002</b>	whole blood cells from a male donor and a female donor	the whole blood cells from a male donor and a female donor were either only exposed to 2450-MHz microwaves (5.0 mW/cm <sup>2</sup> ) for 2 h or only exposed to MMC (0.0125 µg/mL, 0.025 µg/mL and 0.1 µg/mL) for 24 h; and the samples were exposed to MMC for 24 h after exposure to MW for 2 h	single cell gel electrophoresis (SCGE) assay (COMET assay) and cytokinesis-blocked micronucleus (CBMN) test in vitro		the low-intensity 2450-MHz microwave radiation can not induce DNA and chromosome damage, but can increase DNA damage effect induced by MMC in COMET assay.
<b>Rudiger et al. 2003</b>	cultured human fibroblasts	1800 MHz (either CW, GSM, intermittent, or talk-modulated) at SARs of 1.2 or 2 W/kg for up to 24 hours. Wave guide system sXc1800, Temperature: 37 ± 0.1 °	single strand breaks by neutral COMET assay and double strand breaks by alkaline COMET assay		increased DNA damage was reported by both alkaline and neutral COMET assay after 16 and 24 hour exposures, with a maximal effect of 8-9% increase in comet tail

					migration. GSM, intermittent, and talk modulated caused more damage than CW alone
<b>Mashevich et al. 2003</b>	primary human lymphocytes	830 MHz (CW) RF for 72 hours at average SARs from 1.6 – 8.8 W/kg. At the highest average SAR, high frequency structure simulation (HFSS) computations showed peak SAR estimated in the range of 22.46 W/kg. Exposure resulted in temperatures of 34.5 - 37.5 °C, and at the highest exposure level the incubator temperature had to be set at 33.5 °C to insure the exposed culture temperature did not exceed 38 °C  <b>thermal effect? dosimetry?</b>	analysis of chromosome replication / aneuploidy via in situ hybridization		the authors report a linear increase with exposure level and aneuploidy of chromosome 17 as detected by using alpha-satellite probes and in situ hybridization (in the earlier BEMS presentation, the authors reported data using probes for chromosome 17 genes p53 and EGFR / HER2-neu). The threshold for these effects was reported at 2.9 ± 0.35 W/kg. The authors also reported dose dependent asynchronous replication with increased exposure. The authors suggest non-thermal epigenic alterations are involved in SAR dependent genetic toxicity

<b>Diem et al., 2005</b>	human diploid fibroblasts	waveguide, R18 rectangular 1800 MHz a) C.W., SAR 2 W/kg, 4, 16 and 24 h b) C.W., intermittent 5 min on/10 min off, SAR 2 W/kg, 4, 16 and 24 h c) pulsed, intermittent 5 min on/10 min off, SAR 2 W/kg, 4, 16 and 24 h d) pulsed, continuous, SAR 1.2 W/kg, 4, 16 and 24	alkaline and neutral COMET assay		significant differences after 16 h exposure at all modulations, intermittent exposure effect > continuous exposure effect
<b>Baohong et al., 2005</b>	human lymphocytes	TEM cell 1800 MHz, C.W. pulsed at SAR 3 W/kg for 2h controls: sham-exposure, 4 chemical mutagens as positive controls (mitomycin C MMC, bleomycin BLM, methyl methanesulfonate MMS, 4-nitroquinoline-1-oxide 4NQO for 3 h)  additionally: RF-exposure together with chemical mutagen	COMET assay  DNA damage detected at 2 incubation times (0 and 21 h after treatment)		a) RF-EMF alone: no statistically significant difference between exposure and sham-exposure at 0 and 21 h b) co-exposure of RF-EMF + chemical mutagen: <i>MMC / RF-MMC</i> : significant difference at 0 and 21 h <i>NQO / RF-4NQO</i> : significant difference at 0 and 21 h <i>MMS / RF-MMS as well as BLM / RF-BLM</i> : no statistically significant difference c) RF-EMF (1800 MHz, 3W/kg for 2h) does not induce human lymphocyte DNA damage but enhances the one induced by the chemical mutagens MMC and 4NQO
<b>Chemeris et al.,</b>	human whole	high power microwave pulses:	alkaline single cell		no statistically significant

<b>2006</b>	blood leukocytes and isolated lymphocytes	rectangular waveguide continuous exposure to pulsed 8800 MHz RF-EMF signal for 40 minutes , average SAR 1.6 kW/kg, 180 ns pulse width, peak power 65 kW, pulse repetition frequency 50 Hz, steady state temperature rise: $3.5 \pm 0.1^\circ \text{C}$ (initial temperature in cell suspension: $23 \pm 1^\circ \text{C}$ , within 10-15 seconds $27 \pm 1^\circ \text{C}$ ) temperature control cells (negative controls): $23^\circ \text{C}$ and $27^\circ \text{C}$ and $37^\circ \text{C}$ (30 min) positive controls: alkylating agent ethylmethanesulfonate	gel electrophoresis (SCGE) assay (COMET assay)		effects found
<b>Sakuma et al., 2006</b>	human glioblastoma A172 cells  human IMR-90 fibroblasts	anechoic chamber, horn antenna low level exposure to 2142.5 MHz RF-EMF signal A172 cells a) CW pulsed b) W-CDMA at SAR 0.08, 0.25 and 0.8 W/kg for 2 and 24 h  IMR-90 fibroblasts: a) CW c) W-CDMA at SAR 0.08 W/kg for 2 and 24 h  sham exposure	alkaline single cell gel electrophoresis (SCGE) assay (COMET assay)		no statistically significant differences between exposure and sham-exposure
<b>Speit et al. 2007</b>	human fibroblasts (ES1 cells)	waveguide, R18 rectangular 1800 MHz a) CW, 5min on/10 min off, for 1,4, 18 and 24 h, SAR 2 W/kg	single cell gel electrophoresis (SCGE) assay		no independent replication the REFLEX data on human fibroblasts published by Diem et al. , 2005:

	Replication study	<p>b) CW, 5min on/10 min off, for 4, and 22 h, SAR 1 W/kg, SAR 2 W/kg</p> <p>c) CW, pulsed (GSM basic modulation), 24 h, SAR 1 W/kg, SAR 2 W/kg</p> <p>Positive control 2Gy gamma radiation (4Gy/min)</p>	(COMET assay) and cytokinesis-blocked micronucleus (CBMN) test in vitro		genotoxic effects could NOT be detected
<b>group 3</b>	<b>animal cells</b>			<b>+/- data on cell growth</b>	
<b>Li et al. 2001</b>	murine C3H 10T1/2 cells	2, 4 or 24 h exposure to 847.74 MHz CDMA and 835.62 MHz FDMA modulated radiations in RTL irradiators, to 37.0 ± 0.3 °C, SAR: 3.2-5.1 W/kg	alkaline COMET assay		exposure of cells at 37 °C CDMA or FDMA at SAR values of up to 5.1 W/kg did not induce DNA damage
<b>Bisht et al. 2002</b>	murine C3H 10T1/2 cells	835.62 MHz frequency division multiple access (FDMA) or 847.74 MHz code division multiple access (CDMA) modulated RF radiation. Exponentially growing cells or plateau-phase cells were exposed to CDMA (3.2 or 4.8 W/kg) or FDMA (3.2 or 5.1 W/kg) RF radiation for 3, 8, 16 or 24 h.	micronuclei with cytochalasin B at a concentration of 2 µg/ml for 22 h was found to yield the maximum number of binucleated cells in C3H 10T1/2 cells		no exposure condition was found by analysis of variance to result in a significant increase relative to sham-exposed cells either in the percentage of binucleated cells with micronuclei or in the number of micronuclei per 100 binucleated cells. No significant exposure-

					related differences for either plateau-phase cells or exponentially growing cells
<b>Park and Kim 2002 (Principal invest.)</b>	C3H10T1/2 (mouse fibroblasts) and other cell lines	exposed to 836.5 MHz (CDMA) at SAR up to 36.5 W/kg and 1.765 GHz (CDMA) at SAR up to 38.2 W/kg for up to 72 hours	on assay and chromosome aberrations		no effect on transformation or chromosome aberrations was reported
<b>Koyama et al. 2003</b>	Chinese hamster ovary CHO-K1 cells	(1) exposed to RF-EMF for 18 h at average SARs of 13, 39 and 50 W/kg with input power 7.8 W, and were compared with a sham-exposed control; (2) the cells were exposed to a RF-EMF at SARs of 78 and 100 W/kg with input power 13 W, and were compared with a sham-exposed control; (3) the cells were treated with bleomycin alone or with bleomycin followed by exposure to a RF-EMF for 18 h at SARs of 25, 78 and 100 W/kg, and were compared with a bleomycin-treated positive control. The cells treated with bleomycin alone were compared with sham-exposed controls; and (4) a high temperature control, CHO-K1 cells were incubated at 39 °C for 18 h. Exposure source: cavity  Location: Cells in the annular culture plates were exposed to RF-EMF in the cavity.  Exposure time: C.W. for 18 h; sham	the MN frequency in cells in the inner, middle and outer wells of an annular culture plate was determined for the following four conditions during cell division		these results indicate that cells exposed to a RF-EMF at a SAR of 78 W/kg and higher form MN more frequently than sham-exposed cells, while exposure to a RF-EMF at up to 50 W/kg does not induce MN formation. In addition, a RF-EMF at a SAR of 78 W/kg and higher may potentiate MN formation induced by bleomycin-treatment

		Exp. was performed			
<b>Lagroye et al. 2004</b>	murine C3H 10T1/2 cells	2-h exposure to 2450 MHz CW; SAR of 1.9 W/kg in RTL or 1 mM cisplatin (CDDP, a positive control for DNA crosslinks), 4 Gy of gamma rays ( <sup>137</sup> Cs.).	single-cell gel electrophoresis assay (COMET assay)		no evidence for the induction of DNA-protein crosslinks
<b>Komatsubara et al., 2005b</b>	murine m5S cells	waveguides a) 2450 MHz continuous wave for 2 h at SAR 5, 10, 20, 50 and 100 W/kg  b) 2450 MHz, pulsed, intermittent for 2 h : 1 sec on / 8 or 17 sec off SAR 50 W/kg (1 sec on, 17 sec off) SAR 100 W/kg (1 sec on, 8 sec off)  Controls: sham-exposure, mitomycin C (0.1µg/ml) positive control, 3 Gy gamma radiation positive control	chromosomal aberrations	mitosis index	no significant difference in frequency of chromosomal aberrations between RF-exposed and sham-exposed cells  no difference in chromosomal effects between continuous wave and pulsed signal
<b>Diem et al., 2005</b>	transformed rat granulosa cells GFSH-R17	waveguide, R18 rectangular 1800 MHz a) C.W., SAR 2 W/kg, 4, 16 and 24 h  b) C.W., intermittent 5 min on/10 min off, SAR 2 W/kg, 4, 16 and 24 h  c) pulsed, intermittent 5 min on/10 min off, SAR 2 W/kg, 4, 16 and 24 h  d) pulsed, continuous, SAR	alkaline and neutral COMET assay		significant differences after 16 h exposure at all modulations, intermittent exposure effect > continuous exposure effect

		1.2 W/kg, 4, 16 and 24			
<b>Nikolova et al., 2005</b>	Embryonal stem cells (ES R1 cells)	waveguide, R14 signal generator 1710 GHz (GSM), pulsed (217 Hz), intermittent exposure (5 min on/30 min off)  at SAR 1.5 W/kg  for 6 and 48 h	alkaline and neutral COMET assay Chromosomal aberrations Sister chromatid exchange  (differential staining FPG-technique)	cell proliferation (BrdU incorporation)	RF-EMF 6 h short-term, but not 48 h exposure of murine embryonal stem cells induced a small and transient increase in DNA double strand breaks  not influence on cell proliferation could be detected
<b>Speit et al. 2007</b>	Chinese hamster fibroblasts V79	waveguide, R18 rectangular 1800 MHz d) CW, 5min on/10 min off, for 1,4, 18 and 24 h, SAR 2 W/kg e) CW, 5min on/10 min off, for 4, and 22 h, SAR 1 W/kg, SAR 2 W/kg f) CW, pulsed (GSM basic modulation), 24 h, SAR 1 W/kg, SAR 2 W/kg positive control 2Gy gamma radiation (4Gy/min)	single cell gel electrophoresis (SCGE) assay (COMET assay) and cytokinesis-blocked micronucleus (CBMN) test in vitro		be found no genotoxic effect could

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## **WP1:**

What gaps and what uncertainties exist in the ELF- and RF-EMF cancer risk assessment?

- ▶ RF-EMF and genotoxicity
  - ▶ underlying mechanism ?
    - ▶ **reactive oxygen species (ROS) hypothesis**

**Tabelle 1:**

<b>citation</b>	<b>cell type</b>	<b>exposure conditions</b> (duration, frequency, SAR, additional characteristics)	<b>detection methods / endpoints</b>	<b>information on cell proliferation / cell growth</b> (analytical method)	<b>results</b>
<b>group 1</b>	<b>human cells</b>			<b>data on cell growth included</b>	
–	–	–	–	–	–
<b>group 2</b>	<b>human cells</b>			<b>no data on cell growth</b>	
<b>Stopczyk et al., 2002</b>  <b>Article in Polish, just English abstract</b>	human blood platelets	900 MHz for 1,3,5,7 minutes SAR ? signal ? control cells  no further informations available	superoxide dismutase activity (SOD-1)  malonyldialdehyde MDA concentrations		at 1,5 and 7 minutes SOD activities and MDA concentration were significantly depleted, at 3 minutes of RF-EMF exposure SOD activities and MDA concentrations increased as compared to control cells
<b>Stopczyk et al., 2005</b>  <b>Article in Polish, just English abstract</b>	human blood platelets	900 MHz for 1,3,5,7 minutes SAR ? signal ? control cells  no further informations available	superoxide dismutase activity (SOD-1)		at 1,5 and 7 minutes SOD activities were significantly depleted, at 3 minutes of RF- EMF exposure SOD activities increased as compared to control cells
<b>Lantow et al., 2006a</b>	human Mono Mac 6 and K562 cells	1800 MHz, C.W. GSM-non DTX (speaking only) GSM- DTX (hearing only) GSM Talk (34% speaking, 66% hearing)	superoxide radical ELISA, ROS (and Hsp70) flow cytometry		no significant difference in ROS production after RF- EMF and controls GSM-DTX signal significant difference in ROS formation when compared to sham-,

		<p>specific SARs: 0.5, 1, 1.5, 2 W/kg</p> <p>controls: sham-exposure, incubator controls positive controls: PMA, LPS, heat (40° C) and co-exposure conditions</p>			<p>but not incubator controls !</p> <p>Heat and PMA: significant increase in superoxide radical anions and in ROS production in Mono Mac 6 cells</p> <p>no additional effects on superoxide radical anion formation after co-exposure to RF-EMF/PMA and RF-EMF/LPS</p> <p>no significant effects of RF-EMF exposure at different conditions on Hsp70 expression</p>
<b>Lantow et al., 2006b</b>	human umbilical cord-derived monocytes and lymphocytes	<p>1800 MHz, cavity resonator, waveguide C.W., different GSM signals (GSM-DTX, GSM-Talk) at 2 W/kg, for 30 or 45 min of continuous or intermittent exposure ( 5 min On/5 min OFF)</p> <p>incubator control, sham-exposure RF-EMF exposure PMA 1µM as positive control</p>	flow cytometric analysis of ROS formation (or Hsp70 expression)		<p>following C.W. and intermittent GSM-DTX exposure at 2 W/kg human monocytes showed a significant generation of ROS as compare to sham-exposure (but: lower level of sham ROS value in monocytes !)</p> <p>in human lymphocytes no difference was detected</p> <p>Hsp70 showed no differences</p>
<b>Simko et al., 2006</b>	human Mono Mac 6 cells	<p>1800 MHz C.W. alone or Pulsed (217 Hz) or GSM-non DTX), each 60 min at SAR 2 W/kg Positive control: heat treatment (42-43° C, 1h)</p> <p>Exposure alone or as co-exposure with RF-EMF: ultra fine particles (UFP)</p>	<p>Hsp70: Flow cytometry, Western Blot</p> <p>ROS formation: cytochrome C assay</p> <p>Incorporation of UFPs:</p>		<p>no effect of any of the RF-EMF exposure conditions applied on ROS formation</p> <p>co-exposure with UFP or UFP alone showed no induction of ROS and superoxide radical anion</p>

			differential-interference-contrast-microscopy		
<b>Kiel et al., 1984</b>	human erythrocytes	radial waveguide 2450 MHz, pulsed (3.333 kHz) duty factor 0.02 average SAR 0.4 W/kg power flux density 5 mW/cm <sup>2</sup> exposure at 37° C, 42°C, 48° C for 20 min  a part of the cells was sensitized to oxidative damage by treatment with 1-chloro-2,4-dinitrobenzene (CDNB) and/or by coating with wheat germ agglutinin-horseradish peroxidase (WGA-HRP) conjugate	spontaneous hemolysis of erythrocytes, detection by spectrophotometry at 410 nm		RF-EMF significantly decreased spontaneous hemolysis of unsensitized cells at 42° C, but not at 37° or 48° C. RF-EMF significantly enhanced a CDNB membrane stabilizing effect at 42°, but not at 37° or 48° C. At 42° C RF-EMF increased hemolysis of WGA-HRP coated cells. Cells treated with both WGA-HRP and CDNB showed no change in fragility at 42° C, but increased fragility at 48° C without a RF-EMF effect. The RF-EMF effects observed appear to involve perturbation of the thermal threshold for oxidative hyperthermic hemolysis
<b>group 3</b>	<b>animal cells</b>			<b>+/- data on cell growth</b>	

<p><b>Kiel et al., 1986</b></p>	<p>sheep red blood cells</p>	<p>radial waveguide 2450 MHz C.W. SAR: 91 W/kg exposure time: 10 min</p> <p>temperature was held constant at 25, 37, 40, 42 or 45 ° C with an airflow heat system</p>	<p>decrease of residual base-activated chemiluminescence (CL) as indication of infield oxidase activity source of chemiluminescence: oxidation of luminol by superoxide, hydrogen peroxide, hydroxyl free radicals, generated by thermally induced autoxidation of oxyhemoglobin</p>		<p>air heating: significant decrease in residual CL at temperatures &gt; 37° C</p> <p>RF-EMF inhibited the decline &gt; 37° C in residual CL</p> <ul style="list-style-type: none"> <li>a) either reversibly alteration of thermodynamics of oxygen binding to hemoglobin</li> <li>or</li> <li>b) failure to energize a significant portion of hemoglobin molecules in each sample to the thermal threshold of hemoglobin autoxidation</li> </ul>

<b>Deng et al., 2000</b>	pig retinal pigment epithelial cells (RPE cells)	2450 MHz 10, 20 and 30 mW/cm <sup>2</sup> exposure for 1 h  protective effect of zinc (ZnSO <sub>4</sub> ) at 30 mW/cm <sup>2</sup>	activity of SOD  content of malonyldialdehyde MDA as indicator of lipid peroxidation		induction of lipid peroxide damage in RPE cells  SOD activity decreased significantly as compared with control group  Zn can enhance antioxidation ability of cells and alleviates the damage to some extent
<b>Zmyslony et al., 2004</b>	rat lymphocytes	GTEM cell 930 MHz C.W. power density : 5 W/cm <sup>2</sup> theoretical calculated SAR: 1.5 W/kg acute exposure: 5 and 15 min  co-exposure of lymphocytes with FeCl <sub>2</sub> (induction of ROS by FeCl <sub>2</sub> (10µg/ml)) and RF-EMF	intracellular ROS measured by fluorescent probe dichlorofluorescein diacetate (DCF-DA)		ROS production was not affected by acute exposure to RF-EMF alone  co-exposure of lymphocytes with FeCl <sub>2</sub> and RF-EMF revealed a significant increase in ROS production

<p><b>Hook et al., 2004</b></p>	<p>murine macrophage cell line J774.16</p>	<p>FMCW (frequency-modulated continuous-wave with carrier frequency of 835.62 MHz)</p> <p>CDMA (code division multiple access centered on 847.74 MHz)</p> <p>exposure duration: 20-22h SAR: 0.8 W/kg</p> <p>Temperature : 37.0 ± 0.3° C</p> <p>Positive controls: gamma-interferon and LPS</p>	<p>oxidant levels (Oxidation of thiols: by measuring accumulation of glutathione disulfide GSSG)</p> <p>Antioxidant levels (SOD activity CuZnSOD and MnSOD, catalase activity, glutathione peroxidase activity)</p> <p>Oxidative damage Nitric oxide production Oxidation of thiols: by measuring accumulation of glutathione disulfide (GSSG)</p>	<p>trypan blue exclusion assay for detection of changes in cell viability</p>	<p>no indication for effects of RF-EMF on parameters of oxidative stress</p>

<p><b>Zeni et al., 2007</b></p>	<p>murine L929 fibrosarcoma cells</p>	<p>900 MHz C.W., 10 min, SAR 0.3 and 1 W/kg CW., 30 min, SAR 0.3 and 1.0 W/kg GSM, 10 min, SAR 0.3 and 1 W/kg GSM, 30 min, SAR 0.3 and 1 W/kg</p> <p>RF-EMF alone or with 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX, a potent environmental carcinogen produced during chlorination of drinking water; applied at a subtoxic level of 500 µM; RF-Exposure during the first 10 or 30 minutes of chemical treatment)</p> <p>sham-exposure for each exposure condition</p>	<p>fluorimetric measurement of the generation of reactive oxygen species up to 60 min following RF-exposition / co-exposition</p>		<p>MX treatment alone at each incubation interval tested leads to a significant increase in the generation of reactive oxygen species</p> <p>no induction in the generation of ROS by RF-EMF exposure alone or in combination with MX</p>

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