Final Report

Title of the project: In vivo Research on Possible Health Effects of the Use of Mobile Telephones and Base Stations (Carcinogenicity Studies in Rats and Mice)

Acronym of the project **PERFORM-A**

0 Summary

Data of published long-term animal studies investigating the effects of mobile phone use and base station exposure on the organism as a whole are not sufficient for a joint risk assessment. In response to this, the European Commission (through its Fifth Framework Program), the Swiss and Austrian governments, the GSM Association and the Mobile Manufacturers Forum have been supporting research addressing potential long-term health implications from the use of mobile phones. The research program with the acronym PERFORM-A included two NTP-type carcinogenicity studies being conducted in both sexes of mice and rats. The physical agents simulating handset exposure from the dominant mobile communications systems in Europe, i.e., GSM (Global System for Mobile Communications) and DCS (Digital Personal Communications System), were applied at three exposure levels (and sham) to allow the detection of a potential dose response relationship. Two subprojects included mice (**PERFORM-A1**) and rats (**PERFORM-A2**), both exposed either to GSM or to DCS. These subprojects were performed as “classical” combined chronic toxicity and carcinogenicity studies, equivalent to studies routinely performed to evaluate the health risks of chemicals, pharmaceuticals or environmental agents. Two additional PERFORM-A studies were conducted using animals predisposed to tumor [e.g., mammary tumor (**PERFORM-A3**) or lymphoma (**PERFORM-A4**)] development. To assure well characterized exposure conditions over the entire exposure period, two new setups optimized for uniform whole-body exposure were developed and employed in all PERFORM-A studies by the Foundation for Research on Information Technologies in Society, Zurich, Switzerland [IT'IS Foundation], (contractor **PERFORM-A5**) assisted by the Radio Communications Laboratory, Dept. of Physics, University of Thessaloniki, Greece (contractor **PERFORM-A6**) and ARC Research GmbH, Seibersdarf, Austria (contractor **PERFORM-A3)**.

The results of PERFORM-A are expected to play an important role in the health risk assessment of the use of mobile phones and base stations undertaken by the European Union (EU), International Agency for Research on Cancer (IARC) and World Health Organization (WHO).

In more detail, the following four separate animal studies were part of the PERFORM-A program:

PERFORM-A1: A Combined Chronic Toxicity / Carcinogenicity Study of 900 MHz GSM & 1800 MHz DCS Wireless Communication Signals In B6C3F1 Mice (performed by Fraunhofer ITEM, Hannover, Germany).

PERFORM-A2: A Combined Chronic Toxicity / Carcinogenicity Study of 900 MHz GSM & 1800 MHz DCS Wireless Communication Signals In WISTAR Rats (performed by RCC Ltd, Itingen, Switzerland).

PERFORM-A3: Evaluation of 900 MHz GSM Wireless Communication Signals on DMBA-Induced Mammary Tumours in Sprague Dawley Rats (performed by ARC Research GmbH, Seibersdorf, Austria).

PERFORM-A4: Evaluation of 900 MHz GSM Wireless Communication Signals on Lymphoma Induction in Eμ-Pim 1 Transgenic Mice (performed by Istituto di Ricerche Biomediche "A. Marxer" (RBM), Colleretto Giacosa, Italy).

The IT'IS Foundation realized the technical aspects of the RF-exposure with their (sub) project **PERFORM-A5**: Exposure System Design, Construction & Dosimetry To Support Studies A1-A4 (performed by IT'IS, Zurich, Switzerland).

All animal studies, including histopathology, were performed blind to all individuals involved except for the IT'IS staff controlling/monitoring the daily RF exposure. Reversely the IT'IS staff did not know the group identifier. The key codes and identifier were not disclosed until completion of the histopathological evaluation and handover of the still blinded raw data to the representatives of the sponsors.
The studies were performed in compliance with the Principles of Good Laboratory Practice (GLP) and are presented in separate reports, provided as appendices to the present PERFORM-A Final Report, which summarizes the main findings of the separate studies.

Uniform whole-body exposure was optimized by restraining the animals in tubes at fixed positions in the exposure setup. Rodents were exposed to three whole-body SARs levels (SAR: Specific Absorption Rate) or sham exposed during the entire exposure period. The exposure units ("wheels") consisted of two parallel stainless steel metal plates at a defined distance. A conical antenna was placed in the center between the plates. Encased between the plates there were cylindrical (plexi-glass) tubes arranged radially around the antenna. Animals were placed in polycarbonate tubes with adjustable backstops. Each exposure was connected with a ventilation system to provide the restraint animals with fresh air. Temperature and humidity were monitored continuously within the exposure units. All the exposure equipment, including necessary amplifiers, signal generator and other electronic devices, was supplied by Foundation for Research on Information Technology in Society (IT'IS)-Zurich (Switzerland). IT'IS also assured the continuous monitoring of the exposure system, including data transmission and dosimetry.

The results can be summarized as follows.

(PERFORM-A1): During the in-life phase of the B6C3F1 mice studies, parameters evaluated included clinical signs, body weight gain, food consumption and mortality revealed no RF-related effects. Chronic toxicity investigations performed after 12 months of RF exposure, analyzing organ weights, hematology, gross pathology and histopathology, showed no RF-related abnormalities. In the carcinogenicity study of GSM and DCS wireless communication signals in B6C3F1 mice, regarding the organ-related tumor incidence after up to 2 years of RF-exposure, the pairwise Fisher test did not show any significant increase of a specific tumor type in the RF exposed groups as compared to the sham-exposed group. A comparison with historical control data from B6C3F1 mice in NTP carcinogenicity studies (Haseman et al. 1999) shows that the tumor rates observed in the present studies are within the range of the NTP tumor data, although for some organs (liver, Harderian glands, hematopoietic system) differences between both data sets exist. The main tumor types observed in the present studies were also well in line with those found in untreated B6C3F1 mice from a transgeneration carcinogenicity study, recently conducted at Fraunhofer ITEM (Dasenbrock et al. 2005).

In conclusion, the PERFORM-A1 study produced no evidence that the exposure of male and female B6C3F1 mice to electromagnetic fields (EMF) of GSM and DCS at an absorption rate of up to 4.0 W/kg for two hours per day, 5 days per week, over a period up to 24 months had any adverse health effect or any influence on the incidence or severity of the background non-neoplastic and neoplastic lesions. The study thus did not provide any evidence of RF possessing a carcinogenic potential.

(PERFORM-A2): The Wistar rat studies, revealed no clinical signs or palpable masses, body weight, food consumption, ophthalmic findings, macroscopic findings or organ weight changes considered to be related to exposure to 902 MHz GSM or 1747 MHz DCS wireless communication signals. There were also no changes in hematological, clinical biochemical or urinalysis parameters considered to be related to exposure to 902 MHz GSM or 1747 MHz DCS wireless communication signals. The increased/decreased incidences of several non-neoplastic and neoplastic findings are regarded incidental rather than exposure-related. The incidence of prostate adenomas (4 / 50) in the high dose (1747 MHz - group) was not statistically different from the incidence in the sham control (0 / 50). However, prostate adenomas are uncommon in the Wistar rat. For this reason the prostate gland of the cage control males were also examined. Since this examination revealed 3 / 50 adenomas, it is concluded that the finding in the 1747 MHz High dose group was incidental.

Consequently, under the conditions of study PERFORM-A2, Wistar rats exposed to 902 MHz GSM wireless communication signals at SAR levels of up to 0, 0.44, 1.33 or 4.0 W/kg or 1747 MHz DCS wireless communication signals at SAR levels of 0.41, 1.23 or 3.7 W/kg for 2 hours/day and 5 days/week over a period of up to 24 months produced no evidence of any adverse health effect or any influence on the incidence or severity of the background non-neoplastic and neoplastic lesions. The study thus did not provide any evidence of RF possessing a carcinogenic potential.

(PERFORM-A3): In the DMBA-induced mammary tumour study in Sprague Dawley rats, for histopathology endpoints, the following main findings were observed:
When compared with the sham exposed groups, there were statistically significantly

- less animals with benign neoplasms in all EMF-exposed groups,
- more animals with malignant neoplasms in the high EMF-dose group,
- more adenocarcinoma (in total No.) in the low EMF-dose group,
- more malignant neoplasms (in total No.) in the low and the high EMF-dose group,
- more animals with adenocarcinoma (any number) in the high EMF-dose group,
- less animals with one (or any number of) fibroadenoma in the low and the mid EMF-dose group.

In a study of this dimension with numerous parameters determined, isolated findings, which are seemingly treatment related are to be expected, as there may be several "incidental" significant differences between the groups, even in the absence of any biologically effective agent.

Except for the mammary gland effects, there were also significant differences in some isolated organ weights between any of the EMF-exposed groups and the sham exposed groups. None of them is given biological relevance attributed to the EMF-exposure.

In the mammary glands and their neoplastic lesions there were some significant differences between one or more of the EMF-exposed groups and the sham exposed groups, especially:

- more palpable tissue masses,
- more animals with malignant neoplasms,
- less animals with benign neoplasms.

This indicates, that there might be an effect of the exposure to EMF with respect to a shift in the number and dignity of the tumours formed, while all other aspects (time of onset, total number, multiplicity, size, etc.) remained unaffected. The most pronounced differences noted in this study were those between the sham exposed group and the cage control group.

Consequently, for study PERFORM-A3 it is concluded, that this study produced a borderline evidence of long term repeated exposure to 902 MHz GSM signals affecting the DMBA-induced mammary tumour response in rats with an equivocal biological relevance.

(PERFORM-A4): In the lymphoma induction study using transgenic mice exposed to pulsed 900 MHz electromagnetic fields, histological investigation revealed that the exposure of Eμ-*Pim I* transgenic mice to a pulsed 900 MHz electromagnetic field (EMF) for eighteen months at absorption rates of 0.5 W/kg and 1.4 W/kg was not considered to have affected the incidence of any neoplastic finding. In particular, the incidence of malignant lymphoma in animals exposed to EMF was not significantly different from that seen in cage or sham controls. A dose-related positive trend in the incidence of males bearing a Harderian gland adenoma ($p<0.0028$, one tailed test) with four of six cases occurring in males exposed to 4.0 W/kg and the remaining two in males exposed to 1.4 W/kg contrasted with the result in females where four of the six cases occurred in controls and the two others in mice exposed to 0.5 W/kg. The statistically significant positive trend in males bearing a Harderian gland adenoma was considered to have arisen fortuitously and not as a result of exposure to EMF.

None of the non-neoplastic findings encountered in this study were considered to have been affected by exposure to EMF. The range of findings encountered was broadly similar to that commonly observed in ageing mice.

In summary, under the conditions of study PERFORM-A4, exposure of *Pim 1* transgenic mice to a pulsed 900 MHz electromagnetic field (EMF) at an absorption rate of 0.5, 1.4 or 4.0 W/kg, daily for one hour, over a period of not less than 18 months produced no evidence that exposure had any effect on the incidence or severity of any neoplastic or non-neoplastic condition.

As an overall conclusion, three out of four studies produced no evidence that exposure had any adverse health effect or any influence on the incidence, severity or time of appearance of any neoplastic or non-neoplastic condition. The only effect observed is a borderline one found in the DMBA rat mammary tumour model assay.

1 Introduction

The European Commission (through the Fifth Framework Program), Swiss and Austrian Governments, the GSM Association and the Mobile Manufacturers' Forum have supported research addressing potential long-term health implications from the use of mobile phones and base stations. The research program called PERFORM-A is expected to play an important role in the health risk assessment undertaken by the European Union (EU) and World Health Organization (WHO).

This research program includes two NTP-type [NTP: National Toxicology Program of the (US-American) National Institute of Environmental Health Sciences / National Institutes of Health] carcinogenicity mouse and rat studies being conducted in both sexes, involve different exposure levels and use as exposure agents signals which best represent current cellular communications based RF. The aim of this PERFORM-A study was to evaluate putative carcinogenic effects in mice and rats exposed to radio-frequency (RF) for up to 2 hours per day, 5 days per week over a period of up to two years. The applied signal simulated the exposure from GSM (GSM: Global System for Mobile Communication) and DCS (DCS: Digital Personal Communications System) handsets, including the low-frequency amplitude-modulation components as occur during speaking (GSM Basic), listening (DTX) and moving within the environment (Handovers, Power Control). The carrier frequency was set to the center of the system's uplink band, i.e., 902 Megahertz (MHz) for GSM and 1747 MHz for DCS.

The following four separate animal studies were part of the PERFORM-A program:

PERFORM-A1: A Combined Chronic Toxicity / Carcinogenicity Study Of 900 MHz GSM & 1800 MHz DCS Wireless Communication Signals In B6C3F1 Mice (performed by Fraunhofer ITEM, Hannover, Germany).

PERFORM-A2: A Combined Chronic Toxicity / Carcinogenicity Study Of 900 MHz GSM & 1800 MHz DCS Wireless Communication Signals In WISTAR Rats (performed by RCC Ltd, Itingen, Switzerland).

PERFORM-A3: Evaluation of 900 MHz GSM Wireless Communication Signals on DMBA-Induced Mammary Tumours in Sprague Dawley Rats (performed by ARC Research GmbH, Seibersdorf, Austria).

PERFORM-A4: Evaluation of 900 MHz GSM Wireless Communication Signals on Lymphoma Induction in Eμ-Pim 1 Transgenic Mice (performed by Istituto di Ricerche Biomediche "A. Marxer" (RBM), Colleretto Giacosa, Italy).

All studies were performed in compliance with the Principles of Good Laboratory Practice (GLP) and are presented in separate reports. These reports are provided as appendices to the present PERFORM-A Final Report, which summarizes the separate studies.

2 Material and methods

PERFORM-A1: The B6C3F1 mouse studies of GSM and DCS wireless communication signals comprised eight exposure groups and a cage control group consisting of 65 males and 65 females each.

The applied signal simulated the exposure from GSM and DCS handsets, including the low-frequency amplitude modulation components as they occur during speaking (GSM Basic), listening (DTX) and moving within the environment (handovers, power control). The carrier frequency was set to the center of the system's uplink band, i.e., 902 megahertz (MHz) for GSM and 1747 MHz for DCS.

Uniform whole-body exposure was achieved by restraining the mice in tubes at fixed positions in the exposure setup. Mice were exposed to three whole-body SARs levels or sham exposed for 2 hours per day, 5 days per week during the entire 2-yr exposure period.
The exposure units ("wheels") consisted of two parallel stainless steel metal plates at a distance of 117 mm. A conical antenna was placed in the center between the plates. Encased between the plates there were 65 cylindrical (plexi-glass) tubes arranged radially around the antenna., The mice were placed in the exposure wheels in polycarbonate tubes with adjustable backstops for two hours daily. Each exposure was connected with a ventilation system to provide the restraint mice with fresh air. Temperature and humidity were monitored continuously within the animal exposure units. All the exposure equipment, including necessary amplifiers, signal generator and other electronic devices, was supplied by the IT'IS Foundation who also assured the continuous monitoring of the exposure system, including data transmission and dosimetry.

With the exception of the daily tube restrainment (EMF exposure: 2h/d, 5d/w), the animals were maintained under controlled standard animal room conditions (22 $\pm$ 2°C, 30-70% humidity, 12-hour light/dark cycle) on absorbent softwood in Polycarbonate Type II cages, having free excess to food and water.

During the in-life phase of the studies, parameters evaluated included clinical signs, body weight gain and food consumption. Chronic toxicity investigations with 15 male and female mice per group were performed after 12 months of RF-exposure, analyzing organ weights, hematology, gross pathology and histopathology, as the remaining 50 mice per group were sacrificed after up to 24 months EMF exposure.

After histopathological examination, a selection of slides, selected by an external advisor, was examined by a (small scale) Pathology Working Group (PWG) and consensus diagnosis was reached on single questionable cases.

The study including histopathology was performed blind to all individuals involved except for the IT'IS staff, and the key codes were disclosed only after completion of histopathology evaluation.

PERFORM-A2: In the 902 MHz GSM and 1747 MHz DCS rat study, groups of 65 male and 65 female Wistar rats were exposed to target levels of wireless communication signals of 4 SAR W/kg (high dose), 1.33 SAR W/kg (mid dose), 0.4 W/kg (low dose) and 0 SAR W/kg (sham control). Exposure was performed 2 hours a day, 5 days/week for 52 consecutive

weeks (15 male and 15 female rats/group), or for 104 consecutive weeks (50 male and 50 female rats/group). One additional group of 65 males and 65 females was kept unexposed and served as cage control for the same intervals.

The exposure wheel consisted of a circular cascade of 17 sectoral waveguides, all excited by one quarter-loop antenna placed in the center. The wheels were sealed by stainless steel wires on the side. During exposure the rats were restrained in metal-free polycarbonate tubes in the horizontal position. Air from the animal room was supplied to each rat by a ventilation system. Environmental parameters of oxygen, relative humidity and temperature were recorded. All the exposure equipment, including necessary amplifiers, signal generator and other electronic devices, was supplied by Foundation for Research on Information Technology in Society (IT'IS), Zurich (Switzerland). IT'IS also assured the continuous monitoring of the exposure system, including data transmission and dosimetry.

Parameters evaluated included clinical (mortality, clinical signs, palpable mass observation, body weight, food consumption, ophthalmoscopic examination and clinical pathology) and post mortem (organ weight, macroscopic and microscopic pathology) examinations.

Microscopic examination was performed on all collected tissues of all animals excluding the cage controls (except prostate gland).

After histopathological examination, a selection of slides, selected by an external advisor, was examined by a (small scale) Pathology Working Group (PWG) and consensus diagnosis was reached on single questionable cases.

The study including microscopic examination was performed blind to all individuals involved except for IT'IS staff, and key codes were disclosed only after completion of the microscopic evaluation.

PERFORM-A3: The aim of the study 902 MHz GSM wireless communication signals: effects on DMBA-induced mammary tumours in rats was to detect a possible modification by long term exposure to 902 MHz GSM on incidence, nature, latency period, multiplicity or growth of mammary tumours, induced by an initial administration of DMBA. The "DMBA induced mammary tumour"-model is a well established model to investigate the influence of factors on tumour development.

Five groups of 100 female Sprague Dawley Rats each were treated once orally with 17 mg/kg 7,12-dimethylbenz(a)anthracene (DMBA) at an age of 46-48 days. From the day after the DMBA dosing onwards they were treated with 902 MHz GSM signals as follows:

Sham exposure group: No exposure to electromagnetic fields (EMF), but transferred to and kept in (like the dosed groups) the exposure setup tubes for 4 h per day. This group served as a negative control group for the exposed group.
Low dose group: Exposed to 0.44 W/kg body weight for 4 h per day on 5 days a week for 6 months.
Mid dose group: Exposed to 1.33 W/kg body weight for 4 h per day on 5 days a week for 6 months.
High dose group: Exposed to 4.00 W/kg body weight for 4 h per day on 5 days a week for 6 months.

Cage control group: No exposure to electromagnetic fields (EMF), kept continually in their home cages. This group served to give baseline data of the animals without the restriction in the exposure units.

The investigations performed included daily animal observation, detailed weekly clinical observations, weekly examination for palpable subcutaneous tissue masses, weekly body weights, selected hematology parameters at terminal necropsy, necropsy with gross pathological examination of all animals selected organ weights at terminal necropsy, as well as histopathology of all gross lesions, some selected organs plus 12 mammary gland sections per animal.

PERFORM-A4: The aim of the study lymphoma induction and carcinogenicity study in Pim 1 transgenic mice exposed to pulsed 900 MHz electromagnetic fields was to determine whether long-term exposure to three different levels of pulse-modulated RF fields similar to those used in digital mobile telecommunications would increase the incidence of lymphoma in *Pim 1* transgenic mice. These animals express elevated levels of the Pim-1 transgene in their lymphoid compartments, and as a result are predisposed to develop lymphomas.
This experiment was performed in order to clarify the results of a previously published study (Repacholi et al., 1997). In addition, the properties of these RF fields to induce tumors other than lymphomas in this mouse model were investigated in the study, which was conducted in compliance with the main Guidelines regarding carcinogenicity studies.

In the present study groups of 50 male and 50 female Pim-1 transgenic mice were exposed to different EMF levels, i.e.: 4 W/kg (high level group), 1.4 W/kg (medium level group), 0.5 W/kg (low level group) and 0 W/kg (sham group). Exposure was performed 1 hour a day, 7 days/week for 18 consecutive months. One additional group of 50 males and 50 females was kept unexposed and served as cage control.
The exposure units ("wheels") consisted of two parallel stainless steel metal plates at a distance of 117 mm. A conical antenna was placed in the center between the plates. Encased between the plates there were 65 cylindrical (plexi-glass) tubes arranged radially around the antenna. Mice were placed in polycarbonate tubes with adjustable backstops. Each exposure was connected with a ventilation system. All the exposure equipment, including necessary amplifiers, signal generator and other electronic devices, was supplied by Foundation for Research on Information Technology in Society (IT'IS)-Zurich (Switzerland). IT'IS also assured the continuous monitoring of the exposure system, including data transmission and dosimetry.
Parameters evaluated included clinical (clinical signs, palpable mass observation, body weight, food consumption and clinical pathology) and post mortem (organ weight, gross pathology and histology) examinations.
Histology was performed on all tissues of all animals including the cage controls. After histological examination, a selection of slides was examined by a Pathology Working Group (PWG).
The study including histology was performed blind to all scientists involved except for IT'IS staff, and key codes were disclosed only after completion of histopathology evaluation.

3 Results

The results can be summarized as follows.

PERFORM-A1: Combined Chronic Toxicity / Carcinogenicity Studiy of GSM and DCS Wireless Communication Signals in B6C3F1 Mice.

Within two years, complete exposures (2h/d) were performed in 98 % and 99% of the expected target days in the GSM study and DCS study, respectively.
Bacteriological investigations revealed positive results on the superficial surfaces of single animal without clinical relevance. Parasitological and virological examinations during the course of the study revealed no abnormalities, indicating an undisturbed animal study.

Main clinical findings throughout this long-term study were atrophy of the hair follicles, hyperkeratosis of the hind feet and osteoathropathy (joint stiffening) of the knee joints (all of slight severity) which are restrainment-related, though they were observed with an increasing incidence during the course of the study in all (Sham-) Exposure groups. Compared to the Sham-Exposure group, a significantly altered food intake was detected in various EMF exposure groups: differences (increased and decreased consumption) were limited to few and singular weeks, revealing no continuity in time or in the different/increased EMF-dose levels.

Repeated measurements analysis of variance as a global test showed significant differences in the body weight gain for the complete course of the study. Nevertheless, compared to the Sham-Exposure group, the significant differences are only detected at some singular measurements and revealed no continuity in respect of time or EMF-dose level.

The incidence of mortality (including sacrifice of moribund animals for ethical reasons) throughout the study was higher in the female groups than in the male groups exposed to GSM and DCS signals. At the terminal sacrifice time point (after the 2-year exposure period), the incidence of mortality in tube-restrained males was between 10% and 20% and between 20% and 30% of the females were dead. Comparing the mortality of the sham and three EMF Exposure groups statistically, Kaplan Meier Test revealed no remarkable differences in the males and females of the GSM - and DCS study.

Hematological analysis after 12 months EMF-exposure revealed no abnormalities.

Relative weights of the brain, heart, lungs, liver, spleen, adrenals, kidneys and gonads were analyzed after 12 months EMF exposure and revealed no EMF-exposure related effects. Significant differences were found in the lung weights of the males in the DCS-study (decreased mean lung weight of the Medium-Dose group compared to the Sham-Exposure group), exclusively.

The histopathological results after 12 months exposure revealed a large variety of sporadic findings, all within the normal range of background alterations commonly seen in mice of this age and strain. Restrainment related lesions were detected in all exposure groups (including Sham-Exposure groups).

After two years EMF-exposure, among various non-neoplastic findings which did not show any exposure-related increases, a high frequency of chronic osteoarthropathy of the knee joint(s) together with pododermatitis (skin) was observed in both studies. Etiologically, these lesions were considered to be related to restrainment of the animals in the exposure tubes.

Regarding the organ-related tumor incidence, the pairwise Fisher test did not show any significant increase of a specific tumor type in the radiofrequency exposure groups as compared to the sham-exposed group, either in the GSM or in the DCS study.

PERFORM-A2: Combined Chronic Toxicity / Carcinogenicity Study of GSM and DCS Wireless Communication Signals in WISTAR Rats.

Of the number of intended exposures more than 98% (902 MHz) or 96.6% (1747 MHz) were successfully completed.

The estimated doses in terms of specific whole body absorption rate (SAR) were 0.44, 1.33 and 4.0 W/kg for 902 MHz groups and 0.41, 1.23 and 3.7 W/kg for the 1747 MHz groups at the low, mid and high doses respectively.

The incidence of animals which died or were killed before the end of the treatment period did not indicate an effect related to exposure to 902 MHz GSM or 1747 MHz DCS wireless communication signals.

There were no clinical signs or palpable masses, body weight, food consumption, ophthalmic findings, organ weight changes, or macroscopic and microscopic findings considered to be related to exposure to 902 MHz GSM or 1747 MHz DCS wireless communication signals. There were also no changes in hematological, clinical biochemical or urinalysis parameters considered to be related to exposure to 902 MHz GSM or 1747 MHz DCS wireless communication signals.

PERFORM-A3: Evaluation of GSM Wireless Communication Signals on DMBA-Induced Mammary Tumours in Sprague Dawley Rats.

There was no EMF-exposure related effect on observations in life, clinical and functional observations as well as on the survival or the causes of death. All EMF-exposed groups had, at several terms, significantly more palpable tissue masses. There was no EMF-exposure related effect on body weights, hematology endpoints and organ weights. There was also no EMF-exposure related effect found on gross pathology at necropsy.

For histopathology endpoints, the following main findings were observed: When compared with the sham exposed group, there were significantly

- less animals with benign neoplasms in all EMF-dosed groups,
- more animals with malignant neoplasms in the high EMF-dose group,
- more adenocarcinoma (in total No.) in the low EMF-dose group,
- more malignant neoplasms (in total No.) in the low and the high EMF-dose group,
- more animals with adenocarcinoma (any number) in the high EMF-dose group,
- less animals with one (or any number of) fibroadenoma in the low and the mid EMF-dose group.

PERFORM-A4: Evaluation of GSM Wireless Communication Signals On Lymphoma Induction in Eμ-Pim 1 Transgenic Mice.

75 males and 92 females died or were killed before the end of the treatment period. The distribution of unscheduled deaths across the groups indicated that, in comparison to controls, there was poorer survival in all the male groups exposed to EMF and in females exposed to 0.5 W/kg. Since the decreased survival was not dose-related it was considered incidental. There was no evidence from the histopathology of decedents that exposure to EMF was responsible for the early death of any animal.
No effects on body weight, food consumption and palpable masses that could be related to EMF exposure were found.
In the hematology investigations, no changes in WBC differential count, total blood cell count and related parameters were noted. No organ weight changes and no macroscopic changes that could be related to EMF exposure were found.
Histological investigation revealed that the exposure of *Pim I* transgenic mice to a pulsed 900 MHz electromagnetic field (EMF) for eighteen months at absorption rates of 0.5 W/kg and 1.4 W/kg was not considered to have affected the incidence of any neoplastic finding. In particular, the incidence of malignant lymphoma in animals exposed to EMF was not significantly different from that seen in cage or sham controls.

A dose-related positive trend in the incidence of males bearing a Harderian gland adenoma ($p<0.0028$, one tailed test) with four of six cases occurring in males exposed to 4.0 W/kg and the remaining two in males exposed to 1.4 W/kg contrasted with the result in females where four of six cases occurred in controls and the two others in animals exposed to 0.5 W/kg.

4 Discussion

PERFORM-A1: Concerning the tumour incidence in the carcinogenicity study of GSM and DCS wireless communication signals in B6C3F1 mice, a comparison with historical control data from B6C3F1 mice in NTP carcinogenicity studies (Haseman et al. 1999) shows that the tumor rates observed in the present studies are within the range of the NTP tumor data, although for some organs (liver, Harderian glands, hematopoietic system) marked differences between both data sets exist. The main tumor types observed in the present studies were also well in line with the corresponding tumor incidences in untreated B6C3F1 mice from a transgeneration carcinogenicity study, recently conducted at Fraunhofer ITEM (Dasenbrock et al. 2005).

PERFORM-A2: The increased/decreased incidences of several non-neoplastic and neoplastic findings in the study 902 MHz GSM and 1747 MHz DCS wireless communication signals: combined chronic toxicity / carcinogenicity study in the Wistar rat are regarded incidental rather than exposure-related.

The incidence of prostate adenomas (4 / 50) in the high dose (1747 MHz - group) was not statistically different from the incidence in the sham control (0 / 50). However, prostate adenomas are uncommon in the Wistar rat. For this reason the prostate gland of the cage control males were also examined. Since this examination revealed 3 / 50 adenomas, it is concluded that the finding in the 1747 MHz High dose group was incidental.

PERFORM-A3: For giving the histopathological results of the study "902 MHz GSM wireless communication signals": effects on DMBA-induced mammary tumours in rats a relative weight, a comparison of the sham exposed group vs. the cage control group is added:
Among the two not EMF-exposed groups repeatedly significant differences were noted.

The cage control group had, when compared with the sham exposed group:
A marginally higher mean body weight at some terms
Higher mean adrenal gland weights
More animals with palpable tissue masses in the mammary gland (actually the highest number of all groups)
More tissue masses in the mammary gland at necropsy (actually the highest number of all groups)
More animals with hyperplasia or neoplasia (actually the highest number of all groups)
More animals with malignant neoplasms
More benign neoplasms in the mammary gland (actually the highest number of all groups)
More malignant neoplasms in the mammary gland (and, of course, more neoplasms of any dignity), (actually the highest number of all groups)
A higher number of adenocarcinomas and of fibroadenomas (actually the highest number of all groups) in the mammary gland
Some other significant differences in tumour distribution, in general with the higher number than the sham exposed group.

The almost identical body weights of the two control groups indicate, that the manipulation and restriction in the exposure setups did not stress the animals severely. No cause for the higher tumour formation in the cage control animals could be identified.

In a study of this dimension with numerous parameters determined, isolated findings, which are seemingly treatment related are to be expected, as there may be several "incidental" significant differences between the groups, even in the absence of any biologically effective agent.

Except for the mammary gland effects, there were significant differences between any of the EMF-exposed groups and the sham exposed groups only in some isolated organ weights found. None of them is given biological relevance nor is it attributed to the EMF-exposure.

In the mammary glands and their neoplastic lesions there were some significant differences between one or more of the EMF-exposed groups and the sham exposed groups found, especially:
More palpable tissue masses
More animals with malignant neoplasms
Less animals with benign neoplasms

This indicates, that there might be an effect of the exposure to EMF with respect to a shift in the number and dignity of the tumours formed, while all other aspects (time of onset, total number, multiplicity, size, etc.) remained unaffected.

In this context it is important to include the cage control group for comparison of the effects and to establish their relative biological importance. In fact, in all the above mentioned parameters with significant effects, the cage control group had equal or even worse results than the worst EMF-exposed group (please note: “worse” stands here for more tumours or a higher malignancy of the tumours).

The most pronounced differences noted in this study were those between the sham exposed group and the cage control group.

PERFORM-A4: In the lymphoma induction and carcinogenicity study in Pim 1 transgenic mice exposed to pulsed 900 MHz electromagnetic fields, the statistically significant difference in the incidence of males bearing a Harderian gland adenoma was considered to have arisen fortuitously and not as a result of exposure to EMF.

None of the non-neoplastic findings encountered in this study were considered to have been affected by exposure to EMF. The range of findings encountered was broadly similar to that commonly observed in ageing mice.

5 Conclusions

Under the conditions of study **PERFORM-A1**, the exposure of male and female B6C3F1 mice to electromagnetic fields (EMF) of GSM and DCS wireless communication signals at a whole body absorption rate of up to 4.0 W/kg, two hours per day, 5 days per week, over a period of up to 24 months produced no evidence that the exposure had any adverse health effect or any influence on the incidence, severity, or time of appearance of the background non-neoplastic and neoplastic lesions observed.

Under the conditions of study **PERFORM-A2**, Wistar rats exposed to 902 MHz GSM Wireless Communication Signals at SAR levels of up to 0.44, 1.33 or 4.0 W/kg or 1747 MHz DCS Wireless Communication Signals at SAR levels of 0.41, 1.23 or 3.7 W/kg for 2 hours/day and 5 days/week over a period of up to 24 months produced no evidence that the exposure had any adverse health effect or any influence on the incidence, severity, or time of appearance of the background non-neoplastic and neoplastic lesions observed.

Under the conditions of study **PERFORM-A3** it is concluded, that this study produced a borderline evidence of long term repeated exposure to 902 MHz GSM signals affecting the DMBA-induced mammary tumour response in rats with an equivocal biological relevance.

Under the conditions of study **PERFORM-A4**, exposure of *Pim 1* transgenic mice to a pulsed 900 MHz electromagnetic field (EMF) at an absorption rate of 0.5, 1.4 or 4.0 W/kg, daily for one hour, over a period of not less than 18 months produced no evidence that exposure had any effect on the incidence or severity of any neoplastic or non-neoplastic condition.

As an overall conclusion, three out of four studies produced no evidence that exposure had any effect on the incidence or severity of any neoplastic or non-neoplastic condition. The only effect observed is a borderline one in the study investigating effects on the DMBA-induced mammary tumour response.

6 Exploitation and dissemination of results

The results of all four studies will be published in peer reviewed journals and thus be accessible for the whole scientific community. Moreover, it is expected that the results will be used

for a better risk assessment and communication worldwide. For the European Union, the results of the present project will be used within the sixth framework program coordination action entitled "Effects of the exposure to electromagnetic fields: from science to public health and safer workplace (EMF-NET)".

7 Policy related benefits

Wireless technology has clearly become well rooted in the European lifestyle, and is expected to become an important motor for communication growth and innovation over the next decade in Europe. The potential economic impact of wireless Communications technology in Europe is addressed in the Bangemann Group report (Europe and the Global Information Society-Recommendations to the European Council, 26 May 1994), which identified it as a necessary building block of the Information Society, and recommended strengthening its potential. European wireless equipment manufacturers, and network operators are in the vanguard of corporations providing this technology to Europe as well as the rest of the world. In summary, mobile and personal cellular communications is a vital and robustly growing industry within the European Union.

Recent public concern that cellular telephony might be linked to specific and non-specific health disorders, however, must be addressed in order for this technology to remain a vital component of the advancing European society. The potential economic impact of unanswered health questions, however, could also be considerable for Europe. Unfounded fears could result in limiting the growth of wireless Communications technology. Alternatively, the persistence of undetected health problems could result in needless health care costs and public stress. Public concern over adverse health conditions which might be caused or precipitated by the use of wireless communication devices originated in the United States in late 1992 with an anecdotal report of brain cancer developing in a cellular telephone user. Since then, public concern that cellular telephony might be linked to specific and non-specific health disorders (including cancer, headaches, sleep disturbances and memory loss) has been raised in Europe. Although such claims are unsubstantiated by scientific evidence, they remain a concern due to the lack of a comprehensive research database sufficient for public health agencies to make a conclusive human health risk analysis. While a number of scientific and standard setting bodies around the world have reviewed the available literature and concluded that no health hazard exists when wireless equipment is designed, manufactured and operated in conformance with internationally-recognised exposure limits, there have been attempts to further regulate or require warning labels on cellular Communications devices. New policies addressing wireless communication require sound evaluation of a complete database of studies, such as those set forth in the research agenda of the World Health Organization (WHO), in order to make a conclusive human health risk analysis.

In responding to this issue in 1995, the European Commission called upon eight experts to prepare an action plan designed to investigate possible human health effects of wireless telecommunications. The agenda included epidemiological research, animal bioassays (NTP type rodent bioassays involving two species and both sexes), human provocation studies, and replication of previously reported positive study findings. Currently, an assemblage of epidemiological data is planned through a large multinational case control study directed by International Agency for Research on Cancer (IARC). This study will involve data collection from sites in 14 different countries and will examine the correlation between cellular telephone use and brain tumours, head & neck tumours, and leukemia & lymphomas.

The remaining major studies listed in the WHO agenda were proposed to the 5 Framework program by the present research consortium. The present consortium comprised of labs in 6

different European countries, and had the sponsorship of the cellular Communications industry, the Mobile Manufacturers Forum, and the GSM Association to guarantee adequate financial support. Approval and remaining support of the proposed studies by a government directed research program assured public confidence in the overall results. Further, the data generated by these studies, in combination with the research initiated largely by industry over the past few years, provide the necessary and sufficient database (as described in the WHO research agenda) for human health risk analysis by public health agencies. Such an evaluation to determine the human cancer risk from cellular telephone radiofrequency exposure is currently performed by IARC.

Based on these considerations, and taking into account the perspectives described in paragraph 6, it can be considered that the initial intentions and objectives of the project were fully met.

8 Literature cited

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9 Appendix

Study Reports:

Appendix A:
Carcinogenicity Study of GSM (902 MHz) and DCS (1747 MHz) Wireless Communication Signals in B6C3F1 Mice (PERFORM A1, performed by Fraunhofer ITEM, Germany)

Appendix B:
902 MHz GSM and 1747 MHz DCS Wireless Communication Signals: Combined Chronic Toxicity / Carcinogenicity Study in the WISTAR Rat (PERFORM A2, performed by RCC Ltd, Switzerland)

Appendix C:
"902 MHz GSM Wireless Communication Signals": Effects on DMBA-Induced Mammary Tumours in Rats (PERFORM A3, performed by ARC Research GmbH, Austria)

Appendix D:
Lymphoma Induction and Carcinogenicity study in Pim 1 Transgenic Mice Exposed to Pulsed 900 MHz Electromagnetic Fields (PERFORM A4, performed by Istituto di Ricerche Biomediche "A. Marxer" (RBM), Colleretto Giacosa, Italy)