Overview of the epidemiologic studies on the health effects of ELF magnetic and electric fields published in the first trimester of 2020.

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1. Reviews

Symptoms associated with environmental factors" (SAEF) - Towards a paradigm shift regarding idiopathic environmental intolerance" and related phenomena. Haanes JV, Nordin S, Hillert L, Witthöft M, van Kamp I, van Thriel C, Van den Bergh O. *J Psychosom Res. 2020 Feb 5;131:109955.*

Health conditions characterized by symptoms associated with chemical, physical and biological environmental factors unrelated to objectifiable pathophysiological mechanisms are often labelled by the general term "idiopathic environmental intolerances". More specific, exposure-related terms are also used, e.g. "multiple chemical sensitivities", "electromagnetic hypersensitivity" and "candidiasis hypersensitivity". The prevalence of the conditions varies from a few up to more than 50%, depending on definitions and populations. Based on evolving knowledge within this field, the authors provide arguments for a paradigm shift from terms focusing on exposure and intolerance/(hyper-)sensitivity towards a term more in line with the perceptual elements that seem to underlie these phenomena. Symptoms caused by established pathophysiologic mechanisms should not be included, e.g. allergic or toxicological conditions, lactose intolerance or infections. The authors discuss different alternatives for a new term/concept and end up proposing an open and descriptive term, "symptoms associated with environmental factors" (SAEF), including a definition. Conclusions: The authors propose a new descriptive term "Symptoms associated with environmental factors" which is in line with the current knowledge and acknowledge the experiences of the afflicted persons. The proposed concept is likely to facilitate therapy and communication between health professionals and afflicted persons, and to provide a base for better understanding of such phenomena in healthcare, society and science.

2. Residential exposure

Relationship between distance to overhead power lines and calculated fields in two studies. *J Radiol Prot. 2020 Feb 17;40(2):431-443.*

There is some evidence that both distance from transmission lines and measured or calculated magnetic fields are associated with childhood leukemia. Because distance is a key component when calculating the magnetic field generated by power lines, distance from lines and calculated fields based on lines tend to be highly correlated. Socioeconomic status (SES) and dwelling type are also associated with magnetic field exposure. The authors used exposure data from two large studies of childhood leukemia and other cancers, in the US and the UK, to describe a relationship between distance and magnetic fields across the population within 100 meters (m) of power lines as a whole and evaluate potential modifiers such as SES and type of dwelling. There were 387 subjects living within 100 m of an overhead power line. There was no significant difference in mean calculated fields or distance to 200+ kV lines within 100 m by study. Within the range where the power-line field is expected to be significant compared to other sources, which was taken as 100 m, distance to high-voltage lines

predicted magnetic field (MF) variation in both studies better than other functions of distance tested in both linear and logistic regression. There were no differences between high and low SES or dwelling types (single-family home versus other).

Conclusions: The authors found that calculated fields do appear to diminish linearly with increasing distance from overhead power lines, up to 100 m, particularly those 200+ kV and above. These results are stronger in the UK study. Within 100 m, distance to high-voltage lines continues to be highly correlated with calculated MFs and each can be a proxy for the other.

3. <u>Occupational exposure</u>

Case-control study of paternal occupational exposures and childhood bone tumours and soft-tissue sarcomas in Great Britain, 1962-2010. Kendall GM, Bunch KJ, Stiller CA, Vincent TJ, Murphy MFG. *Br J Cancer. 2020 Feb 26.*

This nationwide study investigated associations between paternal occupational exposure and childhood bone tumours and soft- tissue sarcomas. The UK National Registry of Childhood Tumours provided cases of childhood sarcomas born and diagnosed in Great Britain, 1962-2010. Control births, unaffected by childhood cancer, were matched on sex, birth period and birth registration sub-district. Fathers' occupations were assigned to one or more of 33 exposure groups and coded for occupational social class. 5,369 childhood sarcoma cases and 5380 controls were analysed. Total bone tumours, total soft-tissue sarcomas and the subgroups osteosarcoma, rhabdomyosarcoma and Ewing Sarcoma Family of Tumours (ESFT) were considered separately. Significant positive associations were seen between rhabdomyosarcoma and paternal exposure to EMFs (odds ratio = 1.67, CI = 1.22-2.28) and also for ESFT and textile dust (1.93, 1.01-3.63). There were putative protective effects on total bone tumours of paternal dermal exposure to hydrocarbons, metal, metal working or oil mists.

Conclusions: Despite the large size and freedom from bias of this study, these results should be interpreted with caution. Many significance tests were undertaken, and chance findings are to be expected. Nevertheless, the finding of associations between ESFT and paternal exposure to textile dust may support related suggestions in the literature.

4. Human experimental studies

Extremely Low Frequency Magnetic Fields Do Not Affect LTP-Like Plasticity in Healthy Humans. Capone F, Pellegrino G, Motolese F, Rossi M, Musumeci G, Di Lazzaro V. *Front Hum Neurosci. 2020 Feb 5;14:14.*

Several studies explored the biological effects of extremely low-frequency magnetic fields (ELF-MFs) in vitro, reporting the induction of functional changes in neuronal activity. In particular, ELF-MFs can influence synaptic plasticity both in vitro and in animal models but some studies reported an increase in long-term potentiation (LTP) whereas others suggested its reduction. However, no specific study has investigated such effect on humans. The aim of this study was to evaluate whether ELF-MFs affect the propensity of the human cortex to undergo LTP-like plasticity. The authors designed a randomized, single-blind, sham-controlled, cross-over study on 10 healthy subjects. Cortical plasticity was induced by intermittent theta burst stimulation (iTBS) before and after 45-min ELF-MFs (75 Hz; 1.8 mT) or sham exposure and was estimated by measuring the changes of motor evoked potentials (MEP) amplitude before and after each iTBS. No adverse events were reported. No significant effects of ELF-MFs on cortical plasticity were found.

Conclusions: Whole-brain exposure to ELF-MFs (75 Hz; 1.8 mT) is safe and does not seem to significantly affect LTP-like plasticity in human motor cortex.

Phantom Model Testing of Active Implantable Cardiac Devices at 50/60 Hz Electric Field. Gerçek C, Kourtiche D, Nadi M, Magne I, Schmitt P, Roth P, Souques M. *Bioelectromagnetics. 2020 Feb;41(2):136-147.*

Exposure to external extremely low-frequency (ELF) electric and magnetic fields induces the development of electric fields inside the human body, with their nature depending on multiple factors including the human body characteristics and frequency, amplitude, and wave shape of the field. The objective of this study was to determine whether active implanted cardiac devices may be perturbed by a 50 or 60 Hz electric field and at which level. A numerical method was used to design the experimental setup. Several configurations including disadvantageous scenarios, 11 implantable cardioverter-defibrillators, and 43 cardiac pacemakers were tested in vitro by an experimental bench test up to 100 kV/m at 50 Hz and 83 kV/m at 60 Hz.

Conclusions: No failure was observed for ICNIRP public exposure levels for most configurations (in more than 99% of the clinical cases), except for six pacemakers tested in unipolar mode with maximum sensitivity and atrial sensing. The implants configured with a nominal sensitivity in the bipolar mode were found to be resistant to electric fields exceeding the low action levels, even for the highest action levels, as defined by the Directive 2013/35/EU.

5. Human experimental studies

None

6. Leukaemia studies

Cesarean section and risk of childhood leukemia: a systematic review and meta-analysis. Jiang LL, Gao YY, He WB, Gan T, Shan HQ, Han XM. *World J Pediatr. 2020 Feb 11.*

A large number of studies pointed that being delivered by cesarean section (CS) would affect the health outcomes of offspring, however, whether CS would affect the risk of childhood leukemia remained uncertain. This study conducted a meta-analysis to quantitatively evaluate whether being delivered by CS would influence the onset of childhood leukemia. PubMed, Embase and Web of Science databases were searched from 3rd June, 1950 to 13th October, 2019 to identify the literature, which examined the relationship between CS and childhood leukemia. This study used Newcastle-Ottawa Scale to assess the quality of literature. Subgroup analyses were conducted on region, mode of delivery, design of the study and number of confounders adjusted. Egger's test and Begg's test were performed to evaluate possible publication bias. The pooled odds ratio (OR) estimates illustrated that children delivered by CS had a higher risk of developing leukemia [OR 1.10, 95% confidence interval (CI) 1.04-1.17, P = 0.002] and lymphoblastic leukemia (OR 1.12, 95% CI 1.03-1.23, P = 0.009), while a significant association for myeloid leukemia was not observed (OR 1.05, 95% CI 0.92-1.20, P = 0.451). Results of subgroup analyses indicated that elective CS would increase the risk of childhood lymphoblastic leukemia (OR 1.16, 95% CI 1.06-1.27, P = 0.002). However, a statistical relationship between emergency CS and lymphoblastic leukemia was not observed (OR 1.07, 95% CI 0.93-1.23, P = 0.364).

Conclusions: CS would increase the risk of childhood lymphoblastic leukemia. It is worth noting that subgroup analyses shows that elective CS rather than emergency CS increases the risk of lymphoblastic leukemia in offspring.

Prenatal pesticide exposure and childhood leukemia - A California statewide case-control study. Park AS, Ritz B, Yu F, Cockburn M, Heck JE. *Int J Hyg Environ Health. 2020 Feb 19;226:113486.*

A number of epidemiologic studies with a variety of exposure assessment approaches have implicated pesticides as risk factors for childhood cancers. In this study the authors explore the association of pesticide exposure in pregnancy and early childhood with childhood acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) utilizing land use and pesticide use data in a sophisticated GIS tool. The authors identified cancer cases less than 6 years of age from the California Cancer Registry and cancer-free controls from birth certificates. Analyses were restricted to those living in rural areas and born 1998-2011, resulting in 162 cases of childhood leukemia and 9,805 controls. Possible carcinogens were selected from the Environmental Protection Agency's classifications and pesticide use was collected from the California Department of Pesticide Regulation's (CDPR) Pesticide Use Reporting (PUR) system and linked to land-use surveys. Exposures for subjects were assessed using a 4000m buffer around the geocoded residential addresses at birth. Unconditional logistic and hierarchical regression models were used to assess individual pesticide and pesticide class associations. Elevated risks for ALL were observed with exposure to any carcinogenic pesticide (adjusted Odds Ratio (aOR): 2.83, 95% CI: 1.67-4.82), diuron (single-pesticide model, adjusted (OR): 2.38, 95% CI: 1.57-3.60), phosmet (OR: 2.10, 95% CI: 1.46-3.02), kresoxim-methyl (OR: 1.77, 95% CI: 1.14-2.75), and propanil (OR: 2.58, 95% CI: 1.44-4.63). Analyses based on chemical classes showed elevated risks for the group of 2,6-dinitroanilines (OR: 2.50, 95% CI: 1.56-3.99), anilides (OR: 2.16, 95% CI: 1.38-3.36), and ureas (OR: 2.18, 95% CI: 1.42-3.34).

Conclusions: These findings suggest that in rural areas of California exposure to certain pesticides or pesticide classes during pregnancy due to residential proximity to agricultural applications may increase the risk of childhood ALL and AML. Future studies into the mechanisms of carcinogenicity of these pesticides may be beneficial.

Infections and the development of childhood acute lymphoblastic leukemia: a population-based study. Hwee J, Sutradhar R, Kwong JC, Sung L, Cheng S, Pole JD. *Eur J Cancer Prev. 2020 Feb 4.*

An infectious trigger for childhood acute lymphoblastic leukemia is hypothesized. The authors assessed the association between the rate, type, and critical exposure period for infections and the development of acute lymphoblastic leukemia. They conducted a matched case-control study using administrative databases to evaluate the association between the rate of infections and childhood acute lymphoblastic leukemia diagnosed between the ages of 2-14 years from Ontario, Canada and using a validated approach to measure infections. In 1600 cases of acute lymphoblastic leukemia, and 16 000 matched cancer-free controls aged 2-14 years, having >2 infections/year increased the odds of childhood acute lymphoblastic leukemia by 43% (odds ratio = 1.43, 95% confidence interval 1.13-1.81) compared to children with ≤0.25 infections/year. Having >2 respiratory infections/year increased odds of acute lymphoblastic leukemia by 28% (odds ratio =1.28, 95% confidence interval 1.05-1.57) compared to children with ≤0.25 respiratory infections/year. Having an invasive infection increased the odds of acute lymphoblastic leukemia by 72% (odds ratio =1.72, 95% confidence interval 1.31-2.26). Having an infection between the age of 1-1.5 years increased the odds of acute lymphoblastic leukemia by 20% (odds ratio = 1.20, 95% confidence interval 1.04-1.39).

Conclusions: Having more infections increased the odds of developing childhood acute lymphoblastic leukemia and having an infection between the ages of 1-1.5 years increased the odds of childhood acute lymphoblastic leukemia.

Occupational livestock or animal dust exposure and offspring cancer risk in Denmark, 1968-2016. Hall C, Hansen J, von Ehrenstein OS, He D, Olsen J, Ritz B, Heck JE. *Int Arch Occup Environ Health. 2020 Feb 5.*

The objective of this study was to examine associations with occupational livestock or other animal dust exposure and offspring cancer risk. In a population-based case-control study of Danish children aged < 17 years old, 5078 childhood cancer cases diagnosed 1968-2016 were matched to cancer-free controls by birth year and sex (n = 123,228). Occupational livestock or animal dust exposure was identified using a job-exposure matrix. Multivariable conditional logistic regression models were employed to estimate associations with offspring cancer for births 1968-2016 and 1989-2016, with the latter timeframe reflecting a period of presumed higher exposure due to changes in Danish farming practices. Sensitivity analyses considered place of birth (urban areas vs. rural areas and small towns). For births 1968-2016, paternal exposure from offspring birth to cancer diagnosis was associated with central nervous system tumors (adjusted odds ratio [OR] = 1.30, 95% confidence interval [CI] 1.04-1.63) and germ cell tumors (OR = 1.82, 95% CI 1.05-3.27), while maternal pregnancy exposure was associated with astrocytoma (OR = 1.89, 95% CI 1.00-3.57). For births 1989-2016, paternal exposure from offspring birth to cancer diagnosis was negatively associated with acute lymphoid leukemia (OR = 0.58, 95% CI 0.33-1.00). For births in rural areas only, maternal exposure from offspring birth to cancer diagnosis was positively associated with acute myeloid leukemia (OR = 2.16, 95% CI 1.09-4.29).

Conclusions: This study suggests that paternal occupational animal exposure is associated with offspring germ cell tumors, and maternal pregnancy exposure with astrocytomas. The results are mixed with respect to leukemia subtypes.

Early immune stimulation and childhood acute lymphoblastic leukemia in Costa Rica: A comparison of statistical approaches. Figueroa SC, Kennedy CJ, Wesseling C, Wiemels JM, Morimoto L, Mora AM. *Environ Res. 2020 Mar;182:109023.*

Although epidemiologic studies suggest that early immune stimulation is protective against childhood leukemia, evidence for this relationship is equivocal for Hispanic children, who are disproportionately affected by this disease. The complex biological processes underlying immune stimulation and leukemogenesis may benefit from novel statistical approaches that account for mixed exposures and their nonlinear interactions. In this study, the authors utilized targeted machine learning and traditional statistical methods to investigate the association of multiple measures of early immune stimulation with acute lymphoblastic leukemia (ALL) in Costa Rican children. They used data from a population-based case-control study conducted in Costa Rica (2001-2003). Cases of ALL (n = 240) were diagnosed in 1995-2000 (age >1 year and <15 years at diagnosis) and were identified through the National Cancer Registry and National Children's Hospital. Population controls (n = 578) were frequency-matched to cases by birth year and drawn from the National Birth Registry. Data on surrogate measures of early immune stimulation were collected through in-home interviews. Multivariable models were fitted, utilizing targeted causal inference (varimpact), unconditional logistic regression, and latent class analysis (LCA). In varimpact analysis, contact with any pet [risk difference (RD) = -0.17, 95% CI: -0.25, -0.10)] or any farm animal (RD = -0.07, 95% CI: -0.13, 0.00) and allergies (RD = -0.08, 95% CI: -0.17, 0.01) were associated with a reduced risk of ALL, whereas experiencing a fever longer than one week was associated with an increased risk (RD = 0.23, 95% CI: 0.12, 0.33). In unconditional logistic regression models, contact with any pet or farm animal and a complete vaccination scheme were inversely associated with odds of ALL (OR = 0.44, 95% CI: 0.31, 0.62; OR = 0.66, 95% CI: 0.49, 0.90; OR = 0.45, 95% CI: 0.24, 0.83; respectively), whereas experiencing a fever longer than one week was positively associated with ALL (OR = 2.44, 95% CI: 1.61, 3.70). Two-class and three-class LCA revealed a group with elevated risk for ALL whose exposure profile was mainly characterized by reduced exposure to pets and farm animals.

Conclusions: Using distinct statistical approaches, the authors observed that exposure to pets and farm animals was inversely associated with ALL risk, whereas having a fever longer than one week (a putative proxy of severe infection) was associated with an increased risk. For multifactorial diseases such as childhood leukemia, the authors recommend estimating the joint effects of multiple exposures by applying diverse statistical methods and interpreting their results together. Overall, they found support for the hypothesis that early immune stimulation offers protection against childhood ALL.

Parental occupational exposure to pesticides, animals and organic dust and risk of childhood leukemia and central nervous system tumors: Findings from the International Childhood Cancer Cohort Consortium (I4C). Patel DM, Jones RR, Booth BJ, Olsson AC, Kromhout H, Straif K, Vermeulen R, Tikellis G, Paltiel O, Golding J, Northstone K, Stoltenberg C, Håberg SE, Schüz J, Friesen MC, Ponsonby AL, Lemeshow S, Linet MS, Magnus P, Olsen J, Olsen SF, Dwyer T, Stayner LT, Ward MH; International Childhood Cancer Cohort Consortium. *Int J Cancer. 2020 Feb 15;146(4):943-952.*

Parental occupational exposures to pesticides, animals and organic dust have been associated with an increased risk of childhood cancer based mostly on case-control studies. The authors prospectively evaluated parental occupational exposures and risk of childhood leukemia and central nervous system (CNS) tumors in the International Childhood Cancer Cohort Consortium. They pooled data on 329,658 participants from birth cohorts in five countries (Australia, Denmark, Israel, Norway and United Kingdom). Parental occupational exposures during pregnancy were estimated by linking International Standard Classification of Occupations-1988 job codes to the ALOHA+ job exposure matrix. Risk of childhood (<15 years) acute lymphoblastic leukemia (ALL; n = 129), acute myeloid leukemia (AML; n = 31) and CNS tumors (n = 158) was estimated using Cox proportional hazards models to generate hazard ratios (HR) and 95% confidence intervals (CI). Paternal exposures to pesticides and animals were associated with increased risk of childhood AML (herbicides HR = 3.22, 95% CI = 0.97-10.68; insecticides HR = 2.86, 95% CI = 0.99-8.23; animals HR = 3.89, 95% CI = 1.18-12.90), but not ALL or CNS tumors. Paternal exposure to organic dust was positively associated with AML (HR = 2.38 95% CI = 1.12-5.07), inversely associated with ALL (HR = 0.55, 95% CI = 0.31-0.99) and not associated with CNS tumors. Low exposure prevalence precluded evaluation of maternal pesticide and animal exposures; no significant associations with organic dust exposure was observed.

Conclusions: This first prospective analysis of pooled birth cohorts and parental occupational exposures provides evidence for paternal agricultural exposures as childhood AML risk factors. The different risks for childhood ALL associated with maternal and paternal organic dust exposures should be investigated further.