Reviewer's report

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

Version: 2 Date: 27 April 2011

Reviewer: Chu-Chih Chen

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The proposed estimating equation for non-steady-state exposure estimation appears to be useful, though the restrictive assumptions need to be implemented to be applied in practice. Some comments are as follows:

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.

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.

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.

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 (n²+n)/2, rather than n².

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 what was done in the simulations of is desired. It is suggested that the authors clarify this fact further in the same paragraph.

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.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.