Author's response to reviews

Title: Estimating equations for biomarker based exposure estimation under non-steady-state conditions

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Author's response to reviews: see over
Response to second round of reviewer comments for MS 6186704284631047: “Estimating equations for biomarker based exposure estimation under non-steady-state conditions”

The authors would like to thank the reviewers for their additional comments and suggestions. Thanks also to the editor for extending the deadline for our response during both rounds of revisions.

Reviewer #1

Major Compulsory Revisions:
1. The authors have provided the estimate of exposure based on a simplified (one-compartment) biokinetic model when the steady-state assumption holds (3rd paragraph, Methods). They have also performed simulation studies of their exposure mean and variance estimates under non-steady-state conditions. It is thus interesting to compare the steady-state estimate with the proposed estimate under non-steady-state conditions, so that the bias using the steady-state estimate can be assessed.

We have added text reviewing the performance of the steady-state method on page 14, including closed-form bias and precision formulas for the steady-state estimator.

2. The additional files 1 to 4 as Tables 1 to 4 are difficult to read. It is the author’s responsibility to provide sufficient information of their results in tabulated form (as part of the text), so that readers can assess the performance of their estimates numerically. One or two summary tables in addition to Figures 1 to 4 should be sufficient, which should not duplicate the readings from the figures.

Tables 1-3 are now embedded in the main document. Table 4 is omitted entirely, as it is easily summarized in a single sentence on page 13.

Minor Essential Revisions:
1. To distinguish vector of parameters or matrix with scalar parameter, it is suggested that the former should be typed in bold-face, as is commonly adopted in statistical literature.

We changed vectors and matrices to bold-face throughout the manuscript, as suggested by the reviewer.

2. (Page 11, 5th paragraph of Algorithm) If the estimated covariance matrix in vector form includes the upper diagonal elements of , then the dimensions of should be $(n^2+n)/2$, rather than $n^2$.

We agree and have corrected the dimensions throughout this paragraph, clarifying that only the upper diagonal elements of the covariance matrix $\mathbf{V}$ are included in this expression. We thank the reviewer for his careful attention.
3. Following 2, the dimension of is reduced to \( n \) under independent assumption. Because only one biomarker measurement per person is assumed, estimate of variance in exposures need to borrow information from between-subject variations. Therefore, further simplification of the dimension of to 1 as was done in the simulations of is desired. It is suggested that the authors clarify this fact further in the same paragraph.

We changed the text to clearly indicate that only one estimating equation is used for \( \alpha \), omitting the unnecessary \( q \) to simplify the notation. Page 11 now includes additional discussion regarding the borrowing of information from between-subject variation in biomarker measurements.

Discretionary Revisions:

The assumption of the same fraction \( f \), blood volume \( v \), and excretion rate \( k \) for each individual is unrealistic. A hierarchical Bayesian approach assuming that these parameters follow a statistical distribution population-wise may be adopted, as has been well established for PBPK model parameter estimation (see, e.g., Bois 1996 Environ. Health Perspect.) Some discussion of this issue is suggested.

Additional discussion of model extension to accommodate biokinetic variability has been added to page 16.

**Reviewer #2**

Discretionary Revisions:

Reword last sentence of Abstract to say "..at any reasonable sample size,.." or the like

We changed the abstract as suggested by the reviewer.