

## Statistical Methods for Evaluating Exposure-Biomarker Relationships

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Levels of exposures and biomarkers vary greatly within and between persons; these levels are subject to measurement error, exposure-biomarker relationships can be nonlinear, and levels of exposures and biomarkers can lie below analytical limits of detection. This combination of factors has limited useful applications of biomarkers for characterizing human health risks. The purpose of this project is to develop and evaluate appropriate statistical models for elucidating the true relationships between exposures to organic toxicants, notably volatile organic compounds, and biomarkers. We apply toxicokinetic theory and models to propose a regression model relating the mean-individual-biomarker level to the mean-individual-exposure level, while allowing both exposure levels and biomarker levels to vary within and between persons. The model permits questions related to saturable metabolism, low-dose linearity, and interindividual variability to be explicitly evaluated. Then, we develop maximum likelihood methods, and the associated computational algorithms, for estimating key regression model parameters, with appropriate adjustments for measurement errors in levels of exposure and biomarkers and with provisions for handling levels below analytical limits of detection. We investigate the validity and precision of these methods using a combination of simulation studies and regression diagnostic methods. Finally, we apply these maximum likelihood methods, and related regression diagnostics to existing exposure-biomarker data sets involving a host of chemical contaminants and biomarkers.

**Implications:** The methods developed in this study should provide the structure required for useful applications of biomarkers to investigate the nature of risks associated with organic contaminants.

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### Presentations:

Rappaport, S.M., Kupper, L.L., Taylor, D.T., Johnson, B.J., and Lin, Y.S. (2004). Statistical methods for evaluating exposure-biomarker relationships. Poster presented at the LRI Annual Science Meeting, Miami, FL, May 5–6, 2004.

Rappaport, S.M., Kupper, L.L., and Lin, Y.S. (2004). On the importance of cumulative exposure to the doses of volatile organic compounds. Presented at XPASS 2004 (International Symposium on Exposure Assessment), Utrecht, Netherlands, June 16, 2004.

Rappaport, S.M., Kupper, L.L., and Lin, Y.S. (2004). Dose versus dose rate in assessing chemical exposures – are 'peaks' important? Presentation at Center for Occupational and Environmental Health, University of Manchester, Manchester, United Kingdom, June 25, 2004.

Rappaport, S.M. (2005). Dose-response modeling for benzene. Presentation at Workshop on Representations of Dose-Response Relationships for Chemicals Associated with Non-Cancer Effects and their Policy Implications, Oakland, CA, January 27–28, 2005.

Rappaport, S.M., Kupper, L.L., and Lin, Y.S. (2005). Air sampling versus biomarkers for assessing chemical exposures. The Fifth International Symposium on Modern Principles of Air Monitoring, Loen, Norway, June 12–16, 2005.

Rappaport, S.M., Kupper, L.L., and Lin, Y.S. (2005). Recent applications of PBPK models to determine the impact of exposure variability (peak exposures) on the long term doses of VOCs (benzene, perchloroethylene, acetonitrile) and their metabolites. First International Course on Peak Exposure and Human Health, Loen, Norway, June 16–19, 2005.

Rappaport, S.M., Kupper, L.L., and Lin, Y.S. (2005). Air samples versus biomarkers for epidemiology. Presentation at the Epidemiology Branch, National Institute for Environmental Health Sciences, Research Triangle Park, NC, November 21, 2005.

Rappaport, S.M., Kupper, L.L., and Lin, Y.S. (2005). Are biomarkers better measures of exposure than air samples for epidemiology studies? Symposium of the U.K. Molecular Epidemiology Group, Imperial College London, United Kingdom, December 8, 2005.

Rappaport, S.M., Kupper, L.L., and Lin, Y.S. (2005). Are biomarkers better measures of exposure than air samples for epidemiology studies? Bilateral French-American Workshop on Biomarkers, Office of Science and Technology, Embassy of France in the United States, Charleston, SC, January 17, 2006.

Rappaport, S.M., Kupper, L.L., and Lin, Y.S. (2006). Air samples versus biomarkers for epidemiology. Presentation at U.S. Environmental Protection Agency, HEASD, Research Triangle Park, NC, March 1, 2006.

Rappaport, S.M., Kupper, L.L., Taylor, D.J., and Johnson, B.A. (2006). Statistical methods for evaluating exposure-biomarker relationships, Making Sense of Human Biomonitoring Data. Presentation at the ICCA Workshop on Interpreting Biomonitoring Data, Minneapolis, MN, July 26–27, 2006.

Johnson, B.A., Kupper, L.L., Taylor, D.J., Lin, Y.-S., and Rappaport, S.M. (2006). Population-averaged nonlinear regression models for epidemiologic exposure studies of volatile organic compounds. XXIIIrd International Biometric Conference, Montreal, Canada, July 2006.

#### **Peer-reviewed publications:**

Rappaport, S.M., Kupper, L.L., and Lin, Y.S. (2005). On the importance of exposure variability to the doses of volatile organic compounds. *Toxicol Sci.* 83: 224-236.

Lin, Y.S., Kupper, L.L., and Rappaport, S.M. (2005). Air Samples versus biomarkers for epidemiology. *Occ Env Med.* 62: 750-760.

Johnson, B.A., Kupper, L.L., Taylor, D.J., and Rappaport, S.M. (2005). Modeling exposure-biomarker relationships: Applications of Linear and Nonlinear Toxicokinetics for Understanding Genotoxic Metabolism and Carcinogenesis. *J Agric Biol Environ Stat.* 10(4): 440-459.

Johnson, B.A. and Rappaport, S.M. On modeling metabolism-based biomarkers of exposure: A comparative analysis of nonlinear models with few repeated measurements. *Stat Med.* (In press).

Taylor, D.J., Kupper, L.L., Johnson, B.A., Kim, S., and Rappaport, S.M. Parametric methods for evaluating nonlinear exposure-biomarker relationships when the predictor and the response variables are measured with error. *J Agric Biol Environ Stat.* (In press).

**Other publication(s):** None.

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