Author's response to reviews

Title: Hematological and Hepatic Alterations in Nonsmoking Residents Exposed to Benzene Following a Flaring Incident at the British Petroleum Plant in Texas City

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Version: 3 Date: 9 October 2014

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Responses to Reviewers' comments

Reviewer # 1

**General**: The authors provide an excellent report of the metabolic changes (complete blood count, liver and kidney profile) observed among non-smoking subjects exposed to Benzene.

**Response**: We thank the reviewer for his/her appreciation of our work.

1. **Comment**: However, it was unclear whether lab testing was repeated among subjects with metabolic dysfunction to determine whether these changes were persistent with long-term follow-up.

   **Response**: This was a retrospective cross sectional evaluation in which metabolic dysfunction was examined in subjects exposed to benzene in comparison to control subjects. Although the long-term follow up analysis is important to determine the persistent harmful effects of benzene, the work presented in this manuscript is limited to the cross sectional evaluation. Longitudinal analysis of this work is planned and we will report the outcomes in the future.

2. **Comment**: I suggest modifying the title to (for example): acute metabolic changes observed among non-smoker exposed to Benzene following a refinery accident. Health risks imply that the damage was permanent and requires long-term follow-up.

   **Response**: Since the health effects of benzene were not assessed immediately after its exposure, it may not be appropriate to use the term “acute” in the title. Similarly, the event at BP may not be considered as an accident. Moreover, the term metabolic dysfunction refers to a broad term for several metabolic pathways. Therefore, while keeping the reviewer’s suggestion in mind, the title is modified as “Hematological and Hepatic Alterations among Nonsmoking Residents Exposed to Benzene Following a Flaring Incident at the British Petroleum Plant in Texas City” in the revised manuscript.

3. **Comment**: Please describe how the subjects who were exposed to Benzene should be followed to assess long-term damage to the bone marrow, liver, kidney and second malignancy in the discussion. Longitudinal data is required to determine whether these metabolic changes are transient or permanent. If they are permanent, should individuals who develop permanent liver dysfunction undergo more testing such as liver biopsy for example. The authors would provide valuable service to the community exposed to future accidents.

   **Response**: We appreciate this recommendation from the reviewer. As suggested by the reviewer, we have included a paragraph how the subjects who were exposed to benzene should be followed to assess long-term damage to the bone marrow, liver, kidney and second malignancy in the discussion section of the revised manuscript while keeping in mind that this work is not longitudinal analysis.
Reviewer # 2

General: Mark A. D’Andrea et al provide an interesting paper that evaluates the health risks attributed to benzene exposure among non-smoking adults in Texas City following a flaring incident. This is an important topic in occupational epidemiology. The design of this molecular epidemiology study is strong, particularly the use of non-smoking adults, the random selection of unexposed subjects (30 to 50 miles from exposure site), and markers of impact on the subjects' hematological profiles, and kidney and liver function. The overall design, methods, and interpretation of the study are good with potential limitations described.

Response: We appreciate the reviewer’s thoughtful comments on our work. However the paper could be further strengthened if the following are considered:

1. **Comment:** As few high quality molecular epidemiological studies of occupational exposures exist, the authors should add an explanation in the abstract and introduction for why these particular biochemistries or hematological profiles were examined and how they bear effects on potential carcinogenesis.

   **Response:** As suggested by the reviewer, we have included an explanation on the importance of the hematological and hepatic profiles in the introduction/abstract of the revised manuscript.

2. **Comment:** The authors report that the exposed and unexposed groups are comparable in age. Where other demographic variables considered are potential confounders?

   **Response:** We have looked at the age and gender differences between the exposed and unexposed groups to benzene and the findings are reported in the manuscript. However, given the limitations and pit falls of retrospective design, we could not control many other variables of the study and thus, due to lack of detailed information on other demographic variables, we could not determine the effect of other potential confounders.

3. **Comment:** Tables 2-4 provide estimates of risk among exposed groups. These results, however, would be strengthened by adjusting for age, gender, and other relevant confounders.

   **Response:** This is a good suggestion. However, as responded to the above comment, this is a retrospective study and lack complete data on other variables to do the logistic regression analysis for the determination of the effect of the relevant confounders. We are planning to do this analysis on a larger study involving over 3000 subjects who were exposed to benzene from this refinery accident and the findings will be reported in the future.

4. **Comment:** The authors should provide support for the biological plausibility of their biochemical markers in relation to the health effects attributed to benzene exposure.
**Response:** As responded to the other reviewer’s comment # 3, the biological plausibility of the biochemical markers i.e., damage to the bone marrow, liver, kidney and second malignancy is included in the discussion section of the revised manuscript.

**Minor Comments:**

1. P-values should be provided in appropriate scientific notation (i.e., not P = 0.0000).
   **Response:** As suggested by the reviewer, the p values are now provided as P = 0.01 or 0.001.

*We sincerely thank reviewers for their valuable time, effort and greatly appreciate their thoughtful suggestions as well as encouraging comments which we have addressed in the revised manuscript.*