Letters to the Editor

Correspondence re: Navas-Acien *et al.*, Interactive Effect of Chemical Substances and Occupational Electromagnetic Field Exposure on the Risk of Gliomas and Meningiomas in Swedish Men. *11:* 1678–1683, 2002

Letter

Lucio G. Costa

Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, Washington 98105

A. Navas-Acien, M. Pollan *et al.* recently reported that combined exposures to extremely-low-frequency (ELF) EMFs[1] and certain toxic chemicals can act synergistically to increase brain cancer risks, more specifically, gliomas (1). The risk for gliomas was increased 50% by exposure to solvents, 2-fold by pesticides/herbicides and 4-fold by lead. A large number of previous epidemiological studies had indicated that exposure to EMF may pose a small risk for brain cancer (2). However, skepticism has also been raised on the validity and significance of such findings (3). One of the problems of many such epidemiological studies is that brain tumors were lumped together, without a full appreciation for their different etiology and cellular characteristics. Indeed, when gliomas were singled out, the relative risk associated with EMF was greater, and even more so in the case of astrocytomas, which are the most common type of brain tumors (4). The biological basis for such an association, *i.e.*, the cellular and molecular mechanisms underlying these effects of EMF, are, however, still poorly understood. A prevailing hypothesis is that EMFs may not initiate cancer but may, instead, act as promoters. In this respect, our recent findings that EMFs can increase the proliferation of human astrocytoma cells *in vitro* may be of some relevance (5). Indeed, the mitogenic effect of EMFs seemed to be mediated by protein kinase C (PKC), which is the intracellular receptor for tumor promoters such as the phorbol esters. Furthermore, EMF strongly potentiated the effect of other mitogens acting through the PKC pathway. Of interest also was the finding that EMFs did not increase DNA synthesis in rat cortical astrocytes, *i.e.*, in similar nontransformed cells, lending support to the hypothesis that EMFs are unlikely to be cancer initiators but might act as tumor promoters. It should be also noted in this regard that, compared with nonmalignant glial cells, all human glioma cell lines express a high level of PKC activity, and that PKC-dependent pathways are believed to be the major determinants for proliferation of glioma cells (6).

Received 5/2/03; accepted 7/1/03.

[1] The abbreviations used are: EMF, electromagnetic field; PKC, protein kinase C.

The article by Novas-Acien *et al.* adds a new aspect to the issue, *i.e.*, the possible interactive effect of concomitant exposure to EMF and certain toxic chemicals. In particular, the almost 4-fold increased risk found with combined exposure to lead and EMF is noteworthy. Exposure to lead has also been associated with an increased risk for brain cancer, most notably astrocytomas (7), but the overall evidence is still inconclusive. Lead also does not seem to act as a tumor initiator but is believed to act as a promoter. Recently, we have found that lead can significantly increase the proliferation of human astrocytoma cells by a mechanism that involves the activation of PKC (8). Similar to EMF, lead was not mitogenic in nontransformed glial cells. Whether, in this *in vitro* model, EMF and lead may interact in an additive or synergistic manner remains to be investigated. These considerations, however, point out that, as new approaches and hypotheses are needed in epidemiological studies to bring a better understanding of the possible association between EMF exposure and the risk of gliomas (1), attention should be also given to mechanistic studies that may provide biological plausibility for current findings and novel insights for future studies.

References

1. Navas-Acien, A., Pollan, M., Gustavsson, P., Floderus, B., Plato, N., and Dosemeci, M. Interactive effect of chemical substances and occupational electromagnetic field exposure on the risk of gliomas and meningiomas in Swedish men. Cancer Epidemiol. Biomark. Prev., *11:* 1678–1683, 2002.

2. Kheifets, L. I., Afifi, A. A., Buffler, P. A., and Zhang, Z. W. Occupational electric and magnetic field exposure and brain cancer: a meta-analysis. J. Occup. Environ. Med., *37:* 1327–1341, 1995.

3. Savitz, D. A. Invited commentary: electromagnetic fields and cancer in railway workers. Am. J. Epidemiol., *153:* 836–838, 2001.

4. Wrensch, M., Bondy, M. L., Wiencke, J., and Yost, M. Environmental risk factors for primary malignant brain tumors: a review. J. Neuroncol., *17:* 47–64, 1993.

5. Wei, M., Guizzetti, M., Yost, M., and Costa, L. G. Exposure to 60-Hz magnetic fields and proliferation of human astrocytoma cells *in vitro.* Toxicol. Appl. Pharmacol., *162:* 166–176, 2000.

6. Baltuch, G. M., and Yong, V. W. Signal transduction for proliferation of glioma cells *in vitro* occurs predominantly through a protein kinase C-mediated pathway. Brain Res., *710:* 143–149, 1996.

7. Anttila, A., Heikkila, P., Nykyri, E., Kauppinen, T., Pukkala, E., Hernberg, S., and Hemminki, K. Risk of nervous system cancer among workers exposed to lead. J. Occup. Environ. Med., *38:* 131–136, 1996.

8. Lu, M., Guizzetti, M., and Costa, L. G. Inorganic lead stimulates DNA synthesis in human astrocytoma cells: role of protein kinase C α. J. Neurochem., *78:* 590–599, 2001.

Correspondence re: Navas-Acien *et al.*, Interactive Effect of Chemical Substances and Occupational Electromagnetic Field Exposure on the Risk of Gliomas and Meningiomas in Swedish Men. *11:* 1678–1683, 2002

Lucio G. Costa

Cancer Epidemiol Biomarkers Prev 2003;12:950.