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Mobile telephony radiation exerts genotoxic action and significantly enhances the effects of gamma radiation in human cells

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Abstract. I previously reported chromosomal damage in human peripheral blood lymphocytes (HPBLs) induced by: a) mobile telephony (MT) electromagnetic fields (EMFs)/electromagnetic radiation (EMR), b) a high caffeine dose, and c) the combination of the two stressors. HPBLs from the same subjects exposed to gamma radiation at doses 0.1, 0.3, or 0.5 Gy, displayed more aberrations than those exposed to MT EMFs or the high caffeine dose in a dose-dependent manner. When the cells exposed to these gamma radiation doses were pre-exposed to a single 15-min MT EMF exposure, the number of aberrations increased significantly more than the sum number of aberrations induced by the individual stressors in all subjects. Thus, MT EMF exposure at a power density ~136 times below the latest International Commission on Non-Ionizing Radiation Protection (ICNIRP) exposure limit, apart from the fact that it is genotoxic by itself, significantly enhanced the genotoxic action of gamma radiation. Since gamma radiation at similar doses is applied for diagnostic and therapeutic purposes, people should be aware of the increased risk during treatment periods. Comparison of the genotoxic action between MT EMF and gamma radiation shows that the ICNIRP limits are, at least, ~4.5×10^4 times less stringent than the limits for gamma radiation.

Key words: Electromagnetic fields — Mobile phone radiation — Gamma radiation — Human lymphocytes — Chromatid aberrations — DNA damage

Abbreviations: CW, continuous-wave; DECT, Digitally Enhanced Cordless Telecommunications; ELF, Extremely Low Frequency; EMF, electromagnetic field; EMR, electromagnetic radiation; GSM, Global System for Mobile telecommunications; HPBLs, human peripheral blood lymphocytes; IARC, International Agency for Research on Cancer; ICNIRP, International Commission on Non-Ionizing Radiation Protection; IFO, ion forced-oscillation; LTE, UMTS Long-Term Evolution; M, Mitosis; MIMO, multiple input multiple output; MT, mobile telephony; NR, New Radio; OS, oxidative stress; PHA, phytohaemagglutinin; RF, Radio-Frequency; ROS, reactive oxygen species; S, Synthesis; SAR, Specific Absorption Rate; SSB, synchronization signal blocks; ULF, Ultra Low Frequency; UMTS, Universal Mobile Telecommunications System; UV, ultraviolet; VGIC, voltage-gated ion channel; WC, wireless communications; Wi-Fi, Wireless Fidelity; 2G/3G/4G/5G, second/third/fourth/fifth generation of MT/WC.

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Introduction

Wireless communication electromagnetic fields and health effects

The peer-reviewed scientific literature already includes a great number of studies on the adverse effects of anthropogenic electromagnetic fields (EMFs), especially those employed in modern wireless communications (WC) including mobile telephony (MT) devices and base antennas, wireless domestic phones called Digitally Enhanced Cordless Telecommunications (DECT) phones, Internet connection routers called Wireless Fidelity (Wi-Fi), "Bluetooth" wireless connections among electronic devices, etc. All WC EMFs always combine Radio-Frequency (RF)/microwave carrier waves (of the order of GHz in most cases) with Extremely Low Frequency (ELF) (3–3000 Hz) modulation and pulsation. The pulsation is used in order to increase the amount of various transmitted information (speech, text, images, video, Internet, etc.), and the number of users communicating simultaneously with the same antenna and performing different tasks (called multiplexing). Moreover, all WC signals display random variability mainly in the Ultra Low Frequency (ULF) band (0–3 Hz) (Panagopoulos et al. 2022a). There is ample evidence that the most bioactive components of the complex WC signals are the ELF/ULF components of modulation, pulsation and variability (Markkanen et al. 2004; Mansourian et al. 2020; Panagopoulos et al. 2022a).

Both RF (actually WC) and pure ELF EMFs have been classified by the International Agency for Research on Cancer (IARC) as possibly carcinogenic to humans (Group 2B) (IARC 2002, 2013; Baan et al. 2011). Based on more recent scientific evidence after the 2011 IARC classification for RF EMFs, several studies have suggested that RF (actually WC) EMFs should be re-evaluated and classified as probably carcinogenic (Group 2A) or carcinogenic (Group 1) to humans (Yakymenko et al. 2011, 2016, 2018; Hardell et al. 2013; Carlberg and Hardell 2017; Hardell 2017, 2019; Miller et al. 2018, 2019; Panagopoulos 2019a, 2019b, 2020; Hardell and Carlberg 2020; Hardell and Nyberg 2020; Panagopoulos et al. 2022b; Yakymenko and Tsibulin 2022a, 2022b). Moreover, it is shown that the majority of studies performed with simulated WC EMFs with fixed parameters emitted by generators (following IARC's recommendations) grossly underestimate the biological activity of real-life highly variable WC EMF exposures by commercially available devices and antennas (Panagopoulos et al. 2015a, 2022a; Leach et al. 2018; Panagopoulos 2019a, 2019b, 2020; Kostoff et al. 2020; McCredden et al. 2022, 2023).

Universal Mobile Telecommunications System (UMTS), applied in third and fourth generation (3G and 4G) MT/WC EMFs/electromagnetic radiation (EMR) emitted by commercially available mobile phones and base antennas, is a common type of modern MT/WC EMFs/EMR. While 2G Global System for Mobile telecommunications (GSM) is still in use, and 4G – a combination of UMTS or GSM for voice and an enhancement of UMTS with carrier frequency up to 2.6 GHz for broadband Internet access called UMTS Long-Term Evolution (LTE) – is today the most widely in use, the installation of the 5G MT/WC system by the telecommunications industry called New Radio (NR) is well underway. This involves, apart from the already existing carrier frequencies, even higher ones (up to 100 GHz), additional ELF pulsations called synchronization signal blocks (SSB), multi-stream transmissions called "multiple input multiple output" (MIMO), antenna arrays for directional beams of potentially increased intensity, and a much denser network of base antennas of potentially increased power in order to compensate for the energy scattering loss due to the higher carrier frequencies (Sesia et al. 2011; Dahlman et al. 2018; Hardell and Carlberg 2020; Hardell and Nyberg 2020; Kostoff et al. 2020; Panagopoulos et al. 2022a; Betta et al. 2023). Many experts on the biological/health effects of EMFs have expressed strong objections to 5G roll out with concerns of highly increased health risk based on the aforementioned differences from previous MT/WC systems (McClelland and Jaboin 2018; Miller et al. 2018, 2019; Panagopoulos 2019a, 2019b, 2020, 2023; Hardell and Carlberg 2020; Hardell and Nyberg 2020; Kostoff et al. 2020; Balmori 2022; Jagetia 2022; McCredden et al. 2022, 2023; Miller 2022; Yakymenko and Tsibulin 2022a, 2022b). Those scientists have asked for a moratorium in 5G roll out and urgent application of the Precautionary Principe (Read and O'Riordan 2017).

Numerous studies have reported genotoxic effects of both RF/microwave (actually WC) and pure ELF EMFs on a variety of organisms and cell/tissue types (see reviews in Phillips et al. 2009; Panagopoulos 2019b, 2023; Lai 2021; Jagetia 2022). The genetic damage is accompanied by oxidative stress (OS) due to reactive oxygen species (ROS) generation and recent data point that actually genetic damage is due to OS in the cells (Yakymenko et al. 2016; Panagopoulos et al. 2021; Yakymenko and Tsibulin 2022b). Long-term animal carcinogenicity studies have recently shown that rodents exposed to simulated 2G or 3G MT EMFs developed brain and heart cancer accompanied by significantly increased DNA damage (strand breaks) in the brains of exposed animals (Falcioni et al. 2018; NTP 2018; Melnick 2019; Smith-Roe et al. 2020), confirming the fact that DNA damage is the main cause of environmentally-induced cancer. Two studies that compared the bioactivity between 2G and 3G MT EMFs/radiation emitted by an active mobile phone, found that both types of MT EMFs induced DNA damage and histological changes on the developing liver and brain of chick embryos, with the 3G

(UMTS) being even more genotoxic/bioactive than the 2G (GSM) (D'Silva et al. 2017, 2021).

Gamma and other types of ionizing radiation

While anthropogenic ELF and RF (actually WC) EMFs are categorized as non-ionizing and classified by IARC (2002, 2013) as "possibly carcinogenic" (Group 2B), the carcinogenic/lethal effects of radioactivity (alpha particles which are high-energy helium nuclei $^{4}He^{2+}$ consisting of two protons and two neutrons, beta particles which are high-energy electrons, and gamma radiation which consists of high-energy photons) (Klimov 1975; Burcham and Jones 1995; Prasad 1995) were recognized soon after its discovery in 1896 when pioneer scientists died from cancer not knowing its danger at that time (Hall and Giaccia 2006). Radioactivity is emitted by unstable nuclei of naturally existing atoms (such as ^{235}U, ^{226}Ra, etc.), and after the early 1930s it is also emitted by artificial radionuclides formed in atomic particle accelerators by high-energy collisions, or in nuclear reactors (Klimov 1975; Burcham and Jones 1995). Apart from alpha, beta, and gamma radiation, high-energy neutrons and protons are also forms of radioactivity, and x-rays and even ultraviolet (UV) (to a lesser degree) are also forms of ionizing EMR. Finally, cosmic ionizing radiation consists of various types of ionizing particles like mesons, neutrons, etc., and gamma radiation. The kinetic energies of ionizing particles, or the photon energies of gamma radiation (≥1 MeV) are usually of the order of several MeV) and of x-ray photons usually of the order 1–100 keV, while the energies of the chemical bonds between the outer (valence) electrons and their nuclei in atoms/molecules are of the order of a few eV. UV is significantly less energetic than x-rays with energies approximately 3–100 eV but still capable of producing ionization to a smaller degree. All living organisms on Earth are constantly exposed to small doses of natural radioactivity/ionizing radiation of cosmic/solar and terrestrial origin (Prasad 1995; Nias 1998).

All types of radioactivity and x-rays are classified by IARC (2000) as "carcinogenic" (Group 1), even though x-rays are constantly used for diagnosis, and gamma radiation at significant doses (up to ~1 Gy) is also used for medical diagnosis and therapeutic treatment of cancer in patients (Hall and Giaccia 2006). Their action in any absorbing media including biological tissue is briefly that the high-energy particles (alpha, beta, neutrons, etc.) or photons (gamma, x, and even UV) can readily break chemical bonds and ionize the atoms/molecules of the exposed materials (Prasad 1995; Nias 1998). The established metric for the absorption of ionizing radiation by living tissue is the "absorbed dose" (in Gy or mGy) defined as the amount of energy absorbed by unit mass of tissue (1 Gy = 1 J/kg).

The exposure limit to any type of ionizing radiation for the general population is given in terms of the "effective dose" *per* year, and it is 1 mSv/year, but the doses from medical exposures and natural background radioactivity are excluded from this limit. Also, it seems there is a lack in the literature regarding a corresponding limit for acute irradiation. Taking a certain dose acutely is normally much more detrimental than taking the same total dose in many fractions and allowing recovery of the organism in the time intervals between the fractions (Prasad 1995; Nias 1998; Hall and Giaccia 2006; IAEA 2011).

The effective dose (in Sv or mSv) for a specific tissue type and for a specific type of ionizing radiation is equal to the absorbed dose (in Gy or mGy) multiplied by the effectiveness of the specific type of ionizing radiation (called radiation weighting factor – W_R), and also multiplied by the sensitivity of the specific tissue that absorbs the radiation (called tissue weighting factor – W_T) (Prasad 1995; Nias 1998; Hall and Giaccia 2006). Thus:

$$1\ \text{Sv} = 1\ \text{Gy} \times W_R \times W_T \quad (1)$$

Human peripheral blood lymphocytes and reported genotoxic effects

Human peripheral blood lymphocytes (HPBLs) naturally arrested in G_0 phase and usually stimulated for Mitosis (M) – have been established as a model biological system for the assessment of genotoxicity of various environmental agents such as ionizing radiation, chemicals, smoking, pharmaceuticals. While the effects of ionizing radiation on HPBLs are intense and well-known for decades including all types of chromosomal aberrations in a dose-dependent manner (IAEA 2011), several studies have been conducted to search the effects of WC EMFs on HPBLs, both *in vitro* and *in vivo*. Most of these studies have found genotoxic effects induced by the WC EMFs alone or in combination with other genotoxic agents. A review of such studies can be found in Panagopoulos (2019a, 2020, 2022a). One of these studies found DNA strand breaks and chromosomal aberrations induced by UMTS-like MT EMF at degrees increasing with longer exposure duration. The effects were attributed to OS induced by the EMF exposure (El-Abd and Eltoweissy 2012). In an older study (Ji et al. 2004) volunteers were exposed *in vivo* by talking on their GSM (2G) mobile phones for 4 hours. After the exposure, DNA damage in their blood samples was significantly increased compared to their blood samples before the exposure. Two more recent studies examined HPBLs from people residing in the vicinity of MT/WC base stations and thus exposed *in vivo* to real-life MT/WC EMFs/EMR emitted by the base antennas. Both studies Gulati et al. (2016) and Zothansiama et al. (2017) found significantly increased genetic damage compared to control groups residing at longer distances from the antennas/cell towers.

A sensitive assay to record genotoxic effects of environmental stressors on HPBLs is the so-called "G_2 assay". This allows observation at metaphase of unrepaired DNA damage induced during G_2 or early M phase and converted during the M phase into chromatid-type aberrations in cells activated for mitosis (Terzoudi and Pantelias 2006; Pantelias and Terzoudi 2010, 2011; Terzoudi et al. 2011; Panagopoulos 2019a, 2020). The reason for the increased sensitivity of the G_2 phase of the mitotic cycle is related to the existence of a checkpoint which is a most sensitive stage of the cell cycle along with the other known checkpoint at the end of G_1 phase (Pantelias and Terzoudi 2011).

I recently reported that a 15-min single exposure of human peripheral blood lymphocytes to UMTS EMF emitted by a commercially available mobile ("smart") phone during an active phone call in "talk" mode at 1 cm distance from the blood samples induced chromatid breaks (terminal deletions) and chromatid gaps (achromatic lesions) at highly significant percentages (up to +275%) compared to the sham-exposed (control) samples in all six healthy subjects tested. Wi-Fi and Bluetooth functions were turned off in the device. The lymphocytes were stimulated to enter the mitotic cycle. Those exposed during the G_2 or early M phase were arrested at metaphase by colcemid treatment and observed by light microscopy (Panagopoulos 2019a). More recently, I reported that the numbers of chromatid aberrations induced by the mobile phone EMF exposure were comparable and even greater than those induced by an extreme caffeine dose ~290 times higher than the permitted single caffeine dose for an adult individual, and that the combination of this caffeine dose with the mobile phone exposure increased the number of aberrations on the same subjects significantly more than the sum of the individual effects induced by each stressor alone (Panagopoulos 2020).

Combining WC EMFs with ionizing radiation. Purpose of the study

Comparing the biological effects of WC EMFs with those of other genotoxic agents such as gamma radiation or the high caffeine dose in my previous publication with HPBLs and examining the combined effects is very important since people are today in most cases exposed to combined stressors with one of them being WC EMFs. Several studies have already compared the effects or examined the combination of WC EMF exposures with radioactivity/ionizing radiation. Most of them have found synergistic effects in various biological systems.

One study exposed yeast cells to continuous-wave (CW) or pulsed RF EMF (same RF frequency and amplitude but provided in pulses with 217 Hz repetition rate like in GSM MT), in both cases combined or not with exposure to UV radiation and examined the induction of cell death. The study found that the pulsed RF EMF (with 217 Hz GSM pulses) significantly enhanced cell death induced by UV radiation while the CW RF EMF did not induce any such enhancement (Markkanen et al. 2004). Another study found that simulated UMTS EMF exposure enhanced the x-ray-induced chromosomal damage in HPBLs (Manti et al. 2008). Another study examined the combined effect of GSM 900 (2G) mobile phone EMF exposure and gamma radiation on human glioma cell line (SHG44) cells and found that pre-exposure to the 2G MT EMF significantly enhanced the decrease in cell proliferation rate and the increased rate of apoptosis induced by gamma radiation exposure, and resulted in a synergistic effect by triggering stress response and OS in the cells (Cao et al. 2009). Another study compared the genotoxic effects between plutonium-239 alpha-particle radiation (nominal activity 3.0×10^4 Bq) and 2G (GSM 900) EMF exposure from a commercially available mobile phone on Allium cepa newly emerged roots. The study found very intense genotoxic effects (mitotic abnormalities, chromosome aberrations, micronuclei, etc.) induced by the 2G MT EMF and increasing with longer exposure duration, even though they were less intense, as expected, than the corresponding effects of the alpha radioactivity which is a known human carcinogen (Pesnya and Romanovsky 2013). A recent study found that simultaneous exposure to Wi-Fi EMF and gamma radiation for 72 h increased the number of DNA double-strand breaks in rat peripheral blood lymphocytes (Khodamoradi et al. 2022). A more recent study examined the combined effect of UV radiation and Wi-Fi EMF in inducing inflammation in human skin cells as assessed by increases in cytokine concentrations, and found that Wi-Fi exposure observably, but not significantly, further increased the cytokine concentrations that were already increased by the prior UV exposure (Szilágyi et al. 2023). Other studies did not find a synergistic effect between RF/WC EMF and ionizing radiation exposures (Maes et al. 2000; Stronati et al. 2006; Juutilainen et al. 2007).

The purpose of the present study was to compare the genotoxicity of UMTS (3G/4G) MT/WC EMFs/EMR described in my previous reports (Panagopoulos 2019a, 2020), with that of gamma radiation at doses comparable to those used for diagnostic and cancer treatment purposes, and test the genotoxicity of the combination of the two stressors on HPBLs of the same subjects and under identical conditions and experimental procedures. The experiments of the present study were carried out at the same time with those of Panagopoulos (2019a, 2020) but the analyses of the results were carried out separately and published in separate reports. This is the third report addressing the comparison and combination of the UMTS MT EMF with gamma radiation. No other study has until now compared the genotoxicity or investigated the combined effect of gamma radiation and

real-life 3G/4G MT EMF exposure on HPBLs, and therefore the present study is novel.

Materials and Methods

Blood culture and separation into individual samples/groups

After obtaining consent, blood samples were collected from six healthy non-smoker adult donors (one sample from one donor in each experiment) in heparinized glass tubes for analysis of chromosomal sensitivity to the various stressors under test. The subjects were both males and females, 28–42 years old, with "moderate" mobile phone use (no more than ~30 min total daily conversation on their mobile phones), and no reported history of major illnesses or any regular medication. Apart from this, no specific differences between the subjects were addressed, since each subject had its own control sample. Whole blood samples were cultured in RPMI 1640 medium (Biochrom AG, Germany) containing 10% fetal bovine serum (FBS), 1% L-glutamine (2 mM), and 1% antibiotics (penicillin: 100 U/ml; streptomycin: 100 μg/ml). Phytohaemagglutinin (PHA) 2% of the final medium volume (dissolved in water at a concentration of 0.24 mg/ml) was added to stimulate the lymphocytes (normally arrested in the G_0 phase) to enter the mitotic cycle (Panagopoulos 2019a, 2020).

For each subject, a single culture was prepared in a 200 ml flask (which was later divided into individual samples/groups) to ensure identical culture conditions and treatment for all individual samples/groups in each experiment. The culture was incubated for 72 h, at 37°C in a humidified incubator with an atmospheric content of 5% CO_2 and 95% air.

After 72 h of incubation the single blood culture was subdivided into individual samples/groups in identical 30 ml rectangular plastic flasks. (Each individual group contained: 0.5 ml blood, 5 ml culture medium, 100 μl PHA). One sample was exposed to the UMTS EMF-alone for 15 min, and another one was sham-exposed as previously described (Panagopoulos 2019a). Three additional samples were exposed to the UMTS EMF and then to gamma radiation 0.1, 0.3, and 0.5 Gy, and another three exposed to the same gamma radiation doses and sham-exposed to the UMTS EMF for 15 min.

EMF and gamma radiation exposure systems

EMF-exposures were performed by a UMTS (3G/4G) commercially available "smart" mobile phone handset in order to test the effects of real-life exposures. For description of the parameters of the UMTS EMF (modulation, pulsing, etc.) see Panagopoulos (2019a, 2020). The Specific Absorption Rate (SAR) value of the handset for the human head, according to the manufacturer, was 0.66 W/kg. The Internet connection (data)/Wi-Fi, and Bluetooth functions of the "smart" phone were disabled like previously (Panagopoulos 2019a, 2020).

The power density in the RF band emitted by the handset during the exposures was measured at 1 cm distance from the handset by a Cornet ED85EXpluss RF meter (Cornet Microsystems Inc., USA), and a Spectran HF-4040V3 spectrum analyzer (Aaronia AG, Germany), both with a near-field antenna. The ELF electric and magnetic field intensities (ELF-E and ELF-B) emitted by the handset were measured at 1 cm distance by a Spectran NF-1010E (Aaronia AG, Germany) spectrum analyzer. Representative average peak power density (from five representative peak instant measurements excluding background) in the RF band ± standard deviation (SD) was 92 ± 27 μW/cm^2. Averaged power density over six min (as in the guidelines issued by ICNIRP (1998; 2020) was 29 ± 14 μW/cm^2, which is ~136 times below the latest ICNIRP (2020) corresponding limit (4000 μW/cm^2). The carrier frequency was variable ~1920–1960 MHz during the exposures. Representative average ELF-E and ELF-B (from five representative instant measurements excluding background) ± SD at 100 Hz was 12 ± 4.2 V/m, and 0.9 ± 0.4 mG, respectively. Corresponding average ELF-E and ELF-B (from five instant measurements excluding background) ± SD at 1500 Hz was 8 ± 4.6 V/m, and 0.06 ± 0.02 mG, respectively (Panagopoulos 2019a, 2020). All measurements were carried out separately from the exposures in order to have the measuring devices at the same location with the samples during the exposures.

The samples were exposed to gamma radiation within a special metallic gamma chamber containing ^{60}Co (GammaCell 220 irradiator, Atomic Energy of Canada Ltd., Ottawa, Canada) at room temperature. The absorbed dose was evaluated by an electrometer "Victoreen r-meter" 570A (Victoreen Instruments Co, Cleveland, Ohio, USA). The gamma radiation doses selected for the experiments to study their effects alone or combined with mobile phone radiation were 0.1, 0.3, and 0.5 Gy. The exposure durations in the gamma chamber corresponding to these doses were 18, 52, and 85 s respectively.

For gamma radiation $W_R = 1$ in Equation 1, and $W_T = 1$ for whole body absorption which is the case for circulating blood that has absorbed the dose (Hall and Giaccia 2006). Thus, the effective doses corresponding to 0.1, 0.3, and 0.5 Gy used in the present experiments are 0.1, 0.3, and 0.5 Sv, respectively which are 100, 300, and 500 times greater than the permitted annual limit of 1 mSv. Considering that any corresponding limit for an acute dose should be at least tens of times smaller, we could very conservatively conclude that the doses used in the present experiments were at least ~1000, 3000, and 5000 times greater than a reasonable allowable acute dose for gamma radiation.

Gamma radiation and mobile phone exposure procedures

The specific samples that were to be exposed to UMTS, alone or in addition to gamma radiation, were taken to the "exposure room" and exposed for 15 min by the UMTS mobile phone handset at 1 cm distance from the proximal flask wall during an active phone-call in "talk" mode (Panagopoulos 2019a, 2020). This took place in the exposure room so that the controls (in the culture room) would not be exposed. After all the exposed samples were back in the culture room, the corresponding control (sham-exposed) samples were also transferred to the exposure room for 15 min at the same location as the exposed samples, without being exposed to the MT EMF. This was done because the background ELF-E and ELF-B and the light conditions in the two rooms were not identical as explained before (Panagopoulos 2019a, 2020).

Temperature increases within the blood samples during the 15 min exposures did not exceed 0.1ºC as measured within an identical culture and flask by a HANNA Check-Temp 1 calibrated electronic thermometer (USA).

Then, all blood samples within the identical 30 ml plastic flasks were transferred within a thermally insulated box to where the special chamber for gamma radiation exposures was installed. Those samples which would not be exposed to gamma radiation were placed in a room next to the room of the gamma chamber with the same temperature but no gamma radiation. The specific samples exposed to gamma were taken to the room with the gamma chamber and inserted in the chamber for a certain time (s) corresponding to the specific doses (0.1, 0.3, and 0.5 Gy), and then placed back with the other samples. Thus, all samples were subjected to identical environmental influences apart from the gamma exposure. After gamma exposures were completed, all samples were transferred back within the thermally insulated box to the "culture room" of the laboratory.

Metaphase arrest, fixation and observation

After exposures/sham-exposures were completed (~60 min after the separation into individual samples) and all the exposed and sham-exposed samples were returned back to the culture room, all individual groups/samples were treated with colcemid (50 μl added to each sample) for 60 min, to arrest dividing cells at metaphase. Colcemid prohibits dividing cells from proceeding from metaphase to anaphase by preventing the formation of the attractus. Keeping the cells in metaphase makes their condensed chromosomes clearly observable by light microscopy for possible aberrations. The duration of colcemid treatment (60 min) right after the termination of exposure/sham-exposure plus the exposure/sham-exposure time (~2 h in total) determines in which phases of the cell-division cycle the arrested in metaphase lymphocytes were exposed. In this case, the ~2-h period determines that the metaphase cells collected for observation were normally at the mid-late G_2 or early M (prophase) stages during the exposure/sham-exposure.

Cells were then collected by centrifugation, treated for 10 min with hypotonic KCl solution 75 mM (Sigma-Aldrich, USA), fixed in methanol: glacial acetic acid (3:1 v/v), and stained for 10 min with 5% Giemsa solution (Merck, Germany) to be observed by light microscopy. Light microscopy was coupled with an image analysis system (Ikaros MetaSystems, Germany) to facilitate scoring.

Chromosomal damage was evaluated by the number of chromatid gaps (achromatic lesions) and chromatid breaks (terminal deletions) in cells at metaphase. For each of the 8 samples of each subject described above, 400 metaphases identically processed from 4 different slides (100 cells from each slide), were blindly scored for chromatid-type aberrations. Mean values of total number of aberrations (gaps and breaks) *per* cell and SD in all samples were calculated for each individual. Gaps were scored only when extended across the full chromatid width. An aberration was considered as a break when the gap width was equal to or greater than the chromatid width.

Statistical analysis

Results were statistically analyzed by application of the Student's *t*-test for unequal variances (Microsoft Excel program) between exposed and control groups (samples) or between differently exposed groups for each individual. The *p*-values smaller than 0.05, for the probability that differences between groups are due to random variations, were accepted as statistically significant.

Results

The results of experiments with the HPBLs of the six healthy subjects (No. 1–6) are listed in Table 1 and presented graphically in Figure 1. A single 15-min exposure by the UMTS (3G/4G) mobile phone during a phone call in "talk" mode at 1 cm distance, increased the total number of chromosomal aberrations (chromatid gaps and breaks) by 100–275% compared to the sham-exposed/control samples, with the vast majority of aberrations being gaps. All UMTS-exposed samples differed significantly from the corresponding control/sham-exposed samples (in all cases $p < 0.03$) as reported in Panagopoulos (2019a) and shown in Table 1. As expected the samples that were exposed to the gamma radiation displayed significantly greater numbers of aberrations (both chromatid gaps and breaks) than those exposed to the UMTS EMF and differed even more significantly, by 344%–2900%, from the corresponding con-

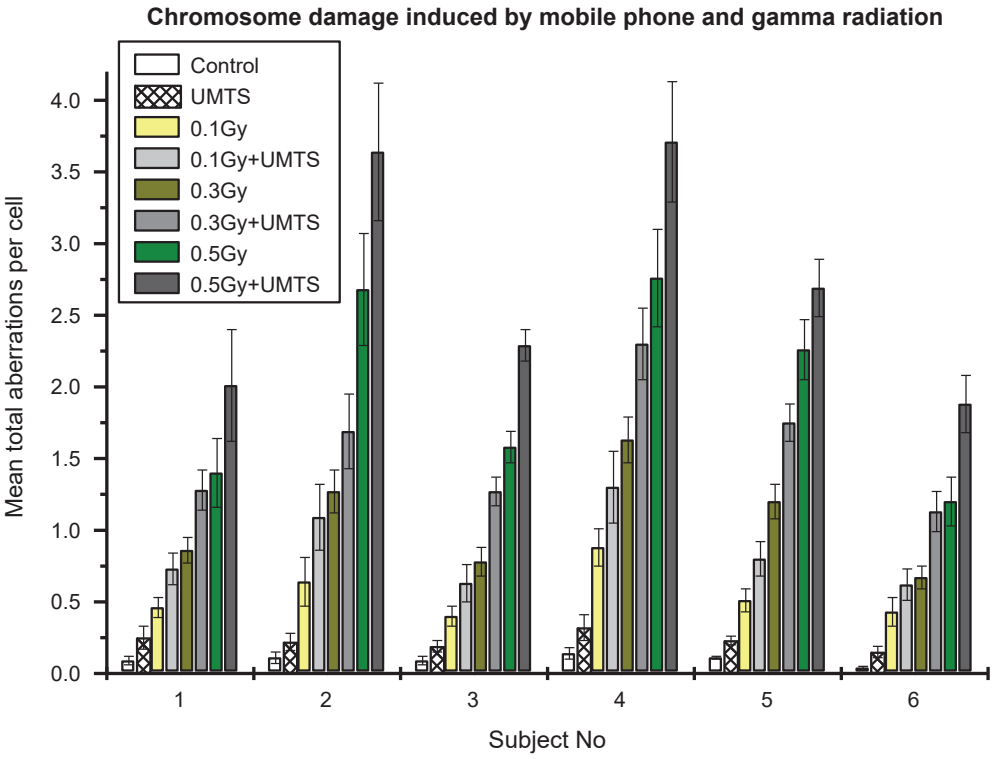


Figure 1. Mean total number of chromatid-type aberrations (gaps and breaks) *per* cell ± SD in 400 cells (peripheral blood lymphocytes) of each group (blood sample), for each one of the 6 subjects (No. 1–6): Sham-exposed (Control); exposed to UMTS 15 min (UMTS); exposed to 0.1 Gy gamma radiation (0.1Gy); exposed to 0.1 Gy and UMTS 15 min (0.1Gy+UMTS); exposed to 0.3 Gy (0.3Gy); exposed to 0.3 Gy and UMTS 15 min (0.3Gy+UMTS); exposed to 0.5 Gy (0.5Gy); exposed to 0.5 Gy and UMTS 15 min (0.5Gy+UMTS).

trol/sham-exposed samples (in all cases $p < 0.01$) (Table 1, Fig. 1). Even though in most samples exposed to gamma radiation alone or in combination with the UMTS EMF the number of gaps (achromatic lesions) was still greater than the number of breaks (terminal deletions) (Table 1), the percentage of breaks was significantly greater than in the samples exposed to the MT EMF and/or to caffeine (Panagopoulos 2019a, 2020). The genetic damage induced by gamma radiation was dose-dependent and increased with increasing doses from 0.1 to 0.5 Gy. The combined exposure to the UMTS EMF and then to gamma radiation increased the number of aberrations (gaps and breaks) in all subjects significantly more than the exposure only to gamma radiation (in all cases $p < 0.05$), and significantly more than the sum of aberrations induced by the individual exposures (gamma, UMTS) (Table 1, Fig. 1). This clearly shows that living tissue is more vulnerable when subjected to conditions of combined stress than when subjected to individual stressors, and the adverse effect in the case of combined stress is greater than the sum of the individual effects from the separate exposures to each stressor.

In Figure 2A, a metaphase of a control (sham-exposed) blood sample is shown from subject No. 6 (male). This is a representative picture of a metaphase from a control (sham-exposed) sample/group with all 46 chromosomes intact. Figure 2B shows a metaphase of a blood sample of the same subject, exposed to UMTS MT EMF (15 min) with one chromatid achromatic lesion – gap (g). Figure 2C shows a metaphase of a blood sample of the same subject (No. 6) exposed to gamma radiation 0.1 Gy with one chromatid terminal deletion – break (b) with displaced fragment (shorter arrow) toward the counter chromatid and one chromatid gap (g). Figure 2D shows a metaphase of a blood sample of the same subject, exposed to gamma radiation 0.1 Gy and UMTS MT EMF (15 min) with two gaps (g) and one break (b). Figure 2E shows a metaphase of a blood sample of the same subject, exposed to gamma radiation 0.3 Gy with two breaks (b) and one gap (g). Figure 2F shows a metaphase of a blood sample of the same subject, exposed to gamma radiation 0.3 Gy and UMTS MT EMF (15 min) with two gaps (g), and two breaks (b). The one break at the lower right part of the picture is with a displaced fragment (shorter arrow) toward the counter chromatid, and the other in the lower left part of the picture is an isochromatid break (a break at the same point in both chromatids). [Isochromatid (double) aberrations are counted as one aberration and are considered to occur during the Synthesis (S) phase of the cell cycle. Thus, it seems that the particular cell was at the S phase during the exposure and proceeded to the M phase faster than most other cells]. Figure 2G shows a metaphase of a blood sample of the same subject, exposed to gamma radiation 0.5 Gy with four breaks (b), the three of them with fragments displaced toward the counter chromatids (shorter arrows), and one gap (g). Finally, Figure 2H shows a metaphase of a blood

Table 1. Chromatid-type aberrations in human lymphocytes induced by UMTS mobile phone or/and gamma radiation

Subject No. (age, sex)	Groups (Samples)	Gaps in 400 cells	Breaks in 400 cells	Total Aberr. in 400 cells	Mean Total Aberr. *per* cell ±SD	Deviation from Control (%)	*p*-value*	Deviation from Gamma (%)***	*p*-value**
1 (42, Male)	Control	30	5	35	0.09 ± 0.03				
	UMTS	84	17	101	0.25 ± 0.08	+178	<0.02		
	0.1 Gy	92	92	184	0.46 ± 0.07	+411	<0.01		
	0.1 Gy + UMTS	140	153	293	0.73 ± 0.11	+711	<0.01	+59	<0.01
	0.3 Gy	165	181	346	0.86 ± 0.09	+856	<0.01		
	0.3 Gy + UMTS	271	241	512	1.28 ± 0.14	+1322	<0.01	+49	<0.01
	0.5 Gy	275	286	561	1.40 ± 0.24	+1456	<0.01		
	0.5 Gy + UMTS	407	398	805	2.01 ± 0.39	+2133	<0.01	+44	<0.05
2 (33, Female)	Control	37	7	44	0.11 ± 0.04				
	UMTS	70	19	89	0.22 ± 0.06	+100	<0.03		
	0.1 Gy	143	113	256	0.64 ± 0.17	+482	<0.01		
	0.1 Gy + UMTS	257	179	436	1.09 ± 0.23	+891	<0.01	+70	<0.03
	0.3 Gy	269	240	509	1.27 ± 0.15	+1055	<0.01		
	0.3 Gy + UMTS	325	302	627	1.69 ± 0.26	+1436	<0.01	+33	< 0.04
	0.5 Gy	591	436	1027	2.68 ± 0.39	+2336	<0.01		
	0.5 Gy + UMTS	733	724	1457	3.64 ± 0.48	+3209	<0.01	+36	<0.03
3 (28, Male)	Control	28	9	37	0.09 ± 0.03				
	UMTS	63	15	78	0.19 ± 0.04	+111	<0.02		
	0.1 Gy	79	83	162	0.40 ± 0.07	+344	<0.01		
	0.1 Gy + UMTS	118	133	251	0.63-± 0.13	+600	<0.01	+57	<0.04
	0.3 Gy	162	151	313	0.78 ± 0.10	+767	<0.01		
	0.3 Gy + UMTS	263	247	510	1.27 ± 0.10	+1311	<0.01	+63	<0.01
	0.5 Gy	343	290	633	1.58 ± 0.11	+1656	<0.01		
	0.5 Gy + UMTS	451	464	915	2.29-± 0.11	+2444	<0.01	+45	<0.01
4 (40, Male)	Control	43	15	58	0.14 ± 0.04				
	UMTS	102	26	128	0.32 ± 0.09	+129	<0.03		
	0.1 Gy	222	130	352	0.88 ± 0.13	+529	<0.01		
	0.1 Gy + UMTS	335	185	520	1.30 ± 0.25	+829	<0.01	+48	<0.04
	0.3 Gy	393	258	651	1.63 ± 0.16	+1064	<0.01		
	0.3 Gy + UMTS	495	424	919	2.30 ± 0.25	+1543	<0.01	+41	<0.01
	0.5 Gy	615	490	1105	2.76 ± 0.34	+1871	<0.01		
	0.5 Gy + UMTS	819	665	1484	3.71 ± 0.42	+2550	<0.01	+34	<0.02
5 (35, Female)	Control	42	2	44	0.11 ± 0.01				
	UMTS	82	12	94	0.23 ± 0.03	+109	<0.01		
	0.1 Gy	136	69	205	0.51 ± 0.08	+364	<0.01		
	0.1 Gy + UMTS	200	120	320	0.80 ± 0.12	+627	<0.01	+57	<0.02
	0.3 Gy	267	212	479	1.20 ± 0.12	+991	<0.01		
	0.3 Gy + UMTS	396	306	702	1.75 ± 0.13	+1491	<0.01	+46	<0.01
	0.5 Gy	535	368	903	2.26 ± 0.21	+1955	<0.01		
	0.5 Gy + UMTS	639	439	1078	2.69 ± 0.20	+2345	<0.01	+19	<0.03
6 (30, Male)	Control	15	2	17	0.04 ± 0.01				
	UMTS	56	5	61	0.15 ± 0.04	+275	<0.01		
	0.1 Gy	94	77	171	0.43 ± 0.07	+775	<0.01		
	0.1 Gy + UMTS	135	112	247	0.62 ± 0.11	+1450	<0.01	+44	<0.04
	0.3 Gy	142	127	269	0.67 ± 0.08	+1575	<0.01		
	0.3 Gy + UMTS	229	225	454	1.13 ± 0.14	+2725	<0.01	+69	<0.01
	0.5 Gy	256	223	479	1.20 ± 0.17	+2900	<0.01		
	0.5 Gy + UMTS	411	340	751	1.88 ± 0.20	+4600	<0.01	+57	<0.01

Aberr., aberrations; * probability of the "null hypothesis" for the difference between each exposed sample and the control/sham-exposed sample; ** probability of the "null hypothesis" for the difference between samples exposed to gamma + UMTS radiation and corresponding samples exposed only to gamma radiation; *** deviation of samples exposed to gamma + UMTS radiation from corresponding samples exposed only to gamma radiation.

sample of the same subject, exposed to gamma radiation 0.5 Gy and UMTS MT EMF (15 min) with four breaks (b), the two of them with fragments displaced toward the counter chromatid (short arrows), and three gaps (g).

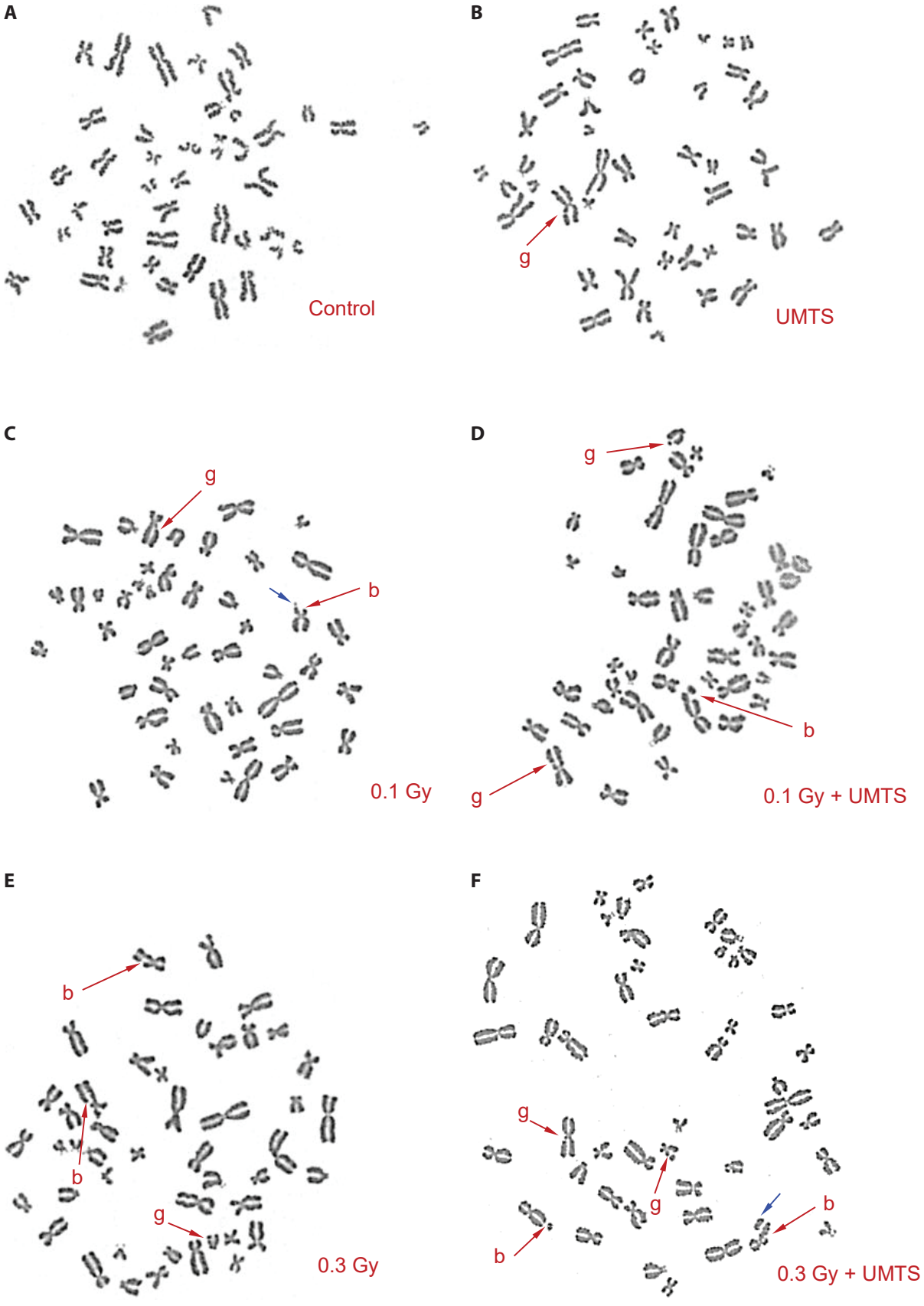
Figures 2B–2H are indicative of the damage caused in the chromosomes, in the form of chromatid gaps and breaks, by the various stressors examined (mobile phone EMF, 0.1, 0.3, 0.5 Gy gamma radiation, and the combination of the mobile phone EMF with the same gamma radiation doses).

Discussion

In a previous report of my experiments with HPBLs from the same donors, and under identical conditions and experimental procedures, it was shown that a single 15-min UMTS exposure alone at 1 cm distance from an active 3G/4G mobile phone during an active phone-call in "talk" mode, increased the chromatid-type aberrations from 100% up to 275% with respect to the control/sham-exposed samples (Panagopoulos 2019a). In the present study it was shown that gamma radiation at doses 0.1, 0.3, and 0.5 Gy increased chromatid-type aberrations in HPBLs of the same 6 healthy donors from 344% up to 2900% in a dose-dependent manner with respect to the control/sham-exposed samples. The same doses of gamma radiation combined with the 15-min UMTS exposure increased chromatid-type aberrations from 600% up to 4600% with respect to the control/sham-exposed samples. In other words, the combination of various doses of gamma radiation with a 15-min exposure to a 3G/4G mobile phone (with disabled Wi-Fi and Bluetooth functions) increased greatly and in some cases nearly doubled the effects of gamma radiation in all subjects. The number of aberrations induced by the combined exposure was significantly greater than the sum number of aberrations induced by the individual stressors in all subjects (Table 1). Thus, MT EMF exposure ~136 times below ICNIRP (2020) limits, apart from the fact that it is genotoxic by itself, significantly enhanced the genotoxic action of gamma radiation when the two stressors were combined. The synergistic action of MT EMF exposure and gamma radiation is in agreement with the findings of other studies that examined the combination of various types of WC EMFs with various types of ionizing radiation in a variety of biological models (Markkanen et al. 2004; Manti et al. 2008; Cao et al. 2009; Pesnya and Romanovsky 2013; Khodamoradi et al. 2022; Szilágyi et al. 2023). Since gamma radiation in similar doses is used for diagnostic and cancer treatment purposes, this result suggests that people/patients who are subjected to diagnostic or therapeutic treatment with ionizing radiation should be prudently advised by their oncologists/radiologists not to use their mobile/"smart" phones for a few days before, during, and after such treatments. Moreover, it becomes evident that medical/radiology practitioners should be specifically educated on the effects of anthropogenic EMFs in addition to those of ionizing radiations which are already part of their education. The biological/health effects of ionizing radiations are well known for more than a century. Nowadays there is an urgent need to address the effects of the "non-ionizing" anthropogenic EMFs which prevail today in everyday life compared to most (if not all) other stressors. Exploring more details of the already recorded effects is needed to be carried out by scientists without conflicts of interest. Although anthropogenic EMFs are not directly ionizing, they become ionizing and genotoxic indirectly in living tissue through the action of the ROS that generate in the living cells (Yakymenko et al. 2016; Panagopoulos et al. 2021, 2022b).

Apart from the increase in chromatid-type aberrations from 100% up to 275% due to the 15-min 3G/4G MT/WC EMF exposure (Panagopoulos 2019a, and Table 1), it was also shown previously that the corresponding increase induced by an extreme caffeine dose under identical conditions and experimental procedures ranged from 89% up to 250% (Panagopoulos 2020). Thus, it was shown that a single MT EMF exposure ~136 times lower than the most recent ICNIRP (2020) limit induced chromosomal aberrations in a slightly higher degree than a caffeine dose ~290 times higher than the permissible single caffeine dose for an adult human (Panagopoulos 2020). Assuming linearity for the effects of the UMTS EMF and the caffeine as the best possible approximation, and assuming the caffeine single dose limit to be correct (since the effects of caffeine on human organism are fast and evident in contrast to EMF-effects), this comparison suggested that, the exposure limits set for microwave EMFs by ICNIRP (2020) may be enormously less stringent (~136×290 or ~40000 times) than those for caffeine, and thus, should be lowered by (at least) ~40000 ($= 4\times10^4$) times.

In the present study, gamma radiation 0.1 Gy, (which as explained already is at least ~1000 times greater than a reasonable acute dose limit), induced an increase in chromatid-type aberrations from 344% up to 775% compared to the control samples which is (in an average) less than three times greater than the corresponding increase induced by the 15-min exposure to the mobile phone EMF with a power density ~136 times lower than the corresponding exposure limit (Table 1). Again, assuming linearity for the effects of the UMTS EMF and for those of the gamma radiation, and accepting the dose limit for gamma radiation as correct since its lethal effects are known for more than 120 years, this comparison suggests that the exposure limits set for microwave EMFs by ICNIRP (2020) may be enormously less stringent (~136×1000/3 or $\sim4.5\times10^4$ = 45000 times) than those for gamma radiation. This is very similar to the finding of my previous study deduced from comparison with caffeine (Panagopoulos 2020). Thus, in


A
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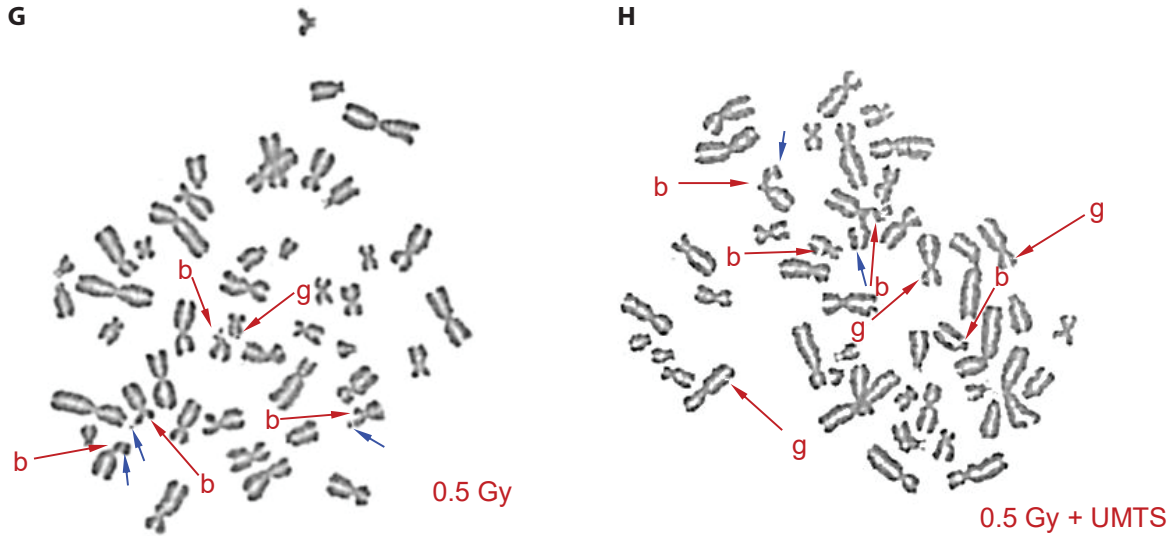

Figure 2. A. A metaphase from the Control (sham-exposed) blood sample of subject No. 6 (male) with all 46 chromosomes intact. **B.** A metaphase from the blood sample of the same subject exposed to UMTS MT EMF for 15 min with 1 achromatic lesion – gap (g). **C.** A metaphase from a blood sample of the same subject exposed to 0.1 Gy with 1 terminal deletion – break (b) with displaced fragment (short arrow), and 1 achromatic lesion – gap (g). **D.** A metaphase from a blood sample of the same subject exposed to combination of gamma radiation 0.1 Gy and UMTS MT EMF 15 min, with 1 terminal deletion – break (b), and 2 achromatic lesions – gaps (g). **E.** A metaphase from a blood sample of the same subject exposed to gamma radiation 0.3 Gy with 2 terminal deletions – breaks (b), and 1 achromatic lesion – gap (g). **F.** A metaphase from a blood sample of the same subject exposed to combination of gamma radiation 0.3 Gy and UMTS MT EMF 15 min, with 2 terminal deletions – breaks (b) (one isochromatid break and one with displaced fragment-short arrow), and 2 achromatic lesions – gaps (g). **G.** A metaphase from a blood sample of the same subject exposed to gamma radiation 0.5 Gy with 4 terminal deletions – breaks (b), the three of them with fragments displaced toward the counter chromatid (short arrows), and 1 achromatic lesion – gap (g). **H.** A metaphase from a blood sample of the same subject exposed to combination of gamma radiation 0.5 Gy and UMTS MT EMF 15 min, with 4 terminal deletions – breaks (b), the two with displaced fragments (short arrows), and 3 achromatic lesions – gaps (g).

order for the ICNIRP limits for WC EMF exposure to be compatible with the caffeine limit should be lowered by (at least) 40000 times, and in order to become compatible with the ionizing radiation limit should be lowered by (at least) 45000 times. These results suggest an impressive inadequacy of the ICNIRP limits for WC EMFs.

By lowering the 2020 ICNIRP limit of 4000 μW/cm^2 (for 2 GHz averaged for 6 min exposure) by 4×10^4 (or 4.5×10^4) times the limit would become 0.1 μW/cm^2 (or 0.08 μW/cm^2 which is very close) for short-term exposures. Thus, comparison with either caffeine or ionizing radiation dictates approximately the same limit for WC EMF short-term exposures (~0.1 μW/cm^2). By lowering this further by at least 100 for long-term exposures it becomes 0.001 μW/cm^2. These limits for short- and long-term exposures apart from the fact that they are compatible with both the caffeine consumption limit and the limit for ionizing radiation, are indeed relevant as protection limits according to experimental results in the EMF-bioeffects literature including also *in vivo* experiments (Panagopoulos et al. 2010; Panagopoulos 2019b, 2022a), and in agreement with limits suggested by other experts (see Table 3 in Belyaev et al. 2016).

It should be noted that while the average power density of the mobile phone was found to be ~136 times below the latest ICNIRP (2020) power density limit, the SAR level of the device is only ~3 times below the corresponding SAR limit (2 W/kg). This shows the discrepancy between the incident power density which can be directly and objectively measured by any credible EMF meter available in the market, and the SAR which refers to the absorbed power by the human tissue and is calculated by simplistic simulation methods utilizing human head models made of plastic and filled with water. Moreover, it shows the inadequacy of SAR as a meter for EMF bioactivity. While the power density (or radiation intensity) is independent of thermal or non-thermal effects, the SAR is applicable only to thermal effects, which in this case are totally insignificant (Gandhi et al. 2012; Panagopoulos et al. 2013, 2022a).

Like in the previous study which examined the combination of MT EMF exposure with a high caffeine dose, the present study showed that when the MT EMF was combined with gamma radiation the number of induced chromatid-type aberrations was dramatically increased compared to the effect of each stressor alone (Table 1, Fig. 1). The results of

the previous study (Panagopoulos 2020) showed that heavy coffee consumption combined with mobile phone use may significantly increase health risks and that the combination of two (or more) separate stressors (called co-stress condition) may have much greater biological effect than the sum of the individual effects of each stressor alone. Similarly, the results of the present study show that exposure to ionizing radiation combined with exposure to MT EMFs has much greater biological effect than the sum of the individual effects of each stressor alone. The effect of the combined stress being greater than the sum of the individual effects is probably due to the fact that the first stressor makes the organism weaker, and thus, more vulnerable to the second one than if the second stressor acted alone, in line with Knudson's famous "two-hit hypothesis" for carcinogenesis (Knudson 1971; Panagopoulos et al. 2022b).

Since anthropogenic EMF exposure at different frequency bands of the spectrum (RF, ELF, etc.) constitutes a new reality in daily life for everyone, its combination with a variety of other existing stressors on human/biological systems (such as development, aging, sickness, infections, ionizing radiation, chemicals, pharmaceuticals, smoking, coffee drinking, psychological stress, etc.) should be examined as a priority by future studies.

Like previous studies have shown that the effects of MT EMF exposure on humans/animals are dose-dependent and increase almost linearly with exposure duration (Panagopoulos and Margaritis 2010; El-Abd and Eltoweissy 2012; Panagopoulos 2020), the present study confirmed once again that the effects of gamma radiation are dose-dependent and increase with increasing doses (Prasad 1995; Nias 1998; Hall and Giaccia 2006). In previous studies of my group, exposure of fruit flies to 2G (GSM) mobile phone EMFs induced extensive DNA damage in the gametes leading to cell death and reproductive decline (Panagopoulos et al. 2007, 2010; Chavdoula et al. 2010; Panagopoulos 2012). Since DNA damage is converted into chromosomal damage during the early M phase of the cell division cycle (Terzoudi and Pantelias 2006; Pantelias and Terzoudi 2010; Terzoudi et al. 2011; Tian et al. 2018), the recorded chromosomal damage induced by the UMTS (3G/4G) MT/WC EMF and/or caffeine and/or gamma radiation, is evidently due to DNA damage caused by these stressors.

The recorded effects on HPBLs are in complete agreement with previous results of my group that found extensive DNA damage in fruit fly ovarian cells after *in vivo* exposure to GSM (2G) MT radiation from a mobile phone (Panagopoulos et al. 2007, 2010; Chavdoula et al. 2010; Panagopoulos 2012, 2019b), as well as with *in vivo* studies that found OS and genetic damage in HPBLs (Ji et al. 2004; Gulati et al. 2016; Zothansiama et al. 2017), showing once more that MT/WC EMFs are very genotoxic/bioactive, able to induce DNA damage and consequent chromosomal damage in both human and animal cells, *in vitro* or *in vivo*. This should be anticipated since cells are essentially the same in all animals (including humans), and all biological/health effects are initiated at the cellular level (Panagopoulos 2019b). It is important to note that the *in vitro* exposure of human blood cells to MT EMFs, and comparison either with caffeine or with gamma radiation exposure, dictates the same limit 0.1 $\mu W/cm^2$ for short-term exposures (and respectively 0.001 $\mu W/cm^2$ for long-term exposures) for MT/WC EMFs as the previous studies of my group based on *in vivo* animal exposures (Panagopoulos et al. 2010).

The main type of aberrations, induced by either MT EMF exposure, caffeine, or the combination of the two stressors, were chromatid gaps (achromatic lesions). Gamma radiation induced both gaps and breaks but in a higher degree than MT EMF or caffeine. Moreover, the percentages of breaks over gaps were significantly increased with exposure to gamma radiation and increased with increasing doses (Table 1). While chromatid breaks are more intense damages and easier to be recognized (Conger 1967), both gaps and breaks are damages of the same nature and, actually, gaps are incomplete breaks (Brecher 1977). While among many researchers working with ionizing radiation effects on chromosomes it has been accepted that only breaks (and not gaps) are "true" chromosome aberrations (Gileva 2002; IAEA 2011), my present and previous studies (Panagopoulos 2019a, 2020) have shown that under weaker clastogenic influences such as those from non-ionizing radiation and anthropogenic EMFs or caffeine, both breaks and gaps (total number of aberrations) should be counted in evaluating genotoxic effects. Ignoring the gaps and counting only the breaks, may be one of the reasons why certain previous studies did not find statistically significant effects of MT/WC EMFs in human blood lymphocytes, in addition to exposing during more resistant cell conditions (e.g. during the G_0 phase instead of during the cell division cycle and especially its most sensitive phases M, G_2), and to employing simulated MT/WC signals instead of real-life signals. For a review of such studies see Panagopoulos (2019a, 2020). Even though in the case of ionizing radiation the counting of breaks alone is enough to show the effects and the procedure of counting becomes a lot easier and faster, the counting of both gaps and breaks seems to be necessary for the cases of the milder clastogenic agents (such as non-ionizing and non-thermal EMF exposure or caffeine), and perhaps, even in the case of ionizing radiations, it would provide a more detailed and accurate estimate of the genetic damage.

The recorded chromatid-type aberrations induced by the MT EMF exposure is a non-thermal effect since it was not accompanied by any significant temperature increase of the exposed blood samples. The 0.1°C highest temperature increase during the 15 min exposures is absolutely insignificant as previously explained (Panagopoulos 2019a, 2020). The under deployment 5G technology with significantly higher

carrier frequencies up to 100 GHz, much denser antenna networks, and more intense and collimated radiation beams, is expected to induce significant thermal effects in addition to the non-thermal ones which may not be tolerated by the human/animal body (Neufeld and Kuster 2018; Hardell and Carlberg 2020; Panagopoulos et al. 2022a). This may represent a great threat to public health which the health authorities should carefully investigate before allowing 5G installation.

It is shown that real-life WC EMFs emitted by commercially available mobile phone devices, Wi-Fi routers, DECT phones, or base antennas/cell towers are by far more bioactive than simulated corresponding signals with invariable parameters emitted by generators (Panagopoulos et al. 2015a; Panagopoulos 2017, 2019b; Leach et al. 2018; Kostoff et al. 2020; McCredden et al. 2022, 2023). This is an additional reason why in some previous studies no effects of simulated MT EMFs on human lymphocytes were reported (Zeni et al. 2003, 2012; Stronati et al. 2006; Schwarz et al. 2008), while in my studies, in which a real 3G/4G WC EMF exposure was employed, a very intense effect was found (up to 275% increase in chromatid aberrations compared to the control samples). From six previous studies with human lymphocytes exposed to real-life MT EMFs (Ji et al. 2004; Gulati et al. 2016; Danese et al. 2017; Zothansiama et al. 2017; Panagopoulos 2019a, 2020), five found effects (Ji et al. 2004; Gulati et al. 2016; Zothansiama et al. 2017; Panagopoulos 2019a, 2020) in agreement with the majority of the lymphocyte studies, while one study (Danese et al. 2017) did not. This is the only study found in the literature employing real-life WC EMF exposure that reported no effect on human lymphocytes, and one of the very few on any biological model (Panagopoulos 2017, 2019b). In this study, in addition to other issues discussed before (Panagopoulos 2020), they exposed the cells during their resting G_0 phase, alike Stronati et al. (2006), instead of exposing them during the cell division cycle, and especially the most sensitive phases M, G_2 (Nias 1998; Terzoudi et al. 2011).

The studies that found real-life UMTS (3G/4G) exposure to be even more genotoxic than real-life GSM (2G) (D'Silva et al. 2017, 2021) are in line with the fact that newer types of MT/WC EMFs (3G, 4G, 5G) transmit increasingly higher amount/density of variable information (speech, text, images, video, Internet) making the signal increasingly complicated, unpredictably varying each moment, and thus, increasingly more bioactive due to the inability of the living organisms to adapt to a highly variable stressor. Thus, the effects of the under deployment 5G MT EMF are expected to be even more intense than those of 2G, 3G, 4G. This should have been seriously considered by the responsible public health authorities.

Since the health effects of all WC EMFs (including MT, Wi-Fi, DECT phones, Bluetooth wireless connections etc.) are of utmost importance in our days, studies should be conducted to test the most sensitive biological conditions with real-life exposures, and in combination with other environmental stressors, otherwise the results may be misleading in terms of public health protection. Exposures by any type of simulated signals and within any type of exposure chambers used to produce "uniform" exposures, such as "reverberation chambers" or "TEM chambers" (Ardoino et al. 2005; Wu et al. 2009) do not represent real-life exposure conditions and may produce misleading outcomes toward "no effect" findings (Panagopoulos 2019b, 2023). The use of generators and exposure chambers provided by companies for exposure of biological samples to simulated WC EMFs without knowing and measuring the physical details of the generated EMFs is a major problem in experimental studies (Panagopoulos 2023). The simulated WC EMFs with fixed parameters (intensity, frequency, pulsations, etc.) are in fact very different than the real-life extremely variable WC EMFs. The meaning of studying the effects of WC EMFs is to assess the biological action of the real-life WC EMFs and not of idealized simulated EMFs that produce smaller or no effects. Even in the cases that the experimenters want to test the bioactivity of certain parameters of the signal, and thus the use of idealized signals may be justified, the experimenters need to measure the signal details by themselves and not rely on what the manufacturer of such devices announces.

The disruption of cell electrochemical balance by man-made (polarized and coherent) EMFs through irregular gating of voltage-gated ion channels (VGICs) in cell membranes is described by the "ion forced-oscillation and VGIC dysfunction" mechanism (IFO-VGIC mechanism) (Panagopoulos et al. 2000, 2002, 2015b, 2021; Panagopoulos 2022b). According to this mechanism, the mobile ions in the cells are forced to oscillate in parallel and in phase with the applied man-made oscillating EMFs and this coordinated oscillation of electric charge exerts constructive Coulomb forces on the channel sensors of the VGICs similar to those exerted by membrane voltage changes that physiologically gate the VGICs. This causes irregular gating, and thus, dysfunction of the VGICs, which leads to intracellular release of ROS that finally cause genetic/cellular damage (Panagopoulos et al. 2021, 2022b). This is in line with the attribution of the DNA and chromosome damage to OS by El Abd and Eltoweissy (2012), the confirmed connection of anthropogenic EMF exposures with OS (Phillips et al. 2009; Pall 2013; Yakymenko et al. 2016), and the known effect of ROS on DNA and other cellular macromolecules (Barzilai and Yamamoto 2004). Although certain other studies have reported no connection between simulated WC EMF signals and OS (Poulletier de Gannes et al. 2011), today there is compelling evidence that man-made (including WC) EMF exposures, and mostly real-life exposures, induce a variety of biological/health effects which are in most, if not in all, cases

accompanied by OS (Yakymenko et al. 2016; Yakymenko and Tsibulin 2022b).

What has been referred to by Pall (2018) as voltage-gated calcium channel activation mechanism ("VGCC activation mechanism") is no other than the IFO-VGIC mechanism specifically on the calcium voltage-gated ion channels, and should not be reported as a different mechanism. Pall claimed he suggested a different mechanism simply because he hypothesized that the VGICs are gated by "direct" forces on their voltage-sensors by "penetrating" RF EMFs instead of ELF forces exerted by the oscillating ions in close proximity to the sensors. The impossibility of Pall's claims is analyzed in commentary papers (Foster and Balzano 2021; Panagopoulos 2021; Arribas et al. 2022).

Basic conclusions of the present study are: 1) MT EMF exposure, apart from the fact that it is genotoxic by itself, significantly enhanced the genotoxic action of gamma radiation in combined exposure; 2) People/patients who are subjected to diagnostic or therapeutic treatment with ionizing radiation should be prudently advised to avoid using WC devices for a few days before, during, and after such treatments; 3) Medical/radiology practitioners should be specifically educated on the risks of anthropogenic EMF-exposures in addition to those of ionizing radiations; 4) Comparison with caffeine and gamma radiation suggests that the ICNIRP (2020) limits for WC EMF exposure should be lowered by 40000 and 45000 times, respectively; 5) The limit for short-term (acute) exposure should then become 0.1 $\mu W/cm^2$ and accordingly for long-term exposure 0.001 $\mu W/cm^2$; 6) The combined effects of real-life man-made EMFs with a variety of other environmental stressors should be examined as a priority by next studies.

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Conflict of interest. The author declares no actual or potential competing financial interests.

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