Author's response to reviews

Title: Higher urine 1-hydroxy pyrene glucuronide (1-OHPG) is associated with tobacco smoke exposure and drinking mate in healthy subjects from Rio Grande do Sul, Brazil

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To the Editors:

We have examined the second list of questions/suggestions from the reviewer and we have given a point-by-point response to the comments raised by the reviewer. Since there are only three questions raised by this third reviewer (no questions from the other two reviewers) and this manuscript has been under review in BMC Cancer for several months, we hope that the editors can make a decision on this manuscript based on our responses.

Sincerely,

Renato Fagundes

1. The authors in the methods section only inform about 10 ml spot urines but not the timing of the day for sampling of these spot urines. If all sampled as first or second morning void the argument of same degree of hydration may be used. If however the sampling are spread over the day the creatinine (and dilution) may differ significantly. I recommend this to be further clarified by the authors.

We enrolled subjects as the first part of our morning work each day of enrollment. We did not record how many times, if any, the subject had urinated prior to providing our sample. We have clarified the sentence in the methods section to state that all samples were collected in the morning. As we previously argued, creatinine adjustment is particularly useful when comparing 1-OHPG distributions between populations which might have systematic differences in hydration. A systematic difference in hydration among the participants of this study is unlikely by any of the categories we examined. If there are random errors, they should make the study null rather than positive. It can be argued that consuming high amounts of mate increases hydration and diuresis. If this argument is correct, then one would expect that mate drinkers would have diluted urine samples and therefore lower concentrations of urine 1-OHPG. However, our study showed much higher concentrations of 1-OHPG in urine samples of mate drinkers. Therefore, we think our analysis is sufficient as is.

2. The conclusion that mate contaminant and not just thermal injury may help explain the increased risk of ESCC could/should be further justified. Such information would be needed for risk management.
We have extensively discussed why PAH contaminants of mate may cause esophageal cancer. On page 3, we mention that PAHs are carcinogens in animals and humans. In the discussion section, on page 7, we cite previous reports of high urine 1-OHPG in populations at high risk for ESCC. For much of page 8 we discuss the previously reported association between mate and ESCC and the inconsistent findings about mate temperature and the hypothesis that thermal injury from hot mate is the mechanism whereby drinking mate increases the risk of ESCC. Then, later on pages 8 and 9 we cite prior evidence of mate contamination with benzo[a]pyrene. We conclude on page 9 that our findings suggest that the association between mate drinking and ESCC could be mediated by carcinogenic PAHs in the mate. We think that this is an essentially complete examination of the hypothesis.

3. Also mate intake, smoking and barbequeing tested in other multivariate models could provide attributable risks strengthening the conclusions.

Attributable risks are used to estimate the proportion of disease that can be attributed to a specific exposure. In this study we have examined only a healthy population, not esophageal cancer cases, therefore we cannot calculate an attributable risk or a relative risk. The main result of this manuscript was that mate drinkers were exposed to PAHs almost as much as smokers were. The relative importance of each exposure in contributing to the total variance in urine 1-OHPG exposure can be determined by examine the regression coefficient estimates in table 2.