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Overview of the epidemiologic studies on the health effects of ELF electric and magnetic fields (ELF-EMF) published in the first quarter of 2023.

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Index

1. Reviews and meta-analyses 3
2. Residential exposure 4
3. Occupational exposure 5
4. Exposure assessment 7
5. Leukaemie studies 8

1. Reviews and meta-analyses

1.1 Urbanization, air pollution, and water pollution: Identification of potential environmental risk factors associated with amyotrophic lateral sclerosis using systematic reviews.

Saucier, D., Registe, P.P.W., Bélanger, M., O'Connell, C. (2023). Frontiers in Neurology, 14:1108383. https://doi.org/10.3389/fneur.2023.1108383

Background and Objective: Despite decades of research, causes of ALS remain unclear. To evaluate recent hypotheses of plausible environmental factors, the aim of this study was to synthesize and appraise literature on the potential associations between the surrounding environment, including urbanization, air pollution and water pollution, and ALS.

Methods: The authors conducted a series (n = 3) of systematic reviews in PubMed and Scopus to identify epidemiological studies assessing relationships between urbanization, air pollution and water pollution with the development of ALS.

Results: The combined search strategy led to the inclusion of 44 articles pertaining to at least one exposure of interest. Of the 25 included urbanization studies, four of nine studies on living in rural areas and three of seven studies on living in more highly urbanized/dense areas found positive associations to ALS. There were also three of five studies for exposure to electromagnetic fields and/or proximity to powerlines that found positive associations to ALS. Three case-control studies for each of diesel exhaust and nitrogen dioxide found positive associations with the development of ALS, with the latter showing a dose-response in one study. Three studies for each of high selenium content in drinking water and proximity to lakes prone to cyanobacterial blooms also found positive associations to ALS.

Conclusion: Whereas markers of air and water pollution appear as potential risk factors for ALS, results are mixed for the role of urbanization.

Comment by dr. Els De Waegeneer: The authors include the next paragraf, stating "After rural areas, urbans areas, and level of urbanization, electromagnetic fields and/or proximity to powerlines was the next most studied urbanization risk factor among included studies. Once adjusted for confounders, only three out of five of these studies found a significant positive association between ALS and electromagnetic fields and/or high-voltage infrastructure such as powerlines. However, one of these three positive studies used an ecological approach (51), while the positive case-control study had under 100 ALS cases and was subject to recall bias as it was the only study of five to ascertain the exposure with a self- administered questionnaire. The study finding no association at all between ALS and electromagnetic fields/powerlines had a more substantial number of cases (n = 703) and controls (n =2,737) and utilized geospatial data." These remarks, that recognize the flaws in the studies that report a positive association between proximity to powerlines and ALS, seem to contrast with the conclusion that ELF-EMF is considered as a risk factor for ALS.

2. Residential exposure

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3. Occupational exposure

3.1 Occupational Exposure to Physical and Chemical Risk Factors: A Systematic Review of Reproductive Pathophysiological Effects in Women and Men

Ramezanifar, S., Beyrami, S., Mehrifar, Y., Ramezanifar, E., Soltanpour, Z., et al. (2023). Safety and Health at Work, 14, 17-30. https://orcid.org/0000-0002-0100-7971

Background and Objective: The human reproductive system can be affected by occupational exposure to many physical and chemical risk factors. This study was carried out to review the studies conducted on the issue of the pathophysiological effects of occupational physical and chemical risk factors on the reproductive system of females and males.

Methods: In this systematic review, the databases such as “Google Scholar,” “Pub-Med,” “Scopus,” and “Web of Science” were used. Following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA 2020), the studies included in our study were published between 2000 and 2021. In order to extract the required data, all sections of the articles were reviewed.

Results: Out of 57 articles we reviewed, 34 articles were related to field studies and 23 articles to clinical studies. Among them, 43 studies dealt with the pathophysiological effects of chemical agents, six studies dealt with the pathophysiological effects of physical factors, and 8 studies dealt with the pathophysiological effects of physicochemical factors on the human reproductive system.

Conclusion: Physical (noise, heat, and radiofrequency radiation) and chemical (such as carbamate and organophosphate pesticides, benzene, toluene, xylene, formaldehyde,NO2, CS2,manganese, lead, nickel, and n-hexane) risk factors had pathophysiological effects on the human reproductive system. The presence of these risk factors in the workplace caused damage to the human reproductive system. The rate of these negative pathophysiological effects can be reduced by performing appropriate managerial, technical, and engineering measures in work environments.

Comment dr. Els De Waegeneer: This publication has quite some methodological flaws when it comes to reviewing the effect of ELF-EMF on reproductive performance of individuals. It does not take in consideration the majority of peer-reviewd publications on this topic, but only uses a few articles to take into account. Therefore, the conclusion of the authors should be met with caution.

3.2 Can extremely low frequency magnetic field affect human sperm parameters and male fertility?

Muti, N.D., Salvio, G., Ciarlino, A. et al. (2023). Tissue and Cell.
https://doi.org/10.1016/j.tice.2023.102045

Background and Objective: Exposure to extremely low frequency magnetic fields (ELF-MF) may have different effects on spermatozoa depending on the waveform, magnetic flux density, frequency of ELF-MF, and duration of exposure. In this study, the authors investigated the possible role of ELF-MF (50 Hz; 1 mT) exposure in altering sperm parameters.

Methods: Semen samples (n = 30) were obtained from healthy donors. At the end of the ELF-MF treatment, exposed and control samples were coded and transferred to an operator that, in a blinded condition, routinely processed them using light microscope to determine sperm quality of each aliquot. According to the World Health Organization (WHO) criteria (2021), normal sperm parameters were defined as sperm cell concentration ≥ 16 × 106 cells/ml; and sperm cells with typical morphology > 4 %; 'a+b' type motility or progressive motility ≥ 30 %; 'c' type motility or non-progressive sperm motility. Reactive oxygen species (ROS) levels in spermatozoa were investigated.

Results: Following exposure of the samples, the averages of the sperm parameters studied were compared. At first, no statistical differences were found for the mean of sperm concentration, while a statistically significant decrease was observed in the mean percentage of spermatozoa with typical morphology (13.3 % vs 15.6 %). The authors found a statistically significant difference in total sperm motility and in the average percentage of progressive motility of the exposed samples (26.2 %) compared to the unexposed ones (38.4 %). They also found a statistically significant decrease in the average percentage of non-progressive motility of the exposed samples (10.9 %) compared to the non-exposed ones (12.6 %). Finally, the authors investigated the effects of ELF-MF in inducing oxidative stress. They found that ELF-MF exposure significantly increased the ROS production (18.0 %) in the exposed samples compared to non-exposed ones.

Conclusion: The study states that exposure to ELF-MF at the frequency of 50 Hz (1 mT) for two hours induces statistically significant alterations in progressive motility, morphology and reactive oxygen species (ROS) production of human spermatozoa, suggesting a role of ELF-MF in altering reproductive function of spermatozoa. Occupational exposure to the sine waveform 1 mT 50 Hz ELF-MF used in this study is possible in the workplace. Moreover, these electromagnetic fields are product by many electronic devices and household appliances. Thus, alterations of progressive motility and morphology of spermatozoa would be important consequences of human exposures to ELF-MF.

Comments: Darbandi et al. reviewed studies on the effects of ELF-MF on male fertilities published from 1978 to 2016 (Darbandi et al., 2018). They concluded that 50 Hz ELF-MF had positive effects on sperm quality, motility, and fertility. Other exposures to 50 or 60 Hz ELF-MF either had no effects or caused adverse effects on sperm quality (Darbandi et al., 2018). The ELF-MF effect on sperm parameters likely depends both on the characteristics of ELF-MF (i.e., frequency and wave type) and on the doses and exposure mode (i.e. flow density and timing). Since some people (e.g. welders) can be exposed to the sine waveform 1mT 50 Hz ELF-MF used in this study, and the alterations found in sperm morphology and progressive motility would be important consequences of exposures to ELF-MF, further investigations are needed.

4. Exposure Assessment

4.1 Estimating exposure to extremely low frequency magnetic fields near high-voltage power lines and assessment of possible increased cancer risk among Slovenian children and adolescents

Zagar, T., Valic, B., Kotnik, T., et al. (2023). Radiology and Oncology, 57 (1), 59-69.

Background and objective: Some previous research showed that average daily exposure to extremely low frequency (ELF) magnetic fields (MF) of more than 0.3 or 0.4 µT could potentially increase risk of childhood leukaemia. This study aimed to develop a new three-dimensional method including precision terrain elevation data to calculate the long-term average ELF MF.

Methods: Data on population of Slovenian children and adolescents and on cancer patients with leukaemia's aged 0–19 years, brain tumours at age 0–29, and cancer in general at age 0–14 for a 12-year period 2005–2016 was obtained from the Slovenian Cancer Registry.

Results: The new method enables relatively fast calculation of the value of low-frequency magnetic fields for arbitrary loads of the power distribution network, as the value of each source for arbitrary load is calculated by scaling the value for nominal load, which also enables significantly faster adjustment of calculated estimates in the power distribution network.

Conclusion: According to the large-scale calculation for the whole country, only 0.5% of children and adolescents under the age of 19 in Slovenia lived in an area near HV PL with ELF MF density greater than 0.1 µT. The risk of cancer for children and adolescents living in areas with higher ELF MF was not significantly different from the risk of their peers.

5. Leukaemia Studies

5.1 Outdoor artificial light at night, air pollution, and risk of childhood acute lymphoblastic leukemia in the California Linkage Study of Early-Onset Cancers

Zhong, C., Wang, R., Morimoto, L.M. (2023). Scientific Reports. https://doi.org/10.1038/s41598-022-23682-z

Background and objective: Acute lymphoblastic leukemia (ALL) is the most common type of cancer in children (age 0‐14 years); however, the etiology remains incompletely understood. Several environmental exposures have been linked to risk of childhood ALL, including air pollution. Closely related to air pollution and human development is artificial light at night (ALAN), which is believed to disrupt circadian rhythm and impact health. This study sought to evaluate outdoor ALAN and air pollution on risk of childhood ALL.

Methods: The California Linkage Study of Early-Onset Cancers is a large population-based case‐control in California that identifies and links cancer diagnoses from the California Cancer Registry to birth records. For each case, 50 controls with the same year of birth were obtained from birth records. A total of 2,782 ALL cases and 139,100 controls were identified during 2000‐2015. ALAN was assessed with the New World Atlas of Artificial Night Sky Brightness and air pollution with an ensemble-based air pollution model of particulate matter smaller than 2.5 microns (PM2.5).

Results: After adjusting for known and suspected risk factors, the highest tertile of ALAN was associated with an increased risk of ALL in Hispanic children (odds ratio [OR] = 1.15, 95% confidence interval [CI] 1.01‐1.32). There also appeared to be a borderline association between PM2.5 level and risk of ALL among non-Hispanic White children (OR per 10 μ g/ m3 = 1.24, 95% CI 0.98‐1.56).

Conclusion: The authors observed elevated risk of ALL in Hispanic children residing in areas of greater ALAN. Further work is needed to understand the role of ALAN and air pollution in the etiology of childhood ALL in different racial/ethnic groups.

5.2 Neighborhood Deprivation, Indoor Chemical Concentrations, and Spatial Risk for Childhood Leukemia

Wheeler, D.C., Boyle, J., Carli, M. (2023). International Journal of Environmental Research and Public Health, 20, 3582. https://doi.org/10.3390/ijerph20043582

Background and objective: Leukemia is the most common childhood cancer in industrialized countries, and the increasing incidence trends in the US suggest that environmental exposures play a role in its etiology. Neighborhood socioeconomic status (SES) has been found to be associated with many health outcomes, including childhood leukemia. In this paper, a Bayesian index model approach is used to estimate a neighborhood deprivation index (NDI) in the analysis of childhood leukemia in a population-based case-control study (diagnosed 1999 to 2006) in northern and central California, with direct indoor measurements of many chemicals for 277 cases and 306 controls <8 years of age.

Methods: The authors considered spatial random effects in the Bayesian index model approach to identify any areas of significantly elevated risk not explained by neighborhood deprivation or individual

covariates, and assessed if groups of indoor chemicals would explain any elevated spatial risk areas. Due to not all eligible cases and controls participating in the study, a simulation study was conducted to add non-participants to evaluate the impact of potential selection bias when estimating NDI effects and spatial risk.

Results: The results in the crude model showed an odds ratio (OR) of 1.06 and 95% credible interval (CI) of (0.98, 1.15) for a one unit increase in the NDI, but the association became slightly inverse when adjusting for individual level covariates in the observed data (OR = 0.97 and 95% CI: 0.87, 1.07), as well as when using simulated data (average OR = 0.98 and 95% CI: 0.91, 1.05).

Conclusion: The authors found a significant spatial risk of childhood leukemia after adjusting for NDI and individual-level covariates in two counties, but the area of elevated risk was partly explained by selection bias in simulation studies that included more participating controls in areas of lower SES. The area of elevated risk was explained when including chemicals measured inside the home, and insecticides and herbicides had greater effects for the risk area than the overall study. The consideration of exposures and variables at different levels from multiple sources, as well as potential selection bias, are important for explaining the observed spatial areas of elevated risk and effect estimates.

5.3 Evaluation of Maternal Infection During Pregnancy and Childhood Leukemia Among Offspring in Denmark

He, J.-R., Yu, Y., Fang, F., Gissler, M. et al. (2023). JAMA Network Open. Pediatrics. 6(2):e230133. https://doi.org/10.1001/jamanetworkopen.2023.0133

Background and objective: Maternal infection is common during pregnancy and is an important potential cause of fetal genetic and immunological abnormalities. Maternal infection has been reported to be associated with childhood leukemia in previous case-control or small cohort studies. This study wants to evaluate the association of maternal infection during pregnancy with childhood leukemia among offspring in a large study.

Methids: This population-based cohort study used data from 7 Danish national registries (including the Danish Medical Birth Register, the Danish National Patient Registry, the Danish National Cancer Registry, and others) for all live births in Denmark between 1978 and 2015. Swedish registry data for all live births between 1988 and 2014 were used to validate the findings for the Danish cohort. Data were analyzed from December 2019 to December 2021. Maternal infection during pregnancy categorized by anatomic locations identified from the Danish National Patient Registry. The primary outcome was any leukemia; secondary outcomes were acute lymphoid leukemia (ALL) and acutemyeloid leukemia (AML). Offspring childhood leukemia was identified in the Danish National Cancer Registry. Associations were first assessed in the whole cohort using Cox proportional hazards regression models, adjusted for potential confounders. A sibling analysis was performed to account for unmeasured familial confounding.

Results: This study included 2 222 797 children, 51.3%of whom were boys. During the approximately 27 million person-years of follow-up (mean [SD], 12.0 [4.6] years per person), 1307 children were diagnosed with leukemia (ALL, 1050; AML, 165; or other, 92). Children born to mothers with infection during pregnancy had a 35%increased risk of leukemia (adjusted hazard ratio [HR], 1.35 [95%CI, 1.04-1.77]) compared with offspring of mothers without infection. Maternal genital and urinary tract

infections were associated with a 142%and 65%increased risk of childhood leukemia, with HRs of 2.42 (95%CI, 1.50-3.92) and 1.65 (95%CI, 1.15-2.36), respectively. No association was observed for respiratory tract, digestive, or other infections. The sibling analysis showed comparable estimates to the whole-cohort analysis. The association patterns for ALL and AML were similar to that for any leukemia. No association was observed for maternal infection and brain tumors, lymphoma, or other childhood cancers.

Conclusion: In this cohort study of approximately 2.2 million children, maternal genitourinary tract infection during pregnancy was associated with childhood leukemia among offspring. If confirmed in future studies, these findings may have implications for understanding the etiology and developing preventive measures for childhood leukemia.

5.4 Associations between early-life and in utero infections and cytomegalovirus-positive acute lymphoblastic leukemia in children

Gallant, R.E., Arroyo, K., Metayer, C., et al. (2023). International Journal of Cancer, 152, 845‑853. https://doi.org/10.1002/ijc.34292

Background and objective: Childhood infections and cytomegalovirus (CMV) are associated with pediatric acute lymphoblastic leukemia (ALL). CMV dysregulates the host immune system and alters the immune response to subsequent antigenic exposures. The authors suspect that this immune dysregulation contributes to increased numbers of symptomatic infections in childhood allowing for expansion of pre-leukemic clones. This study explored the association between childhood infections, maternal infections during pregnancy and CMV positive ALL.

Methods: Using a droplet digital PCR assay, diagnostic ALL bone marrow samples from the California Childhood Leukemia Study (1995-2015) were screened for the presence of CMV DNA identifying CMV-positive and CMV-negative cases. A case-only analysis (n = 524) was performed, comparing the number and types of childhood infections and maternal infections during pregnancy between CMV-positive and CMV-negative ALL cases using logistic regression.

Results: With increasing numbers of infections in the first 12 months of life, children were more likely to classify to the highest tertile of CMV DNA in the bone marrow at diagnosis (OR: 1.04, 95% CI: 1.01-1.08). Specifically, those reporting cough or flu in the first 12 months were more likely to be CMV-positive at ALL diagnosis (OR: 2.15, 95% CI: 1.06-4.37 and OR: 2.06, 95% CI: 1.17-3.63 respectively). Furthermore, those with a history of maternal infection during pregnancy were more likely to be CMV-positive (OR: 2.12, 95% CI: 1.24-3.62).

Conclusion: The authors hypothesize that children with underlying immune dysregulation develop more symptomatic infections in childhood and ultimately CMV-positive ALL; this underlying immune dysregulation may be due to early immune system alterations via CMV exposure (in utero or early infancy) proposing a potential link between CMV and ALL etiology.

5.5 Maternal anemia and childhood cancer: a population-based case-control study in Denmark

Qureshia, N., Orimoloyeb, H., Hansen, J., et al. (2023). Cancer Epidemiology, 82: 102308. https://doi.org/10.1016/j.canep.2022.102308

Background and objective: Childhood cancer risk is associated with maternal health during pregnancy. Anemia in pregnancy is a common condition, especially in low-income countries, but a possible association between maternal anemia and childhood cancer has not been widely studied.

Methods: This study examined the relation in a population-based study in Denmark (N = 6420 cancer cases, 160,485 controls). Cases were taken from the Danish Cancer Registry, and controls were selected from national records. The authors obtained maternal anemia diagnoses from the National Patient and Medical Births registries. In a separate analysis within the years available (births 1995–2014), cancer risks among mothers taking prescribed vitamin supplements were examined, using data from the National Prescription Register. The risks of childhood cancer were examined using conditional logistic regression.

Results: The risks of neuroblastoma [odds ratio (OR= 1.83, 95% confidence interval (CI): 1.04, 3.22] and acute lymphoblastic leukemia (OR= 1.46, 95% CI 1.09, 1.97) were increased in children born to mothers with anemia in pregnancy. There was a two-fold increased risk for bone tumors (OR= 2.59, 95% CI: 1.42, 4.72), particularly osteosarcoma (OR= 3.54, 95% CI 1.60, 7.82). With regards to prescribed supplement use, mothers prescribed supplements for B12 and folate deficiency anemia (OR= 4.03, 95% CI 1.91, 8.50) had an increased risk for cancer in offspring.