Extreem lage frequente elektromagnetische velden

effecten op de gezondheid: stand van zaken

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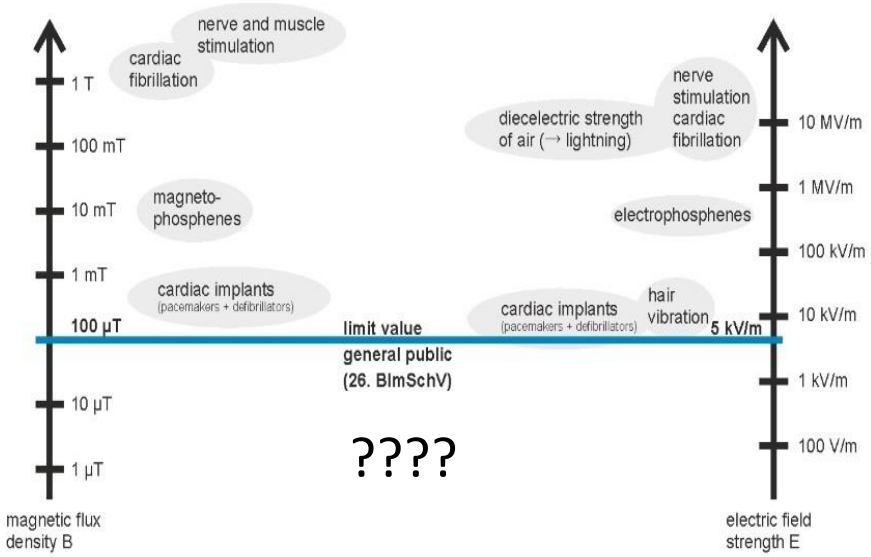
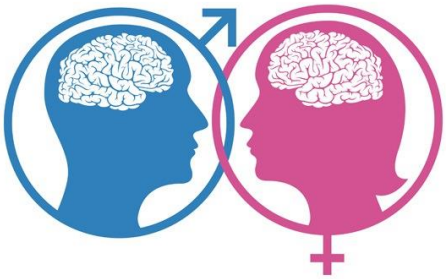


ELF (< 300 kHz)

- Kan men zich aan biologische effecten verwachten?

(< 300V/m et <50µT)

-Niet ioniserend
-Geen verbreking van chemische bindingen
-Geen rechtstreekse DNA schade = geen rechtstreeks genetisch of carcinogeen effect
-Veldsterkten/amplitude <<< gekende electrofysiologische mechanismen (vb. afwijkingen t.h.v. de celmembraan)



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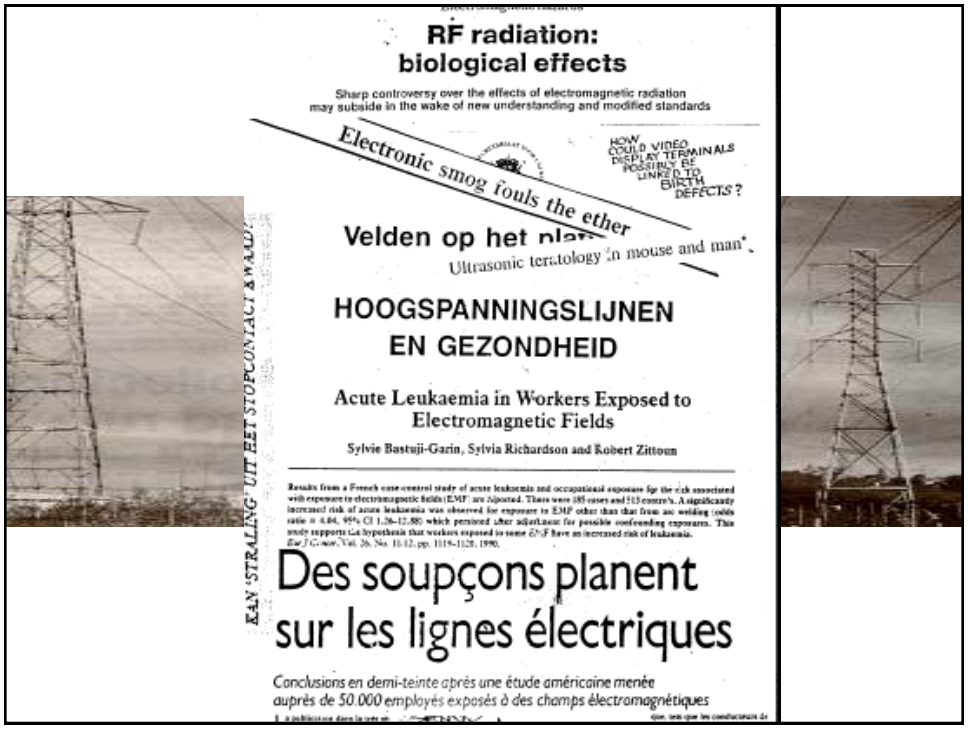
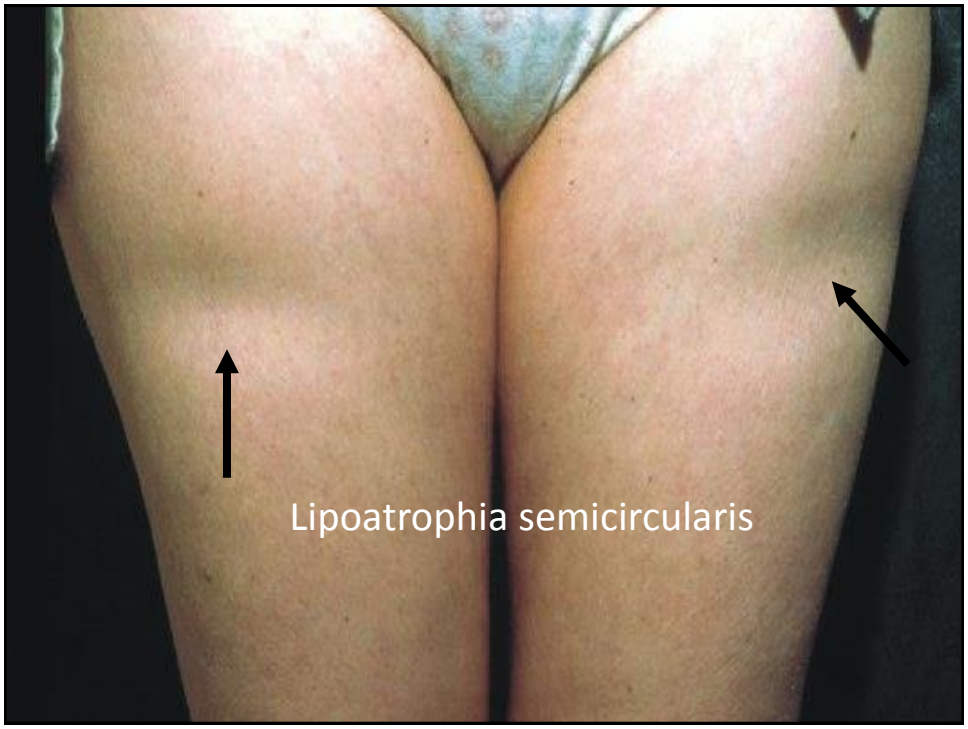


Professor Ivan BEALE of the Auckland University has linked high tension power lines... already assocated with higher rates of leukaemia among children...to asthma and depression in adults. People living within a 20m shadow of high voltage lines are three times as likely to suffer from asthma and twice as likely to have major depression. Researchers believe the danger levels drop rapidly outside the 20m zone. The study also indicates that people have a higher incidence of diabetes and are twice as likely to suffer from immune related illnesses such as allergies

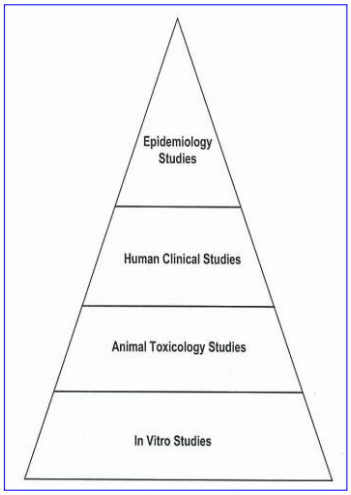


STATE OF THE ART: veel beweringen, weinig zekerheden:

De studie van de biologische effecten van elektromagnetische stralen is een gecompliceerd en zeer breed onderzoeksdomein dat een pluridisciplinaire benadering vereist. Deze complexiteit kan de zeer langzame evolutie van onze kennis ter zake en de persistentie van vele onbekenden verklaren.

1. Verschillende types biologische onderzoeken hebben ieder hun specificiteit, voor- en nadelen

In vitro – in vivo – humaan experimenteel – epidemiologisch



- A single study can form the basis of an hypothesis, but does not provide the basis for hazard identification.
- Confirmation of the results of any study are needed through replication and/or supportive studies.
- The resulting body of evidence forms the basis for science-based judgments by defining exposure levels for
  - adverse health effects and
  - no observable adverse effects.

2. Verschillen in biologisch 'substraat'.

Resultaten kunnen afhangen van het type weefsel dat bestudeerd wordt; bv. de elektrische en magnetische eigenschappen van de weefsels kunnen van het ene weefsel tot het andere verschillen (elektrische geleidbaarheid, permeabiliteit, e.d.), de oriëntatie van het organisme t.o.v. de velden kan ook belangrijk zijn, in sommige gevallen de grootte van het organisme e.d.

3. Verschillen in geassocieerde factoren

Biochemische factoren, zoals de aan- of afwezigheid van een chemische stof of polluent in het lichaam/de cellen (medicatie, verontreinigende stof) of een fysiologische alteratie (eventueel ziekte) kunnen de gevoeligheid aan de velden beïnvloeden. In sommige gevallen werden geen effecten vastgesteld in normale gezonde cellen of organismen maar wel in cellen die op een of andere manier 'uit evenwicht' waren (geïnfecteerd, in herstel of genezing, …).

4. het type blootstelling kan bepalend zijn:

Continue of chronische blootstelling, partiële of totale lichaamsblootstelling, interferenties met andere blootstellingen zijn ook factoren die een eventueel verschil in biologische respons kunnen verklaren.

5. De complexiteit van een wetenschappelijke benadering

Normaal zal een wetenschapper proberen een oorzakelijk verband vast te stellen (blootstelling aan een bepaald magnetisch veld induceert leukemie bv.) maar omwille van alle mogelijke variabelen die een rol kunnen spelen zal een wetenschapper proberen van een vereenvoudiging in zijn experimenteel werk door te voeren waardoor het aantal parameters die een invloed kunnen hebben op het resultaat beperkt worden. Daarom ook zijn *in vitro* studies belangrijk (men houdt het 'biologisch systeem' beter in de hand). Maar dat is dus de realiteit niet meer en het bekomen resultaat is daarom altijd slechts partieel, suggestief, maar niet helemaal zeker.

Daarom zijn resultaten van verschillende studies, die in verschillende laboratoria (en soms zelfs in hetzelfde laboratorium) werden uitgevoerd vaak verschillend. Een verschillende benadering kan leiden tot andere parameters die belangrijk zijn en dus tot een andere uitkomst.

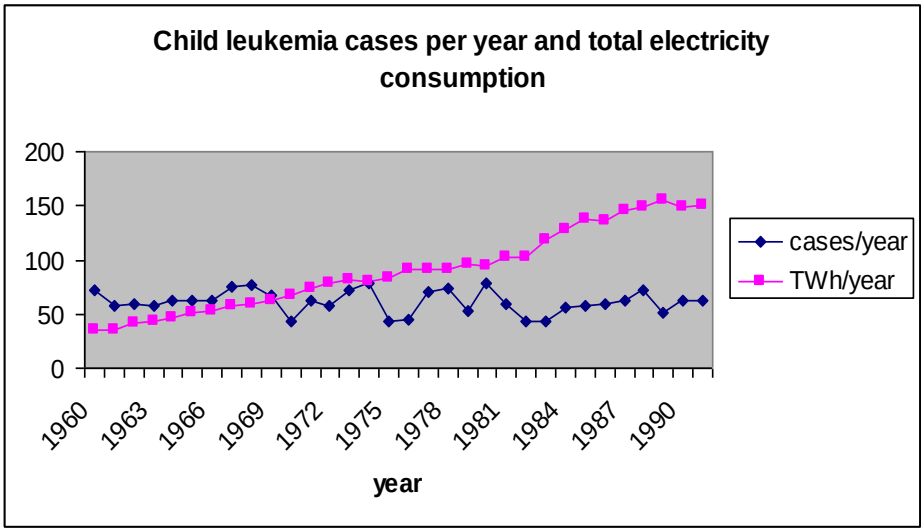
MAGNETISCHE VELDEN EN LEUKEMIE BIJ KINDEREN

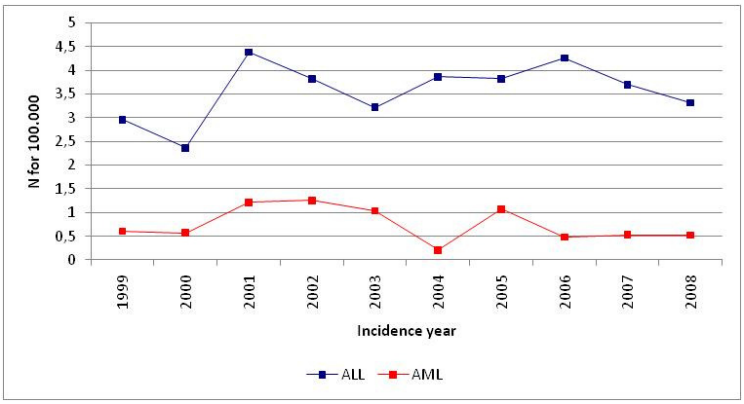
Am J Epidemiol. 1979 Mar;109(3):273-84.
Electrical wiring configurations and childhood cancer.
Wertheimer N, Leeper E.

An excess of electrical wiring configurations suggestive of high current-flow was noted in Colorado in 1976--1977 near the homes of children who developed cancer, as compared to the homes of control children. The finding was strongest for children who had spent their entire lives at the same address, and it appeared to be dose-related. It did not seem to be an artifact of neighborhood, street congestion, social class, or family structure. The reason for the correlation is uncertain; possible effects of current in the water pipes or of AC magnetic fields are suggested.

Epi-studies: beperkingen

-controversiële resultaten
-klein aantal individuen – statistische beperkingen
-vaak "niet blinde" evaluatie (blootstelling, enz.)
-moeilijkheden om directe metingen uit te voeren;
Waar? Voor welke tijdsduur?
-tegenstrijdigheid tussen gemeten velden en de "wire code" in populatiestudies
-vele vergelijkingen; positieve resultaten worden vaak overgeinterpreteerd
- "confounders"
-tegenstrijdigheden tussen positieve resultaten
-onbekend werkingsmechanisme





Trends in incidence of ALL and AML in children (0-14 years)

Flanders

ELF-MF AND CHILDHOOD LEUKAEMIA

$> 0.4\ \mu T$

IARC

Geen andere overtuigende gegevens inzake effecten op de gezondheid.

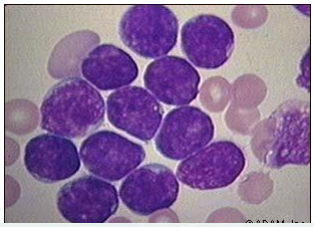
Geen aanwijzingen voor gezondheidseffecten in de beroepsbevolking.

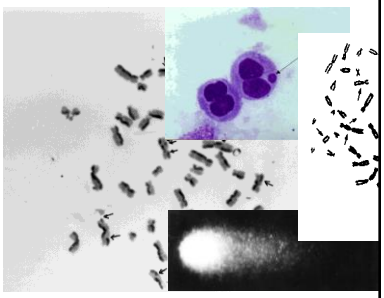
Geen aanwijzingen van schadelijke effecten op de gezondheid voor statische velden (tenzij bij zeer hoge blootstelling.

Epidemiology. 2000 Nov;11(6):624-34.
A pooled analysis of magnetic fields, wire codes, and childhood leukemia. Childhood Leukemia-EMF Study Group.
Greenland S, Sheppard AR, Kaune WT, Poole C, Kelsh MA.

Br J Cancer. 2000 Sep;83(5):692-8.
A pooled analysis of magnetic fields and childhood leukaemia.
Ahlbom A, Day N, Feychting M, Roman E, Skinner J, Dockerty J, Linet M, McBride M, Michaelis J, Olsen JH, Tynes T, Verkasalo PK.

Experimenteel onderzoek in het laboratorium





Honderden studies kunnen geen uitsluitsel brengen

British Journal of Cancer (2010) 103, 931 – 932

www.bjcancer.com

Editorial

The association between extremely low-frequency electromagnetic fields and childhood leukaemia in epidemiology: enough is enough?

S Schmiedel[*,1,2] **and M Blettner**[1]

[1]*Institute for Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center of the Johannes Gutenberg University Mainz, Mainz 55101, Germany;* [2]*Danish Cancer Society, Institute for Cancer Epidemiology, Copenhagen 2100, Denmark*

British Journal of Cancer (2010) **103,** 931 – 932. doi:10.1038/sj.bjc.6605837 www.bjcancer.com

Synoptic Analysis Clarifies Childhood Leukemia Risk from ELF Magnetic Field Exposure

Journal of Electromagnetic Analysis and Applications, 2015, 7, 245-258
Published Online October 2015 in SciRes. http://www.scirp.org/journal/jemaa
http://dx.doi.org/10.4236/jemaa.2015.710026

Norbert Leitgeb

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Email: norbert.leitgeb@tugraz.at

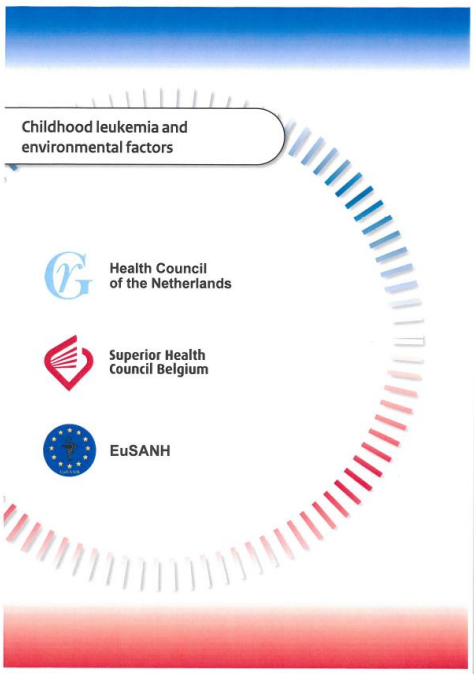
Received 28 August 2015; accepted 19 October 2015; published 22 October 2015

Abstract

In spite of 36 years epidemiologic research, there is still an ongoing controversy about a causal link between childhood leukemia (CL) and exposure to extremely low frequency (ELF) magnetic fields (MF). Public concern has been increased by the fact that ELF MF have been classified as possibly carcinogenic to humans (class 2B) while exposure limits still remain three orders of magnitudes above reported CL risk onset levels. In a new synoptic approach rather than few selected ORs, all reported epidemiological risk estimates (ORs) are analyzed, both pooled together as well as separated into sub-pools of different exposure metric as well as of high and low exposure levels. The results explain the worrying offset of ORs towards increased CL risk as well as the reported puzzling dose-response at low MF levels as an artifact caused by the small-number effect. The synoptic analysis clarifies that ORs critically depend on statistical power. With increasing statistical power ORs decrease and finally converge to and stay at zero risk. This is found consistently at the entire data pool as well as at all sub-pools related to investigated exposure parameters (wire code, distance to MF source, and magnetic field value). Former contradictory results can now be explained. The synoptic analysis provides convincing evidence that the risk of childhood leukemia is not increased by exposure to ELF magnetic fields. IARC's classification of ELF MF needs revision.

Keywords

~~Health Risk, Long-Term Effect, Carcinogenicity, Magnetic Field, Power Line~~



Oorzaken van kinderleukemie (milieu)

Bewezen
-Ioniserende stralen

Waarschijnlijk
-Pesticiden
-Benzeen
-Rookgedrag van de ouders
-PCB's

Mogelijk
-Anorganisch arseen in drinkwater
-Formaldehyde
-Alcoholconsumptie van de ouders
-Weekmakers
-Hoog geboortegewicht
-**Extreem lage magnetische velden**

Review Article

Journal of 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

Herziening van de melatonine hypothese in het licht van recente gegevens over magnetoreceptie

MELATONINE HYPOTHESE

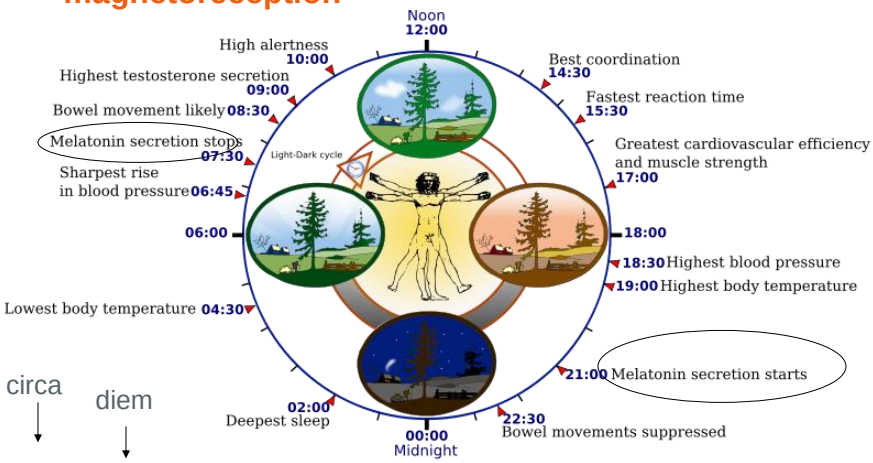
- ✓ MLT (krachtige vrije radicaal* vanger) beschermt tegen (borst)kanker
- ✓ ELF-MV inhiberen de nachtelijke MLT secretie
- ✓ ELF-MV effect op de MLT secretie leidt tot een toename in het risico op borstkanker

→ Deze hypothesis is niet langer weerhouden (geen verdere studies sinds 2004)

Nu kan met zekerheid gezegd worden dat er GEEN associatie bestaat tussen ELF-Mven en borstkanker!

*een molecuul of atoom dat één, of meer, ongepaard elektron heeft. Een dergelijke configuratie is energetisch ongunstig en zal makkelijk naar een gepaarde elektronenstructuur overgaan als dit mogelijk is..

reconsidering the melatonin hypothesis in the light of current data on magnetoreception



Circadiaans ritme

biologisch ritme waarvan de cyclus ongeveer één dag duurt

25

ELF-MV: VERSTORING VAN MAGNETORECEPTIE (het waarnemen van magnetische velden) ??

Er zijn aanwijzingen dat een magnetisch veld van ≥0.5 µT de magnetoreceptie stimuleert en aldus het circadiaans ritme verstoort.

Die ELF-MV-geïnduceerde verstoring zou leukemie bij kinderen kunnen verklaren.

betere correlatie tussen nachtelijke ELF-MV blootstelling en leukemie bij kinderen (t.o.v. 24 uur blootstelling)

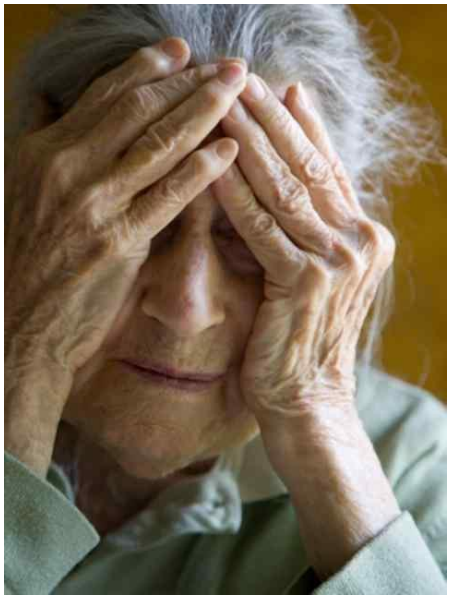
Epidemiologische gegevens:

Geen risico op kinderleukemie bij > 0.3 µT (24u) maar wel bij >0.3 µT ('s nachts) [Wünsch-Filho et al. (2011) Cancer Epidemiol. 35, 534-539].

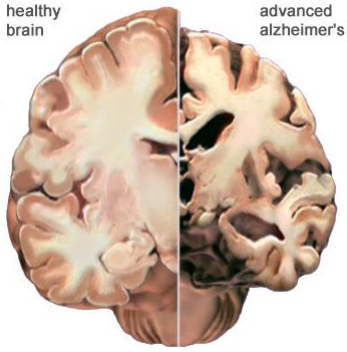
Invloed van de richting van het ELF-MV en de leeftijd (jonge leeftijd versterkt het effect als gevolg van verschillen in 'circadiaanse fysiologie' tussen jongeren en adulten); cf. ratexperimenten:

Salti et al. (2000) J. Clin. Endocrinol. Metab. 85, 2137-2144

Rivkees (2003) Pediatr. Endocrinol. Rev. 1, 38-45.



ALZHEIMER



ANDERE DEGENERATIEVE ZIEKTES?

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

International Journal of Epidemiology 2008;1–12
doi:10.1093/ije/dym295

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,

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.

Published by Oxford University Press on behalf of the International Epidemiological Association

International Journal of Epidemiology 2008;**37**:341–343
doi:10.1093/ije/dyn024

Commentary: Epidemiological research on extremely low frequency magnetic fields and Alzheimer's disease—biased or informative?

Martin Röösli

Accepted 14 January 2008

In 2006 the worldwide prevalence of Alzheimer's disease was estimated to be 26.6 million; and by 2050, Alzheimer's disease prevalence is expected to quadruple because of the increasing life expectancy in many countries.[1] Although the years of life lost per Alzheimer's disease case are relatively small, the disease causes considerable distress for afflicted families. Moreover, Alzheimer's disease patients need substantial care resulting in substantial costs for the health care system.

Little is known about the causes of Alzheimer's disease. Several genetic mutations have been identified to be associated with early-onset as well as late-onset disease.[2] In addition, environmental factors are assumed to play an important role, particularly for the development of late-onset Alzheimer's disease.[3] Many environmental, occupational or lifestyle risk factors assessing long-term exposure to ELF-MF in our everyday environment is complex. There are several occupations where ELF-MF exposure is well characterized and considerably higher than in the everyday environment. It is thus not surprising that all studies on ELF-MF exposure and Alzheimer's disease have focused on occupational exposure and no study has been performed in the general population so far. All epidemiological studies included in the meta-analysis of García *et al.* collected exposure data retrospectively. Collecting retrospective exposure data from Alzheimer's disease patients is particularly problematic if one has to rely on recollection only, being unable to retrieve the information from routine data sources, such as census data or occupation records. In seven of the 14 reviewed epidemiological studies exposure information had to be obtained by

Review

Journal of Applied Toxicology

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(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 aneuploïdy. 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

Mutagenesis vol. 22 no. 1 pp. 15–33, 2007
Advance Access Publication 8 December 2006

doi:10.1093/mutage/gel055

REVIEW

A review of genome mutation and Alzheimer's disease

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Alzheimer's disease (AD) is a complex progressive neurodegenerative disorder of the brain and is the commonest form of dementia. The prevalence of this disease is predicted to increase 3-fold over the next 30 years and to date no reliable and conclusive diagnostic test exists that will identify individuals presymptomatically of susceptibility risk. This review examines the molecular, genetic, dietary and environmental evidence underlying the known pathology of AD and proposes a biologically plausible chromosome instability model to explain some of the features of the disease. Genome damage biomarkers such as aneuploidy of chromosome 17 and 21, oxidative damage to DNA and telomere shortening together with abnormal expression of *APP*, β amyloid and tau proteins are discussed in terms of their potential value as risk biomarkers. These biomarkers could then be used in diagnosis and the evaluation of potentially effective preventative measures.

Introduction

Alois Alzheimer (Figure 1) was born in Markbhrict, Germany on June 14, 1864. He studied medicine at the Universities of Berlin, Tübingen, and Würzberg where he completed his doctoral thesis under the supervision of Albert Kölliker on cerumimal glands in 1887. From 1888 to 1903 Alzheimer worked as a medical resident and then later as a senior physician at the municipal mental asylum in Frankfurt. It was here that he forged his friendship with Franz Nissl, who developed histopathological stains that allowed the histology of nervous tissue from various neurodegenerative disorders to be studied.

On November 25, 1901 a patient called Auguste D was admitted to Frankfurt hospital where she was seen and treated by Alzheimer. She exhibited various behavioural and psychiatric symptoms including paranoia, delusions, hallucinations and impaired memory (1). After having suffered 5 years of illness she died in 1906. Her clinical notes and brain were forwarded onto Alzheimer in Munich, where over the next few months he examined Auguste's brain in great detail. At the 37th Conference of German psychiatrists meeting in Tübingen on November 4, 1906, Alzheimer reported for the first time the histopathological changes that he had witnessed in Auguste's brain. In his journal he wrote *"in the centre of an almost normal cell there stands out one or several fibres due to their characteristic thickness and peculiar impregnability. Numerous small miliary foci are found in the superior layers. They are determined by the storage of a peculiar substance in the cerebral cortex. All in all we have to face a peculiar disease process"* (2).

The impregnable fibres so described by Alzheimer were the neurofibrillary tangles, whereas the miliary foci were to be later referred to as the amyloid based neuritic plaques. Both these structures initially described by Alzheimer are now recognized as the characteristic hallmarks of a disease that now bears his name. In 1910 Emil Kraepelin published the 8th edition of his book *The Handbook of Psychiatry* where he describes a particularly serious form of senile dementia with early age of onset as Alzheimer's disease.

Having worked with Kraepelin in Munich from 1903 to 1912, Alzheimer was appointed to the position of professor of Psychiatry in Breslau, Poland. However with the arrival of the First World War conditions became increasingly more difficult. He found himself under increasing stress until finally his health started to fail. Alois Alzheimer died in a uraemic coma as a result of rheumatic endocarditis on December 19, 1915 at the age of 51. Alzheimer's many years of dedicated research provided the foundation for today's extensive research programmes, into trying to understand a disease that is predicted to make a huge social and financial impact on the 21st Century. Alzheimer's disease (AD) has been classified as a progressive degenerative disorder of the brain and is the most common form of dementia, with between 50 and 70% of all clinically presented cases being histopathologically confirmed as AD at post mortem (3). Worldwide a new case of dementia is diagnosed every 7 s. The global incidence of dementia is estimated to be 24.3 million, with ~4.6 million new cases being diagnosed annually (4,5). Currently between 165 000 and 180 000 Australians suffer from this disease, with an annual cost in 2004 to the Australian government of $3.6 billion dollars in lost productivity and medical care (6,7). These numbers are set to increase 3-fold over the next 30 years as a greater proportion of an already ageing population reaches retirement age. Advancing age is the major contributing factor for increased risk of developing Alzheimer's. After the age of 65 a doubling of risk occurs every 5 years affecting ~30% of individuals aged ≥80 years (3,8,9) It is estimated that by 2025 at least 34 million people worldwide will suffer from AD (10).

Clinical diagnosis

At present, based upon criteria of cognitive impairment and behavioural changes patients can be clinically diagnosed with

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Biomarkers of Alzheimer's Disease Risk in Peripheral Tissues; Focus on Buccal Cells

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Abstract: Alzheimer's disease (AD) is a progressive degenerative disorder of the brain and is the most common form of dementia. To-date no simple, inexpensive and minimally invasive procedure is available to confirm with certainty the early diagnosis of AD prior to the manifestations of symptoms characteristic of the disease. Therefore, if population screening of individuals is to be performed, more suitable, easily accessible tissues would need to be used for a diagnostic test that would identify those who exhibit cellular pathology indicative of mild cognitive impairment (MCI) and AD risk so that they can be prioritized for primary prevention. This need for minimally invasive tests could be achieved by targeting surrogate tissues, since it is now well recognized that AD is not only a disorder restricted to pathology and biomarkers within the brain. Human buccal cells for instance are accessible in a minimally invasive manner, and exhibit cytological and nuclear morphologies that may be indicative of accelerated ageing or neurodegenerative disorders such as AD. However, to our knowledge there is no review available in the literature covering the biology of buccal cells and their applications in AD biomarker research. Therefore, the aim of this review is to summarize some of the main findings of biomarkers reported for AD in peripheral tissues, with a further focus on the rationale for the use of the buccal mucosa (BM) for biomarkers of AD and the evidence to date of changes exhibited in buccal cells with AD.

Keywords: Alzheimer's disease, buccal mucosa, diagnosis, mild cognitive impairment, peripheral biomarkers.

1. NEED FOR PREDICTIVE BIOMARKERS OF AD

Alzheimer's disease (AD) is the sixth leading cause of death in the United States [1] and the most common form of dementia. AD patients have been reported with cognitive impairment characterized by impaired ability to register new information, reasoning, visuospatial abilities and language functions. AD patients also exhibit behavioural symptoms such as for instance, mood fluctuations, apathy, compulsive or obsessive behaviours and loss of interest, often correlated with loss of cognitive functions [2-5]. Previously, clinical diagnosis of AD were based upon criteria outlined by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA), published in 1984 including memory impairments, visuospatial and language impairment (aphasia) as measured by the Mini-Mental State Examination (MMSE) [6]. These criteria were recently revised by the NINCDS-ADRDA to incorporate biomarkers of brain amyloid-beta (cerebrospinal fluid (CSF) Amyloid-β 1-42; positive positron emission tomography (PET) amyloid imaging) and downstream neuronal degeneration (CSF Tau, magnetic resonance imaging of brain atrophy, PET imaging of fluorodeoxyglucose uptake) in the diagnosis of AD [5]. Although NINCDS-ADRDA does not encourage the use of such biomarkers within tests for routine diagnostic purposes, they can and should be used to increase certainty of diagnostic in research and clinical trials. However, the current suite of tests used in clinical diagnosis can only provide a possible or probable diagnostic of AD in living subjects and the definitive diagnostic can only be made during post-mortem. This is achieved by the observation of the extracellular senile plaques and intracellular neurofibrillary tangles (NFTs) in specific areas of the brain such as the entorhinal cortex and hippocampus [7, 8]. The number of new AD cases is dramatically increasing with an estimated 81.1 million people worldwide being affected by dementia by 2040 [9] and since the pathogenic processes of AD are likely to begin years before clinical symptoms are observed, the need of predictive biomarkers has become urgent. Moreover AD does not only alter the quality of life, health and wellbeing of those affected but also leads to a significant social financial burden [10, 11].

2. PERIPHERAL TISSUE AS SOURCE FOR AD BIOMARKERS

A biomarker, as defined by the National Institutes of Health Biomarkers Definitions Working Group, is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [12]. A potential biomarker should be useful for detecting early stages of a disease and exhibit high levels of sensitivity and specificity. The scientific community has been actively

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ELF-MV geïnduceerde GENETISCHE EFFECTEN?

- SCENIHR 2015 e.a.:
  - Geen rechtstreekse DNA schade
  - Geen genetische effecten (chromosoombreuken) bij < 100 µT
  - Co-mutageen effect ?
  - Genoommutaties?
  - …

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The Cytome Assay as a Tool to Investigate the Possible Association Between Exposure to Extremely Low Frequency Magnetic Fields and an Increased Risk for Alzheimer's Disease

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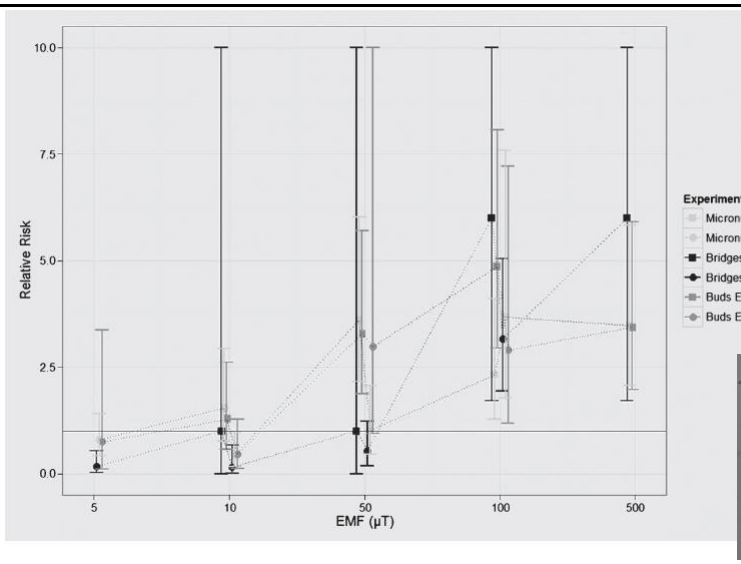
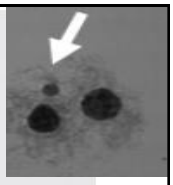
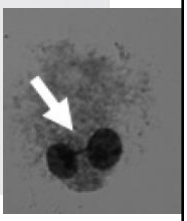
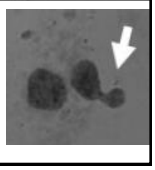








1) Toename in frequentie van micronuclei (struct. en/of numerieke chrom. aberr.) en 'bruggen' (struct. chrom. aberr.) bij >100 µT
2) Toename in frequentie van 'buds' (= gen amplificatie) bij >50 µT
3) Verminderd risico voor genetische schade bij 5 en 10 µT (?)

SCENIHR 2015

"The previous SCENHIR Opinion indicated a possible increase in Alzheimer's disease arising from exposure to ELF, stressing the need for further epidemiological and laboratory investigations".

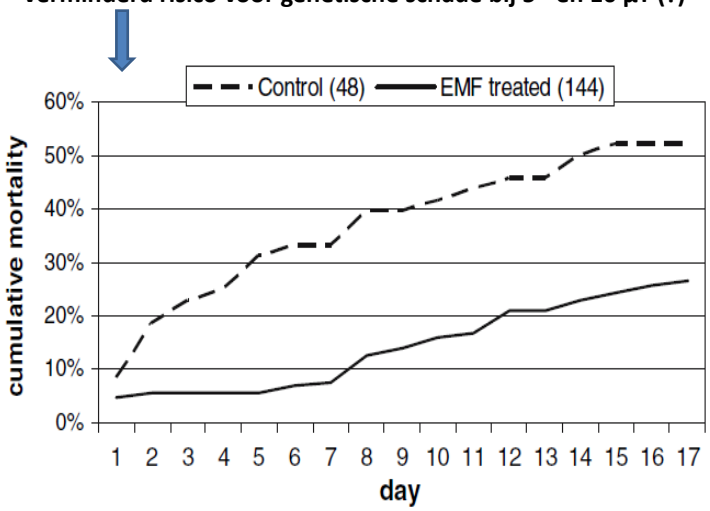
What has been achieved since then?

"Although the new studies in some cases have methodological weaknesses, they do not provide support for the previous conclusion that ELF MF exposure increases the risk for Alzheimer´s disease".

+

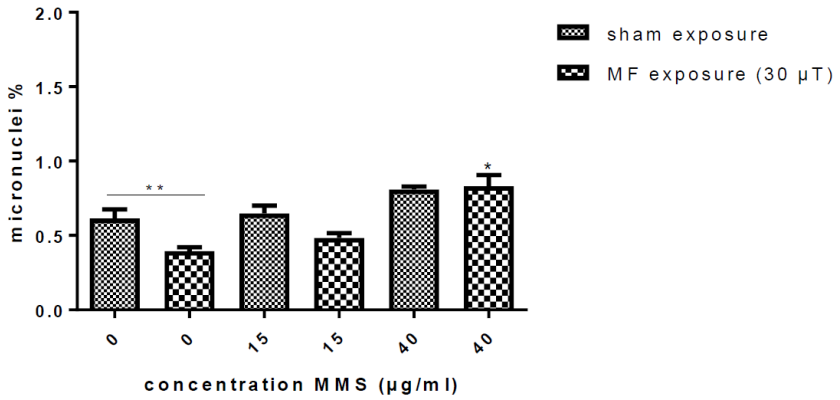
Macedo et al. (2017) Is Sleep Disruption a Risk Factor for Alzheimer's Disease? J Alzheimers Dis. 2017;58(4):993-1002. doi: 10.3233/JAD-161287.
Mechanisms triggered by sleep disruption may be involved in AD development, such as brain hypoxia, oxidative stress, circadian activity rhythms disturbances, overexpression of orexins, and blood-brain barrier impairment.

Verminderd risico voor genetische schade bij 5 - en 10 µT (?)



Cuppen et al., (2007) Environmentalist, DOI 10.1007/s10669-007-9055-2

Intermediaire frequenties: 7,5 kHz magnetisch veld



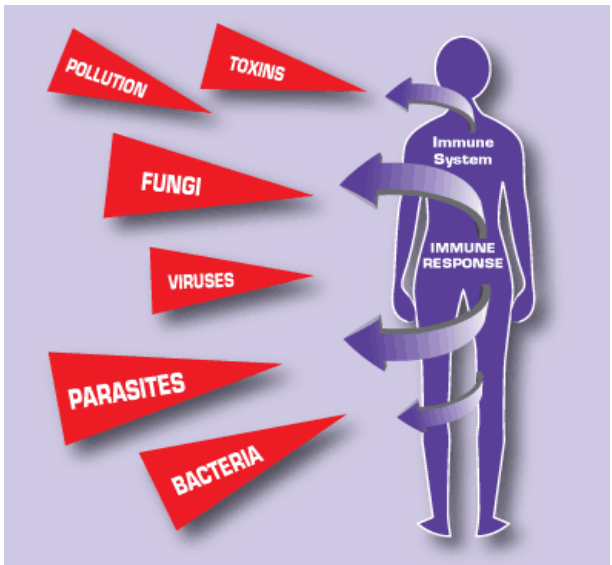
⇒ Lage blootstellingen (aan LF-EMVen en andere omgevingsfactoren) stimuleren de immuun respons en DNA herstel

⇒ Stimulatie is effectiever in **geïnfecteerde weefsels/gestresseerde cellen** (ook niet getoonde gegevens); dus in geval van ziekte of onevenwicht.

EMV-blootstelling heeft minder effect wanneer de cellen gezond zijn!

⇒ HYPOTHESE:

EMVen veroorzaken een zwakke 'stress situatie' in cellen waardoor hun immuun systeem en andere 'alarm' systemen (vb. DNA herstel) 'voortijdig' activeren. Zo zullen zij bv. sneller dan normaal in staat zijn externe dreigingen (pathogenen e.d.) het hoofd te bieden. Pathogenen hebben op die manier minder kans om schadelijk te zijn.



Weinig pathogenen in het lichaam→ verdedigingsmechanismen zijn (nog) niet geactiveerd

Invasie van pathogenen ↓
ALARM

⇒ VERDEDIGING

Wat doen ELF-MVen?

⇒

Weinig pathogenen in het lichaam + EMV ⇒ **ALARM & VROEGE BESCHERMING**
Of weinig « straling » of andere blootstelling

MAAR: wat gebeurt er na langdurige (chronische) blootstelling aan ELF-MVen?

Er zijn beperkte aanwijzingen dat langdurige blootstellingen aanvankelijk leiden tot stimulatie van het immuun systeem maar dat dit nadien afneemt (uitputting?). Andere beperkte gegevens spreken dit dan weer tegen.

Dit is tot op heden nooit voldoende onderzocht!!

BESLUIT

-Relatie tussen ELF-Mven en leukemie bij kinderen 'houdt voorlopig stand' maar er zijn andere, en wellicht belangrijkere oorzaken voor leukemie bij kinderen.

-Aanwijzingen voor een rol van ELF-MVen in het ontstaan van neurologische aandoeningen zoals de ziekte van Alzheimer zijn vooralsnog niet overtuigend maar volledig uitsluiten is (nog) niet mogelijk.

-ELF-MVen kunnen (net als andere stressoren zoals RF-straling maar ook andere fysische en chemische agentia) op korte termijn een milde (ongevaarlijke) 'stress-reactie' oproepen in cellen/organismen maar implicaties op lange termijn zijn vooralsnog onbekend.

DANK U