MMW and biology - a research update

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Thanks to

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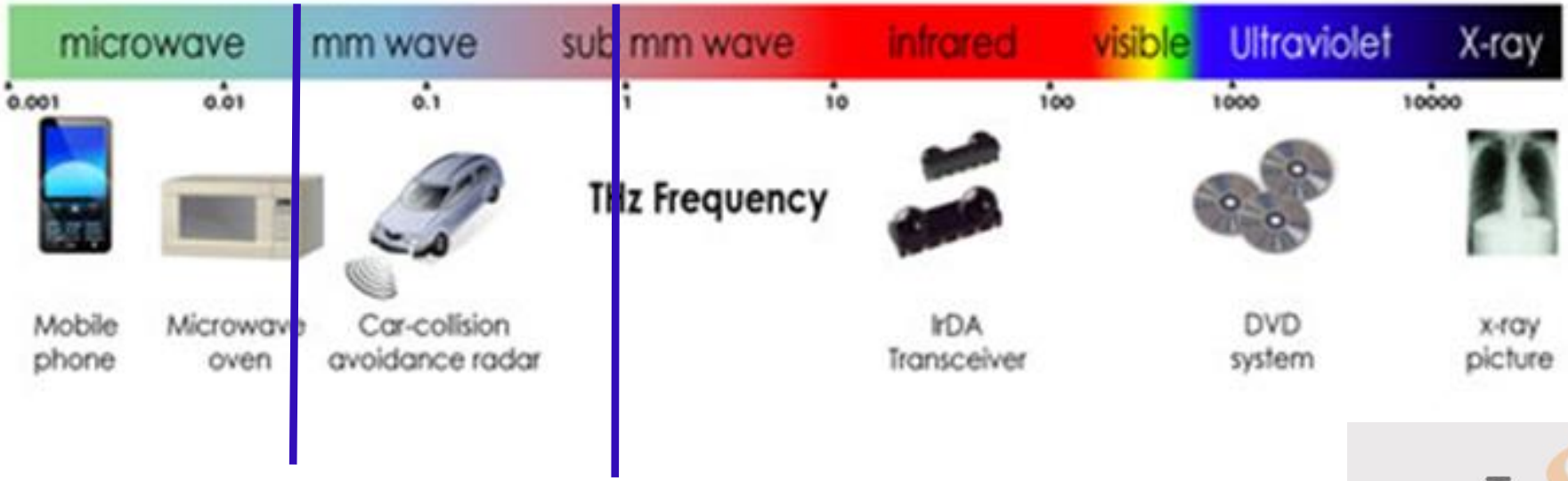
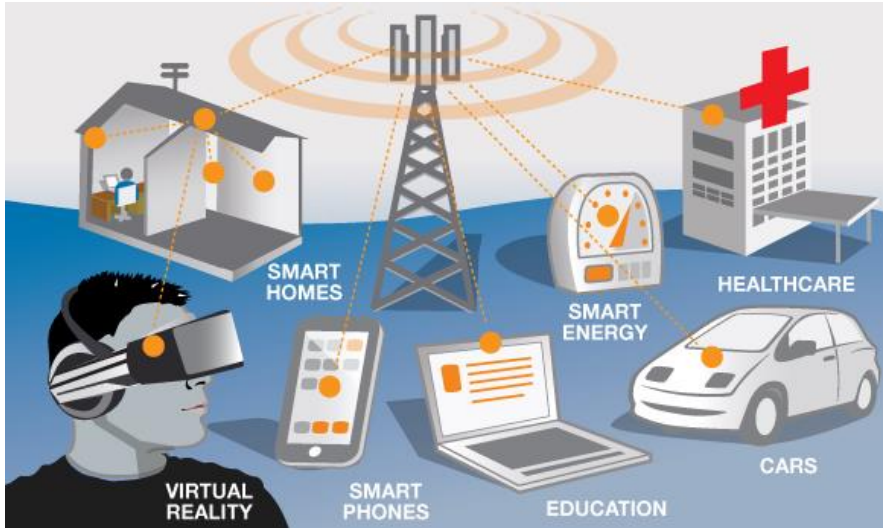
for providing me with most of the material used to set-up this presentation



30 GHz **100 GHz**

early deployment of 5G < 6 GHz (0.7 – 3.8)

now > 6 GHz (24.25 – 71)



The rationale for health risk evaluation

- It is assumed that human exposure to MMW will increase for general public & workers
- the question is if exposure to MMW (in this presentation 6-100 GHz) can induce health effects

These applications will operate with low power and, due to the small penetration depth of the radiation, human exposure pertains superficial tissues

Health risk evaluation

The study of biological effects is crucial to understand the mechanisms governing interactions between such fields and biological tissues, although a distintion must be made:

- **a biological effect** takes place when the exposure induces modifications of the physiological conditions of a biological system
- **a health effect** takes place when the induced biological effect exceeds the capability of the biological system to compensate the modifications

Biological and health effects are consistently different

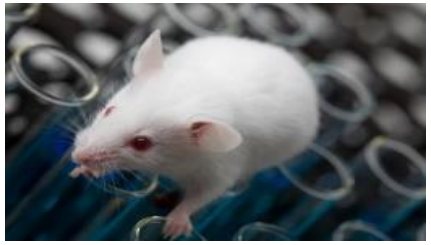
Health risk evaluation

Evaluating the database of studies at different levels

Population

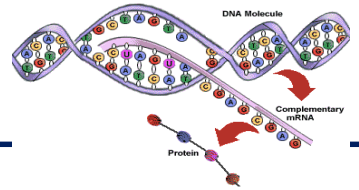
Epidemiological studies

Individual



***In vivo* - Animal and human experiments**

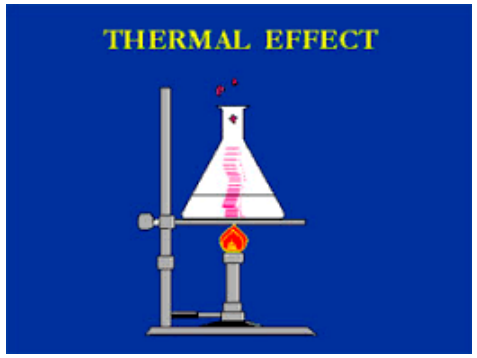
Tissues, cells and molecules



***In vitro* - Cell, biochemical and molecular investigations**

Extablished biological effects

Evident, replicated and consistent



Effects due to **thermal increase** are well understood and well accepted

Hydrated biological tissues strongly absorb radiation at MMW frequency

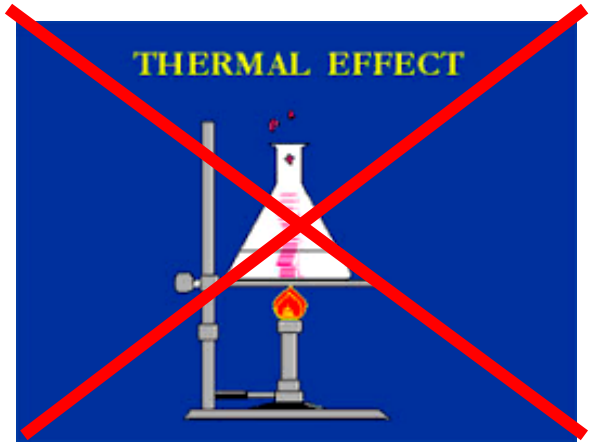
Common effects are tissue coagulation, structural protein damage, cell death, activation of intracellular stress response, and disruption of organelles function

They are acute in nature and occur above given exposure threshold

Therefore, appropriate dosimetry and temperature control are essential to determine the existence of non-thermal effects of MMWs

Non-thermal biological effects

The existence of pure electromagnetic bio-effects, strictly independent of temperature rise, is still controversial



They should provide support to the observed biological effects

but

hypotetical mechanisms have been postulated but not experimentally verified and validated

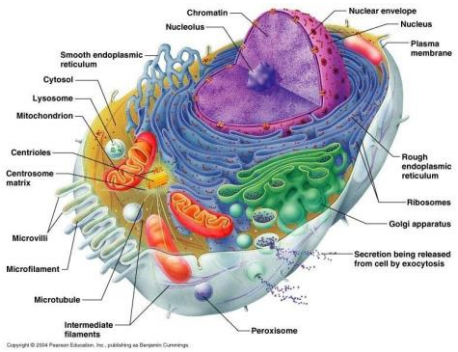
Hypotetical mechanisms of non-thermal interaction @ MMWs

- Analytical and numerical simulations suggest that **MMWs produce a highly non-uniform electric field distribution around the cells, with the highest field gradient concentrating at the plasma membrane**
  (*Liberti et al., IEEE Antennas Wireles Propag Lett, 2009)*

- Theoretical model has been developed that describes the **interaction of MMWs with biological membranes) that is supported by experimental studies on biomembranes**
  (Ramundo Orlando, J. Infrared, Millimeter, Terahertz Waves, 2010; Beneduci et al., Materials , 2013; Beneduci et al., Soft Matter, 2014)

- The **water dipoles are the key MMW absorbers** in biological tissues due to their abundance and high dielectric permittivity
  (Beneduci et al., 2008, in Bioelectrochem Res Develop, Nova Science, 2008)

MMWs – main results *in vitro*

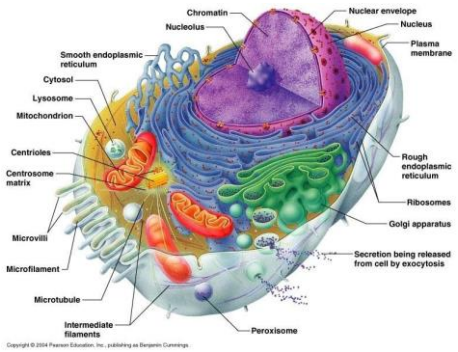


On different cell models **effects on neuronal activity, apoptosis, cell metabolism**, as well as **effects on genomic instability and genetic damage, cell proliferation** (antiproliferative effects) @ short exposures duration in the range 40-100 GHz and up to 60 mW/cm^2 PD

REFERENCES

Korenstein-Ilan, et al., 2008 *Radiat. Res.,* 170, 224–234
Romanenko et al.,2014 *J. Neurophysiol.*, 112, 2423–2431
Chidichimo et al.,2002 *Anticancer Res*., 22, 1681–1688.
Beneduci et al., 2007 *Bioelectrochemistry*, 70, 214–220
Beneduci et al., 2009 *Cell Biochem. Biophys*. 55, 25–32
Li et al., 2010 *Int. J. Mol. Med*. 25 393–399
Li et al., 2010 *Int. J. Mol. Med*. 26 77–84.
Li et al., 2012 *Int. J. Mol. Med*. 29 823–831

MMWs – main results *in vitro*

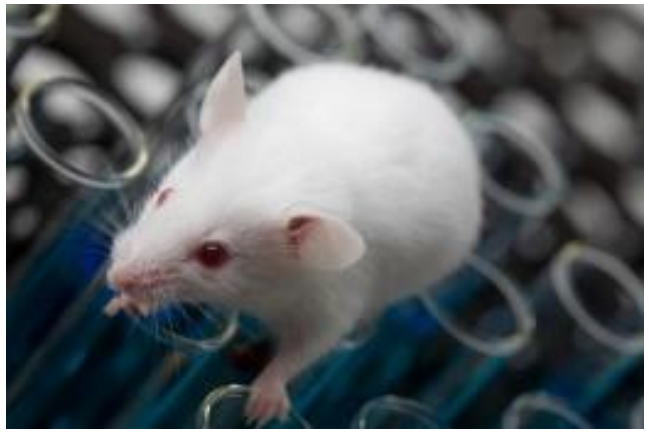


No effects in different cell models on **cell cycle, gene expression, genotoxicity, apoptosis@** exposures in the range 40-130 GHz and 0.3-20 mW/cm^2 PD

REFERENCES

Koyama et al., 2016, *Int. J. Environ. Res. Public Health,* 13, 802
Le Quément et al., 2012, *Bioelectromagnetics*, 33(2):147–158
Zhadobov et al., 2007, *Bioelectromagnetics*, 28(3):188–196
Beneduci et al., 2009, *Cell Biochem. Biophys*., 55, 25–32
Haas et al., 2016, *Neurosci. Lett*., 618, 58–65
Vijayalaxmi et al., 2004, *Radiat. Res.,* 161, 341–345
Zeni et al., 2007, *Health Phys*, 92(4), 349-57

MMWs – main results *in vivo*



Absence of genotoxicity @42.2 GHz at 31 mW/cm^2 PD

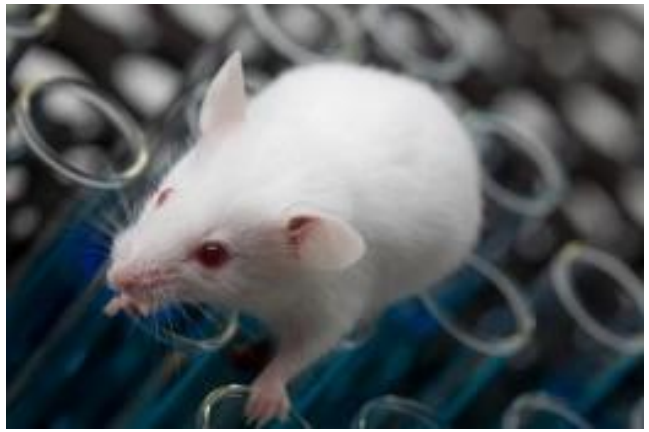
Reduction in tumor metastasis via activation of NK cells

Beneficial effects in cancer treatment

REFERENCES

Logani et al., 2004 *Radiat. Res.* 161(3):341–345
Logani et al., 2006 *Bioelectromagnetics*. 27: 258–264
Radzievsky et al., 2004 *Bioelectromagnetics* 25 466–473
Makar et al., 2005 *Bioelectromagnetics* 26 10–19

MMWs – main results *in vivo*



Using a model of local acute inflammation in mice, **anti-inflammatory actions** have been described @ 42-GHz at 0.1 mW/cm^2

These anti-inflammatory effects seem to be **strongly dependent on the frequency, intensity, and exposure duration**

REFERENCES

Logani et al., 2004 *Radiat. Res.* 161(3):341–345
Logani et al., 2006 *Bioelectromagnetics*. 27: 258–264
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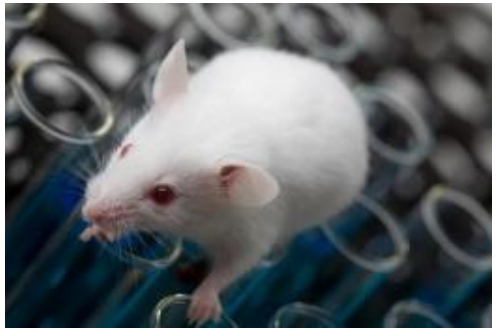
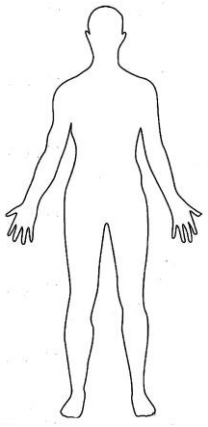
Makar et al., 2005 *Bioelectromagnetics* 26: 10–19

MMWs – main results *in vivo*



Evidences have been accumulated that MMW exposure @ 40-60 GHz is capable in **enhancing animal and human immune system,** and this is in line with the MMW biomedical applications mainly in Eastern Europe



Hypoalgesic effects were found in animals and humans with MMW exposures to acupuncture points, or by exposing skin areas with high nerve endings concentration. The **peripheral neural system is supposed to be the link between MMWs and pain treatment** (results by different labs under controlled conditions)

Investigations reviewed in:

Rojavin et al., 1998, *Q. J. Med*., 91(1), 57–66
Zhadobov et al.,2011, *Int. J. Microwave Wireless Technol*. 3(2), 237–247
Le Dréan et al., 2013, *Comptes Rendus Physique* 14(5), 402–411

Literature Review - Methods

PubMed - *https://www.ncbi.nlm.nih.gov/pubmed/*

EMF-Portal - *https://www.emf-portal.org/*

Both ***in vivo*** and ***in vitro*** studies have been considered

94 relevant publications identified and used for further analysis (no epidemiological studies)

Parameters recorded in a summary table:

Reference
Animal/tissue/cell (primary, cell line, health status)
Frequency, power density, SAR, exposure duration
Endpoint
Effect
Quality control (sham, dosimetry, positive control, blind, T°)

Literature Review - Results

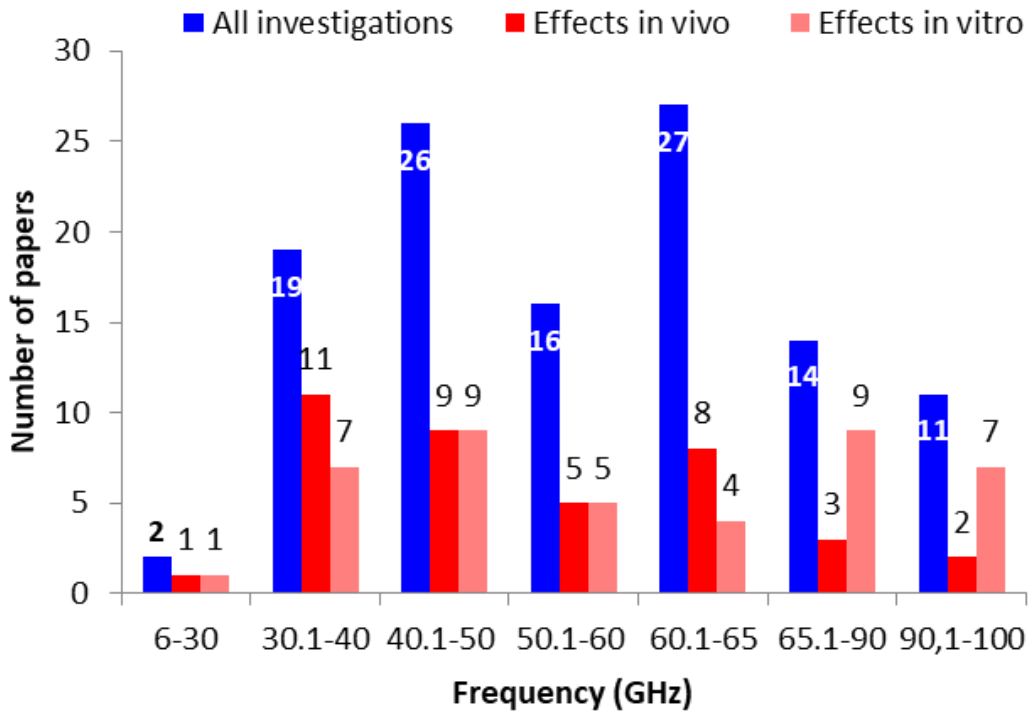
Publication type (n=94)	Total	No effects	Effects
In vivo	**45**	**10**	**35 (80%)**
In vitro	**53**	**22**	**31 (58%)**
-primary cells		6	18
-cell lines		16	13
Epidemiology	**0**		

To counteract thermal effect, cooling of the samples was present in several *in vitro* studies

Such cooling is not possible in *in vivo* studies

detrimental / beneficial effect

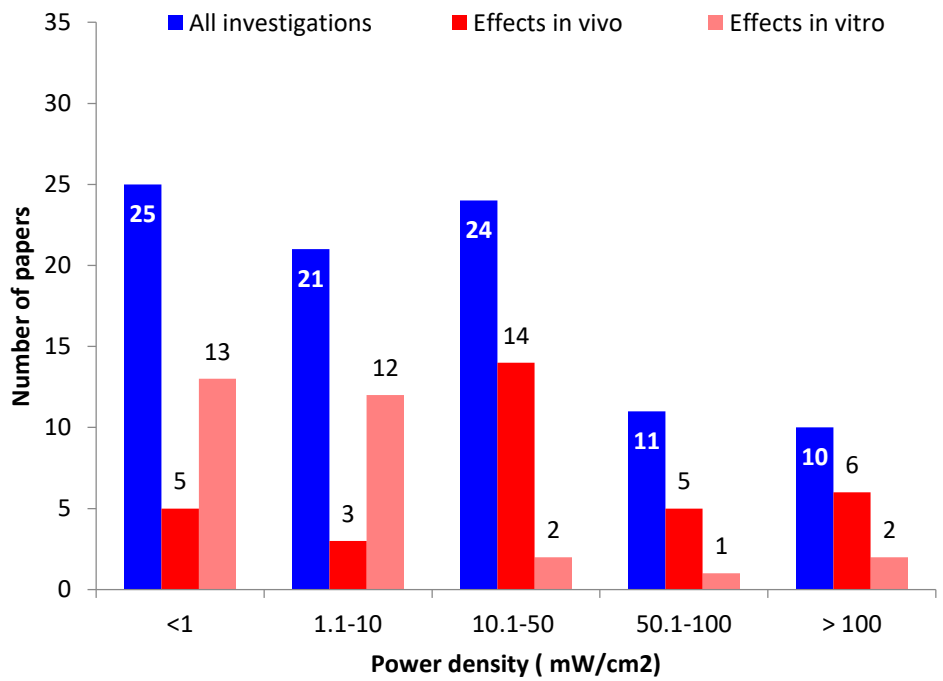
Literature Review – Results/frequency



In most cases, effects **independent from the frequency**

More than half of the studies performed in the frequency ranges 40.1 – 50 and 60.1 – 65 GHz, with a perspective on possible medical applications

Literature Review – Results/power density

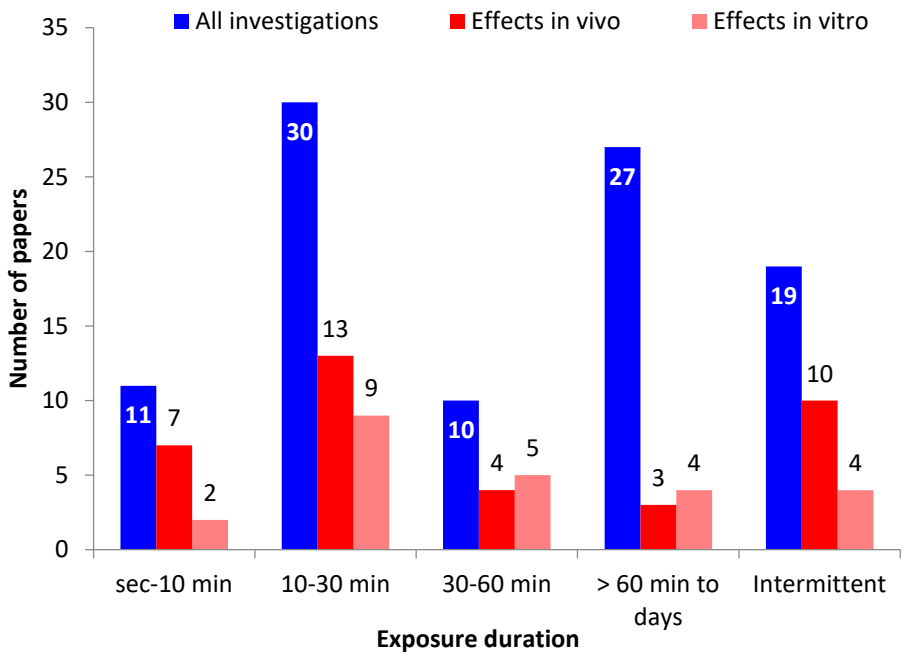


In most cases, effects **independent from the power density**

About half of the studies performed at or below 10 mW/cm^2.

The available data do not allow to conclude that higher power densities have larger effects

Literature Review – Results/exposure duration



In most cases, effects **independent from the exposure duration**.

in the group **> *60 minutes up to days*** lower response rates

(23/27 studies were *in vitro*, employing sample cooling, which can have affected the outcome, counteracting thermal effects)

Brief analysis of the results

A wide range of investigated end-points

- ✓ **In vivo** – most organ systems
- ✓ **In vitro** – cell proliferation, viability, cell cycle progression, morphology, DNA integrity, genotoxicity, gene and protein expression, protein function, cell signalling, metabolism, oxidative stress

Majority of studies indicate biological responses

No consistent correlation with exposure conditions (frequency, power density, exposure duration)

- reflecting real situation or result of publication bias?

- is heating the main reason for the observed effects?

Brief analysis of the results

- Most of the literature report on beneficial effects from low-level exposure

- Well-controlled and reproducible studies with an appropriate dosimetry are still needed to well characterize and quantify the biological effects of MMWs and their thresholds to discriminate the thermal and non-thermal effects

- Mechanisms still unknown

About quality

International Journal of *Environmental Research and Public Health*

MDPI

Review

Quality Matters: Systematic Analysis of Endpoints Related to "Cellular Life" in Vitro Data of Radiofrequency Electromagnetic Field Exposure

Myrtill Simkó [1,*], Daniel Remondini [2], Olga Zeni [3] and Maria Rosaria Scarfi [3]

Apoptosis & proliferation = *cellular life*

108 peer reviewed papers from 1995 to 2015

About 500 different experiments (EM and biological)

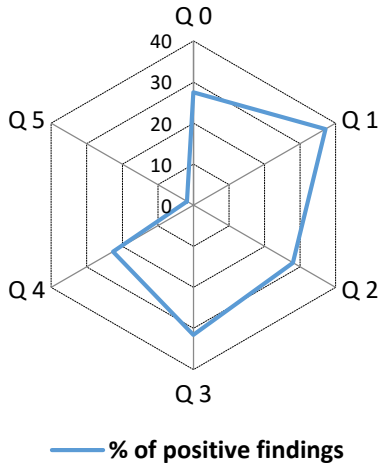
All responses (positive or negative) considered separately, independently on the size or direction

5 quality criteria (Q): sham, dosimetry, temperature measurement, blinded, positive control

The percentage of positive responses to RF exposure is between 22-37% in all experiments in which part of the quality criteria are satisfied.

The experiments where all criteria are satisfied have less than 2% positive responses (2 exp out of 109).

Fisher test: strongly significant association of positive outcomes and low-quality ($p=10^{-10}$) exists



The lower the quality, the higher the % of positive findings

To achieve their full potential, *in vivo* and *in vitro* studies must be well designed, taking care of both biological and EM aspects

Knowledge gaps and research recommendations

- Accurate **dosimetry** of the **skin** for relevant frequency ranges, including the consideration of short intense pulses (bursts).
- Investigations of **inflammatory reactions emanating** from the **skin** and associated tissues.
- *In vivo* studies on the influence of a **possible tissue temperature increase** (employing e.g. nude mice or hairless mice models).
- *In vivo* **dose-response studies** of heat development.
- Use of ***in vitro* models** (3D models) of the skin.
- Clarification of the question of **non-thermal effects** (*in vitro*).
- Questions regarding the **environmental impact** with possible consequences for human health.

Summary & conclusions

- The available studies do **not provide suffficient and adequate** information for meaningful safety assessment.
- The question about the possibility of **non-thermal effects can not be answered** as there are no relevant data.
- There is an **urgent need** for research in the fields of biomedicine and dosimetry.
- There are **major gaps in knowledge** regarding local heat development on small biological surfaces, e.g. on the skin or on the eye, which can lead to specific health effects.
- In order to make future studies more informative and relevant for safety assessment, **design and implementation must be significantly improved** (the presence of sham control and appropriate dosimetry and temperature controls are minimal requirements).

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9th International THz-Bio Workshop
April 30 - May 3, 2020
Erice, Sicily, Italy

Topics: Spectroscopic measurements on biological systems of increasing complexity, mechanisms of interaction and effects induced by the electromagnetic field, safety issues, technological developments of terahertz active & passive instrumentations and THz-Bio sensing & imaging

Co-chairs:

Gian Piero Gallerano, **ENEA-Frascati** ***and Olga Zeni,*** **CNR-IREA, Naples**

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Thank you !!!