Marginal Analysis of Exposure Data with Repeated Measures and Non-Detects

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Abstract

Exposure data with repeated measures from occupational studies are commonly right-skewed and in the presence of detection limits. The use of linear mixed effects models incorporating maximum likelihood method for repeated measures data with non-detects has been discussed to model log-normal exposure outcomes. However, this modeling has a disadvantage that assumes a correctly specified distribution for the random effect, which is practically unknown, and the estimation methods can result in bias and imprecision in finite-sample data even when distributional assumptions are met.

In contrast with random effects modeling, which addresses subject-specific means by explicitly modeling subject-to-subject heterogeneity for the regression parameters, marginal modeling provides an alternative to analyzing data with repeated measurements, in which the parameter interpretations are with respect to marginal or population-averaged means. The interpretations are the same as for the ordinary linear regression, but in the presence of correlated data.

In this study, we outline the theories of three marginal models, i.e., generalized estimating equations (GEE), quadratic inference functions (QIF), and generalized method of moments. With these approaches, we propose to incorporate the fill-in methods, including single and multiple value imputation techniques, such that any measurements less than the limit of detection are assigned values. In a simulation study and application examples, we demonstrate that the GEE method works well in terms of estimating the regression parameters, particularly in small sample sizes, while the QIF outperforms in large-sample settings, as parameter estimates are consistent and have relatively smaller mean squared error. No specific fill-in method can be deemed superior as each has its own merits.

Key words: marginal analysis, left censoring, right skewness, limit of detection, repeated measures, environmental exposure.

1. Introduction

In environmental or occupational studies, repeated concentration measurements not detected or falling below limits of detection (LOD) of laboratory instruments are called left-censored repeated measures data. The unquantified non-detects are generally low-level concentrations with values between zero and LOD. Statistical models continue to arise for industrial hygienists to analyze left-censored exposure data with repeated measures in cluster and longitudinal studies because the estimation of the effect of exposure on risk of disease and the importance of within- and between-worker variability in occupational exposure have been increasingly acknowledged. Analytical results from laboratories, environmental contaminants, and occupational exposures, e.g., the concentration of an analyte in a biological urine or serum sample, or an environmental hand wipe or personal breathing zone air sample, are often subject to non-detects or left censoring and the data are skewed to the right. These measurements are usually collected from the same subject or the same study site. In such cases, statistical modeling of exposure data can be complicated when repeated measurements are collected in a cluster or longitudinal study.

The use of linear mixed effects models incorporating maximum likelihood (ML) method for left-censored data with repeated measurements has been discussed for modelling log-normal data in longitudinal infectious disease studies, in which correlation among measures is modeled using a random effect (Thi´ebaut and Jacqmin-Gadda, 2004; Thi´ebaut et al., 2006; Vaida and Liu, 2009). Another study recommended the use of mixed effects model for occupational exposure data with repeated measures while accounting for different levels of censoring (Jin et al., 2011). Nevertheless, this modeling has a disadvantage that assumes a correctly specified distribution for the random effect, which is practically unknown, and the existing literature assumes the data with correlated outcomes were log-normally distributed. Therefore, the data are transformed using the natural logarithm to follow a log-normal distribution (Leidel et al., 1977). However, the estimation methods can result in bias and imprecision in finite-sample data even when distributional assumptions are met (Helsel, 1990).

In contrast with random effects modeling, which address subject-specific means by explicitly modeling subject-to-subject heterogeneity for the regression parameters, generalized estimating equations (GEE) are a special type of marginal analysis for data with repeated measurements, in which the parameter interpretations are with respect to marginal or population-averaged means. The interpretations are the same as for ordinary linear regression, but in the presence of correlated data. Consistent regression parameter estimates can often be obtained under the assumption of a mis-specified working correlation structure (Liang and Zeger, 1986). However, accurately modeling of the correlation structure can improve estimation efficiency, i.e., smaller standard errors (SEs) of regression parameters (Wang and Carey, 2003). Another method of marginal analysis discussed in this manuscript is the generalized method of moments (GMM) (Hansen, 1982), which takes advantage of all estimating equations and has widely developed in econometrics. Additionally, based on GEE and GMM methods, the quadratic inference functions (QIF) method (Qu et al., 2000) has been proposed to improve efficiency of estimators when the working correlation structure is mis-specified and in large-sample settings. This method rewrites GEE as a linear combination of sets of unbiased estimating equations for representing the inverse of the working correlation matrix. These marginal models are promptly available and regularly used for quantifying repeated measures data without censoring; however, they have not been carried out for data with repeated measurements and non-detects.

Statistical methods have been continuously proposed to analyze left-censored data sets. The substitution or single value imputation method, e.g., assigning a value (LOD/2 or LOD/$\sqrt{2}$) (Burstyn and Teschke, 1999; Hornung and Reed, 1990) for measurements less than the LOD, is commonly adopted by industrial hygienists. Unfortunately, there is no unique replaced value for this substitution or single value imputation method, and regression parameter estimation of the substitution method can be biased for high censoring proportion (Hornung and Reed, 1990). This substitution approach is also not advisable unless less than 10% of values are below the LOD (Lubin et al., 2004). Comparatively, the multiple random value imputation technique, e.g., creating imputed values based on throughout scatter of the dataset, has been advocated (Baccarelli et al. 2005; Huybrechts et al. 2002; Lubin et al., 2004). In addition, the use of a ML approach has been shown to perform best in terms of producing less biased estimates for the mean and standard deviation (Amemiya, 1973; Helsel, 1990, 2006; Hewett and Ganser, 2007), but this method performs poorly for small data sets with fewer than 50 detectable values (Helsel, 2006) and highly skewed data under log-normal and Weibull assumptions (Gilliom and Helsel, 1986; Helsel and Cohn, 1988; Shoari et al., 2015), even though the data distribution is correctly specified (Shoari et al., 2015). The nonparametric Kaplan-Meier (KM) method which assumes no distribution for the data has been recommended over the ML method for sample sizes less than 50 and censoring less than 50% (Helsel, 2005). Alternatively, the ML method outperforms the KM method when the data are log-normal and are generated by combining two lognormal distributions (Hewett and Ganser, 2007). Recently, the β-substitution method was presented to produce results comparable to the ML method, even when sample sizes were less than 20 (Ganser and Hewett, 2010). Another multiple imputation method utilized the actual data distribution to generate the relatively conjunct and ordered values has also been added to the approaches for handling left censoring (Pleil, 2016a, 2016b).

In this manuscript, we outline the theories of three marginal models, i.e., GEE, GMM, and QIF, and with these approaches, we propose to incorporate the fill-in methods, including single and multiple value imputation techniques, and β-substitution method such that any measurements less than the LOD are assigned values. We also will consider small-sample bias corrections for the empirical covariance estimators of regression parameter estimates (Chen and Westgate, 2017; Ford and Westgate, 2017, 2018; Mancl and DeRouen, 2001; Westgate, 2012, 2013a, 2016). Therefore, the resulting approaches will have the potential to perform better than the existing methods in small-sample settings. Secondly, we conduct a simulation study to compare the proposed methods and evaluate how well they estimate regression parameters for exposure data with repeated measurements under a range of sample sizes and LOD proportions. Finally, we illustrate the proposed methods using a longitudinal chlorpyrifos dataset and a cluster flame retardant exposure dataset.

2. Materials and methods

In this section, we described the marginal models popularly used for analyzing repeated measures data without censoring, the substitution approaches proposed for filling in left-censored data without repeated measures, and the proposed methods for data with repeated measures and non-detects. With these proposed approaches, a simulation study will be presented later to examine the validity of inference and two motivating applications will be demonstrated.

Suppose we have a cluster or longitudinal study in which *N* independent subjects have *M* distinct number of cluster sizes or time points for ease of illustration. For example, in a cluster study, *M* biological samples (dependent variable) of study participants measured for each of the *N* independent companies are used to examine their association with hand wipe or breathing zone air samples (independent variable). Repeated measures from the same company are typically positively correlated, which must be accounted for when performing data analysis. The measures are equally correlated because no ordering occurs with the participants within the company or industry, hence, the outcomes should be equally correlated. In a longitudinal study, *M* samples are collected over time for each of the *N* participants. Here the correlation between any two time points decreases as the time lag increases. Note that unbalanced repeated measures (cluster sizes or time points) are permitted with the discussed study designs.

Marginal models. Generalized estimating equations (GEE) provide consistent regression parameter estimates as long as the mean structure is assumed to be correctly specified. Although the data analyst is required to incorporate a working correlation structure within the GEE, the structure need not be correctly clarified. However, accurately modeling this structure has the impact on improving estimation, i.e., reduce SEs of regression parameters (Wang and Carey, 2003). We denote the observed exposure outcome for the *i*th subject as $\boldsymbol{Y}_i = [Y_{i1},...,Y_{iM}]^T$, which connects to a marginal mean given by $E(\boldsymbol{Y}_i|\boldsymbol{X}_i) = \boldsymbol{\mu}_i$. The marginal mean is linked to independent variables via a function, $f(\mu_{ij}) = \mathbf{x}_{ij}^T\boldsymbol{\beta}$, where $\mathbf{x}_{ij} = [1,\mathrm{x}_{1ij},...,\mathrm{x}_{pij}]^T$ and $\boldsymbol{\beta} = [\beta_0,\beta_1,...,\beta_p]^T$, *i* = 1, ..., *N*; *j* = 1, ..., *M*. The working covariance matrix for $\boldsymbol{Y}_i$ is $\boldsymbol{V}_i = \boldsymbol{A}_i^{1/2}\boldsymbol{R}_i\boldsymbol{A}_i^{1/2}$, diagonal matrix $\boldsymbol{A}_i = \mathrm{diag}\left[\phi\upsilon(\mu_{i1}), ..., \phi\upsilon(\mu_{iM})\right]$ represents marginal variances, including a scale parameter, ϕ, assuming common dispersion and a known function, $\upsilon(.)$, and $\boldsymbol{R}_i$ is asymmetric working correlation matrix. Let $\boldsymbol{R}_i = \partial\boldsymbol{\mu}_i/\partial\boldsymbol{\beta}^T$ and incorporate the GEE approach into marginal model, the estimates of regression parameters, $\hat{\boldsymbol{\beta}}_{\boldsymbol{GEE}}$, can be obtained by iteratively solving $\sum_{i=1}^{N}\boldsymbol{D}_i^T\boldsymbol{A}_i^{-1/2}\boldsymbol{R}_i^{-1}\boldsymbol{A}_i^{-1/2}(\boldsymbol{Y}_i - \boldsymbol{\mu}_i) = \boldsymbol{0}$. [1]

Generalized Method of Moments (GMM) method constructs a vector, $\mathbf{g}_i(\boldsymbol{\beta})$, consisted of all moment conditions from *i*th subject, *i* = 1, …, *N*, corresponding to the *p*+1 parameters' estimation such that $E[\mathbf{g}_i(\boldsymbol{\beta})] = \mathbf{0}$. The vector is created by stacking all M^2 valid moments according to each parameter so that the maximum length of $\mathbf{g}_i(\boldsymbol{\beta})$ is $M^2 \times (p+1)$. The GMM estimator, $\hat{\boldsymbol{\beta}}_{\boldsymbol{GMM}}$, derived by minimizing the quadratic form, $N\overline{\mathbf{g}}_{\boldsymbol{N}}^{\boldsymbol{T}}(\boldsymbol{\beta})\boldsymbol{C}_{\boldsymbol{N}}^{-\mathbf{1}}(\boldsymbol{\beta})\overline{\mathbf{g}}_{\boldsymbol{N}}(\boldsymbol{\beta})$, asymptotically resolves the estimating equations $N\dot{\mathbf{g}}_{\boldsymbol{N}}^{\boldsymbol{T}}(\boldsymbol{\beta})\boldsymbol{C}_{\boldsymbol{N}}^{-\mathbf{1}}(\boldsymbol{\beta})\overline{\mathbf{g}}_{\boldsymbol{N}}(\boldsymbol{\beta}) = \mathbf{0}$, where $\dot{\mathbf{g}}_{\boldsymbol{N}}(\boldsymbol{\beta}) = E[\partial\overline{\mathbf{g}}_{\boldsymbol{N}}(\boldsymbol{\beta})/\partial\boldsymbol{\beta}^T]$, $\overline{\mathbf{g}}_{\boldsymbol{N}}(\boldsymbol{\beta}) = (1/N)\sum_{\boldsymbol{i}=\mathbf{1}}^{\boldsymbol{N}}\mathbf{g}_i(\boldsymbol{\beta})$, and $\boldsymbol{C}_{\boldsymbol{N}}(\boldsymbol{\beta}) = (1/N)\sum_{\boldsymbol{i}=\mathbf{1}}^{\boldsymbol{N}}\mathbf{g}_i(\boldsymbol{\beta})\mathbf{g}_{\boldsymbol{i}}^{\boldsymbol{T}}(\boldsymbol{\beta})$ is an empirical covariance matrix (Hansen, 1982).

Quadratic inference functions (QIF) method rewrites GEE as a linear combination of k sets of unbiased estimating equations through correlation structures such that $\boldsymbol{R}_i^{-1} \approx \sum_{r=1}^{k}\alpha_{ri}\boldsymbol{M}_{ri}$. With this approach, $\boldsymbol{M}_{ri}$, *r* = 1, …, *k*; *i* = 1, …, *N*, are known basis matrices and α_{ri} are functions of correlation parameters that can be neglected. These estimating equations can then be optimally, linearly stacked through the GMM method (Qu et al., 2000). Two basis matrices are typically employed for exchangeable and first-order autoregressive (AR-1) working correlation structures used in cluster and longitudinal studies, correspondingly. For both structures, $\boldsymbol{M}_{1i}$ is an identity matrix. $\boldsymbol{M}_{2i}$ is a matrix with 0 on the diagonal and 1 elsewhere for exchangeable structure, and with 1 on the sub-diagonal and 0 elsewhere for AR-1 structure.

The robust and empirical sandwich estimator of marginal models increasingly used in practice is because it provides consistency for estimates of regression parameter SEs whether the working correlation structure is correctly specified. However, when the number of subjects, *N*, is not large, this estimator can be negatively biased because the estimated residuals, $\hat{\boldsymbol{e}}_i = \boldsymbol{Y}_i - \hat{\boldsymbol{\mu}}_i$, *i* = 1, …, *N*, are too small on average (Mancl and DeRouen, 2001) and, when estimating $\boldsymbol{\beta}$, the covariance inflation, increasing estimation variability, for $Cov(\hat{\boldsymbol{\beta}})$ results from the use of estimated correlation parameters in $\boldsymbol{R}_i$ or estimated covariance parameters in $\boldsymbol{C}_{\boldsymbol{N}}$ (Westgate, 2012, 2016; Windmeijer, 2005). Therefore, corrections were utilized for the bias from the use of residual vectors, such as the corrections of Mancl and DeRouen (2001) and Kauermann and Carroll (2001). The two well-known methods, along with other corrections, have been demonstrated to outperform for bias correction. Nonetheless, in practice, either the correction of Kauermann and Carroll (2001) and the average of these two corrected methods from Ford and Westgate (2018) may be most desirable (Ford and Westgate, 2018; Westgate, 2016). Adjustment to any covariance inflation occurring with the use of empirical covariance matrix or correlation matrix for the three estimating equation approaches was also recommended (Chen and Westgate, 2017; Westgate, 2012, 2013a, 2016).

Substitution methods. There are two major imputation techniques that are generally used for exposure assessment samples measured less than or below the LOD. We did not advocate direct truncation for the left-censored values because this method might alter the results of central tendency and variability or dispersion, thus decreasing accuracy and precision. Zero replacement for values below the LOD is also not supportive because the logarithmic zero is undefined if the underlying data distribution is assumed to be log-transformed.

Single value imputation assigning a value to a range between 0 and the LOD is the most popular technique adopted for conducting summary statistics. Most often, the use of LOD/$\sqrt{2}$ as the assigned value was demonstrated to provide more accurate estimation of the mean and standard deviation than the use of LOD/2 when the data are less skewed, while the LOD/2 should be considered when the data are highly skewed or have geometric standard deviation approximately 3.0 or greater (Hornung and Reed, 1990; Burstyn and Teschke, 1999). Another single value imputation technique is β-substitution method (Ganser and Hewett, 2010). The β-substitution method deriving the calculation of a β factor for adjusting each value below the LOD is based on the uncensored data. This β factor relies upon whether the mean or geometric mean is estimated. See section for β-substitution method algorithm of Ganser and Hewett (2010) for detailed calculation steps. Through a simulation study, parameter estimates resulting from the β-substitution method have smaller biases and improved root mean squared errors relative to the LOD/2 and LOD/$\sqrt{2}$ substitution methods.

Multiple value imputation techniques provide an increasingly attractive alternative for the exposure data with left censoring (Baccarelli et al. 2005; Huybrechts et al. 2002; Lubin et al., 2004). They employ a ML estimation and a bootstrap procedure, i.e., randomly sampling with replacement, to estimate distribution parameters based on the uncensored data and the censoring proportion so that a common parametric distribution with the estimated parameters can be used for imputing values for observation below the LOD. Because the imputed values cannot be represented as real measurements, the imputation process is repeatedly computed to create multiple data sets. Once each data set is completely analyzed, the multiple data sets are then independently combined to take into account the uncertainty or variability due to the imputation (Little and Rubin 2002). With these methods, the imputed values can also be generated using a regression of an exposure measurement on covariate(s) (Lubin et al., 2004). More recently, Pleil (2016a, 2016b) proposed multiple order value imputation by depicting the natural logarithm of the uncensored exposure concentration levels versus the Z-scores to fit a linear equation regularly presented in a QQ-plot. The linear best fit equation is then utilized to regress or calculate imputed values for the entries of censored data on the corresponding calculated Z-scores. That is, imputed values are projected onto the space spanned by the Z-scores.

Proposed methods. Because of the popularity of marginal models and lack of the use of these models in exposure assessment, we propose to develop marginal models in which the observations of exposure outcome, $\boldsymbol{Y}_i = [Y_{i1},\ldots,Y_{iM}]^T$, *i* = 1, …, *N*, below the LOD are substituted with either single value imputation, multiple random value imputation, or multiple ordered value imputation method. This outcome or dependent variable represents the exposure level measured for the in *i*th subject at the *j*th measurement. Substitution is performed for each non-detectable *j*th, *i* = 1, …, *M*, observation measured in the *i*th subject. The proposed marginal models then utilize all estimating equations, and estimations of regression parameter, standard error (SE), and correlation parameter in $\boldsymbol{R}_i$ or $\boldsymbol{R}_i^{-1}$ are carried out in the same manner as with marginal models. When repeated measures are in a cluster study, exchangeable or compound symmetry structure is accommodated to the working correlation matrix, $\boldsymbol{R}_i$, while AR-1 will be used in a longitudinal data set. We note that small-sample corrections of estimated residuals and SE, such as the ones discussed for the existing marginal models, can be applied with our modified marginal models.

Simulation study*.* We now compare the performances of finite-sample regression parameter estimation of the proposed approaches featuring combinations of two estimation approaches (GEE and QIF) with an AR-1 working correlation structure and five substitution methods for right-skewed and left-censored exposure data with correlated exposure outcomes. Note that the GMM method performed poorly in terms of finite-sample regression parameter estimation and validity of inference and therefore, we initially do not consider it within this manuscript. Instead, we place its results of estimation and inference in Supplementary Material. The substitution methods include:

(1) Single value imputation with the use of LOD/2.
(2) Single values imputation calculating a β factor to adjust each non-detectable value below the LOD, i.e., LOD/β.
(3) Multiple random value imputation using bootstrapping and omitting covariate information that corresponds to exposure outcome. The imputed values are obtained through the *miWQS* package employing weighted quantile sum regression in the multiple imputation framework (Hargarten and David, 2021).
(4) Multiple random value imputation, also via the *miWQS* package, accounting for covariates that contain cluster identification number used in both cluster and longitudinal studies and order of time points within each cluster regularly required in a longitudinal study.
(5) Multiple ordered value imputation using a linear equation fit in a QQ-plot to obtain the imputed values regressed on the calculated Z-scores.

Settings of the simulation study consist of either 30, 100, or 500 subjects (*N*) presenting small, moderate, and large sample sizes. Each subject contributes three repeated measures (*M*) that represents the size of cluster or the number of time points. Each setting is conducted through 1,000 simulations. All simulations with results provided in Tables 1-4 for the proposed approaches were carried out using R version 4.1.2 (R Core Team, 2021). The results of *N* = 500 were provided in supplementary Tables S1 and S2. Moreover, we utilized one data generating model motivated by the literature of parametric repeated measures models (Chen and Westgate, 2017; Jacqmin-Gadda and Thi´ebaut, 2000; Jin et al., 2011) with the censoring proportions subjected to 10%, 20%, 30%, and 40% censoring. The linear model is generated from $\log Y_{ij} = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \gamma_i + \varepsilon_{ij}$, *i* = 1, …, *N*; *j* = 1, …, *M*, where Y_{ij} is the *j*th measurement for the *i*th subject, x_{1i} and x_{2i} are independent variables following Bernoulli and uniform distributions of *Bernoulli*(0.5) and *Uniform*(0, 1), respectively, and γ_i and ε_{ij}, are mutually independent random effects, in which two scenarios are accounted for in the model. Scenario 1 assumes that the random effects are normally distributed with mean 0 and variance 1 (Tables 1 and 2), whereas a true AR-1 correlation structure is formed in scenario 2 (Tables 3 and 4). Tables 1 and 3 present results of the GEE method, while Tables 2 and 4 are used for the QIF method. Because the working correlation structures employed in this study are AR-1, all structures are mis-specified in scenario 1 but correctly specified in scenario 2. The true values of $\beta_0 = 0$ and $\beta_1 = \beta_2 = 1$ are corresponded to the marginal intercept and slopes. The two scenarios were also carried out using the GMM approach, as the results were shown in Supplementary Material (Tables S3 and S4). If $Y_{ij} < \mathrm{LOD}_{ij}$, then Y_{ij} is replaced using the listed substitution methods. In addition to assume that the random effects are log-normally distributed, we further account for a highly skewed pattern, assuming the random effects follow a chi-squared distribution with two degrees of freedom (d.f.) and the working and true structures are different. The results are provided in Tables S5 and S6 of Supplementary Material.

To assess the differences in estimation performances of the two estimation approaches and the five substitution methods, we present empirical biases, empirical mean squared errors (MSEs), and ratios of MSEs from non-intercept parameters, in which we refer to as relative efficiencies (REs), in Tables 1-4. For any given RE, the numerator is the MSE from the use of LOD/2, and the denominator is the MSE for the other substitution method. The modeling option that performs best therefore has the largest ratio. We also present empirical coverage probabilities (CPs) from corresponding 95% confidence intervals (CIs) which utilize the average of Mancl and DeRouen (2001) and Kauermann and Carroll (2001) corrections from Ford and Westgate (2018), denoted by $\mathrm{CP}_{\mathrm{AVG}}$.

3. Results

Simulation study. For scenario 1 with structures incorrectly specified, the empirical CPs using the average of corrections were around the nominal value of 0.95 for the marginal models utilizing either the GEE or the QIF estimation approach and incorporating different substitution methods when $N \leq 100$ and censoring ≤ 20% (Tables 1 and 2). When censoring reached 30%, only β-substitution and QQ-plot methods resulted in near-nominal empirical CPs. Moreover, the GEE approach had relatively lower MSEs compared to the QIF approach in either sample size setting. The REs indicated that the use of β-substitution method performed best overall in terms of regression parameter estimation. However, when sample size is large (N = 500), the QIF demonstrated an efficiency advantage over the GEE based on the results of MSEs, and the QQ-plot method outperformed the other substitution methods, especially for censoring = 30% (Table S1). When the working and true structures were AR-1 in scenario 2, the QQ-plot method still maintained near-nominal 95% CPs for censoring ≤ 30% (Tables 3 and 4). Regarding censoring ≤ 30%, the CPs of the β-substitution method were close to the value of 0.95 in either N = 30 or 100, whereas the LOD/2 substitution method had appropriate CPs when N = 30. MSE results of the GEE and QIF approaches were similar to the results observed in scenario 1 (result of N = 500 was in Table S2). However, RE results corresponding to the QQ-plot method worked very well among all sample size and censoring settings. When a skewed chi-squared distribution occurred with the exposure outcome data, the GEE approach was recommended for small (N = 30) and moderate (N = 100) sample sizes, while the QIF was favorable for large sample size (N = 500). Based on the simulation results of CPs and REs, both the LOD/2 substitution and β-substitution methods were advocated. The two multiple imputation techniques were also considerable because the empirical CPs were near nominal (Tables S5 and S6).

Motivating examples. We applied the existing and proposed methods to a longitudinal study conducted by the National Institute for Occupational Safety and Health (NIOSH), in which termite control workers who utilized chlorpyrifos-containing termiticides to commercial and residential structures in North Carolina in 1998 (Hines and Deddens, 2001). Thirty-seven male applicators participated in the study (number of independent subjects or N is 37). A total of 184 full-shift breathing zone air samples for determination of exposure levels of chlorpyrifos were measured from each applicator on consecutive days during a five-day workweek (number of repeated measures of M is 5). Only one applicator had four-day air samples (M is 4). The analytic LODs ranged from 0.05 to 0.2 µg/sample and the maximum chlorpyrifos exposure level was 73 µg/sample. All laboratory air mass data in µg/sample were converted to concentrations in µg/m^3 by dividing by the air sample volumes. The percentage of chlorpyrifos levels below the LOD was 1.63%, i.e., only three of 184 samples were censored. The distribution of the concentrations was skewed to the right and, based on an examination of quantile-quantile (Q-Q) plot, the exposure data were considered being log-normally distributed.

The marginal model we adopt was suggested in Hines and Deddens (2001), given by $\mu_{ij} = \beta_0 + \beta_1(x_{1ij} = 1) + \beta_2 x_{2ij}$, where μ_{ij} is the ith applicator's mean log-transformed airborne chlorpyrifos concentration during the jth 5-day workweek, x_{1ij} is an indicator for enclosed crawl space, and x_{2ij} is minutes of chlorpyrifos application on the sample collected day. The data were analyzed using GEE and QIF estimation approaches, along with five substitution methods, with an AR-1 working correlation structure. The GMM approach was excluded because of its low precision in finite-sample estimation. Table 5 provides regression parameter estimates and bias-corrected empirical SE estimates. To explore repeated measures data with higher censoring proportion, the laboratory air mass data were also censored at the 20th percentile (20%). All approaches yield same directions and similar magnitudes for regression parameter estimates when the data were subject to low censoring. Both β-substitution and QQ-plot methods in either GEE or QIF approach produces smaller SE estimates when censoring level reached 20%, revealing the two method's potential for efficiency improvement and being consistent with the simulation results. Specifically, minutes chlorpyrifos applied and whether crawl space was treated were significantly associated with increased chlorpyrifos exposure. The correlation parameter estimates used to construct the

AR-1 correlation structure ranged from 0.50 to 0.56, expressing moderate correlation among air samples collected from the same applicator.

The discussed methods were also carried out in a cluster study of NIOSH, which recruited four nail salons (number of independent subjects) located in the San Francisco area in California in 2016 (Estill et al., 2021). Each nail salon had three workers (number of repeated measures) and a total of twelve workers on site were asked to participate. Workers were required to provide spot urine samples at the workplace prior to their first-day shift and after their second-day shift for determination of exposure level of diphenyl phosphate (DPhP), a metabolite of triphenyl phosphate (TPhP) which is one of the commonly used organophosphorus flame retardants. The analytic LOD was 0.16 µg/L and the maximum DPhP metabolite level was 2.39 µg/L. All urinary sample data in µg/L were converted in µg/g by adjusting for their creatinine levels in mg/dL. There were three of 12 workers' DPhP pre-shift levels subject to censoring or below the LOD, i.e., 25% censoring. A visual determination of the Q-Q plot indicated that the data were normal. Therefore, no transformation was applied to the DPhP pre-shift concentrations.

The marginal model from Estill et al. (2021) was given by $\mu_{ij} = \beta_0 + \beta_1(x_{1ij} = 1)$, where μ_{ij} is the mean concentration collected from the *j*th urine pre-shift sample of the *i*th worker and x_{1ij} is an indicator of whether the worker worked the previous day or worked two or more days ago. We analyze the data using the same methods as in the longitudinal example, but with an exchangeable working correlation structure. Table 6 presents the estimates of regression parameter and empirical SE are presented. Results demonstrated that workers who had last worked two or more days ago had lower DPhP pre-shift concentrations relative to those who worked the previous day. When focusing on the preferable GEE approach for small number of clusters, all substitution methods yield same directions and but have different magnitudes for regression parameter estimates and SE estimates. To choose an appropriate method, we extend the correlation information criteria (CIC) for use in the setting, as it has gained popularity in simultaneously selecting estimation approaches with different working correlation structures (Hin and Wang, 2009; Westgate, 2014; Chen and Westgate, 2017). Specifically, the CIC value is calculated by utilizing the trace of $\hat{\boldsymbol{\Sigma}}_I^{-1}\hat{\boldsymbol{\Sigma}}_{BC}$, in which $\hat{\boldsymbol{\Sigma}}_I = \left(\sum_{\boldsymbol{i}=\boldsymbol{1}}^{\boldsymbol{N}} \boldsymbol{D}_{\boldsymbol{i}}^{\boldsymbol{T}} \boldsymbol{A}_i^{-1} \boldsymbol{D}_i\right)^{-1}$ and $\hat{\boldsymbol{\Sigma}}_{BC}$ denotes finite-sample corrected estimate of $Cov(\hat{\boldsymbol{\beta}})$ for any candidate method under consideration. Therefore, the method yielding the smallest CIC will result in the least variable regression parameter estimates. In short, the CIC values indicate that the methods of β-substitution and multiple random value imputation with covariate of cluster identification number are preferable for this data set (Table 6).

4. Discussion

Exposure data with repeated measurements in longitudinal and cluster studies are known to generally be subject to left censoring. Marginal models are appropriate when focusing on inferences about the population average (Diggle et al., 2002) but these models have not been carried out in the literature on exposure data with repeated measures and non-detects. Therefore, we proposed incorporating available fill-in or substitution methods for utilizing detects below the LOD into three estimating approaches, i.e., GEE, QIF, and GMM, in which consistent regression parameter estimates can be obtained even when a working correlation structure is incorrectly specified (Liang and Zeger, 1986). Additionally, we implemented recently developed small-sample corrections to estimators of covariance matrix corresponding to regression parameter estimates. Through bias corrections, the GEE approach is expected to potentially improve upon the QIF performance when the number of subjects (N) is small. The QIF approach performed better in terms of estimating the regression parameters in moderate and large sample sizes in the simulation study in consequence of its theoretical efficiency. In Supplementary Material, the GMM approach was shown to have invalid inference if the sample size is not large even when small-sample corrections are implemented, for instance, CPs had notable departures from the nominal 0.95 level. The finding was consistent with the study of Newey and Smith (2004), which specified that unreliable inferences for the GMM would result from utilizing many moment conditions, e.g., increasing the number of time points or cluster sizes, relative to the sample size. The GMM was demonstrated to have valid inferences when the sample size is large. However, we do not advocate its use in practice because the validity of inference would be questionable when the number of time points increases.

Even though we only accounted for parsimonious AR-1 and exchangeable working correlation structure for marginal models in this manuscript, other working matrices are available for the GEE approach, including Toeplitz and unstructured working structures (Westgate, 2013a). The unstructured form can also be incorporated with the QIF approach (Westgate, 2013b). Including an AR-1 working structure to longitudinal exposure data with repeated measures and non-detects is an additional advantage because it is favored over the other structures in a longitudinal study. Furthermore, based on literature, random effects models used for analyzing left-censored repeated measures exposure data do not accommodate the use of AR-1 because the covariance matrix of the random error term corresponding to the subject level cannot be clarified (Jin et al., 2011).

Our simulation study and two application examples conducted marginal models for continuous responses and multiple covariates, i.e., univariable and multivariable analyses. The longitudinal example was demonstrated that subjects with varying numbers of time points are allowable. Similarly, unbalanced cluster sizes can also be implemented to any cluster exposure data. Note that software such as the SAS procedure GLIMMIX (SAS Institute Inc.,2011), e.g., which can be used for GEE analyses and data with varying numbers of time points or cluster size, can accommodate the user with the two well-known corrections and further average these two corrections. In the simulations and examples, a single LOD or unique censoring proportion and multiple LODs were also permittable. A follow-up topic for future research using longitudinal data is to account for time-varying covariates and to choose the type of time-dependency a covariate belongs to (Chen and Westgate, 2017, 2018).

The study has some limitations. The substitution methods we considered as options are generally used for calculating summary statistics for real-world left-censored environmental and biological data. Regardless of the chosen method, all imputed values are not real data but rather estimated values for measurements that are subject to LOD of laboratory instruments and contain unobserved errors. Additionally, the methods of multiple imputation and Q-Q plot require a common parametric distribution, e.g., log-normal distribution, with the estimated parameters obtained from the uncensored data to impute values for observations below the LOD. These methods might result in biased or unstable statistics when exposure data are asymmetric after log-transforming (Helsel, 1990). Although the methods of LOD/2 and β-substitution are difficult to perform standard normality tests, they are easier to implement and calculate. Another limitation is that all imputed values for measurements falling below the LOD are assumed to be independent. There is no difference in the estimate of interest when incorrectly ignoring the correlation. However, disregard of the correlation will result in positively biased SE estimates, i.e., incorrect estimates of the sampling variability. In such cases, future work can be developed by imputing values based on truncated multivariate normal distribution for log-normal repeated measures data with non-detects (Lubin et al., 2004) or taking truncated multivariate gamma distribution into account for right-skewed data. However, the desired imputation techniques are still constrained by the distributional assumption. Although the replacement for non-detectable values is warranted, through the simulations, we suggested the uses of β-substitution and QQ-plot methods for log-normal data with repeated measurements and left censoring, and LOD/2 and β-substitution, as well as multiple imputations, were recommended for highly skewed data.

Because of the increasingly multilevel or hierarchical exposure data regarding multiple levels of outcomes, future work for other marginal models is needed. Although the primary focus in this manuscript is on statistical inference, improvement of empirical power can be further considered for other topics of interest corresponding to exposure assessment data. The simulation and application R code and functions for implementing the proposed approaches in this manuscript are presented in Supplementary Material or can be acquired by contacting the author at okv0@cdc.gov.

Disclaimer. The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.

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References

Amemiya, T., 1973. Regression analysis when the dependent variable is truncated normal. *E*conometrica 41, 997–1016.

Baccarelli, A., Pfeiffer, R., Consonni, D., Pesatori, A.C., Bonzini, M., Patterson Jr., D.G., Bertazzi, P.A., Landi, M.T., 2005. Handling of dioxin measurement data in the presence of nondetectable values: overview of available methods and their application in the Seveso chloracne study. *Chemosphere* 60, 898–906.

Burstyn, I., Teschke, K., 1999. Studying the determinants of exposure: a review of methods. *American Industrial Hygiene Association Journal* 60, 57–72.

Chen, IC., Westgate, P.M., 2017. Improved methods for the marginal analysis of longitudinal data in the presence of time-dependent covariates. *Statistics in Medicine* 36, 2533–2546.

Chen, IC., Westgate, P.M., 2018. A novel approach to selecting classification types for time-dependent covariates for the marginal analysis of longitudinal data. *Statistical Methods in Medical Research* 28, 3176–3186.

Diggle, P.J., Heagerty, P.J., Liang, K.Y., Zeger, S.L., 2002. The Analysis of Longitudinal Data, 2nd ed. Oxford University Press, New York.

Estill, C.F., Slone, J., Mayer, A.C., Chen, IC., Zhou, M., La Guardia, M.J., Jayatilaka, N., Ospina, M., Calafat, A.M., 2021. Assessment of Triphenyl Phosphate (TPhP) exposure to nail salon workers by air, hand wipe, and urine analysis. *International Journal of Hygiene and Environmental Health* 231, 113630.

Ford, W.P., Westgate, P.M., 2017. Improved standard error estimator for maintaining the validity of inference in cluster randomized trials with a small number of clusters. *Biometrical Journal* 59, 478–495.

Ford, W.P., Westgate, P.M., 2018. A comparison of bias-corrected empirical covariance estimators with generalized estimating equations in small-sample longitudinal study settings. *Statistics in Medicine* 37, 4318–4329.

Ganser, G.H., Hewett, P., 2010. An accurate substitution method for analyzing censored data. *J Occup Environ Hyg* 7, 233–244.

Gilliom, R.J., Helsel, D.R., 1986. Estimation of distributional parameters for censored trace level water quality data 1. estimation techniques. *Water Resources Research* 22, 135–146.

Hansen, L.P., 1982. Large sample properties of generalized method of moments estimators. *Econometrica* 50, 1029–1054.

Hargarten, P.M., Wheeler, D.C., 2021. miWQS: Multiple Imputation Using Weighted Quantile Sum Regression. R package version 0.4.4. https://CRAN.R-roject.org/package=miWQS

Helsel, D.R., 1990. Less than obvious: statistical treatment of data below the detection limit. *Environmental Science and Technology* 24, 1766–1774.

Helsel, D.R., 2005. Nondetects and Data Analysis: Statistics for Censored Environmental Data. John Wiley, New York.

Helsel, D.R., 2006. Fabricating data: how substituting values for nondetects can ruin results, and what can be done about it. *Chemosphere* 65, 2434–2439.

Helsel, D.R., Cohn, T.A., 1988. Estimation of descriptive statistics for multiply censored water quality data. Water *Resources Research* 24, 1997–2004.

Hewett, P., Ganser, G.H., 2007. A comparison of several methods for analyzing censored data. *Annals of Occupational Hygiene* 51, 611–632.

Hin, L.Y., Wang, Y.G., 2009. Working-correlation-structure identification in generalized estimating equations. *Statistics in Medicine* 28, 642–658.

Hines, C.J., Deddens, J.A., 2001. Determinants of chlorpyrifos exposures and urinary 3,5,6-trichloro-2-pyridinol levels among termiticide applicators. *Annals of Occupational Hygiene* 45, 309–321.

Hornung, R.W., Reed, L.D., 1990. Estimation of average concentration in the presence of nondetectable values. *Applied Occupational and Environmental Hygiene* 5, 46–51.

Huybrechts, T., Thas, O., Dewulf, J., Van Langenhov, H., 2002. How to estimate moments and quantiles of environmental data sets with nondetected observations? A case study on volatile organic compounds in marine water samples. *J Chromatogr A* 975, 123–133.

Jacqmin-Gadda, H., Thi´ebaut, R., 2000. Analysis of left-censored longitudinal data with application to viral load in HIV infection. *Biostatistics* 1, 355–368.

Jin, Y., Hein, M.J., Deddens, J.A., Hines, C.J., 2011. Analysis of lognormally distributed exposure data with repeated measures and values below the limit of detection using SAS. *Annals of Occupational Hygiene* 55, 97–112.

Kauermann, G., Carroll, R.J., 2001. A note on the efficiency of sandwich covariance matrix estimation. *Journal of the American Statistical Association* 96, 1387–1396.

Leidel, N.A., Busch, K.A., Lynch, J.R., 1977. Occupational exposure sampling strategy manual (DHEW [NIOSH] publication no. 77-173). Cincinnati, OH: National Institute for Occupational Safety and Health.

Liang, K.Y., Zeger, S.L., 1986. Longitudinal data analysis using generalized linear models. *Biometrika* 73, 13–22.

Little, R.J.A., Rubin, D.B., 2002. Statistical Analysis with Missing Data. 2nd ed. John Wiley and Sons, New Jersey.

Lubin, J.H., Colt, J.S., Camann, D., Davis, S., Cerhan, J.R., Severson, R.K., Bernstein, L., Hartge, P., 2004. Epidemiologic evaluation of measurement data in the presence of detection limits. *Environmental Health Perspectives* 112, 1691–1696.

Mancl, L.A., DeRouen, T.A., 2001. A covariance estimator for gee with improved small-sample properties. *Biometrics* 57, 126–134.

Newey, W.K., Smith, R.J., 2004. Higher order properties of GMM and generalized empirical likelihood estimators. *Econometrica* 72, 219–255.

Pleil, J.D., 2016a. Imputing defensible values for left-censored 'below level of quantitation' (LoQ) biomarker measurements. *Journal of Breath Research* 10, 045001.

Pleil, J.D., 2016b. QQ-plots for assessing distributions of biomarker measurements and generating defensible summary statistics. *Journal of Breath Research* 10, 035001.

Qu, A., Lindsay, B.G., Li, B., 2000. Improving generalised estimating equations using quadratic inference functions. *Biometrika* 87, 823–836.

R Core Team, 2021. *R: a language and environment for statistical computing.* R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org.

SAS Institute Inc., 2011. *SAS/STAT 9.3 Users Guide*. SAS Institute Inc., Cary, NC.

Shoari, N., Dub´e, J.S., and Chenouri, S., 2015. Estimating the mean and standard deviation of environmental data with below detection limit observations: Considering highly skewed data and model misspecification. *Chemosphere* 138, 599–608.

Thi´ebaut, R., Guedj, J., Jacqmin-Gadda, H., Chenˆe, G., Trimoulet, P., Neau, D., Commenges, D., 2006. Estimation of dynamical model parameters taking into account undetectable marker values. *BMC Medical Research Methodology* 6, 38.

Thi´ebaut, R., Jacqmin-Gadda, H., 2004. Mixed models for longitudinal left-censored repeated measures. *Computer Methods and Programs in Biomedicine* 74, 255–260.

Vaida, F., Liu, L., 2009. Fast implementation for normal mixed effects models with censored response. *Journal of Computational and Graphical Statistics* 18, 797–817.

Wang, Y.G., Carey, V., 2003. Working correlation structure misspecification, estimation and covariate design: implications for generalised estimating equations performance. *Biometrika* 90, 29–41.

Westgate, P.M., 2012. A bias-corrected covariance estimate for improved inference with quadratic inference functions. *Statistics in Medicine* 31, 4003–4022.

Westgate, P.M., 2013a. A bias correction for covariance estimators to improve inference with generalized estimating equations that use an unstructured correlation matrix. *Statistics in Medicine* 32:2850–2858.

Westgate, P.M., 2013b. A bias-corrected covariance estimator for improved inference when using an unstructured correlation with quadratic inference functions. *Statistics and Probability Letters* 83, 1553–1558.

Westgate, P.M., 2014. Criterion for the simultaneous selection of a working correlation structure and either generalized estimating equations or the quadratic inference function approach. *Biometrical Journal* 56, 461–476.

Westgate, P.M., 2016. A covariance correction that accounts for correlation estimation to improve finite-sample inference with generalized estimating equations: A study on its applicability with structured correlation matrices. *Journal of Statistical Computation and Simulation* 86, 1891–1900.

Windmeijer, F., 2005. A finite sample correction for the variance of linear efficient two-step GMM estimators. *Journal of Econometrics* 126, 25–51.

Table 1. Results from scenario 1 for settings in which GEE model with an AR-1 working correlation structure is employed. True structure is constructed by random effects.

			LOD/2 Substitution		Beta-Substitution		Imputation Without Covariates		Imputation With Covariates		QQ-plot	
N	% Censoring		β_1	β_2	β_1	β_2	β_1	β_2	β_1	β_2	β_1	β_2
30	10	Bias	0.005	-0.069	-0.051	-0.112	-0.001	0.026	-0.033	0.001	-0.004	0.025
		MSE	0.188	0.628	0.181	0.604	0.192	0.596	0.197	0.575	0.202	0.660
		RE	1.000	1.000	1.037	1.039	0.977	1.053	0.951	1.092	0.930	0.952
		CP_{AVG}	**0.964**	**0.942**	**0.950**	0.935	**0.951**	**0.946**	**0.942**	**0.952**	**0.949**	**0.941**
	20	Bias	-0.071	-0.113	-0.089	-0.121	-0.039	-0.034	-0.003	-0.054	0.002	-0.055
		MSE	0.193	0.537	0.173	0.495	0.197	0.613	0.196	0.630	0.197	0.680
		RE	1.000	1.000	1.116	1.085	0.981	0.876	0.985	0.852	0.978	0.789
		CP_{AVG}	**0.945**	**0.953**	**0.945**	**0.948**	**0.950**	**0.951**	**0.945**	**0.944**	**0.949**	0.929
	30	Bias	-0.160	-0.129	-0.134	-0.134	-0.069	-0.094	-0.068	-0.018	-0.024	-0.022
		MSE	0.179	0.501	0.180	0.480	0.209	0.604	0.194	0.570	0.202	0.593
		RE	1.000	1.000	0.994	1.044	0.858	0.829	0.924	0.879	0.886	0.844
		CP_{AVG}	0.929	**0.941**	**0.936**	**0.957**	0.932	**0.945**	**0.943**	**0.945**	**0.947**	**0.941**
100	10	Bias	-0.027	-0.034	-0.029	-0.050	-0.002	-0.026	-0.026	-0.006	-0.011	0.003
		MSE	0.056	0.163	0.053	0.161	0.058	0.176	0.059	0.165	0.052	0.175
		RE	1.000	1.000	1.052	1.013	0.961	0.928	0.940	0.990	1.075	0.930
		CP_{AVG}	**0.951**	**0.949**	**0.957**	**0.951**	**0.948**	**0.946**	0.935	**0.946**	**0.958**	**0.949**
	20	Bias	-0.082	-0.071	-0.040	-0.038	-0.033	-0.038	-0.030	-0.051	0.001	-0.016
		MSE	0.058	0.149	0.055	0.160	0.061	0.171	0.054	0.167	0.055	0.170
		RE	1.000	1.000	1.057	0.931	0.948	0.875	1.076	0.895	1.046	0.879
		CP_{AVG}	0.927	**0.946**	**0.943**	**0.942**	**0.938**	**0.944**	**0.944**	**0.940**	**0.958**	**0.949**
	30	Bias	-0.128	-0.152	-0.043	-0.050	-0.074	-0.083	-0.077	-0.078	-0.003	0.001
		MSE	0.060	0.165	0.056	0.160	0.062	0.163	0.067	0.165	0.059	0.165
		RE	1.000	1.000	1.075	1.034	0.969	1.012	0.903	1.000	1.026	1.001
		CP_{AVG}	0.901	0.915	**0.944**	**0.946**	0.922	**0.950**	0.919	**0.946**	**0.940**	**0.953**

N, number of subject; Bias, empirical bias; MSE, empirical mean squared error; RE, relative efficiency is a ratio that, for each sample size (N) and percent censoring, compare the empirical MSE from the LOD/2 substitution method to the MSE from the other substitution method; CP_{AVG}, coverage probability from corresponding 95% confidence intervals which utilize the average of two bias corrections. The coverage probabilities falling within a near-nominal range of 0.936 and 0.964 are highlighted in bold.

Table 2. Results from scenario 1 for settings in which QIF model with an AR-1 working correlation structure is employed. True structure is constructed by random effects.

			LOD/2 Substitution		Beta-Substitution		Imputation Without Covariates		Imputation With Covariates		QQ-plot	
N	% Censoring		β_1	β_2	β_1	β_2	β_1	β_2	β_1	β_2	β_1	β_2
30	10	Bias	0.011	-0.064	-0.038	-0.090	-0.003	0.015	-0.024	0.007	0.003	0.024
		MSE	0.200	0.675	0.187	0.640	0.195	0.642	0.210	0.616	0.215	0.697
		RE	1.000	1.000	1.067	1.055	1.021	1.052	0.949	1.097	0.930	0.970
		CP_{AVG}	0.970	**0.947**	**0.954**	**0.940**	**0.958**	**0.953**	**0.954**	**0.949**	**0.949**	**0.936**
	20	Bias	-0.055	-0.101	-0.069	-0.105	-0.030	-0.018	-0.005	-0.047	0.005	-0.043
		MSE	0.208	0.571	0.185	0.540	0.205	0.639	0.212	0.663	0.204	0.709
		RE	1.000	1.000	1.123	1.058	1.011	0.893	0.982	0.862	1.018	0.805
		CP_{AVG}	**0.944**	**0.954**	**0.948**	**0.956**	**0.958**	**0.953**	**0.948**	**0.944**	**0.952**	0.932
	30	Bias	-0.141	-0.118	-0.125	-0.112	-0.061	-0.081	-0.060	-0.013	-0.014	-0.027
		MSE	0.186	0.549	0.190	0.520	0.222	0.637	0.209	0.604	0.213	0.658
		RE	1.000	1.000	0.978	1.056	0.837	0.862	0.889	0.909	0.874	0.834
		CP_{AVG}	**0.943**	**0.936**	**0.942**	**0.954**	0.928	**0.945**	**0.939**	**0.950**	**0.940**	**0.941**
100	10	Bias	-0.022	-0.031	-0.026	-0.043	0.000	-0.028	-0.027	-0.003	-0.013	0.004
		MSE	0.056	0.162	0.053	0.160	0.059	0.183	0.060	0.169	0.052	0.176
		RE	1.000	1.000	1.062	1.013	0.948	0.888	0.925	0.962	1.074	0.921
		CP_{AVG}	**0.952**	**0.950**	**0.958**	**0.954**	**0.943**	**0.942**	0.935	**0.942**	**0.957**	**0.942**
	20	Bias	-0.077	-0.064	-0.033	-0.036	-0.032	-0.034	-0.028	-0.051	0.000	-0.013
		MSE	0.058	0.151	0.055	0.165	0.062	0.171	0.053	0.171	0.055	0.170
		RE	1.000	1.000	1.066	0.917	0.943	0.886	1.090	0.886	1.065	0.889
		CP_{AVG}	0.922	**0.945**	**0.944**	**0.947**	0.934	**0.944**	**0.947**	**0.947**	**0.958**	**0.952**
	30	Bias	-0.122	-0.144	-0.036	-0.042	-0.072	-0.077	-0.078	-0.074	-0.004	-0.002
		MSE	0.060	0.166	0.056	0.164	0.063	0.164	0.067	0.166	0.059	0.165
		RE	1.000	1.000	1.071	1.015	0.953	1.014	0.899	1.001	1.014	1.007
		CP_{AVG}	0.911	0.924	**0.947**	**0.947**	0.928	**0.939**	0.914	**0.945**	**0.938**	**0.952**

N, number of subject; Bias, empirical bias; MSE, empirical mean squared error; RE, relative efficiency is a ratio that, for each sample size (N) and percent censoring, compare the empirical MSE from the LOD/2 substitution method to the MSE from the other substitution method; CP_{AVG}, coverage probability from corresponding 95% confidence intervals which utilize the average of two bias corrections. The coverage probabilities falling within a near-nominal range of 0.936 and 0.964 are highlighted in bold.

Table 3. Results from scenario 2 for settings in which GEE model with an AR-1 working correlation structure is employed. True structure is AR-1.

			LOD/2 Substitution		Beta-Substitution		Imputation Without Covariates		Imputation With Covariates		QQ-plot	
N	% Censoring		β_1	β_2	β_1	β_2	β_1	β_2	β_1	β_2	β_1	β_2
30	10	Bias	0.030	0.017	-0.050	-0.065	-0.007	-0.021	0.002	-0.022	0.004	0.005
		MSE	0.105	0.345	0.097	0.297	0.107	0.348	0.111	0.340	0.112	0.334
		RE	1.000	1.000	1.083	1.160	0.977	0.991	0.946	1.015	0.937	1.033
		CP_{AVG}	**0.944**	**0.938**	**0.960**	**0.953**	**0.953**	**0.941**	**0.951**	**0.949**	**0.950**	**0.942**
	20	Bias	0.001	-0.009	-0.036	-0.067	-0.018	-0.061	-0.018	-0.058	-0.012	-0.023
		MSE	0.110	0.323	0.104	0.309	0.120	0.327	0.120	0.337	0.104	0.319
		RE	1.000	1.000	1.053	1.045	0.916	0.987	0.918	0.957	1.052	1.010
		CP_{AVG}	**0.940**	**0.951**	**0.942**	**0.953**	0.933	**0.948**	**0.939**	**0.940**	**0.956**	**0.959**
	30	Bias	-0.059	-0.091	-0.031	-0.055	-0.073	-0.100	-0.039	-0.075	-0.025	-0.007
		MSE	0.107	0.292	0.106	0.289	0.129	0.338	0.126	0.320	0.106	0.328
		RE	1.000	1.000	1.009	1.009	0.831	0.862	0.847	0.912	1.013	0.888
		CP_{AVG}	**0.950**	**0.957**	**0.956**	**0.954**	0.914	0.932	0.923	**0.945**	**0.954**	**0.946**
100	10	Bias	0.012	0.004	-0.006	-0.002	-0.006	-0.022	-0.014	-0.010	0.005	-0.014
		MSE	0.033	0.098	0.031	0.089	0.033	0.100	0.032	0.096	0.033	0.090
		RE	1.000	1.000	1.060	1.095	0.974	0.980	1.031	1.023	0.983	1.091
		CP_{AVG}	**0.938**	**0.946**	**0.943**	**0.958**	**0.944**	0.932	**0.937**	**0.945**	**0.945**	**0.954**
	20	Bias	-0.010	-0.037	0.028	0.031	-0.036	-0.041	-0.028	-0.033	-0.005	0.008
		MSE	0.031	0.093	0.033	0.098	0.034	0.099	0.034	0.098	0.032	0.092
		RE	1.000	1.000	0.949	0.944	0.924	0.938	0.920	0.948	0.975	1.008
		CP_{AVG}	**0.947**	0.935	**0.944**	**0.951**	0.930	**0.944**	**0.938**	0.932	**0.943**	**0.953**
	30	Bias	-0.072	-0.095	0.089	0.030	-0.056	-0.066	-0.054	-0.077	-0.011	0.008
		MSE	0.034	0.085	0.048	0.109	0.037	0.102	0.038	0.095	0.034	0.094
		RE	1.000	1.000	0.715	0.782	0.933	0.833	0.904	0.900	1.014	0.912
		CP_{AVG}	0.928	**0.936**	0.895	**0.954**	0.917	0.928	0.911	**0.938**	**0.941**	**0.957**

N, number of subject; Bias, empirical bias; MSE, empirical mean squared error; RE, relative efficiency is a ratio that, for each sample size (N) and percent censoring, compare the empirical MSE from the LOD/2 substitution method to the MSE from the other substitution method; CP_{AVG}, coverage probability from corresponding 95% confidence intervals which utilize the average of two bias corrections. The coverage probabilities falling within a near-nominal range of 0.936 and 0.964 are highlighted in bold.

Table 4. Results from scenario 2 for settings in which QIF model with an AR-1 working correlation structure is employed. True structure is AR-1.

			LOD/2 Substitution		Beta-Substitution		Imputation Without Covariates		Imputation With Covariates		QQ-plot	
N	% Censoring		β_1	β_2	β_1	β_2	β_1	β_2	β_1	β_2	β_1	β_2
30	10	Bias	0.032	0.033	-0.038	-0.051	-0.012	-0.025	-0.001	-0.026	0.002	0.008
		MSE	0.116	0.374	0.104	0.326	0.118	0.379	0.116	0.369	0.117	0.360
		RE	1.000	1.000	1.118	1.147	0.987	0.986	0.997	1.013	0.994	1.038
		CP_{AVG}	**0.949**	**0.943**	**0.956**	**0.957**	**0.953**	**0.942**	**0.954**	**0.946**	**0.950**	**0.949**
	20	Bias	0.016	0.000	-0.021	-0.046	-0.018	-0.068	-0.023	-0.061	-0.013	-0.023
		MSE	0.119	0.341	0.113	0.335	0.120	0.351	0.124	0.355	0.112	0.346
		RE	1.000	1.000	1.047	1.017	0.985	0.972	0.955	0.959	1.060	0.986
		CP_{AVG}	**0.947**	**0.950**	**0.950**	**0.952**	**0.948**	**0.948**	**0.939**	**0.957**	**0.954**	0.965
	30	Bias	-0.038	-0.078	-0.001	-0.035	-0.066	-0.098	-0.039	-0.071	-0.026	-0.008
		MSE	0.112	0.317	0.113	0.318	0.131	0.352	0.133	0.353	0.111	0.371
		RE	1.000	1.000	0.994	0.998	0.853	0.901	0.845	0.898	1.009	0.856
		CP_{AVG}	**0.945**	**0.952**	**0.951**	**0.962**	0.926	**0.939**	0.918	**0.949**	**0.963**	**0.947**
100	10	Bias	0.011	0.005	-0.005	0.001	-0.008	-0.021	-0.016	-0.009	0.004	-0.011
		MSE	0.034	0.101	0.031	0.092	0.034	0.101	0.033	0.097	0.033	0.093
		RE	1.000	1.000	1.090	1.096	1.009	1.004	1.034	1.041	1.019	1.085
		CP_{AVG}	0.931	**0.948**	**0.950**	**0.963**	**0.943**	**0.939**	**0.938**	**0.949**	**0.944**	**0.959**
	20	Bias	-0.005	-0.034	0.033	0.034	-0.037	-0.041	-0.029	-0.036	-0.006	0.008
		MSE	0.033	0.096	0.034	0.102	0.034	0.100	0.034	0.100	0.033	0.095
		RE	1.000	1.000	0.950	0.944	0.959	0.963	0.954	0.957	1.000	1.014
		CP_{AVG}	**0.948**	0.933	**0.944**	**0.951**	**0.939**	**0.946**	0.934	0.929	**0.945**	**0.957**
	30	Bias	-0.065	-0.088	0.100	0.039	-0.056	-0.063	-0.055	-0.078	-0.011	0.009
		MSE	0.034	0.087	0.052	0.115	0.038	0.103	0.039	0.097	0.035	0.097
		RE	1.000	1.000	0.663	0.760	0.891	0.849	0.879	0.897	0.983	0.897
		CP_{AVG}	**0.939**	**0.940**	0.892	**0.955**	0.923	0.930	0.910	**0.943**	**0.942**	**0.948**

N, number of subject; Bias, empirical bias; MSE, empirical mean squared error; RE, relative efficiency is a ratio that, for each sample size (N) and percent censoring, compare the empirical MSE from the LOD/2 substitution method to the MSE from the other substitution method; CP_{AVG}, coverage probability from corresponding 95% confidence intervals which utilize the average of two bias corrections. The coverage probabilities falling within a near-nominal range of 0.936 and 0.964 are highlighted in bold.

Table 5. Parameter estimates, bias-corrected standard error estimates (in parentheses), and corresponding correlation parameter estimates resulting from analyses of the chlorpyrifos data.

% Censoring		Covariate	LOD/2 Substitution	Beta-Substitution	Imputation Without Covariates	Imputation With Covariates	QQ-plot
1.63	GEE	Minutes Applied	0.006 (0.002)	0.006 (0.002)	0.006 (0.002)	0.006 (0.002)	0.006 (0.002)
		Crawl Space Treated	0.612 (0.103)	0.614 (0.102)	0.614 (0.102)	0.613 (0.102)	0.618 (0.102)
		Estimated Correlation	0.546	0.557	0.558	0.555	0.568
	QIF	Minutes Applied	0.008 (0.002)	0.007 (0.002)	0.007 (0.002)	0.007 (0.002)	0.007 (0.002)
		Crawl Space Treated	0.638 (0.105)	0.636 (0.104)	0.635 (0.104)	0.636 (0.104)	0.635 (0.104)
20	GEE	Minutes Applied	0.008 (0.002)	0.007 (0.002)	0.008 (0.002)	0.007 (0.002)	0.005 (0.002)
		Crawl Space Treated	0.713 (0.130)	0.664 (0.116)	0.726 (0.129)	0.549 (0.159)	0.540 (0.090)
		Estimated Correlation	0.556	0.553	0.532	0.501	0.564
	QIF	Minutes Applied	0.009 (0.002)	0.008 (0.002)	0.009 (0.003)	0.007 (0.002)	0.007 (0.002)
		Crawl Space Treated	0.725 (0.137)	0.683 (0.120)	0.734 (0.132)	0.621 (0.143)	0.568 (0.091)

GEE, generalized estimating equations; QIF, quadratic inference function.

Table 6. Parameter estimates, bias-corrected standard error estimates (in parentheses), and correlation parameter estimates resulting from analyses of the flame retardant data.

	Covariate	LOD/2 Substitution	Beta-Substitution	Imputation Without Covariates	Imputation With Covariates	QQ-plot
GEE	Last Shift Worked					
	Previous Day	Reference	Reference	Reference	Reference	Reference
	Two or More Days Ago	-0.76 (0.17)	-0.72 (0.11)	-0.80 (0.09)	-0.59 (0.12)	-0.36 (0.43)
	Estimated Correlation Parameter in $\boldsymbol{R}_i$	-0.03	-0.21	-0.03	-0.25	-0.29
	CIC	1.67	0.95	1.35	0.89	1.18
QIF	Last Shift Worked					
	Previous Day	Reference	Reference	Reference	Reference	Reference
	Two or More Days Ago	-0.73 (0.08)	-0.69 (0.08)	-0.59 (0.10)	-0.91 (0.17)	-0.71 (0.21)

GEE, generalized estimating equations; QIF, quadratic inference function; CIC, correlation information criteria.