

## **Reviewer's report**

**Title:** Understanding environmental causes of disease: what can we expect from new technologies?

**Version:** 1 **Date:** 19 February 2009

**Reviewer:** Martyn T Smith

### **Reviewer's report:**

The paper nicely summarizes ideas pertinent to the study of the environmental causes of disease. I particularly enjoyed the opening part of the paper as this is a succinct historical perspective of the current status of environmental epidemiology. The discussion of the relative risk contributions of smoking and the nicotinic acetylcholine receptor subunit risk allele frames the genes v. environment argument well. In this section and later the authors address the advantages of the GWAS approach and the challenges of assessing the contribution to risk from the environment. The central theme of his paper is the idea of cumulative exposures and "clinical vulnerability" to later low exposure and this is discussed thoroughly with the differential effects of ETS among ex-smokers and never smokers on disease risk, as an example. This has implications for epidemiology and toxicogenomic studies which can be confounded by cumulative distal exposures and ways to address this are discussed.

The main weakness of the paper is the failure of the paper to really address the "what can we expect from new technologies" in the title. Examples of gene expression profiling, epigenomics, proteomics, and metabolomics are given but their potential isn't really discussed or how we will utilize them appropriately. There is a disconnect between the OMICS section and the rest of the paper.

### **Major Compulsory Revisions**

The second half of the paper could be improved by discussing the challenges we face in using omics technologies in epi studies. Much of the current writing is wishful thinking and the limited examples given are not very convincing. Why if omics can really trace the history of environmental insults has there not been more application of these technologies? The problems with omics include expense, no standard methods for analysis of very large data sets and the utility of the information gained. The latter is usually mechanistic and nothing to date

has been developed to tell us about historical exposures. A more critical review and a discussion of the way forward would be better in my view - epidemiologists may become sanguined about omics otherwise.

#### Minor Essential Revisions

p.11 The field of genomics is far greater than the areas described by the authors. There are functional and evolutionary genomics for example. The authors need to reword this section.

p. 11 In same para proteomics and metabolomics are described as being high-throughput and highly sensitive. Neither is currently true. The authors are making things sound easier than they actually are.

p.12 first para- reference missing?

p.12 The discussion of epigenomics is over simplistic and too limited. Reference is made to a study of benzene exposed individuals in Italy that doesnt use epigenomics at all.

p.13 The same is true for the discussion of proteomics and no critical evaluation is presented.

p.14 The claim is made that metabolomics will be simpler because yeast have fewer than 600 metabolites, but they have only 4,000 genes and are a unicellular organism. Humans will be infinitely more complex and the metabolome will be constantly changing by the minute. How will this inform us about historical insults?

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Declaration of competing interests:**

'I declare that I have no competing interests'