Author's response to reviews

Title: Correcting for the influence of sampling conditions on biomarkers of exposure to phenols and phthalates: a 2-step standardization method based on regression residuals.

Authors:

Marion Mortamais (marion.mortamais@inserm.fr)
Cécile Chevrier (cecile.chevrier@univ-rennes1.fr)
Claire Philippat (claire.philippat@e.ujf-grenoble.fr)
Claire Petit (claire.petit@univ-rennes1.fr)
Antonia M Calafat (aic7@cdc.gov)
Xiaoyun Ye (xay5@cdc.gov)
Manori J Silva (zca2@cdc.gov)
Christian Brambilla (cb Brambilla@chu-grenoble.fr)
Marinus J.C. Eijkemans (M.J.C.Eijkemans@umcutrecht.nl)
Marie-Aline Charles (marie-aline.charles@inserm.fr)
Sylvaine Cordier (sylvaine.cordier@univ-rennes1.fr1)
Rémy Slama (remy.slama@ujf-grenoble.fr)

Version: 3 Date: 29 March 2012

Author's response to reviews: see over
Dear Editor,

We thank you for offering us the opportunity to submit to Environmental Health a revised version of our manuscript entitled:

**Correcting for the influence of sampling conditions on biomarkers of exposure to phenols and phthalates: a 2-step standardization method based on regression residuals.**

We have taken in account the editorial comments and provided a point by point answer (see below).

We thank you again for the careful consideration of our manuscript,

Sincerely,

Marion Mortamais

Rémy Slama, PhD

Regarding the Editorial comments:

1) Please clarify that your study attempts to adjust for within-subject variability from data on between-subject differences.

Reply: We are actually interested in removing the effect of factors (that may have an impact on the individual level) only to the extent that there is *between*-subject variability in these factors. For example, sampling hour would not be a problem if urine had been collected at the same hour for all subjects, and is an issue only because there are *between*-subject differences on sampling hour. The suggested sentence (“WITHIN-participant variations in sampling conditions of these biological samples constitute AN...
UNavoidable potential source of exposure misclassification”) is to this extent somewhat misleading.

Our approach is in principle very common in epidemiology, although seldom applied to sampling conditions. It is similar e.g. to adjusting for gestational age in a study of environmental impacts on birth weight (gestational age is an individual factor assessed only once for each pregnancy, between-subjects variations in gestational age may cause a bias that is removed by assuming that the birth weight differences between pregnancies delivered at 36 and 40 weeks would also apply longitudinally to singles fetuses if their weight could be assessed successively at 36 and 40 weeks), or to adjusting for child's age in a study of environmental effects on neurodevelopment. Therefore, we find the sentence "Between-participant variations in sampling conditions of these biological samples constitute a potential source of exposure misclassification." less ambiguous.

2) Please see below proposed adjusted wording of the abstract. In the Conclusions, please reword the second sentence ('etiologic' studies is not a commonly used term and needs to be changed).

Reply: We corrected the sentence of the conclusion containing the word etiologic:

“This confirms the relevance for studies aiming to characterize the health effect of compounds with a short half-life such as phthalates and phenols to rely on repeated biomarker assays.” (P.19)

3) The last sentence is unclear - do you mean that adjustment is not needed after all?

Reply: The last sentence was just a suggestion for a sensitivity analysis allowing to quantify the impact of correction for measurement error. We agree that it was not very clear; since it repeats something stated in the same page a few lines higher, we deleted it.

4) We are concerned that the tables as currently designed will not fit within the space available and may have to be transferred to 'additional files' that will not be XML converted. Table 1 could be redesigned so that it uses fewer columns, and perhaps some rows can be combined, or information transferred either to the text or to an additional file. Although these concerns will be addressed by the BMC production staff, it would be to your advantage if the table designs are updated now.

Reply: Tables 1 and 2 have been redesigned.