

Reviewer's report

Title: GSTM1 and APE1 genotypes affect arsenic-induced oxidative stress: a repeated measures study

Version: 1 **Date:** 10 October 2007

Reviewer: Karin Broberg

Reviewer's report:

General

The authors of this manuscript investigate the association between arsenic exposure (total urinary arsenic, toenail arsenic and drinking water) and oxidative stress (urinary 8-hydroxy-2'-deoxyguanosine) and possible genetic effect modification (GSTM1, OGG1 and APE1) among 97 women from Bangladesh.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Abstract: There is a lack of information in the methods section regarding which genotypes were analysed and how they were analysed.

Methods: There is no information whether or not these women were related. Kinship may lead to spurious associations between genotype and biomarkers. The authors should present rs-numbers for the polymorphisms. Moreover they should either present primers and probes as well as assay protocol for the Taqman assay or assay id (e.g. from Applied Biosystems). Were samples resulting in unclear results rerun?

Why were heterozygous and homozygous variant genotypes combined? Based on knowledge of functional impact or based on effect estimates in the present data?

Results: The authors present the data with many numbers. Are the analyses so exact that this is justified? Please, use the same number of numbers for the same type of analyses.

For the results presented in tables 3-5 all models have been adjusted for all genotypes. Is this appropriate? Wouldn't it be better to first present the data without taking genotypes into consideration (table 3) and then analyse the genotypes one by one (table 4) and finally when stratifying for GSTM1 genotype (please, see comment below) not to include GSTM1 in the model (table 5)?

The sentence on page 11 "For example, in the model evaluating toenail arsenic concentration, APE1 148..." should be rephrased. Only for toenail arsenic the negative effect was statistically significant.

It would be interesting to see the effect of the other covariates (e.g. BMI, environmental tobacco smoke at home) in order to evaluate how large effect the

genotype has on 8-OHdG levels.

The p-values for the gene-environment interaction analysis are not presented. Was the interaction term (GSTM1 genotype x arsenic exposure) statistically significant? Is the table 5 showing analysis stratifying for GSTM1 without inclusion of an interaction term? Please, clarify in the statistical section of Methods how the effect modification was investigated.

Discussion: How reasonable is it to adjust for creatinine? Creatinine has been shown to correlate to urinary arsenic as well as BMI and this might weaken the association of arsenic to 8-OHdG. Wouldn't it be better to use urinary specific gravity (Nermell et al., Environmental research, in press) for adjusting urinary arsenic, which is not associated with those variables?

The large fraction of data for 8-OHdG below LOD indicates that the ELISA method is rather insensitive. The authors do not address this problem in the discussion and the possibility that it may explain the lack of association between arsenic and 8OHdG.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Abstract: The abbreviation TUA is used without explanation.

(95% CI 033, 1.66) should be (95% CI 0.33, 1.66).

Introduction: Regarding the effect of homozygous deletions of GSTM1: these deletions rather result in lack of enzyme than ineffective enzyme.

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.