Reviewer's report

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

Version: 1 Date: 14 January 2011

Reviewer: Douglas Taylor

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Major Compulsory Revisions

1) General: The authors present an interesting approach to estimating the distribution of toxicant exposure using biomarker data within the framework of a non-steady state model. However, there are limitations which suggest substantially more work is needed before the approach can be recommended outside of settings where exposure distribution is rather homogeneous across subjects. The authors should emphasize, and in some instances spell-out in greater detail, these limitations.

2) Equation 3: x in the numerator of equation (3) should be lij

3) Equation (3): The authors should emphasize that unique a_i and #_i are (presumably) only estimable if they are modeled using fixed covariate effects (e.g. job type), something not explicitly considered in this paper.

4) Equation (3): The authors should state that they are assuming daily exposures are independent within-person, and comment on limitations of this assumption.

5) Line 229: DeGroot (1989) should be added to the reference list.

6) Line 244 (last paragraph under Algorithm): Given that estimating # is one of the main goals of the paper (being a parameter of the exposure distribution), requiring an external estimate of # seems the most important issue. If an external estimate of # is being recommended, then it should be explicitly mentioned as a limitation in the context of the paper as a whole.

7) After Line 276 (4'th paragraph of Testing and Implementation): In the simulation studies the authors have assumed that the distribution of exposure (given that exposure takes place) over 1000 exposure measurement intervals are homogeneous, both within and between subjects. They have also assumed that the residual error variance is small, known, and homogeneous across subjects, and that the frequency of exposure is known for the entire period of 1000 exposure intervals for each subject. Given these rather strong restrictions, the authors should comment on how they might expect their model to perform in general scenarios where exposure levels vary (e.g. based on preliminary simulation results), or the residual model error is not small, or exposure frequency is measured with error. If there's no basis for speculation, then
explicitly mention that performance in more general settings is unknown should be made.

8) Line 294 (first paragraph of Discussion): The statement “It may be possible to extend the estimating equations to handle multiple biomarkers per individual” conflicts with line 288, where the authors recommend multiple biomarker values be sampled per person. If it is possible then state as such; otherwise indicate that this needs to be explored.

9) Discussion: It’s not obvious how biokinetic parameters would be incorporated into the process as random effects (at least not easily, given what the score-equations might look like). Likewise, it is not clear how to incorporate information “…about the nature of exposure related behaviors.” Presumably the latter gets at making the exposure distribution much more general (e.g. incorporating covariates, random exposure effects, unobserved exposure frequency, etc.). The authors should explain how this might actually be done, or emphasize it as future research.

10) Conclusions: A need for caution and future research appears warranted, because the assessment done in this manuscript – although very interesting – seem based on strong assumptions about the exposure process and known exposure frequency over potentially long periods of time. Likewise, emphasize the importance of correctly specifying the biomarker-exposure model, validating exposure distributional assumptions, the need to have external estimates of #2#, etc.

Minor Essential Revisions

1) Line 30: “…each biomarker measurement as a weighted linear…”

2) Line 80: The examples considered in the paper seek to estimate an exposure distribution that is assumed to be common across all subjects (given that exposure takes place). Hence the line ‘estimating individual and population exposures’ is somewhat confusing. Suggest being a little more specific w/r what is being estimated and how (e.g. without using any actual exposure data).

3) Equation (3): it would be helpful to the reader to emphasize that throughout the rest of the paper, the authors will assume that the conditional exposure distribution given exposure takes place (#i=1) is the same for each subject, or that a_i=a and #_i=# for all i..

4) Line 178 (end of Results): it would be helpful to readers unfamiliar with estimating equation methods to emphasize why there’s no need to have exposure measurements to estimate the mean exposure level.

5) Line 228 (6’th paragraph of Algorithm): might mention that using this parameterization, # and # are the logged mean and logged variance, respectively, of the (conditional) exposure distribution.

6) Line 229: Since D is not generally a vector, it might be better to say “…, EY
and D are identical vectors…” rather than “the vectors EY and D are identical,…”

7) Lines 259-260 (first paragraph of Testing and Implementation): introducing still more notation gets confusing. Perhaps use exp(#) and exp(#) rather than µ and #g2.

8) Line 291 (end of Testing and Implementation): To be consistent with paragraph starting with line 242, perhaps say # and #2# here (recognizing that #2g is a function of #).

8) Line 295 (second line of Discussion): “…parameters to be randomly drawn…”

9) Figure 2: Adding a reference line at ‘5’ would help the reader.

Discretionary Revisions:

1) Some of the development of the estimating equations might be better left to an appendix

2) Line 177 (end of Results): It might not be too difficult to express the examples in terms of likelihoods, and maximize using ML methods, if the gamma exposures are independent within subject. In that case Yit = Zit + Xit, where Zit is a scaled (#it) gamma random variable and Xit is normal random variable. Comparing the performance of ML to the estimating equation methods could be interesting.

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