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1. Reviews and meta-analyses

1.1 Exposure to magnetic fields and childhood leukemia: a systematic review and meta-analysis of case-control and cohort studies.

Brabant, C., Geerinck, A., Beudart, C., Tirelli, E., Geuzaine, C., Bruyère, O. (2022). Exposure to magnetic fields and childhood leukemia: a systematic review and meta-analysis of case-control and cohort studies. *Reviews on Environmental Health*. Published online March 15, 2022. doi: 10.1515/reveh-2021-0112

Background and Objective: The association between childhood leukemia and extremely low frequency magnetic fields (ELF-MF) generated by power lines and various electric appliances has been studied extensively during the past 40 years. However, the conditions under which ELF-MF represent a risk factor for leukemia are still unclear. Therefore, the authors have performed a systematic review and meta-analysis to clarify the relation between ELF-MF from several sources and childhood leukemia.

Method: The authors have systematically searched Medline, Scopus, Cochrane Database of Systematic Review and DARE to identify each article that has examined the relationship between ELF-MF and childhood leukemia. They have performed a global meta-analysis that takes into account the different measures used to assess magnetic field exposure: magnetic flux density measurements (<0.2 μT vs. >0.2 μT), distances between the child's home and power lines (>200 m vs. <200 m) and wire codings (low current configuration vs. high current configuration). Moreover, meta-analyses either based on magnetic flux densities, on proximity to power lines or on wire codings have been performed. The association between electric appliances and childhood leukemia has also been examined.

Results: Of the 863 references identified, 38 studies have been included in the systematic review. The global meta-analysis indicated an association between childhood leukemia and ELF-MF (21 studies, pooled OR=1.26; 95% CI 1.06–1.49), an association mainly explained by the studies conducted before 2000 (earlier studies: pooled OR=1.51; 95% CI 1.26–1.80 vs. later studies: pooled OR=1.04; 95% CI 0.84–1.29). The meta-analyses based only on magnetic field measurements indicated that the magnetic flux density threshold associated with childhood leukemia is higher than 0.4 μT (12 studies, >0.4 μT : pooled OR=1.37; 95% CI 1.05–1.80; acute lymphoblastic leukemia alone: seven studies, >0.4 μT : pooled OR=1.88; 95% CI 1.31–2.70). Lower magnetic fields were not associated with leukemia (12 studies, 0.1–0.2 μT : pooled OR=1.04; 95% CI 0.88–1.24; 0.2–0.4 μT : pooled OR=1.07; 95% CI 0.87–1.30). The meta-analyses based only on distances (five studies) showed that the pooled ORs for living within 50 m and 200 m of power lines were 1.11 (95% CI 0.81–1.52) and 0.98 (95% CI 0.85–1.12), respectively. The pooled OR for living within 50 m of power lines and acute lymphoblastic leukemia analyzed separately was 1.44 (95% CI 0.72–2.88). The meta-analyses based only on wire codings (five

studies) indicated that the pooled OR for the very high current configuration (VHCC) was 1.23 (95% CI 0.72–2.10). Finally, the risk of childhood leukemia was increased after exposure to electric blankets (four studies, pooled OR=2.75; 95% CI 1.71–4.42) and, to a lesser extent, electric clocks (four studies, pooled OR=1.27; 95% CI 1.01–1.60).

Conclusion: These results suggest that ELF-MF higher than 0.4 μ T can increase the risk of developing leukemia in children, probably acute lymphoblastic leukemia. Prolonged exposure to electric appliances that generate magnetic fields higher than 0.4 μ T like electric blankets is associated with a greater risk of childhood leukemia. This meta-analysis suggests that exposure to residential magnetic fields higher than 0.4 μ T can increase the risk of leukemia in children. Nevertheless, it is important to emphasize the fact that very few homes are exposed to magnetic fields higher than 0.4 μ T generated by overhead power lines in high income countries. Moreover, the annual incidence of childhood leukemia is very low and ranges between 35 and 50 cases per million children in western European countries and North America. Since the absolute risk of childhood leukemia is very low and children are rarely continuously exposed to magnetic fields higher than 0.4 μ T in high income countries, the increased leukemia risk found in this meta-analysis does not represent a major public health concern in these countries. Magnetic flux densities higher than 0.4 μ T are usually within 50 m of overhead power lines. Magnetic flux density measurements should be performed if children live within 200 m of overhead power lines to guarantee that they are not exposed to ELF-MF higher than 0.4 μ T. In contrast, living more than 200 m away from overhead power lines could be considered a safe distance for children that is not linked to a higher leukemia risk. This systematic review suggests that children from middle income countries like Mexico and Iran are more likely to be exposed to magnetic fields above 0.4 μ T and the risk of leukemia attributable to ELF-MF is probably higher in these countries. It is noteworthy that none of the studies included in this review have been performed in low income countries or in Africa. More research on ELF-MF and childhood leukemia is needed in these countries, particularly in African countries.

This meta-analyses suggest that exposure to electric appliances like electric blankets and bedside electric clocks increase the risk of leukemia in children. However, it is important to note that the studies that have found an association between these electric appliances and childhood leukemia have been performed more than 20 years ago and our findings should be interpreted based on the electric equipment used today. Electric blankets and bedside electric clocks used at the end of the twentieth century could generate magnetic fields higher than 0.4 μ T and children were typically exposed to these electric appliances during several hours in a row. In contrast, hair dryers can also generate magnetic fields higher than 0.4 μ T but are usually used during a shorter period of time and we did not find a significant association between the use of hair dryers and childhood leukemia. These findings are relevant today in the sense that the duration of exposure to ELF-MF plays a role and that children should not be exposed to electric appliances that generate magnetic fields higher than 0.4 μ T during long periods of time. Importantly, Magne and colleagues have measured personal exposure to ELF-MF in French children between 2007 and 2009. They have found that alarm clocks were the main variable linked to the magnetic field exposure of the children. The proportion of children exposed to magnetic fields higher than 0.4 μ T was 3.1% when all children were included in the analysis and 0.8% when the analysis was restricted to children for which no alarm clock had been identified. Taken together, these results and the meta-analysis suggest that “bedside” electric clocks and alarm clocks that generate magnetic fields higher than 0.4 μ T at close distance should be located at least 1 m away from the bed of the child, because the magnetic flux density generated by electric clocks was lower than 0.4 μ T at this distance. There is no recent update of the study by Behrens et al. that has performed reliable magnetic flux density measurements for electric appliances manufactured recently that generate ELF-

MF. Studies with reliable exposure characterization with respect to sources of ELF-MF are needed, especially for the electric appliances manufactured recently that we use on a daily basis.

In summary, this study suggests that exposure to ELF-MF higher than 0.4 μT increases the risk of developing leukemia in children. Acute lymphoblastic leukemia is probably the subtype of leukemia associated with ELF-MF. Prolonged exposure to electric appliances that generate magnetic fields higher than 0.4 μT like electric blankets is associated with a more elevated risk of childhood leukemia. The distance from power lines linked to leukemia is difficult to determine but living more than 200 m away from power lines is likely a safe distance for children not associated with a higher leukemia risk.

1.2 Magnetic Fields and Cancer: Epidemiology, Cellular Biology, and Theranostics.

Maffei, M.E. (2022). Magnetic Fields and Cancer: Epidemiology, Cellular Biology, and Theranostics, *International Journal of Molecular Sciences*, 23, 1339. <https://doi.org/10.3390/ijms23031339>

Background and Objective: Humans are exposed to a complex mix of man-made electric and magnetic fields (MFs) at many different frequencies, at home and at work. Epidemiological studies indicate that there is a positive relationship between residential/domestic and occupational exposure to extremely low-frequency electromagnetic fields and some types of cancer, although some other studies indicate no relationship. In this review, after an introduction on the MF definition and a description of natural/anthropogenic sources, the epidemiology of residential/domestic and occupational exposure to MFs and cancer is reviewed, with reference to leukemia, brain, and breast cancer. The in vivo and in vitro effects of MFs on cancer are reviewed considering both human and animal cells, with particular reference to the involvement of reactive oxygen species (ROS). MF application on cancer diagnostic and therapy (theranostic) are also reviewed by describing the use of different magnetic resonance imaging (MRI) applications for the detection of several cancers. Finally, the use of magnetic nanoparticles is described in terms of treatment of cancer by nanomedical applications for the precise delivery of anticancer drugs, nanosurgery by magnetomechanic methods, and selective killing of cancer cells by magnetic hyperthermia.

Conclusion of the author: Although scientists do not generally agree that there is a cause-effect relationship between exposure to MF and cancer, MFs might not be the direct cause of cancer but may contribute to produce ROS and generate oxidative stress, which could trigger or enhance the expression of oncogenes.

2. Residential exposure

2.1 Residential extremely low frequency magnetic fields and skin cancer.

Khan, M.W., Juutilainen, J., Naarala, J., Roivainen, P. (2022). Residential extremely low frequency magnetic fields and skin cancer. *Occupational Environmental Medicine*, 79, 49-54. doi:10.1136/oemed-2021-107776

Background and Objective: Photoinduced radical reactions have a fundamental role in skin cancer induced by ultraviolet radiation, and changes in radical reactions have also been proposed as a mechanism for the putative carcinogenic effects of extremely low frequency (ELF) magnetic fields (MFs). The authors assessed the association of melanoma and squamous cell carcinoma with residential MF exposure.

Method: All cohort members had lived in buildings with indoor transformer stations (TSs) during the period from 1971 to 2016. MF exposure was assessed based on apartment location. Out of the 225 492 individuals, 8617 (149 291 person-years of follow-up) living in apartments next to TSs were considered as exposed, while individuals living on higher floors of the same buildings were considered as referents. Associations between MF exposure and skin cancers were examined using Cox proportional hazard models.

Results: The HR for MF exposure ≥ 6 month was 1.05 (95% CI 0.72 to 1.53) for melanoma and 0.94 (95% CI 0.55 to 1.61) for squamous cell carcinoma. Analysis of the age at the start of residence showed an elevated HR (2.55, 95% CI 1.15 to 5.69) for melanoma among those who lived in the apartments when they were less than 15 years old. This finding was based on seven exposed cases.

Conclusion of the authors: The results of this study suggested an association between childhood ELF MF exposure and adult melanoma. This is in agreement with previous findings suggesting that the carcinogenic effects of ELF MFs may be associated particularly with childhood exposure.

Comment: The results of this study should be interpreted with caution, due to the exposure assessment. It is not straightforward to interpret the findings as support to the hypothesis that residential MF enhances skin cancer by affecting UV-induced radical reactions. Exposure to solar UV radiation occurs outdoors, so the UV-induced radical reactions cannot be directly affected by the MFs present in residences. Moreover, the mechanistic explanation is still unclear.

3. Occupational exposure

None

4. Human Experimental Studies

4.1 Assessment of cortisol secretory pattern in workers chronically exposed to ELF-EMF generated by high voltage transmission lines and substations .

Touitou, Y., Selmaoui, B., Lambrozo, J. (2022). Assessment of cortisol secretory pattern in workers chronically exposed to ELF-EMF generated by high voltage transmission lines and substations. Environmental International, 161, 107103. <https://doi.org/10.1016/j.envint.2022.107103>

Background and Objective: The authors investigated the effects of extremely-low frequency electromagnetic fields (ELF-EMFs; 50 Hz) on the secretion of cortisol in 14 men (mean age = 38.0 ± 0.9 years) working in extra-high voltage (EHV) substations. The workers dwelt in houses that were close to substations and high-voltage lines. Thus, they had long histories (1–20 years) of long-term exposure to ELF-EMFs.

Method: Magnetic field strength was recorded using Emdex dosimeters worn by the volunteers day and night for seven days; the one-week geometric mean ranged from 0.1 to 2.6 μT . Blood samples were taken hourly from 20:00 to 08:00 the next morning. Cortisol concentrations and patterns were compared to age-matched, unexposed control subjects whose exposure level was ten times lower.

Results: The comparison of the control group (n = 15) and the groups exposed to fields of 0.1–0.3 μT (n = 5) and > 0.3 μT (n = 9), respectively, revealed a significant effect of field intensity on the cortisol secretory pattern. This study revealed that ELF-EMF exposure decreased the peak-time serum cortisol levels, although the general secretory pattern of cortisol was unaffected.

Conclusion of the authors: This study strongly suggests that chronic exposure to ELF-EMFs alters the peak-time serum cortisol levels. Studies are required on the effect of this disruption in high-risk populations such as children, elderly people, and patients.

5. Exposure Assessment

None

6. Leukaemia Studies

6.1 Environmental Risk Factors for Childhood Acute Lymphoblastic Leukemia: An Umbrella Review

Onyije, F.M., Olsson, A., Baaken, D., Erdmann, F., Stanulla, D., Wollschläger, D., Schüz, J. (2022). Environmental Risk Factors for Childhood Acute Lymphoblastic Leukemia: An Umbrella Review, *Cancers*, 14, 382. <https://doi.org/10.3390/cancers14020382>

Background and Objective: Leukemia is the most common type of cancer among children and adolescents worldwide. The aim of this umbrella review was (1) to provide a synthesis of the environmental risk factors for the onset of childhood acute lymphoblastic leukemia (ALL) by exposure window, (2) evaluate their strength of evidence and magnitude of risk, and as an example (3) estimate the prevalence in the German population, which determines the relevance at the population level.

Method: Relevant systematic reviews and pooled analyses were identified and retrieved through PubMed, Web of Science databases and lists of references.

Results: Only two risk factors (low doses of ionizing radiation in early childhood and general pesticide exposure during maternal preconception/pregnancy) were convincingly associated with childhood ALL. Other risk factors including extremely low frequency electromagnetic field (ELF-MF), living in proximity to nuclear facilities, petroleum, benzene, solvent, and domestic paint exposure during early childhood, all showed some level of evidence of association. Maternal consumption of coffee (high consumption/>2 cups/day) and cola (high consumption) during pregnancy, paternal smoking during the pregnancy of the index child, maternal intake of fertility treatment, high birth weight (>4000 g) and caesarean delivery were also found to have some level of evidence of association. Maternal folic acid and vitamins intake, breastfeeding (>6 months) and day-care attendance, were inversely associated with childhood ALL with some evidence.

Conclusion: Only low doses of ionizing radiation in early childhood and maternal exposure to general pesticides during pregnancy showed convincing evidence of an association with childhood ALL. Other risk factors vary in level of association.

Remark from the authors: The results of this umbrella review should be interpreted with caution; as the evidence stems almost exclusively from case-control studies, where selection and recall bias are potential concerns, and whether the empirically observed association reflect causal relationships remains an open question. Hence, improved exposure assessment methods including accurate and reliable measurement, probing questions and better interview techniques are required to establish causative risk factors of childhood leukemia, which is needed for the ultimate goal of primary prevention.

6.2 Environmental Risk Factors for Childhood Cancer in an Era of Global Climate Change: A Scoping Review.

Buser, J.M., Lake, K., Ginier, E. (2022). Environmental Risk Factors for Childhood Cancer in an Era of Global Climate Change: A Scoping Review. *Journal of Pediatric Health Care*, 36 (1), 46-57.

Background and Objective: Contemporary research about environmental risk factors in an era of global climate change to inform childhood cancer prevention efforts is disjointed. Planetary pediatric providers need to establish a better understanding of how the postnatal environment influences childhood cancer. The authors conducted a scoping review of recent scientific literature with the aim of understanding the environmental risk factors for childhood cancer.

Method: Ovid Medline, CINAHL, and Scopus databases were searched with results limited to the English language with publication years 2010–2021. Two independent reviewers screened 771 abstracts and excluded 659 abstracts and 65 full-text articles on the basis of predefined criteria.

Results: The scoping review identified 47 studies about environmental risk factors for childhood cancer with mixed results and limited consensus in four main categories, including air pollution, chemical exposures, radiation, and residential location.

Conclusion of the authors: The body of literature included in this review highlights recent advances about how the postnatal environment influences childhood cancer. However, only a small number of studies were included in each category, highlighting limited research into risk factors and an ongoing gap in the current scientific literature. Results presented in the studies remain fragmented, demonstrating the need for more research as it is not yet possible to clearly and consistently identify environmental risk factors associated with childhood cancer. In an era of climate change, additional research by collaborative international groups of planetary health researchers about environmental risk factors is needed to inform global health policy for childhood cancer prevention efforts.

6.3 Antibiotics in early life and childhood pre-B-ALL. Reasons to analyze a possible new piece in the puzzle

Cardesa-Salzmann, T.M., Simon, A., Graf, N. (2022). Antibiotics in early life and childhood pre-B-ALL. Reasons to analyze a possible new piece in the puzzle. *Discover Oncology*, 13(5). <https://doi.org/10.1007/s12672-022-00465-6>

Background and Objective: Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer with precursor B-cell ALL (pB-ALL) accounting for ~ 85% of the cases. Childhood pB-ALL development is influenced by genetic susceptibility and host immune responses. The role of the intestinal microbiome in leukemogenesis is gaining increasing attention since Vicente-Duenas' seminal work demonstrated that the gut microbiome is distinct in mice genetically predisposed to ALL and that the alteration of this microbiome by antibiotics is able to trigger pB-ALL in *Pax5* heterozygous mice in the absence of infectious stimuli. In this review the authors provide an overview on novel insights on the role of the microbiome in normal and preleukemic hematopoiesis, inflammation, the effect of dysbiosis on hematopoietic stem cells and the emerging importance of the innate immune responses in the conversion from preleukemic to leukemic state in childhood ALL.

Conclusion of the authors: Since antibiotics, which represent one of the most widely used medical interventions, alter the gut microbial composition and can cause a state of dysbiosis, this raises exciting

epidemiological questions regarding the implications for antibiotic use in early life, especially in infants with a preleukemic “first hit”. Shedding light through a rigorous study on this piece of the puzzle may have broad implications for clinical practice.

6.4 Medication-associated Phthalate Exposure and Childhood Cancer Incidence

Ahern, T.P., Spector, L.G., Damkier, P., Esen, B.O., Ulrichsen, S.P., Eriksen, K., Lash, T.L., Sorensen, H.T., Cronin-Fenton, D.P. (2022). Medication-associated Phthalate Exposure and Childhood Cancer Incidence. Journal of the National Cancer Institute. <https://doi.org/10.1093/jnci/djac045>

Background and Objective: Human phthalate exposure is widespread through contact with myriad consumer products. Exposure is particularly high through medications formulated with phthalates. Phthalates disrupt normal endocrine signaling and are associated with reproductive outcomes and incidence of some cancers. The authors measured associations between gestational and childhood medication-associated phthalate exposures and the incidence of childhood cancers.

Method: The authors identified all live births in Denmark between 1997 and 2017, including both children and birth mothers. Using drug ingredient data merged with the Danish National Prescription Registry, they measured phthalate exposure through filled prescriptions for mothers during pregnancy (gestational exposure) and for children from birth until age 19 years (childhood exposure). Incident childhood cancers were ascertained from the Danish Cancer Registry, and associations were estimated with Cox regression models.

Results: Among 1 278 685 children, there were 2027 childhood cancer cases diagnosed over 13.1 million person–years of follow-up. Childhood phthalate exposure was strongly associated with incidence of osteosarcoma (hazard ratio [HR] 2.78, 95% confidence interval [CI] 1.63 to 4.75). The authors also observed a positive association with incidence of lymphoma (HR 2.07, 95% CI 1.36 to 3.14), driven by associations with Hodgkin and non-Hodgkin lymphoma but not Burkitt lymphoma. Associations were apparent only for exposure to low-molecular phthalates, which have purportedly greater biological activity.

Conclusion of the authors: Childhood phthalate exposure was associated with incidence of osteosarcoma and lymphoma before age 19 years. Lingering questions include which specific phthalate(s) are responsible for these associations, by what mechanisms they occur, and to what extent childhood cancer cases could be avoided by reducing or eliminating the phthalate content of medications and other consumer products.