RF and ELF-EMF: Gene-Pathway-Disease Analysis

Christopher J. Portier¹, Fred Parham², Xiaoqing Chang², Reuben Thomas³, Meike Mevissen⁴⁵

¹ National Center for Environmental Health and Agency for Toxic Substances and Disease Registry, Atlanta, GA, USA; ² National Toxicology Program, Research Triangle Park, NC, USA; ³ University of California-Berkeley, Berkeley, CA, USA; ⁴ Division of Veterinary Pharmacology & Toxicology, Vetsuisse Faculty, University of Bern, 3012 Bern, Switzerland; ⁵ To whom correspondence should be sent

Background
Using in-vitro data in human cell lines, several research groups have investigated changes in gene expression in cellular systems following exposure to Extremely Low Frequency (ELF), Low Frequency (LF), and Radio Frequency (RF) ElectroMagnetic Fields (EMF).

Methods
We obtained 5 studies for ELF and LF EMF, for which we had all of the microarray data and 3 studies where the manuscript contained enough information to extract significantly altered genes (see Table 1). In addition, we obtained 13 full data sets and 5 literature datasets for RF EMF (see Table 1). Plausible links between exposure to ELF/LF and RF EMF, and human diseases were identified using a three-step process: a) linking genes associated with classes of human diseases to molecular pathways; b) linking pathways to ELF and RF EMF microarray data; and c) identifying associations between human disease and EMF exposures where the pathways are significantly similar.

Results
(a) A total of 60 pathways were associated with human diseases, mostly focused on basic cellular functions such as jak-stat signaling or metabolic functions such as metabolism by cytochrome P450 enzymes. Cancer was linked with 21 pathways predominantly relating to metabolism (7 pathways), hormone control (2 pathways), DNA repair (3 pathways) and cellular replication (3). Other pathways significantly linked to cancer and known to be important to carcinogenesis included jak-stat signaling, long-term potentiation and adipocytokine signaling. Thus, of the 21 pathways identified, 18 have long-standing links to cancer as a disease process. Cardiovascular disease was linked to 17 pathways, chemical dependency was linked to 11, neurological disorders to 10, metabolic disorders to 22, and reproductive disorders with 12. The other diseases had too few linkages to be included in our analysis. Many pathways were linked to 5 or more diseases and dealt with basic cellular functions such as jak-stat signaling, cytokine-cytokine receptor interaction, and neuroactive ligand-receptor interaction.

(b) In this study, 13 RF EMF (A-M) microarray, 1 LF EMF (n) microarray and 4 ELF EMF (O-R) microarray datasets with human cells for which we had the original data
were analyzed. In addition, two datasets were constructed by pooling 5 RF EMF (dataset S) and 3 ELF EMF (dataset T) microarray studies from the literature in multiple cell lines with multiple field strengths and exposure durations. These literature studies identified all significantly altered genes.

As a general rule, the individual datasets were linked to quite diverse pathways. The total number of linked pathways was also quite diverse ranging from 3 for dataset P to 26 for dataset B. The separate analyses of the individual RF EMF studies showed 31 pathways being significant at $p<0.05$ in more than one study. When all of the RF EMF studies were combined in one analysis, there were 25 significant pathways linked to the exposure.

(c) Psychological disorders show significant linkages to two datasets (B,C) and the same 5 pathways in both cases (tyrosine metabolism; linoleic acid metabolism; calcium signaling pathway; neuroactive ligand-receptor interaction; long-term depression). However, when the datasets were combined (A-N), the significance could not be maintained because the combined dataset no longer linked to tyrosine metabolism and calcium signaling. The other diseases showed minimal links.

The ELF EMF studies did not demonstrate as robust a response as the RF EMF studies. The four individual studies for which we had complete data (O-R) each showed 3 to 14 links. Only 2 pathways were significantly linked in more than one study, both being linked in 2 studies. These two pathways, inositol phosphate metabolism and FC-gamma R mediated phagocytosis are not related. The analysis of all of the ELF EMF data combined (experiments O-R,T) resulted in 15 significantly linked pathways. No obvious pattern in these linked pathways was seen.

None of the complete ELF EMF datasets (O-R) were significantly linked to any disease. Surprisingly, the combined ELF EMF literature dataset (T) was linked to cancer, chemical dependency, metabolic disorders, and neurological disorders, predominantly through linoleic acid metabolism, retinol metabolism, and drug metabolism by cytochrome P450. None of the combined ELF EMF datasets were linked to any disease.

**Discussion and Conclusions**

The greatest strength of this analysis is that it is completely objective in its approach. Data was identified by reviewing literature and all data was handled equally depending on the type of data available for the analysis. The results are all tied to objective statistical methods that demonstrate the strength of the linkage between various pathways and EMF exposure and disease. The major weakness of this analysis is the paucity of the EMF microarray data of the depth and complexity needed to support a more thorough analysis. Thus, at best, this analysis generates hypotheses that must be followed up. Changes in gene expression do not always correlate to changes in the proteins, enzymes and transcription factors that govern cellular signaling and cellular metabolism. In following up with further research, both gene expression studies and studies of protein changes should be considered. RF EMF effects on psychological and neurological function seem to be the most
promising area for further study. In addition, changes to metabolic functions for all forms of EMF appear to be a common theme in these data.