Champs électromagnétiques et la maladie d'Alzheimer : un lien est-il possible ?

A. Maes, R. Anthonissen, H. Moukhliss, L. Verschaeve
WIV-ISP, Bruxelles

.be

Int. J. Epidemiol. Advance Access published February 2, 2008

International Journal of Epidemiology 2008;1–12
doi:10.1093/ije/dyn295

Occupational exposure to extremely low frequency electric and magnetic fields and Alzheimer disease: a meta-analysis

Ana M García,[1,2]* Antonio Sisternas[1,3] and Santiago Perez Hoyos[4]

Accepted 19 December 2007

Background Among potential environmental risk factors for Alzheimer disease (AD), occupational exposures have received some attention, including extremely low frequency electromagnetic fields (ELF-EMF). A systematic review and meta-analysis of published epidemiological studies on this subject was carried out.

Methods The search was concluded in April 2006. Bibliographic databases consulted included PubMed, EMBASE, Cochrane Library and NIOSHTIC2. Pooled estimates were obtained using random-effects meta-analysis. Sources of heterogeneity between studies were explored, as was publication bias.

Results Fourteen different studies (nine case-control and five cohort studies) accomplished inclusion criteria. All these studies followed standardized criteria for AD diagnosis and most of them obtained quantitative estimates of exposure. Pooled estimates suggest an increased risk of AD from case-control studies (OR_{pooled} 2.03; 95% CI 1.38–3.00) and from cohort studies (RR_{pooled} 1.62; 95% CI 1.16–2.27), with moderate to high statistical heterogeneity in both cases (respectively, $I^2 = 58\%$ and $I^2 = 54\%$). Cohort studies showed consistently increased risks for exposed men (RR_{pooled} 2.05; 95% CI 1.51–2.80, $I^2 = 0\%$). Evidence of dose–response relationship was not present. Test for publication bias suggests small study effects,

2

American Journal of Epidemiology Advance Access published November 5, 2008

DOI: 10.1093/aje/kwn297

Original Contribution

Residence Near Power Lines and Mortality From Neurodegenerative Diseases: Longitudinal Study of the Swiss Population

Anke Huss, Adrian Spoerri, Matthias Egger, and Martin Röösli for the Swiss National Cohort Study

Initially submitted May 5, 2008; accepted for publication August 25, 2008.

The relation between residential magnetic field exposure from power lines and mortality from neurodegenerative conditions was analyzed among 4.7 million persons of the Swiss National Cohort (linking mortality and census data), covering the period 2000–2005. Cox proportional hazard models were used to analyze the relation of living in the proximity of 220–380 kV power lines and the risk of death from neurodegenerative diseases, with adjustment for a range of potential confounders. Overall, the adjusted hazard ratio for Alzheimer's disease in persons living within 50 m of a 220–380 kV power line was 1.24 (95% confidence interval (CI): 0.80, 1.92) compared with persons who lived at a distance of 600 m or more. There was a dose-response relation with respect to years of residence in the immediate vicinity of power lines and Alzheimer's disease: Persons living at least 5 years within 50 m had an adjusted hazard ratio of 1.51 (95% CI: 0.91, 2.51), increasing to 1.78 (95% CI: 1.07, 2.96) with at least 10 years and to 2.00 (95% CI: 1.21, 3.33) with at least 15 years. The pattern was similar for senile dementia. There was little evidence for an increased risk of amyotrophic lateral sclerosis, Parkinson's disease, or multiple sclerosis.

dementia; neurodegenerative diseases; radiation, nonionizing

Abbreviations: ALS, amyotrophic lateral sclerosis; CI, confidence interval; ELF-MF, extremely low frequency magnetic field(s); ICD-10, *International Classification of Diseases, Injuries, and Causes of Death*, Tenth Revision.

Review

Applied Toxicology

Received: 18 March 2011, Revised: 11 July 2011, Accepted: 11 July 2011 Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI 10.1002/jat.1724

Can cytogenetics explain the possible association between exposure to extreme low-frequency magnetic fields and Alzheimer's disease?

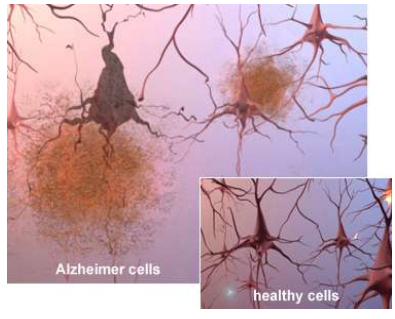
Annemarie Maes and Luc Verschaeve*

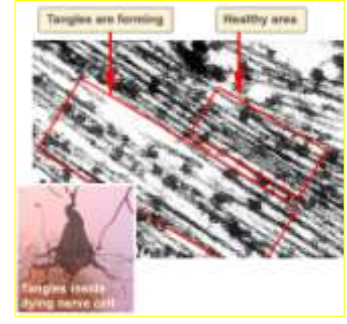
ABSTRACT: Recently, a number of epidemiological studies have suggested that occupational as well as residential exposure to extreme low-frequency electromagnetic fields (ELF-EMFs) may be a risk factor for Alzheimer's disease. This is not proven yet and there are no known biological mechanisms to explain this alleged association. Alzheimer's disease is characterized by a number of events that have, at least partially, a genetic origin. In particular, trisomy of chromosomes 17 and 21 seems to be involved. Overall ELF-EMFs have not been identified as genotoxic agents, but there are some papers in the scientific literature that indicate that they may enhance the effects of agents that are known to induce mutations or tumors. There are also some indications that ELF-EMFs may induce aneuploidy. This opens some perspectives for investigating the alleged association between ELF-EMFs and Alzheimer's. This paper reviews the possibility of a cytogenetic association between the electromagnetic fields and Alzheimer's disease. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: electromagnetic fields; ELF; Alzheimers disease; aneuploidy; genomic instability

BBEMG

isp wiv





Plaques : Amas de peptides amyloïde β entre les neurones (chromosome 21)

Tangles : Protéine Tau – Stabilise le transport intracellulaire, maintenant perturbé (chromosome 17)

Alzheimer's vs. ELF

Maladie d' Alzheimer

Amyloide-β ↑

Mélatonine ↓ ↓

Altérations de l'ADN

Directes ou indirectes ?

Amplification génique (?)

Perturbation de la division cellulaire ?

Trisomie (?)

Exposition aux ELFs

Amyloide-β ↑ (?)

Mélatonine ↓ (?)

Effets directs sur l'ADN???

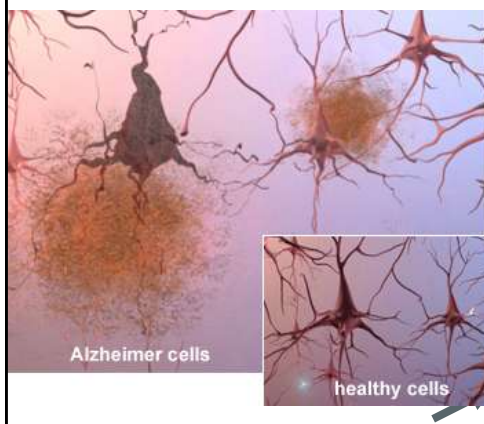
- ADN (cassures d'un ou deux brins) – Effets sur le cerveau
- (indirect) Co-mutagène ??

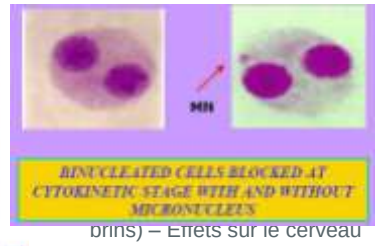
Amplification génique ???

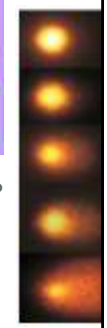
Perturbation de la division cellulaire?

Trisomie?

Alzheimer's vs. ELF







brins) – Effets sur le cerveau

- (indirect) Co-mutagène ??

mplification génique ???

erturbation de la division ellulaire?

risomie?

Available online at www.sciencedirect.com
ScienceDirect
Neuroscience Letters 418 (2007) 9–12
Neuroscience Letters
www.elsevier.com/locate/neulet

Fifty Hertz electromagnetic field exposure stimulates secretion of β-amyloid peptide in cultured human neuroglioma

Elda Del Giudice[a,1], Fabrizio Facchinetti[a,1], Valentina Nofrate[a,b,1], Pasquale Boccaccio[c], Tullio Minelli[b], Mauro Dam[d], Alberta Leon[a,d,*], Giuliano Moschini[b,c]

[a] Research & Innovation (R&I) Company, Padova, Italy
[b] Physics Department, University of Padova, Italy
[c] National Institute of Nuclear Physics (INFN), National Laboratories of Legnaro, Padova, Italy
[d] San Camillo Hospital, IRCCS, Lido, Venezia, Italy

Received 9 November 2006; received in revised form 30 January 2007; accepted 23 February 2007

Abstract

Recent epidemiological studies raise the possibility that individuals with occupational exposure to low frequency (50–60 Hz) electromagnetic fields (LF-EMF), are at increased risk of Alzheimer's disease (AD). However, the mechanisms through which LF-EMF may affect AD pathology are unknown. We here tested the hypothesis that the exposure to LF-EMF may affect amyloidogenic processes. We examined the effect of exposure to 3.1 mT 50 Hz LF-EMF on Aβ secretion in H4 neuroglioma cells stably overexpressing human mutant amyloid precursor protein. We found that overnight exposure to LF-EMF induces a significant increase of amyloid-beta peptide (Aβ) secretion, including the isoform Aβ 1–42, without affecting cell survival. These findings show for the first time that exposure to LF-EMF stimulates Aβ secretion in vitro, thus alluding to a potential link between LF-EMF exposure and APP processing in the brain.

Keywords: Electromagnetic fields; Alzheimer's disease; Amyloid precursor protein; Neuron; Amyloidogenesis; Occupational risk

Melatonin Secretion Rhythm Disorders in Patients with Senile Dementia of Alzheimer's Type with Disturbed Sleep–Waking

Kazuo Mishima, Tozawa Tozawa, Kohtoku Satoh, Yasuhiro Matsumoto, Yasuo Hishikawa, and Masako Okawa

Background: *There is growing evidence that the dysregulation of circadian rhythms may play an important role in irregular sleep–waking in demented elderly. In this study, we investigated daily variation of the pineal hormone melatonin, which has been reported to possess hypnogenic and synchronizing effects, in patients with senile dementia of Alzheimer's type.*

Methods: *Serum melatonin secretion rhythms in inpatients with senile dementia of Alzheimer's type (SDAT group, n = 10, average age = 75.7 years) with disturbed sleep–waking and nondemented elderly (ND group, n = 10, age = 78.3 years) without clinical sleep disorders in the same facility were monitored under a dim light condition without excessive physical exercise.*

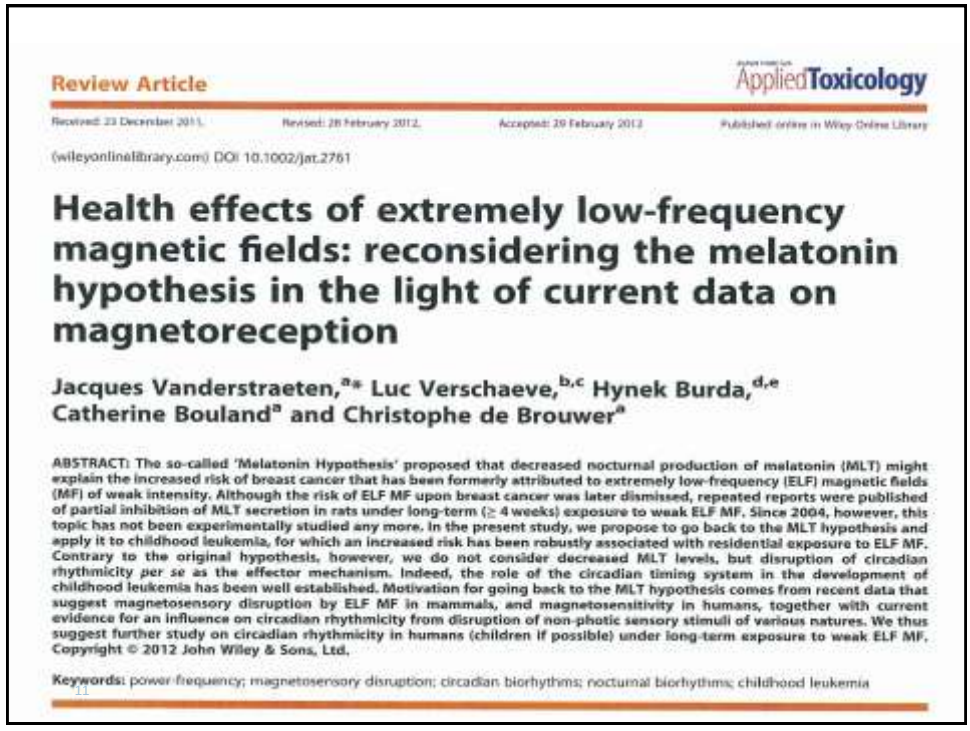
Results: *The SDAT group showed a significantly higher degree of irregularities in actigraphically recorded rest–activity (R–A) rhythm during the 7-day baseline period compared with the ND group. The SDAT group simultaneously showed significantly reduced amplitude, larger variation of peak times, and diminished amount of total secretion in the melatonin secretion rhythm compared with the ND group. There were significantly positive correlations between the severity of R–A rhythm disorder and the reduced amplitude as well as diminished amount of total melatonin secretion.*

Conclusions: *The SDAT patients with disturbed sleep–waking possessed melatonin secretion rhythm disorders that may play an important role in irregular sleep–waking in demented elderly.* Biol Psychiatry 1999;45: 417–421 © *1999 Society of Biological Psychiatry*

Introduction

Many previous reports have suggested that the demented elderly often have a dysregulation of the circadian time-keeping system, which is manifested as disorganized daily overt rhythms of various physiological functions (Dori et al 1994; Nadal et al 1994; Okawa et al 1991; Mishima et al 1997a; Satlin et al 1991; Touitou et al 1986). There is growing evidence that the dysregulation of circadian rhythms may play an important role in irregular sleep–waking and the accompanying behavioral disorders often observed in demented elderly (Aharon-Peretz et al 1991; Okawa et al 1991; Swaab et al 1985; Witting et al 1990). Findings that bright light exposure, which acts as a powerful synchronizer of human circadian rhythms, exhibited significant therapeutic effect for sleep and behavioral disorders in demented elderly support this assumption (Mishima et al 1994; Satlin et al 1992).

Pineal hormone melatonin has been reported to possess synchronizing and hypnogenic actions in human (Dollins et al 1994; Lewy et al 1992; McArthur et al 1991; Mishima et al 1997b;) and is considered to relate to human sleep–waking regulation. The aim of this study is to evaluate the properties of melatonin secretion rhythm under a dim light condition and without excessive physical exercise to exclude masking effects on melatonin rhythms by these factors in patients with senile dementia of Alzheimer's type (SDAT) with disturbed sleep–waking confirmed by continuous monitoring of wrist rest–activity



Review Article

Applied Toxicology

Received: 23 December 2011, Revised: 28 February 2012, Accepted: 29 February 2012 Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/jat.2761

Health effects of extremely low-frequency magnetic fields: reconsidering the melatonin hypothesis in the light of current data on magnetoreception

Jacques Vanderstraeten,[a]* Luc Verschaeve,[b,c] Hynek Burda,[d,e] Catherine Bouland[a] and Christophe de Brouwer[a]

ABSTRACT: The so-called 'Melatonin Hypothesis' proposed that decreased nocturnal production of melatonin (MLT) might explain the increased risk of breast cancer that has been formerly attributed to extremely low-frequency (ELF) magnetic fields (MF) of weak intensity. Although the risk of ELF MF upon breast cancer was later dismissed, repeated reports were published of partial inhibition of MLT secretion in rats under long-term (≥ 4 weeks) exposure to weak ELF MF. Since 2004, however, this topic has not been experimentally studied any more. In the present study, we propose to go back to the MLT hypothesis and apply it to childhood leukemia, for which an increased risk has been robustly associated with residential exposure to ELF MF. Contrary to the original hypothesis, however, we do not consider decreased MLT levels, but disruption of circadian rhythmicity *per se* as the effector mechanism. Indeed, the role of the circadian timing system in the development of childhood leukemia has been well established. Motivation for going back to the MLT hypothesis comes from recent data that suggest magnetosensory disruption by ELF MF in mammals, and magnetosensitivity in humans, together with current evidence for an influence on circadian rhythmicity from disruption of non-photic sensory stimuli of various natures. We thus suggest further study on circadian rhythmicity in humans (children if possible) under long-term exposure to weak ELF MF.

Keywords: power frequency; magnetosensory disruption; circadian biorhythms; nocturnal biorhythms; childhood leukemia

11

BBEMG

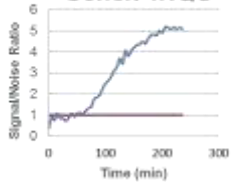
isp wiv

Effets coopératifs des CEM-TBF (50 Hz) avec des mutagènes/cancérogènes connus

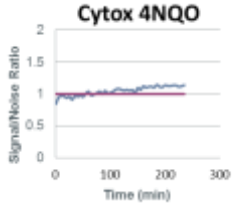
12

.be

Genox 4NQO

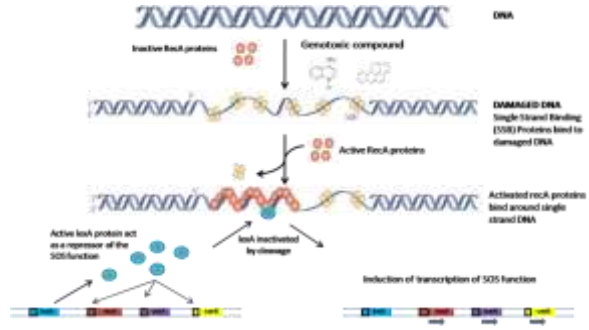


Cytox 4NQO



Vitotox test:Salmonella typhimurium

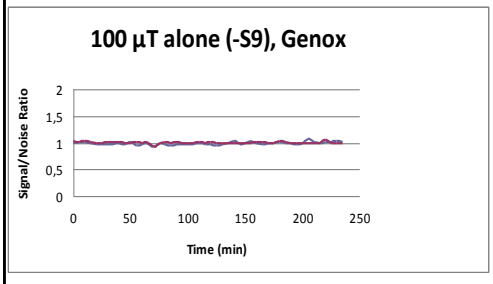
Verschaeve et al. 1999. **Environ. Molec.Mutagen**. 33, 240-248.

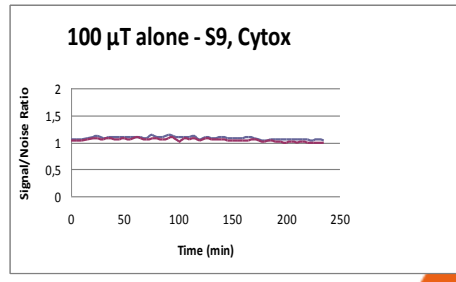


13

.be

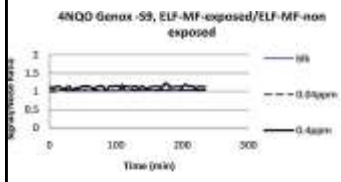
Champs ELF (100 µT – 500 µT) seuls : pas d'effet
exposition combinée : idem

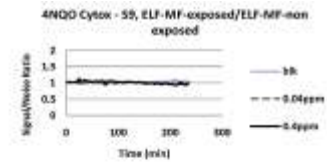


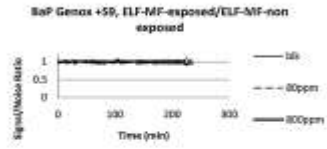


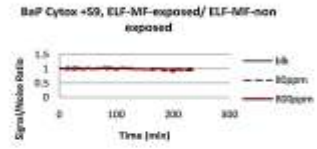
14

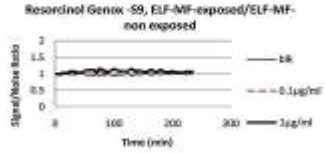
.be

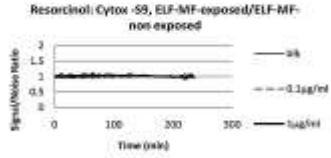


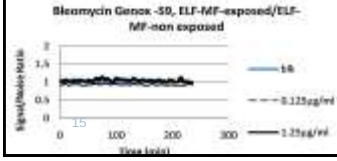


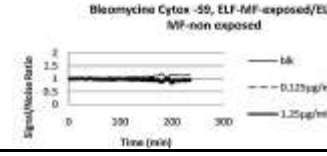












Verschaeve L., Anthonissen R., Gevaert L., Maes A. (2011) Genotoxicity investigation of ELF-magnetic fields in Salmonella typhimurium with the sensitive SOS-based VITOTOX test. **Bioelectromagnetics** 32:580-584.

Verheyen G., Pauwels G., Verschaeve L., Schoeters G. (2003) The effect of co-exposure of 50 Hz magnetic fields and an aneugen on human lymphocytes, determined by the cytokinesis-block micronucleus assay. **Bioelectromagnetics**, 24, 160-164.

15

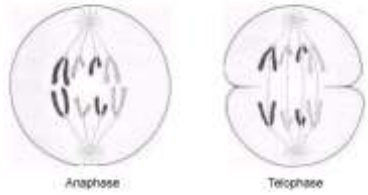
.be

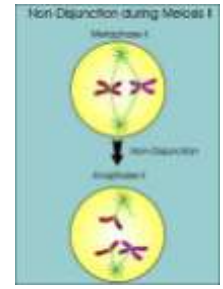
Effets génétiques indirects: effets sur la division cellulaire, l'amplification génique et la trisomie …

16

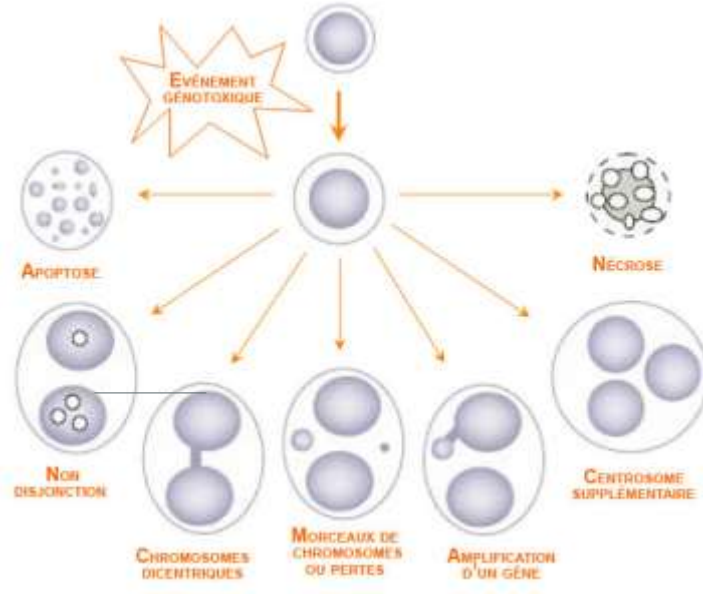
.be


Prophase
Metaphase

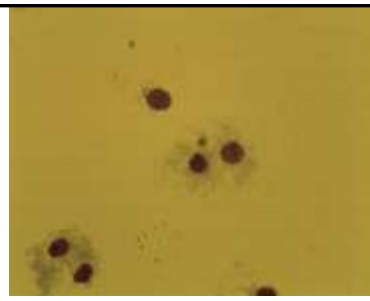

Anaphase
Telophase

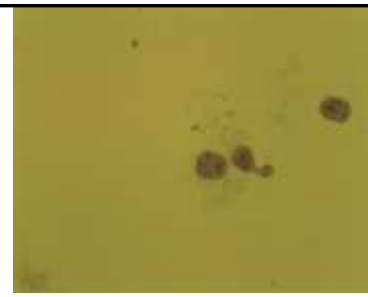

Non-Disjunction during Meiosis II

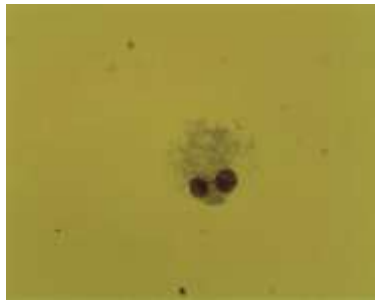
17


Evénement génotoxique
Apoptose
Nécrose
Non disjonction
Chromosomes dicentriques
Morceaux de chromosomes ou pertes
Amplification d'un gène
Centrosome supplémentaire

18





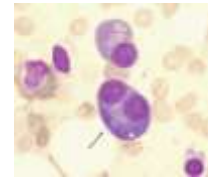


Maes A., Anthonissen R., Verschaeve L. (2012)
Testing chemicals with the cytokinesis-block micronucleus *cytome assay*.
Folia Biol., 58, 215-220.

19

.be

Expositions

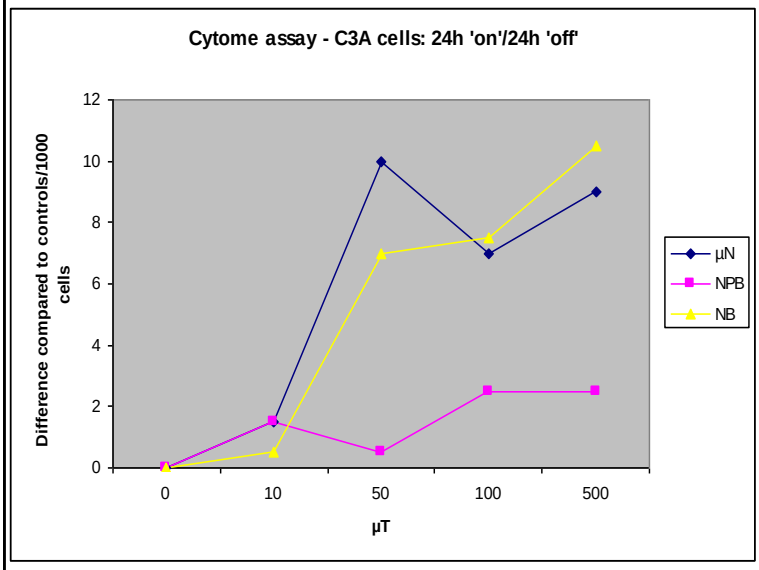


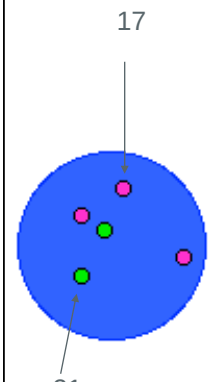
- Exposition continue de 48h
- Exposition 24h suivie de 24h de récupération
- Exposition après 48h

Cellules C3A (ce*llules du foie humain*)
Cellules SH-SY5Y (*neuroblastome humain*)
Cellules IMR-32 (*neuroblastome humain*)

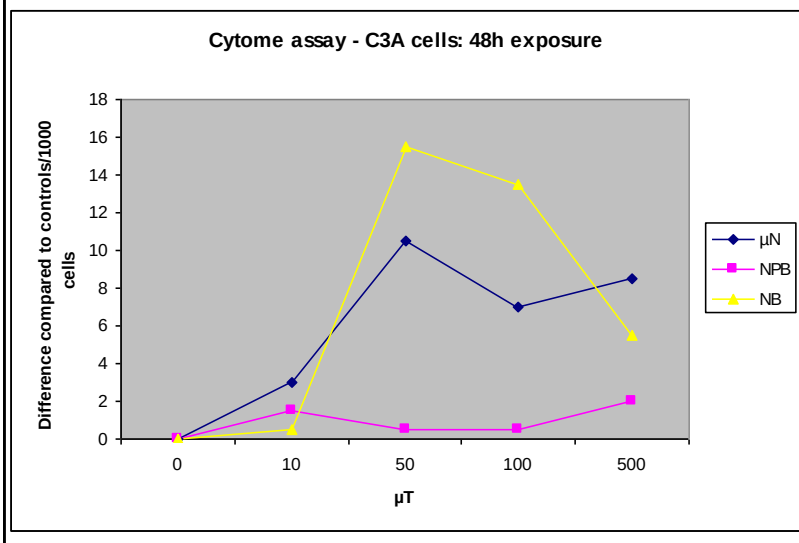
20

.be



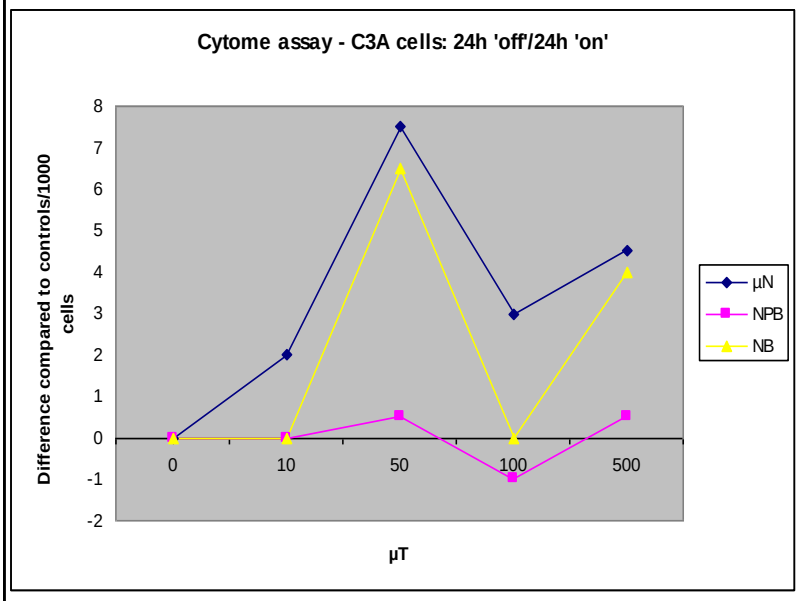


21

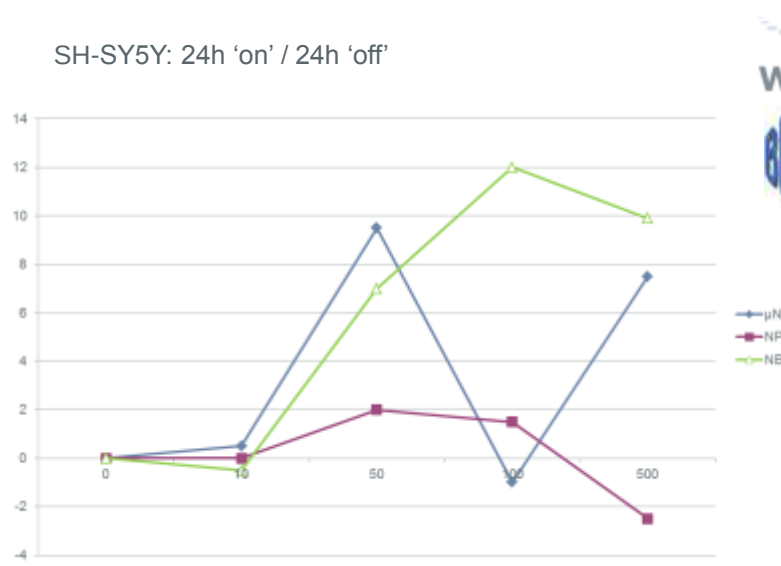


µN = cellules avec micronoyau(x); NPB = avec pont(s) nucléoplasmique(s); NB = avec 'bud(s)' nucléaire (s)

22

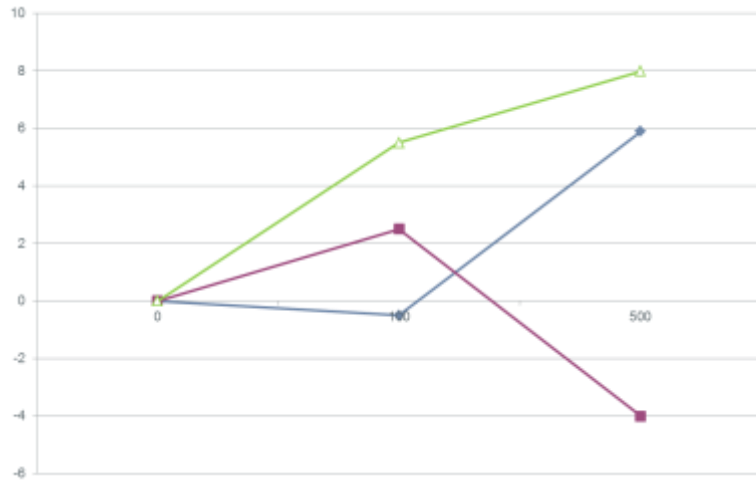

Cytome assay - C3A cells: 24h 'off'/24h 'on'
Difference compared to controls/1000 cells
8
7
6
5
4
3
2
1
0
-1
-2
0
10
50
100
500
µT
µN
NPB
NB

23

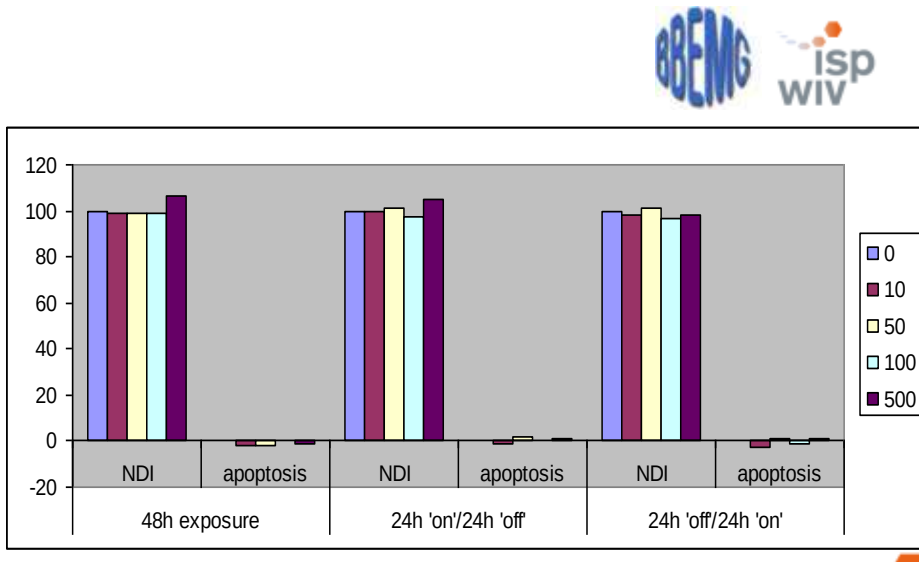

SH-SY5Y: 24h 'on' / 24h 'off'
14
12
10
8
6
4
2
0
-2
-4
0
50
500
µN
NPB
NB
Réponse non-monotonique !

24

SH-SY5Y : 48h ‘on’



25



Index de division cellulaire et apoptose

26

Conclusion provisoire

✓ Absence d'indication claire d'un effet coopératif des CEM-ELFF et des mutagènes chimiques (test Vitotox)
✓ Induction de micronoyaux (larges) et de 'buds' suggérant un effet indirect sur la division cellulaire et l'amplification génique
✓Absence d'effet clair sur la prolifération cellulaire (indice de division) et l'apoptose (mortalité programmée)
✓Pas d'effet spécifique à un type cellulaire précis (?)

Ces résultats montrent qu'une exposition *in vitro* aux CEM-ELF *peut avoir des effets comparables à ceux que l'on trouve dans des cellules de patients avec la maladie d'Alzheimer. Mais les résultats ne prouvent aucun lien certain à ce jour !*

27

.be

Original Contribution

Residential Distance to High-voltage Power Lines and Risk of Neurodegenerative Diseases: a Danish Population-based Case-Control Study

Patricia Frei, Aslak Harbo Poulsen*, Gabor Mezei, Camilla Pedersen, Lise Cronberg Salem, Christoffer Johansen, Martin Röösli, and Joachim Schüz

* Correspondence to Aslak Harbo Poulsen, Danish Cancer Society Research Center, Danish Cancer Society, Strandboulevarden, 2100 Copenhagen Ø, Denmark (e-mail: aslak@cancer.dk).

Initially submitted March 22, 2012; accepted for publication July 23, 2012.

The aim of this study was to investigate the possible association between residential distance to high-voltage power lines and neurodegenerative diseases, especially Alzheimer's disease. A Swiss study previously found increased risk of Alzheimer's disease for people living within 50 m of a power line. A register-based case-control study including all patients diagnosed with neurodegenerative diseases during the years 1994–2010 was conducted among the entire adult population of Denmark. Using conditional logistic regression models, hazard ratios for ever living close to a power line in the time period 5–20 years before diagnosis were computed. The risks for developing dementia, Parkinson's disease, multiple sclerosis, and motor neuron disease were not increased in persons living within close vicinity of a power line. The risk of Alzheimer's disease was not increased for ever living within 50 m of a power line (hazard ratio = 1.04, 95% confidence interval: 0.68, 1.59). No dose-response according to number of years of living within 50 m of a power line was observed, but there were weak indications of an increased risk for persons diagnosed by the age of 75 years. Overall, there was little support for an association between neurodegenerative disease and living close to power lines.

dementia; environmental exposure; magnetic fields; neurodegenerative diseases

28

.be

MERCI

Roel

Annemarie

Hind

Luc